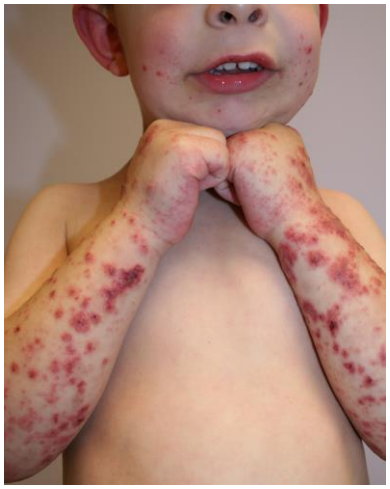
HSP nephritis: when to biopsy?

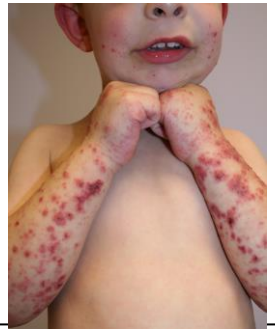


EMEESY Network educational day 2016

Dr. Louise Oni (*nee Watson*)

NIHR Academic Clinical Lecturer in Paediatric Nephrology,
Alder Hey Children's Hospital, University of Liverpool

My background



Henoch Schonlein Purpura – A 5-Year Review and Proposed Pathway

HSP nephritis

HQIP Healthcare Quality Improvement Partnership

PAPER

Urinary monocy… glycoprotei… in juveni…

Disease Activity, Severity, and Damage in the UK Juvenile-Onset Systemic Lupus Erythematosus Coh…

UK JSLE Study Group

Increased Serum Concentration of Sphingosine-1- in Juvenile-onset Systemic Lupus Erythematosus

The pro-inflammatory potential of T cells i… systemic lupus erythematosus

Urine biomarkers in juvenile-onset SLE nephritis

Urine biomarkers for monitoring juvenile lupus nephritis: a prospective longitudinal study

Lupus nephritis

Inflammatory renal disease

Outline

- Background
- When to refer to nephrology
- When would we do a renal biopsy
- What is the management of HSPN?
- Future advances

Henoch Schonlein Purpura (HSP)

Definition:

Vasculitis with IgA-1 dominant immune deposits affecting small vessels; often involving skin, GI tract, arthritis and associated with GN that is indistinguishable from IgA nephropathy

Clin Exp Immunol. 2011 May; 164(Suppl 1): 11–13. PMCID: PMC3095857
doi: 10.1111/j.1365-2249.2011.04358.x

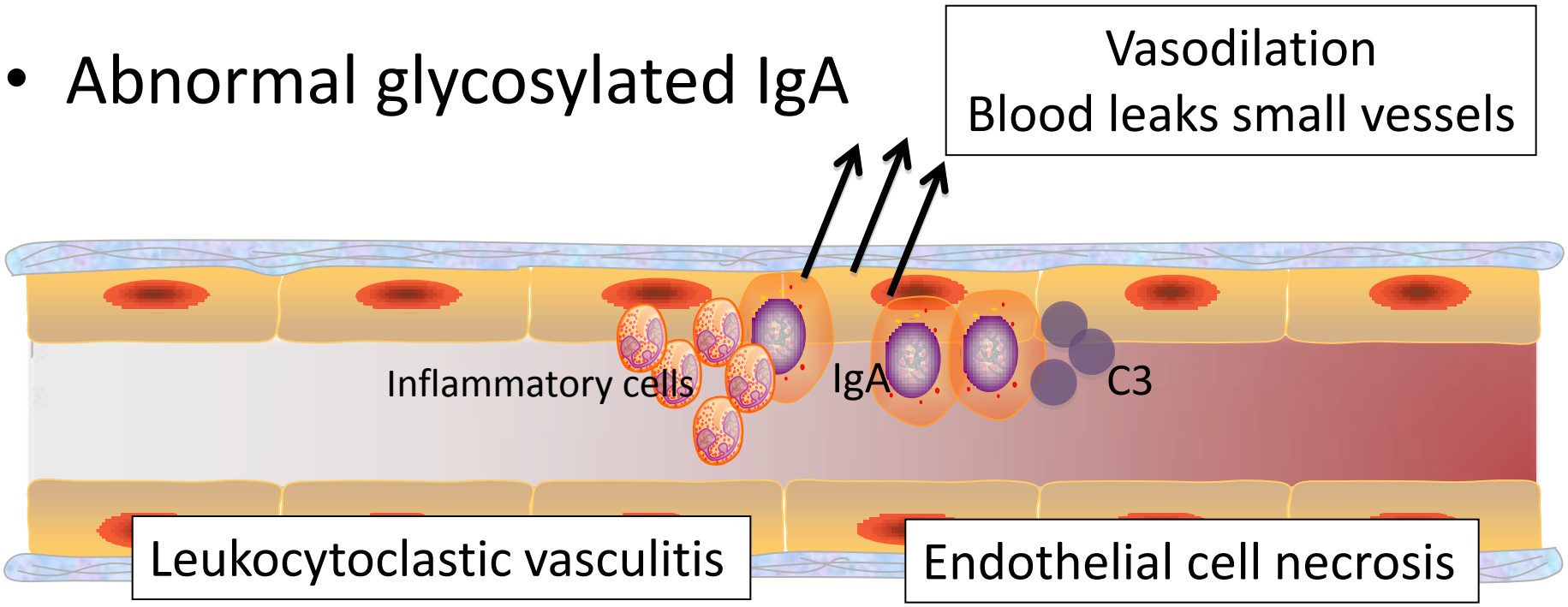
Nomenclature and classification of vasculitis – update on the ACR/EULAR Diagnosis and Classification of Vasculitis Study (DCVAS)

