Renal involvement in vasculitis
Renal involvement in vasculitis

Stephen Marks
Consultant Paediatric Nephrologist

Great Ormond Street Hospital for Children and UCL Institute of Child Health, London, UK.

2nd IPNA-ESPN Master for Junior Classes, Leuven, Belgium Wednesday 2 September 2015
Introduction

• Case presentation
• Classification of AAV
• Management
• Prognosis
Case history - 1

• 12 year old girl presenting with AKI
  – youngest of six children to consanguineous parents
  – sore throat 6 weeks prior to presenting

• S/B GP x 2: cervical lymphadenopathy
• 2 weeks later developed macroscopic haematuria
• admitted to local hospital due to increasing abdominal pain
• discharged on oral antibiotics
• re-admitted following week with worsening abdominal pain
• productive cough of yellow sputum without haemoptysis
• intermittent fevers, reduced appetite, decreased fluid intake
• felt unwell and vomited on the day of her transfer
• reduced urine output on transfer but normal bowel motions
• no rash, headaches, visual disturbances
Examination

• Apyrexial at 36.1°C

• Palpable lymphadenopathy

• Cardiorespiratory examination
  – CRT < 2 seconds
  – HR of 90/min; SBP of 100mmHg; RR of 18/min
  – chest clear
  – no additional sounds
  – slightly congested throat
  – normal ENT

• Abdominal and neurological examinations
  – normal

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<table>
<thead>
<tr>
<th></th>
<th>First admission</th>
<th>Readmission (15 days later)</th>
<th>Readmission (16 days later)</th>
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<tr>
<td>CRP</td>
<td>34.4</td>
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## Local results

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Other investigations

• Blood tests
  – IgG 226.5 (0.8 to 14)
  – IgA 3.65 (0.64)
  – IgM 2.57 (0.6 to 3.2)
  – C3 179 (65 to 190)
  – C4 12.9 (15 to 50)
  – ASOT detected
  – antinuclear IgG negative, < 1 in 80

• Chest x-ray
  – patchy consolidation of the right upper lobe suggestive of infection
  – repeat chest x-ray showed that the consolidation had resolved

• Ultrasound scan
  – right kidney of 10.3cm and a left kidney of 10.6cm with increased echogenicity
  – no evidence of dilatation
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GOSH investigations

- Hb 78g/l
- WCC 7.32 x 10^9/l
- Neutrophil 4.63 x 10^9/l
- Lymphocyte 1.92 x 10^9/l
- Platelet 446 x 10^9/l
- Blood film
  - microcytic and hyperchromic red cells
  - platelet anisocytosis and rouleaux seen on blood film
- ESR 128mm/hour
- CRP 27g/l
- PT 12.0 seconds
- APTT 33.7 seconds
- Thrombin time 13.2 seconds
- Fibrinogen 4.1g/l
GOSH investigations

- Sodium 135mmol/l
- Potassium 3.7mmol/l
- Chloride 100mmol/l
- Bicarbonate 24mmol/l
- Urea 17.3mmol/l
- Creatinine 540µmol/l
- Calcium 2.10mmol/l
- Magnesium 0.75mmol/l
- Phosphate 1.83mmol/l
- Albumin 28g/l
- Bilirubin < 2µmol/l
- ALP 161U/l
- ALT 50U/l
- ASOT 3300
- Anti DNase B 556
  - ASOT titre should be less than 200 and
  - anti DNase B should be less than 300 in school age children
83% (20/24) fibrocellular crescentic GN
Auto-immune profile

- Smooth muscle antibodies: Negative
- GPC antibodies: Negative
- Mitochondrial antibodies: Negative
- Reticulin antibodies: Negative
- LKM antibodies: Negative
- Anti-GBM antibodies: Negative
- Anticardiolipin IgG: Negative
  - 15.4 (normal range 0 to 17) GPL U/ml
- ANA: Negative
- ENA: Negative
# Auto-immune profile

- **pANCA**: Negative
- **cANCA**: Positive
- **PR3**: 61 (Range 0-10) EU/ml
- **C3c**: 1.68 (0.75 to 1.65) g/l
- **C4**: 0.30 (0.14 to 0.54) g/l
- **Immunoglobulins**
  - **IgG**: 20.8 (5.4 to 16.1) g/l
  - **IgA**: 2.77 (0.8 to 2.8) g/l
  - **IgM**: 1.93 (0.5 to 1.9) g/l

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IT’S WEGENER’S GRANULOMATOSIS
ANCA-associated vasculitis

- **Wegener's granulomatosis (WG)**
  - now known as granulomatosis with polyangiitis (GPA)
  - named after Friederich Wegener who described disease in 1936 but due to his Nazi past, reclassification with descriptive name

- **Vasculitis that affects small- and medium-sized vessels in many organs**
  - damage to the lungs and kidneys can be fatal
  - requires long-term immunosuppression
  - 5-year survival up to 87%
  - some of the mortality due to toxicity of treatment
GPA diagnosis

• Clinical features

• Inflammation
  – anaemia, increased ESR and CRP

• cANCA / increased PR3

• Pauci-immune (crescentic GN)

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Treatment of RPGN

- Intravenous methylprednisolone
  - 600mg/m$^2 \times 3$ then
  - high dose oral corticosteroids (60mg/day)

- Intravenous rituximab and cyclophosphamide
  - consideration of oral or intravenous cyclophosphamide

- Plasma exchange (5 daily)

- Broad spectrum antibiotics and antifungals
  - staphylococcus grown in green sputum
  - changed to oral co-trimoxazole

- Aspirin

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Further investigations

- MRI scan of nasal spaces and orbit
  - some thickening of the sinuses

- Pulmonary function tests
  - FVC of 85%
  - FEV 93% of predicted

- High resolution CT chest
  - two nodules in the right upper lobe, one is 6mm and the second is 12mm
Progress

• Nursing staff concerned
  – difficult to engage patient
  – parental education difficult
  – latterly occasional missed clinics

• Converted from 12 week course of oral cyclophosphamide to oral azathioprine as clinically stable
Subsequent investigations

• Glomerular filtration rate
  – 78mls/min/1.73m² via iohexol six months later
  – simultaneous plasma creatinine of 76 µmol/l

• CT chest scan
  – unchanged right upper lobe lesion
  – 2.5 years later

• Normal microlaryngobronchoscopy
  – 3.5 years later
5 year follow-up

• Attending college for one year diploma course in Health and Social care

• Ongoing wheeze
  – well controlled since commenced on montelukast
  – occasional use of inhalers

• Examination
  – weight between 9th - 25th centile
  – height on 25th centile
  – normotensive

• Urine dipstick: 1+ protein (previously 3+), no haematuria
Current medications

- Prednisolone 5mg oral once daily
- Azathioprine 100mg oral once daily
- Enalapril 12.5mg oral once daily
- Aspirin 75mg oral once daily
- Lansoprazole 15mg oral once daily
- Ferrous fumarate 210mg oral once daily
- Co-trimoxazole 720mg oral three times weekly (T/Th/Sat)
- Montelukast (Singulair) 10mg once daily
- Seretide 125/25 250mcg (2 puffs) twice daily (discontinued)
- Salbutamol 200mcg (2 puffs) twice daily up to 10 puffs (discontinued)
**Current eGFR of 82mls/min/1.73m²**