R A Luqmani,* R Suppiah,* P C Grayson,† P A Merkel,† and R Watts‡

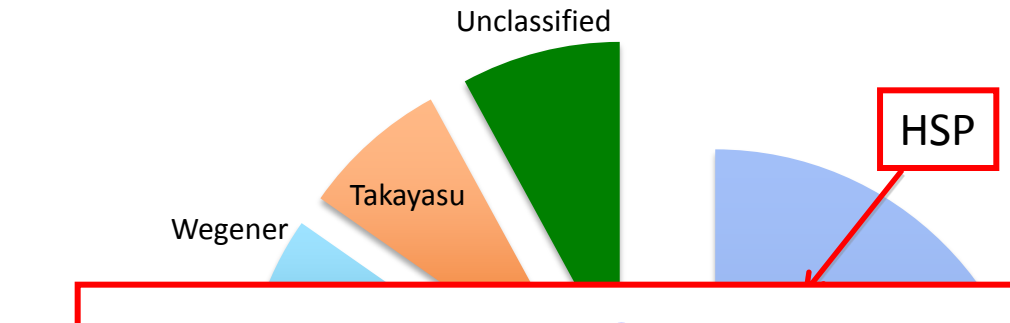
"Immunoglobulin A vasculitis"

Pathophysiology

- Systemic small vessel vasculitis
- Multifactorial
- Abnormal glycosylated IgA



Most common childhood vasculitis



- Child: 3-27 cases/ 100,000
- Onset in Autumn-Winter

s

Average DGH;

- Catchment population of 60,000 children
- ≈ 6-12 cases of HSP/year

Rare for GP population

- 1 case for approx. every 36 GP's

Ruperto et al, Ann Rheum Dis, 2010;69:790-7, Watts et al, Semin Arthrit Rheum, 1995;25(1):28-34

Typical patient

Males>Females
1.5>1

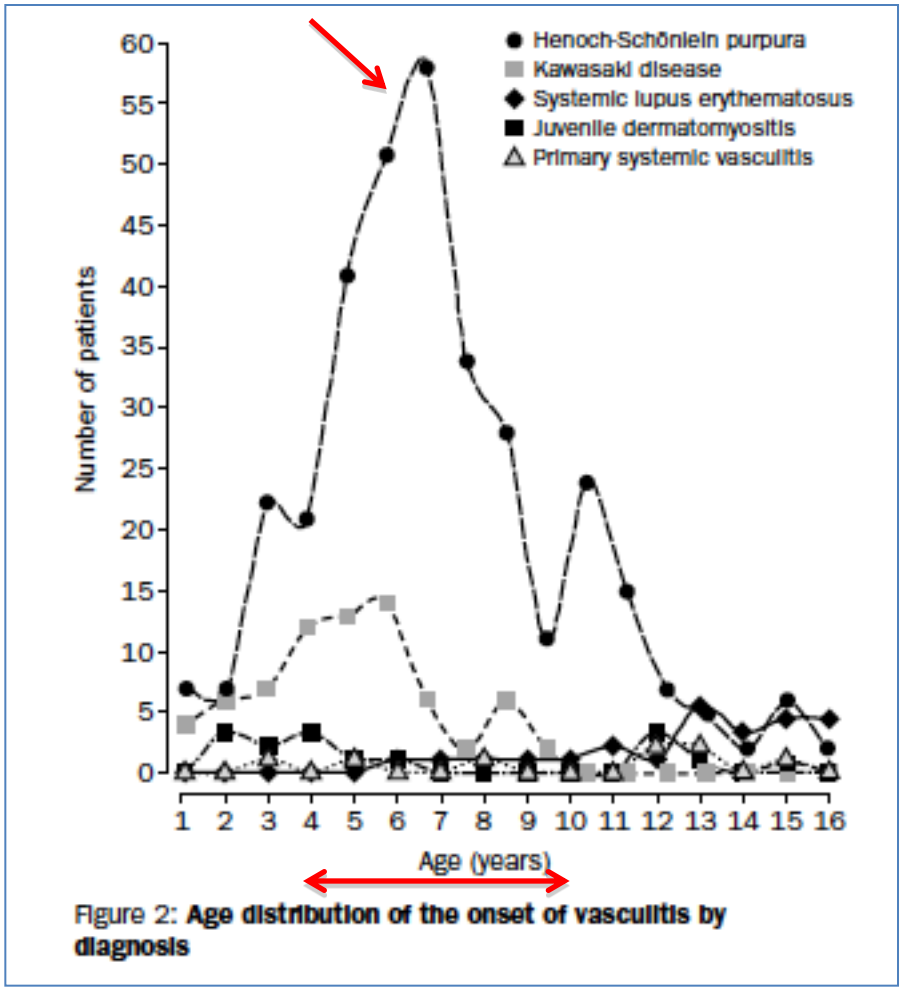
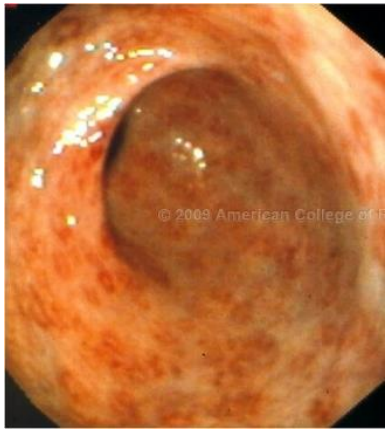


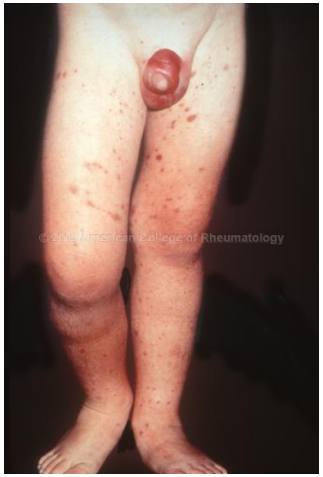
Figure 2: **Age distribution of the onset of vasculitis by diagnosis**