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<tr>
<th>Parameter</th>
<th>Value</th>
<th>Normal Range</th>
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<td>Sodium</td>
<td>140 mmol/L</td>
<td>(137 - 145) mmol/l</td>
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<td>Potassium</td>
<td>4.0 mmol/L</td>
<td>(3.6 - 5.0) mmol/l</td>
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<tr>
<td>Chloride</td>
<td>105 mmol/L</td>
<td>(98 - 107) mmol/l</td>
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<tr>
<td>Total CO2</td>
<td>25 mmol/L</td>
<td>(22 - 30) mmol/l</td>
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<tr>
<td>Urea</td>
<td>4.4 mmol/L</td>
<td>(2.5 - 7.5) mmol/l</td>
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<tr>
<td>Creatinine</td>
<td>64 umol/L</td>
<td>(44 - 80) µmol/l</td>
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<td>Calcium</td>
<td>2.19 mmol/L</td>
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<td>0.82 mmol/L</td>
<td>(0.70 - 1.00) mmol/l</td>
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<td>Phosphate</td>
<td>1.14 mmol/L</td>
<td>(0.81 - 1.45) mmol/l</td>
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<td>Total bilirubin</td>
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<td>ALP</td>
<td>53 (30 - 126) U/l</td>
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<td>ALT</td>
<td>30 (9 - 52) U/l</td>
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<td>Hb</td>
<td>11.6g/l</td>
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<td>WCC</td>
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<td>Neutrophils</td>
<td>6.13 x 10⁹/l</td>
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<td>Platelets</td>
<td>266 x 10⁹/l</td>
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<td>ESR</td>
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<tr>
<td>PR3</td>
<td>0.40 (0 - 1.99) IU/ml</td>
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<tr>
<td>MPO</td>
<td>&lt;0.20 (0 - 3.49) IU/ml</td>
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Not all vasculitis is ANCA-associated vasculitis
Small Vessel Vasculitis

Jennette et al (2012), Arthritis Rheum
Pauci-immune GN in AAV

- 54% of 126 biopsies with AAV showed only weak immune complex deposition on EM

Anti-neutrophil cytoplasmic antibodies

cANCA often against PR3

pANCA often against MPO

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ANCA-associated vasculitis

- Granulomatosis with polyangiitis (GPA)
  - Wegener’s granulomatosis
- Microscopic polyangiitis (MPA)
- Renal limited vasculitis
- Churg-Strauss syndrome
  - Eosinophilic granulomatosis with polyangiitis

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No substantial staining for immunoglobulins

Idiopathic glomerulonephritis

ANCA glomerulonephritis

- No systemic vasculitis
  - ANCA-GN or RLV
- Vasculitis with no asthma or granulomas
  - Microscopic polyangiitis
- Granulomas but no asthma
  - Wegener’s granulomatosis or GPA
- Asthma, granulomas, & eosinophilia
  - Churg-Strauss syndrome

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Analysis of 111 ANCA-Disease Patients

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ANCA-associated vasculitis

- Granulomatosis with polyangiitis (GPA)
  - necrotising, granulomatous vasculitis
  - ocular, upper and lower respiratory tract involvement
  - glomerulonephritis
  - regional - generalised forms
Classification criteria of GPA 2006

- Three out of the below six features

  - abnormal urine dipstick
  - granulomatous inflammation on biopsy
  - nasal sinus inflammation
  - airway stenosis
  - abnormal chest x-ray or CT
  - PR3 ANCA

Ozen S et al (2006); Ann Rheum 65: 936-941

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Classification criteria of GPA 2010

• Three out of the below six features

renal involvement
histopathology
upper airway involvement
laryngo-tracheobronchial stenoses
pulmonary involvement
ANCA positivity

Ozen S et al (2010); Ann Rheum 69: 798-806

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Classification criteria of GPA 2010

- Three out of the below six features
  
  renal involvement
  histopathology
  upper airway involvement
  laryngo-tracheobronchial stenoses
  pulmonary involvement
  ANCA positivity

Sn 93.3%; Sp 99.2%

Ozen S et al (2010); Ann Rheum 69: 798-806

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GPA nasal septal collapse

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Right middle lobe mass in GPA

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ANCA-associated vasculitis

- Microscopic polyangiitis (MPA)
  - multisystem, non-granulomatous necrotising pauci-immune small vessel vasculitis
  - pulmonary capillaritis without upper airway involvement
  - associated with MPO ANCA (pANCA)
  - high frequency of glomerulonephritis (esp. RPGN)
    - renal limited form but can develop other organ involvement
- normal visceral angiography
- not associated with hepatitis B antigenaemia
Alveolar haemorrhage in MPA

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ANCA-associated vasculitis

• Renal limited vasculitis
  • pauci-immune ANCA positive crescentic glomerulonephritis
Treatments of AAV

• To induce remission quickly to minimise active inflammation

• To minimise frequency and severity of relapses with minimal side-effects

• To reduce chronic damage from active and subclinical disease
Diagnosis of AAV

Contraindication to CYC
- Infection
- Fertility Protection
- Previous Urinary Bladder Neoplasia
- Hemorrhagic Cystitis
- High previous CYC exposure