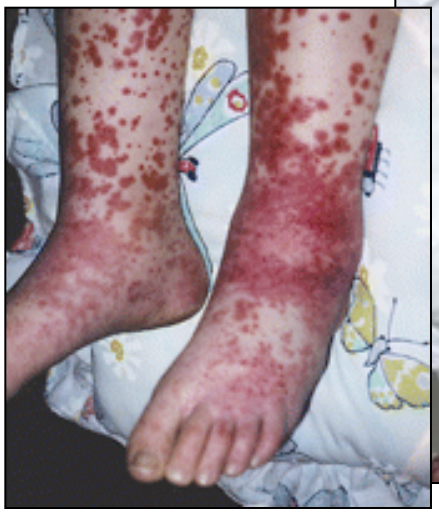
Gardner-Medwin et al, Lancet 2002;360:1197-102

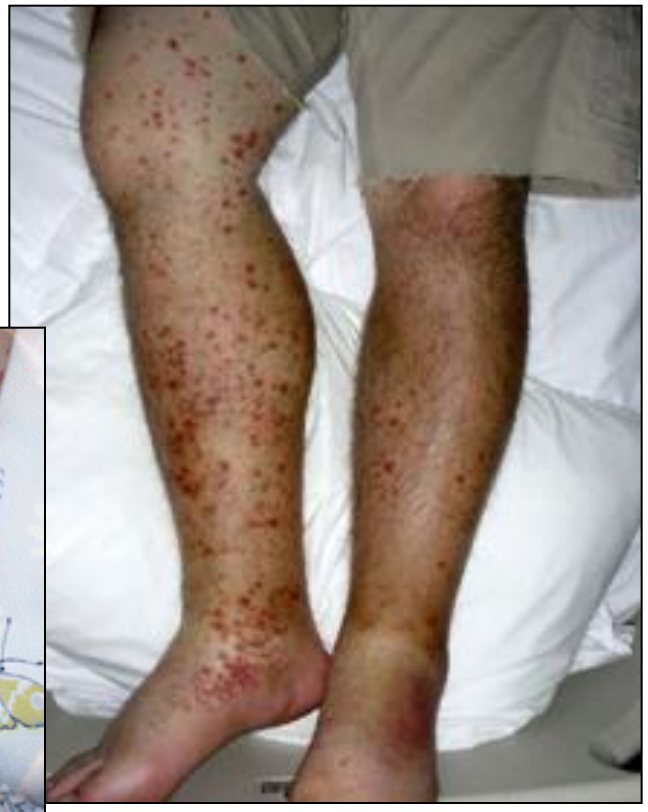
Presents with a rash

- Non-erosive arthritis, arthralgia
- Abdominal pain, bleeding, intussusception
- Scrotal involvement
- Renal involvement
- Rarely neurological, lung

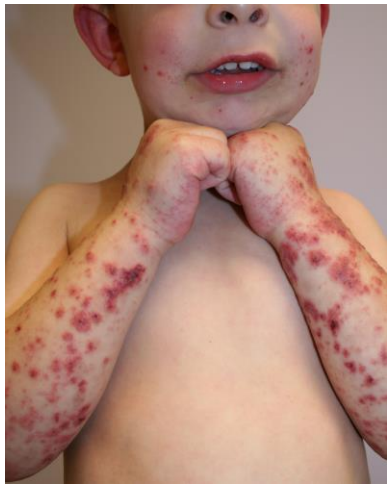








Diagnosis & monitoring



EULAR/PReS Classification of childhood HSP

Table 1 Final EULAR/PRINTO/PRES HSP criteria (with glossary) and classification definition (sample 973)

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
Purpura (mandatory criterion)	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, * not related to thrombocytopenia	89	86	87.5
1. Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding	61	64	62.2
2. Histopathology	Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit	93	89	91.1
3. Arthritis or arthralgias	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion	78	42	59.9
4. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick	33	70	51.4
HSP EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.96)	Purpura or petechiae (mandatory) with lower limb predominance* and at least one of the four following criteria: Abdominal pain Histopathology Arthritis or arthralgia Renal involvement	100	87	93.5

*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.
AUC, area under the curve; EULAR, European League Against Rheumatism; HSP, Henoch–Schönlein purpura; PRES, Paediatric Rheumatology European Society, PRINTO, Paediatric Rheumatology International Trials Organisation.

Ozen et al, Ann Rheum Dis, 2006; 65(7):936-941, Ozen et al, Ann Rheum Dis, 2010; 69(5):798-806

Disease prognosis

- 1/3 symptoms 2 weeks
- 1/3 symptoms 1 month
- 1/3 recurrence

2 years: 94% complete recovery

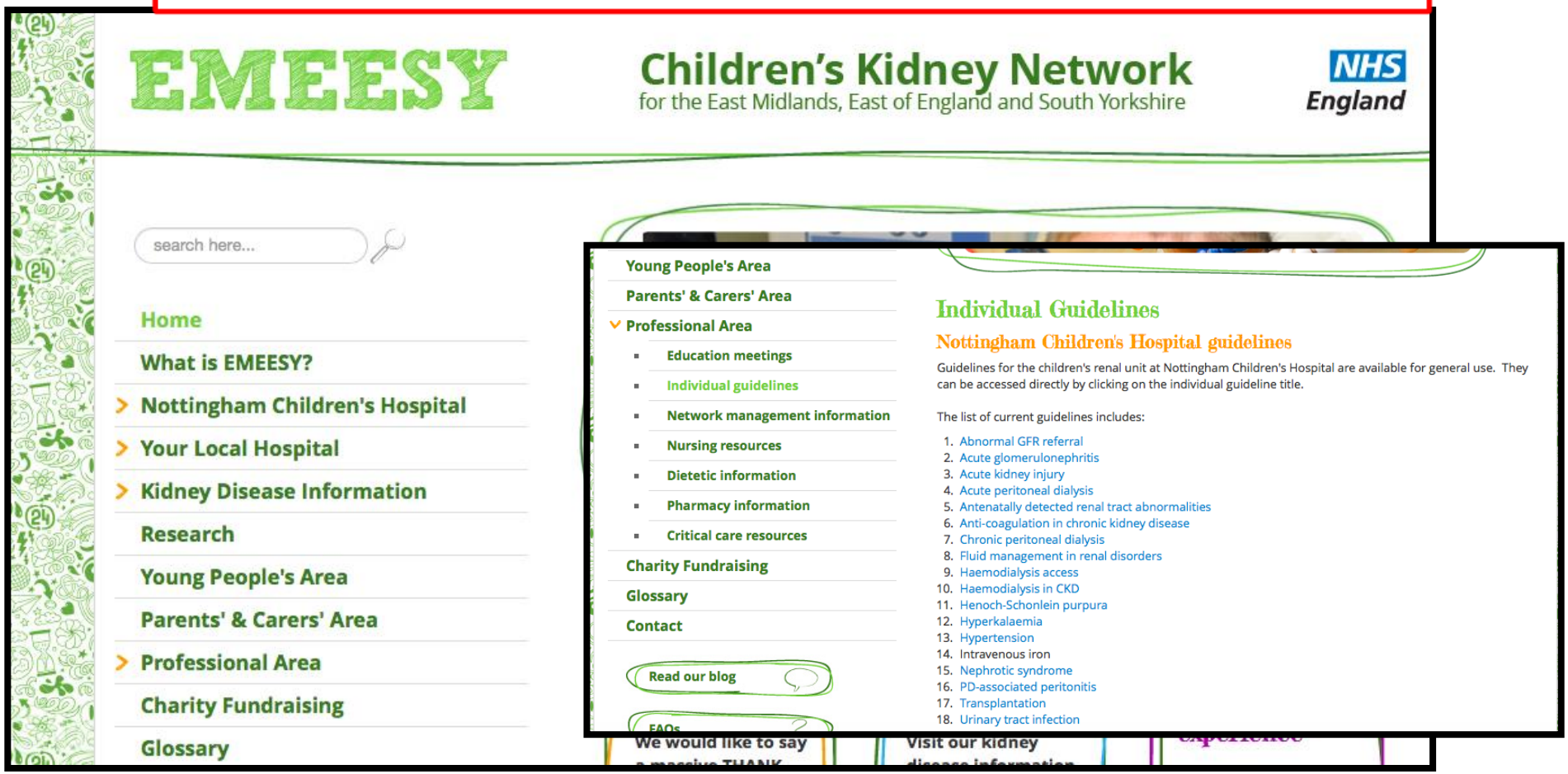
- Early morbidity – GI related
- Late morbidity – renal related
  - Hospital admission related to GI or renal disease

Fidan et al, Ren Fail 2016; Okubo et al, Clin Rheumatol 2015

Renal monitoring

HSP nephritis (HSPN)

Only long term consequence, asymptomatic



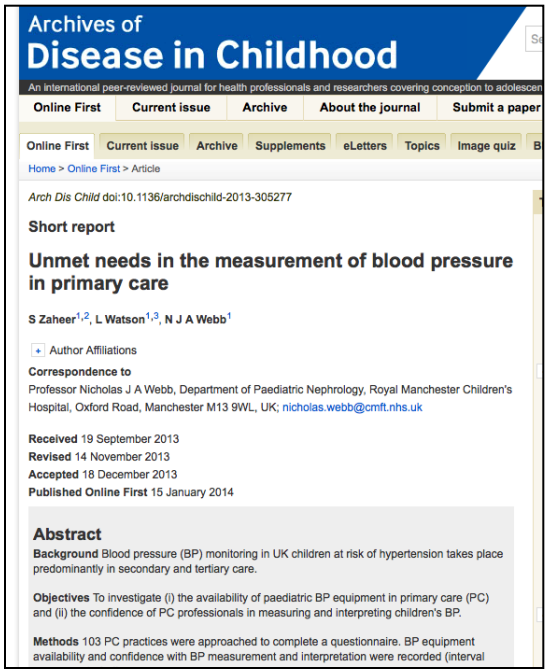
Renal monitoring in primary care

- Availability of BP cuffs
  - GP practices, 4 mile radius of RMCH, n=95
  - 40 (42%) had cuff suitable for a child; small adult cuff
- Confidence in interpreting BP

Self perceived confidence levels	Without normal ranges (mean, 95% CI)	With normal ranges (mean, 95% CI)	p value
Interpreting Children's BP	3.8 (3.3-4.3)	7.4 (6.9-7.9)	p<0.01*

statistically significant

Audit of attendance/compliance



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Arch Dis Child doi:10.1136/archdischild-2013-305277

Short report

Unmet needs in the measurement of blood pressure in primary care

S Zaheer[1,2], L Watson[1,3], N J A Webb[1]

Author Affiliations

Correspondence to
Professor Nicholas J A Webb, Department of Paediatric Nephrology, Royal Manchester Children's Hospital, Oxford Road, Manchester M13 9WL, UK; nicholas.webb@cmft.nhs.uk

Received 19 September 2013
Revised 14 November 2013
Accepted 18 December 2013
Published Online First 15 January 2014

Abstract

Background Blood pressure (BP) monitoring in UK children at risk of hypertension takes place predominantly in secondary and tertiary care.