NO

Induction Treatment
CYC with GCs

Maintenance
AZA/MTX, GCs tapered

Sustained remission

Relapse

Refractory disease

YES

Induction Treatment
RTX with GCs

Maintenance
None or RTX or AZA/MTX

RTX ineffective or contraindicated

Expert advice 3rd line agents

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Alberici Jayne (2014); NDT
Treatments of AAV

• Corticosteroids with cyclophosphamide
  – with or without plasma exchange for crescentic glomerulonephritis or pulmonary vasculitis
  – anti-platelet agent
  – co-trimoxazole for GPA
  – role of intravenous rituximab +/- cyclophosphamide
  -> then azathioprine (as opposed to MMF)
Relapses in Wegener’s granulomatosis: the role of infection

A J PINCHING, A J REES, B A PUSSELL, C M LOCKWOOD, R S MITCHISON, D K PETERS

- 45% (9/20) relapses in patients with GPA 2y to infection
- Treatment of infection alone insufficient
EUVAS randomised clinical trials

- CYCAZAREM 155
- NORAM 100
- MEPEX 150
- CYCLOPS 160
- REMAIN 120
- IMPROVE 170
- RITUXVAS 44
- MYCYC 140
- PEXIVAS 500
- RITAZAREM

Induction: 
Remission: 

MEPEX outcome

Survival no different but renal recovery significantly favours plasma exchange


$p = 0.001$
Azathioprine as maintenance agent after induction with cyc
MYCYC

Remission

- MMF vs CYC for induction

<table>
<thead>
<tr>
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<th>MMF n=70</th>
<th>IV CYC n=70</th>
<th>Difference (90% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Primary</td>
<td>51 (73%)</td>
<td>52 (74%)</td>
<td>-1% (-14 to 11)</td>
<td>0.08</td>
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<tr>
<td>Secondary</td>
<td>63 (90%)</td>
<td>56 (80%)</td>
<td>10% (0 to 20)</td>
<td>&lt;0.001</td>
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</table>

 Cumulative prednisolone dosing at 6 months did not differ but slightly more noncompliance at low doses in the MMF group.
IMPROVE

• Relapses more common in the MMF group (55%) than in the azathioprine group (37.5%)

• Same adverse event rates

Rituximab

- Future to replace cyclophosphamide for induction of remission
  - particularly for relapsing disease
- Similar mortality, serious adverse events and infection rates as cyclophosphamide in short term
- RITAZAREM for intravenous rituximab every 6 months versus azathioprine for maintenance of remission
NHS England funding of MabThera® (rituximab) for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

- MabThera, in combination with glucocorticoids, is now indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener’s; GPA) and microscopic polyangiitis (MPA) - two types of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV).
- NHS England has approved its use in appropriate patients and will fund its use in this indication in certain situations with the aim of reducing inequalities in treatment access.
- The mechanism for funding is through the responsible Area Team at NHS England.
- This applies to the use of MabThera in severe active GPA or MPA only. MabThera will be funded by Clinical Commissioning Groups (CCGs) as the responsible budget holder.

In what situations will NHS England fund the use of MabThera?

MabThera will be routinely funded for the treatment of severe active GPA or MPA in line with the licence in the following situations:

- As an initial remission induction agent in newly diagnosed patients where avoiding the use of cyclophosphamide is desirable.
- As a remission induction agent when cyclophosphamide has not been effective.
- As a remission induction agent at time of first relapse.