Objectives To investigate (i) the availability of paediatric BP equipment in primary care (PC) and (ii) the confidence of PC professionals in measuring and interpreting children's BP.

Methods 103 PC practices were approached to complete a questionnaire. BP equipment availability and confidence with BP measurement and interpretation were recorded (interval

Proposed consensus indications for renal biopsy in first 6 months

1. Proteinuria
   - UPCR >200mg/mmol, repeat increasing trend
   - >4 weeks after diagnosis
   - Spot early morning urine protein:creatinine ratio
2. Nephrotic syndrome
   - Low albumin, oedema, heavy proteinuria
3. Nephritic syndrome
   - Hypertension, haematuria, renal impairment
4. Any of; hypertension, macroscopic haematuria only if with proteinuria

Unpublished, National survey of BAPN units, 2013

Renal histology

ISKDC grade	Pathoanatomical findings	CKD PROGRESSION
I	Minimal alterations	
II	Mesangial proliferation	15%
III A	Focal proliferation or sclerosis with <50% crescents	
III B	Diffuse proliferation or sclerosis with <50% crescents	15%
IV A	Focal proliferation or sclerosis with 50–75% crescents	
IV B	Diffuse proliferation or sclerosis with 50–75% crescents	37%
V A	Focal proliferation or sclerosis with >75% crescents	
V B	Diffuse proliferation or sclerosis with >75% crescents	70%
VI	Membranoproliferative glomerulonephritis	

ISKDC=International Study of Kidney Diseases in Children.

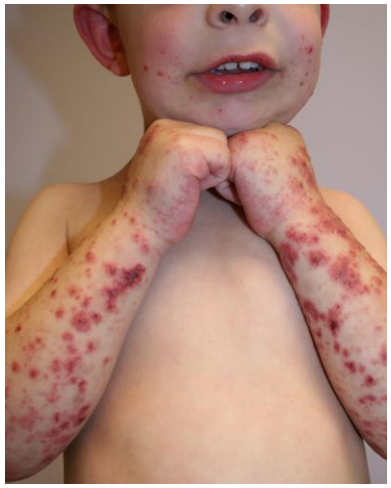
Poor prognostic features

Long term study 49.3 months. End point: eGFR <60ml/min/m^2, >30% reduction renal function, ESRF

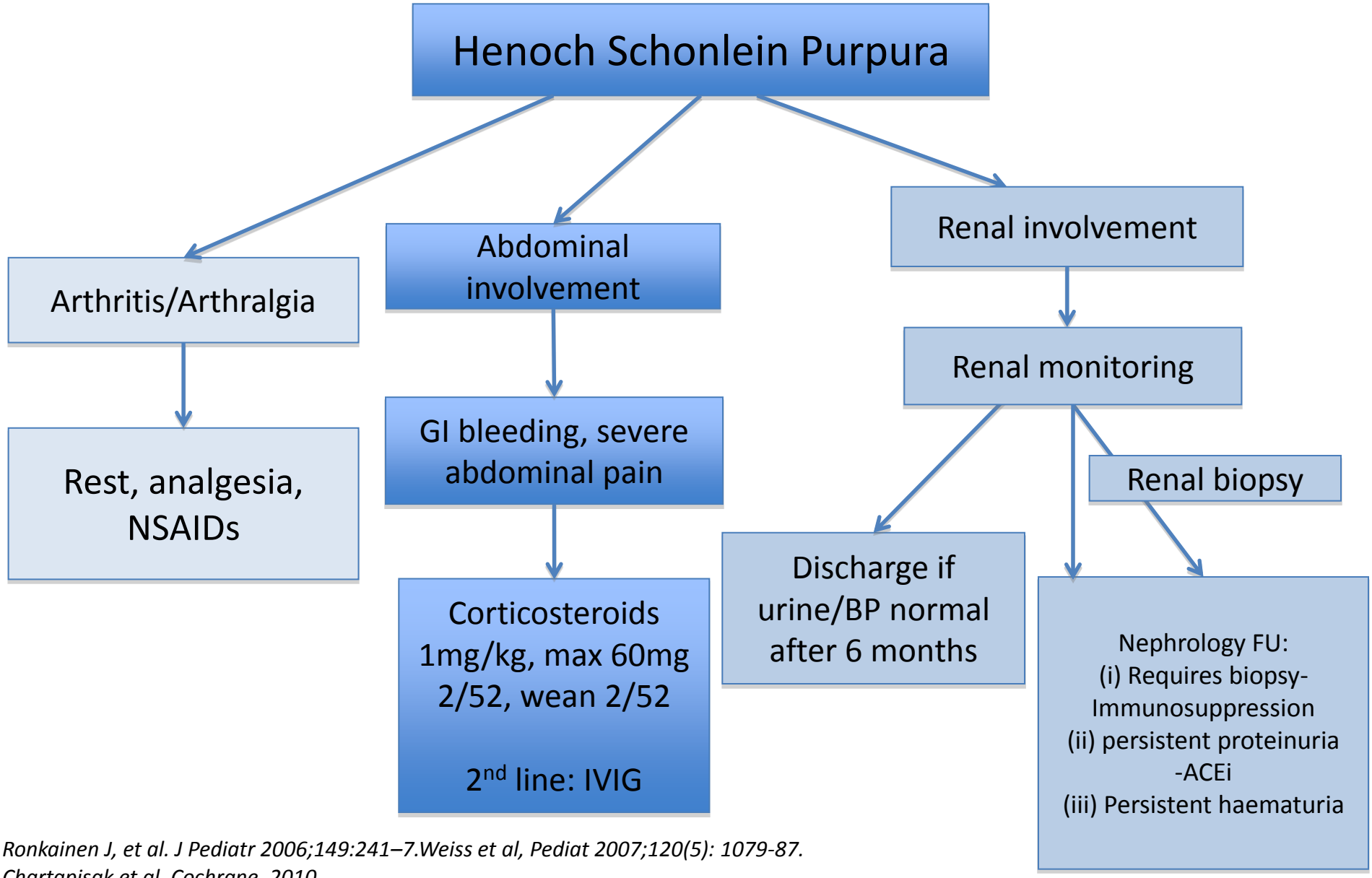
- >50% glomeruli containing crescents
- Endocapillary hypercellularity, tubular atrophy, interstitial fibrosis

Kim et al, Mod Pathol, 2014

Management & prognosis



General management



Ronkainen J, et al. J Pediatr 2006;149:241–7.Weiss et al, Pediat 2007;120(5): 1079-87.
Chartapisak et al, Cochrane, 2010

Treatment of HSPN

Cochrane review (2015): no difference in prevention

- 8 studies, n=746 children
- Early corticosteroids V's placebo, total n=379
- Heparin did reduce kidney disease, 1 study, n=228

Treatment of severe disease

- Cyclophosphamide V's supportive, n=56
- Cyclosporin+MP V's MP, n=15 no difference 6.3 years
- Cyclophosphamide + methylprednisolone, n=12
- Azathioprine + steroids, n=21
- MMF v AZA no difference

- Cochrane: Few RCTs, small numbers, no proven benefit

1. Tizard et al, unpublished, personal communication; Dudley 2007, Huber 2004, Mollica 2004, Ronkainen 2006.2. Jauhola et al, 2011 3. Flynn et al, 2001 4. Bergstein et al, 1998 5. Chartapisak W et al. 2009; Eleftheriou, Brogan, Pediatr Rheumatol online, 2016; Zaffanello et al, Ped Neph 2009.

Suggested treatment:

Severe (renal failure):

- IV MP, cyclophosphamide +/- PEX

Moderate (proteinuria):

- IV MP then oral prednisolone or just prednisolone
- Plus a DMARD
  - AZA/MMF/Cyclophosphamide/Ciclosporin

Biologics and emerging treatments

Target inflammatory injury pathways

- Rituximab: HSP case reports beneficial
  - ➢IgA1 immune complexes
- Complement inhibition: Eculizumab
  - ➢ C3 deposits with IgA
- Fostamatinib: ITP, IgA nephropathy P2 trials
  - – Inhibitor of spleen tyrosine kinase (Syk), blocks IgG receptor signaling in macrophages and B cells

Kistanguri et al, Hematol Oncol Clin North Am 2013, Pillebout et al, NDT 2011

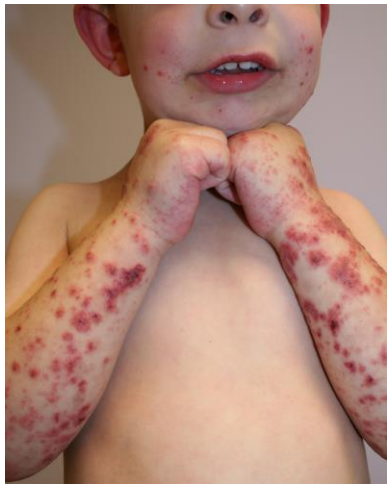
Renal prognosis

- 25–60% will have renal involvement:
  - 76% onset < 4 weeks
  - 97% onset < 3 months
- Isolated microscopic haematuria is benign.
- 82% have normal renal function after 23yr.
- 1.6-3% of all UK childhood ESRF

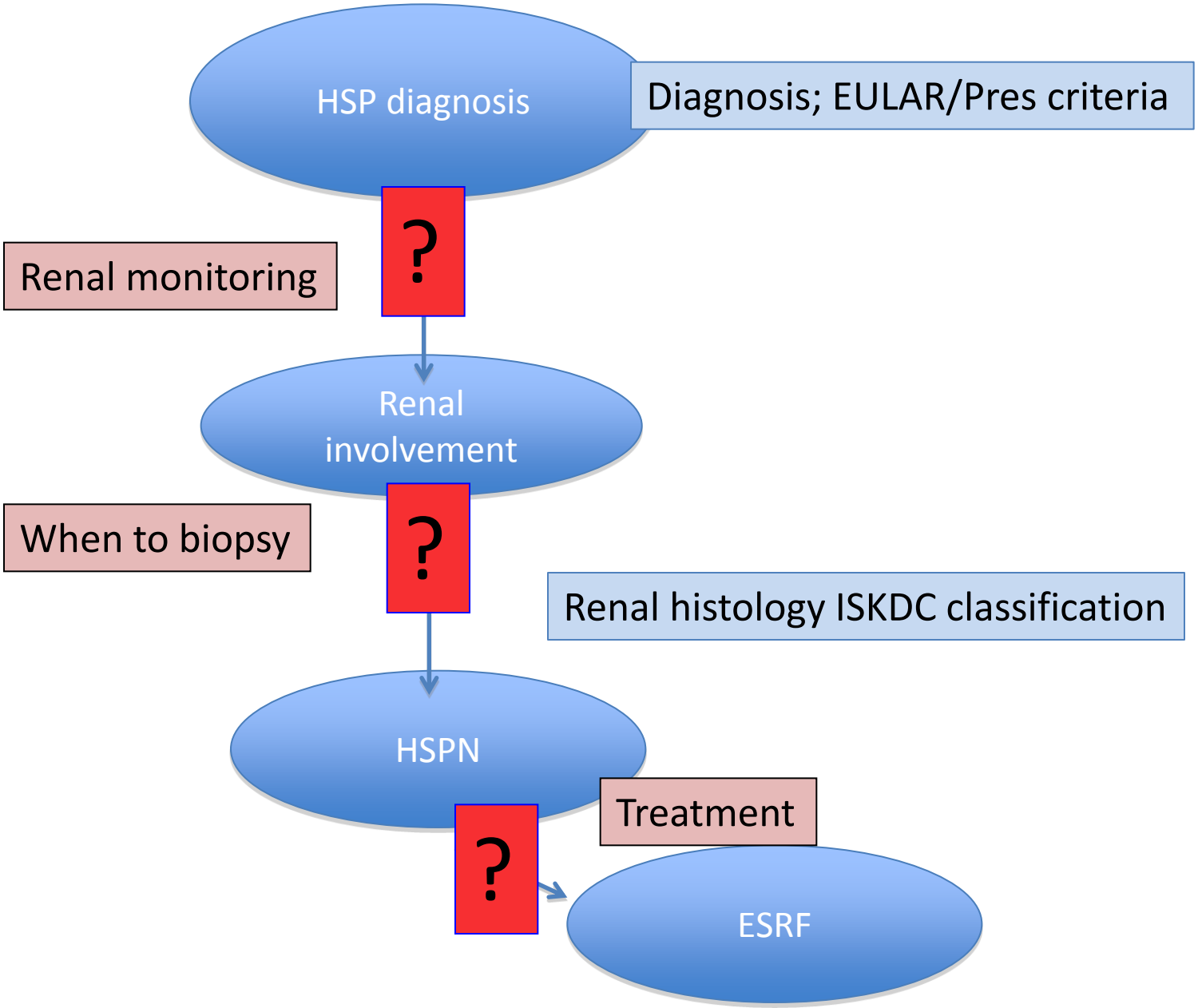
- Mixed nephritic and nephrotic syndrome 20% progress to ESRF
  - 44–50% develop hypertension or CKD.