1. Roche. MabThera Summary of Product Characteristics. April 2013
Rituximab vs Cyclophosphamide Induction (RITUXVAS)
Jones RB et al. NEJM 2010. (EUVAS)

- 44 patients with new ANCA vasculitis with renal involvement.
- RCT, 3:1 assignment.
- IV Rituximab 375mg/m² BSA per week for 4 weeks + 2 IV CYC pulses (no Azathioprine; 33 pts – 18 WG, 12 MPA, 3 renal limited vasc) vs. IV CYC for 3-6 months followed by Azathioprine (11 pts – 4 WG, 4-MPA, 3 RLV).
- Primary end-point: sustained remission at 12 months and SAE.
- Median age: 68 yrs.
- Median baseline GFR: 20 vs. 12
- HD at baseline: 8 vs. 1
- Plasma xchange @ baseline: 8 vs. 3
- Common Rituxan uses: RA (with MTX) and NH-lymphoma
- Results
  - Median BVAS score: 19 vs. 18
  - Pts on 5mg pred @ 9 months: 96% vs. 89%
  - Remission: 91% in both groups
  - Sustained remission at 12 mon: 76% vs. 82% (p=0.68)
  - Median increase in GFR between 0 & 12 months: 19 vs. 15 ml/min (p=0.14).
  - SAE: 42% vs. 36% (p=0.77)
  - Cancer: 6% vs. 0%
  - Serious infxns: 18% in both.
  - SAE req hospitalization: 36% in both
  - Mortality: 18% in both groups (6 pts vs. 1 pt).
  - More leucopenia with CYC

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RITUXIVAS trial

Control Regimen

MP CYC

AZA

RTX Regimen

MP RTX CYC

All Patients

Steroid taper

0 3 6 9 12

Months

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RITUXIVAS remission (BVAS = 0 for 6m)

Time to remission

<table>
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<tr>
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<th>CYC</th>
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<td>Sustained remission</td>
<td>25/33 (76%)</td>
<td>9/11 (82%)</td>
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Jones RB et al (2010); N Engl J Med
Rituximab vs Cyclophosphamide Induction (RAVE-ITN)
Stone JH et al. NEJM 2010. (EUVAS)

- 197 patients; 75% WG, 24% MPA, 49% new dz, 93% white, 66% renal inv
- Severe dz/BVAS 8.2. No limited WG.
- Excluded pts with alveolar hemorrhage requiring vent support &/or creat > 4.0
- 9-center, 1:1 non-inferiority RCT trial
- IV Rituximab 375mg/m² BSA per week for 4 weeks plus daily placebo vs. PO CYC (2mg/kg/d) + placebo inj
- In control group, if remission btwn 3-6 mon: can switch from CYC to azathioprine (2 mg/kg/d).
- -3 pulses of 1g solumedrol, then PO pred (1mg/kg/d). Tapered & discontinued by 5 mon if remission without disease flares.
- Primary end-point: Remission (BVAS of 0) at 6 months off steroids.

Early treatment failure: at 1 month if BVAS not decreased by >1 point or a new dz manifestation.

Results
- 64% vs. 53% reached primary end-point (P<0.001; non-inferiority)
- 67% vs. 42% reached remission of relapsing dz (P<0.001; superiority); persisted after adjustment for ANCA type & clinical site (OR, 1.40; 95% CI, 1.03 to 1.91; P = 0.03).
- Results not different in WG vs. MPA.
In pts with renal inv: CrCl increased by 11.2ml vs. 10.5ml in 6 months. 61 vs. 63% reached primary endpoint (p=0.92)
- More leucopenia with CYC (10 vs. 3)
- More hospitalization (8 vs. 2) cancer with Rituxan (6 vs. 1).
**RAVE results**

<table>
<thead>
<tr>
<th></th>
<th>RTX n = 99</th>
<th>CYC n = 98</th>
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<tbody>
<tr>
<td>Remission at 6 months and discontinuation of corticosteroids</td>
<td>64%</td>
<td>53%</td>
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<tr>
<td>Relapsing disease</td>
<td>67%</td>
<td>42%; p=0.01</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation of therapy</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>Leucopenia (grade 2)</td>
<td>33%</td>
<td>22%; p = 0.01</td>
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<tr>
<td>Deaths</td>
<td>1</td>
<td>2</td>
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</table>
Prognosis of AAV

• Mortality of 10% and 25% at 1 & 5 years
• High remission rates of 90%  
  – suboptimal disease control in 20%
• High relapse rates of 50%  
  – 50% of survivors relapse by 5 years
• Significant risk for ESKD in 30%  
  – post-transplant recurrence in 15 - 20%
• >95% suffer treatment-related toxicities

Dr Stephen Marks, UK
Any questions?

Dr Stephen Marks, UK