Mir et al 2007, Shenoy et al, 2007, Butani et al, 2007. UK Renal Registry 2005

The future

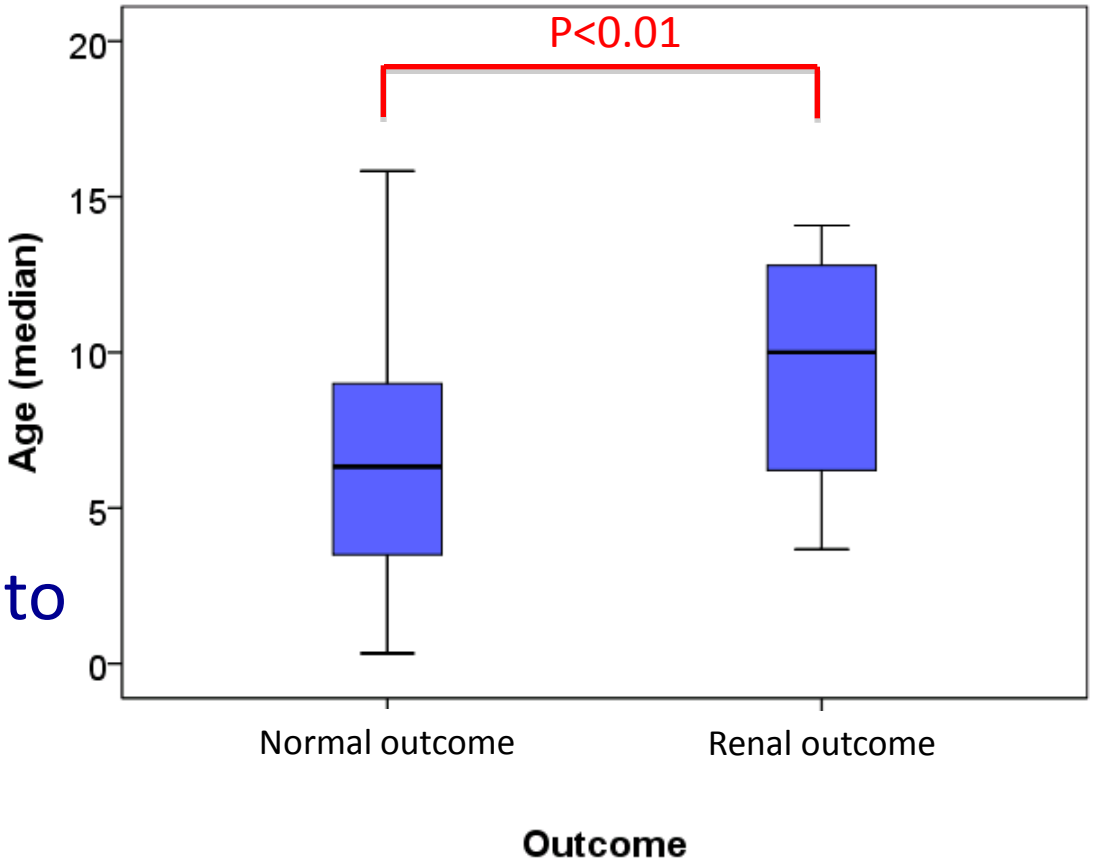


Lots of uncertainty….



Some high risk groups…

Characteristics	Number
Male sex	48%
Caucasian	90%
Age (median)	6.3 years
Cohort recruitment	5.7 years
Cohort size	104
Did not attend	2
Cohort with adequate data	102



Older children more likely to develop HSP nephritis

Watson et al, PlosONE, 2012

Challenges…

Self-limiting course

Trials difficult

Not an adult disease

One-off episode

No animal models

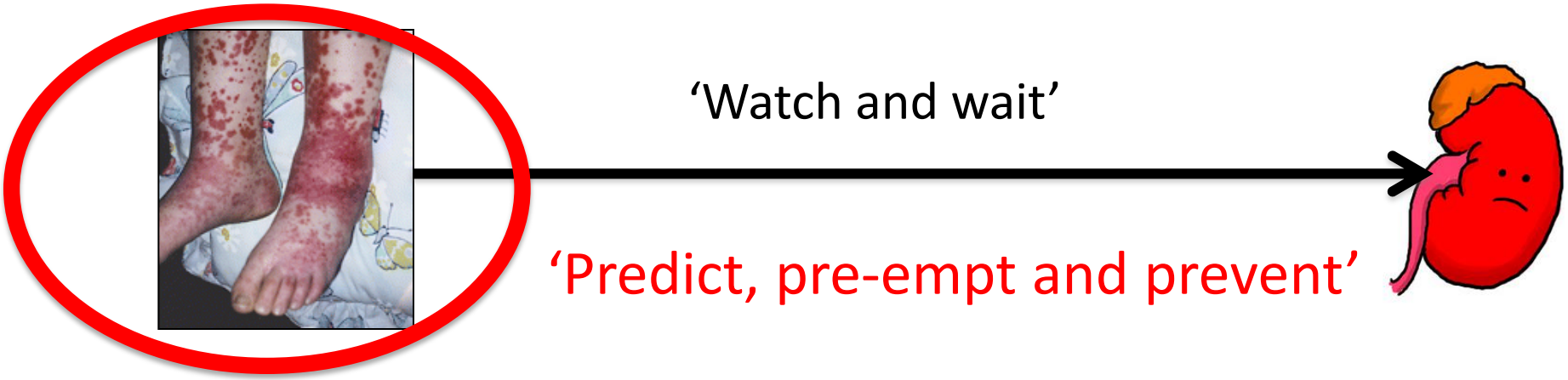
Multi-systemic disease

Presents to numerous centres

No standardised management

Majority excellent outcome

The future…



- Stratify patients
- Better disease biomarkers
- Clinical trials: early intervention
- Listen to our patients & lead adult colleagues

Patient information

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Vasculitis Patient Symposium/Education Day and Gala Charity Ball - March 4th 2017

Posted: 24 Sep 2016

We are delighted to announce that after the huge success of the Vasculitis Patient Symposium in 2015, that we have agreed to arrange another one - which will take place on **Saturday 4th March 2017** in **Manchester**, at the Mercure Piccadilly Hotel.

In 2015 the very first Vasculitis Patient Symposium was held at the London Business Design Centre. The Patient Symposium was held the day prior to the Vasculitis International Conference.

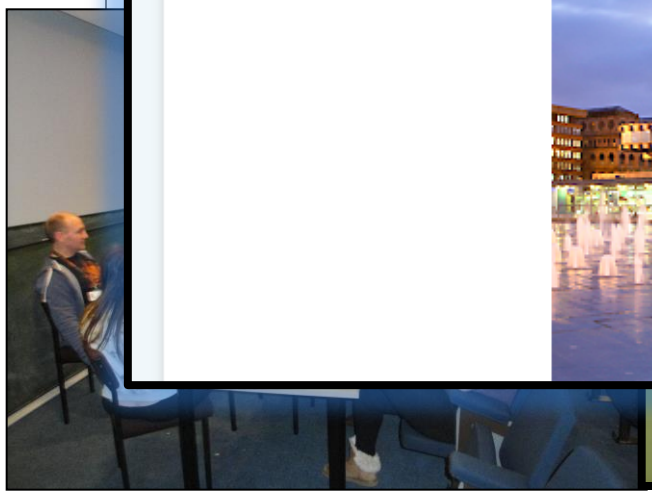
In March 2017 Innov8 Conference Services along with Vasculitis UK will be holding the second National Vasculitis Patient Symposium

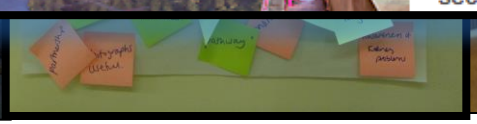
Useful Contacts

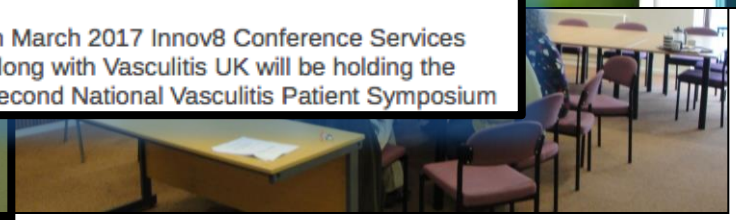
oad a summary

this whole topic

e future







Summary

- HSP common childhood vasculitis
  - Rare for primary care
- Majority self limiting disease, excellent outcome

- Monitoring for HSPN is essential
- Renal biopsy: proteinuria, nephrotic/nephritic
- Histology guides immunosuppression

- Future…can only improve!

Acknowledgements

Patients and families

Original HSP pathway committee:

- Dr. Gavin Cleary
- Dr. Briar Stewart
- Dr. Dave Casson
- Elvina White
- Pauline Stone

UK Paediatric Nephrologists & trainees for contributing to the Delphi survey

UK HSPN Steering group

- Dr. Jane Tizard
- Dr. Paul Brogan
- Prof. Michael Beresford
- Dr. Caroline Jones
- Dr. Richard Holt
- Dr. Amanda Richardson
- Prof. Matthew Peak
- Dr. Theo Anbu
- Dr. Kjell Tullus
- Dr. Rajeev Shukla
- Dr. Milos Ognjanovic
- Dr. Mohan Shenoy

Alder Hey Children's Kidney Fund

Email: louise.oni@liverpool.ac.uk

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