NHS
Birmingham Women's and Children's
NHS Foundation Trust

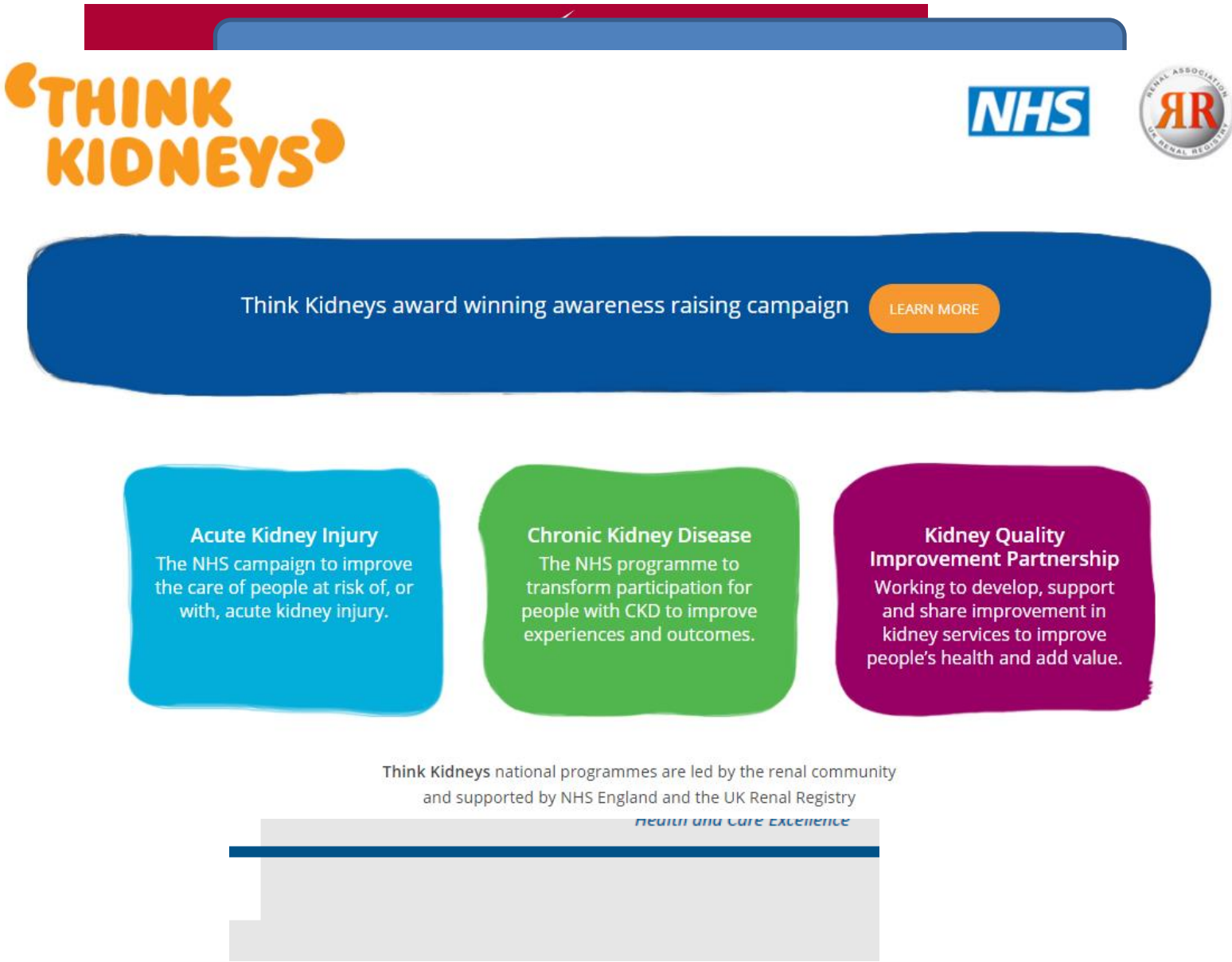
Acute Kidney Injury

David V Milford

WCNPN
2017

let's make it better

The ascendency of AKI



Recognition of AKI

inability to maintain renal homeostasis:

- fluid balance
- Na+/K+
- acid-base
- excretory function

a child with a high creatinine - is it acute or chronic?

- oliguria/anuria favours AKI

(in critical illness usually acute or acute on chronic)

Recognise AKI has a spectrum of severity…

Stage	RIFLE/pRIFLE criteria	AKIN criteria	KDIGO criteria	Urine output[d]
Risk or stage 1	eGFR decrease by ≥ 25% or 50 - 99% Cr rise from baseline within 7 days[g] (1.50-1.99 × baseline)	Rise of ≥ 26 µmol/L[e] within 48h or 50 - 99% Cr rise from baseline within 7 days[g] (1.50-1.99 × baseline)	Rise of ≥ 26 µmol/L[e] within 48h or 50 - 99% Cr rise from baseline within 7 days[g] (1.50-1.99 × baseline)	< 0.5 ml/kg/h for more than 6h (8h for pRIFLE)[f]
Injury or stage 2	eGFR decrease by ≥ 50% or 100 - 199% Cr rise from baseline within 7 days[g] (2.00-2.99 × baseline)	100 - 199% Cr rise from baseline within 7 days[g] (2.00-2.99 × baseline)	100 - 199% Cr rise from baseline within 7 days[g] (2.00-2.99 × baseline)	< 0.5 ml/kg/h for more than 12h (16h for pRIFLE)[f]
Failure or stage 3	eGFR decrease by ≥ 75% or ≥ 200% Cr rise from baseline within 7 days[g] (≥ 3.00 × baseline)	≥ 200% Cr rise from baseline within 7 days[g] (≥ 3.00 × baseline)	≥ 200% Cr rise from baseline within 7 days[g] (≥ 3.00 × baseline)	< 0.3 ml/kg/h for 24h or anuria for 12h
	or Cr rise to ≥ 354 µmol/L[h] with acute rise of ≥ 44 µmol/L	or Cr rise to ≥ 354 µmol/L[h] with acute rise of ≥ 44 µmol/L	or Cr rise to ≥ 354 µmol/L[h] with acute rise of: ≥ 26 µmol/L within 48 h or ≥ 50% rise within 7 days	
	or (pRIFLE only) eGFR <35 ml/min/1.73m^2	or any requirement for renal replacement therapy	or any requirement for renal replacement therapy	

diagnosis of AKI is based on acute rise in serum creatinine and/or fall in urine output

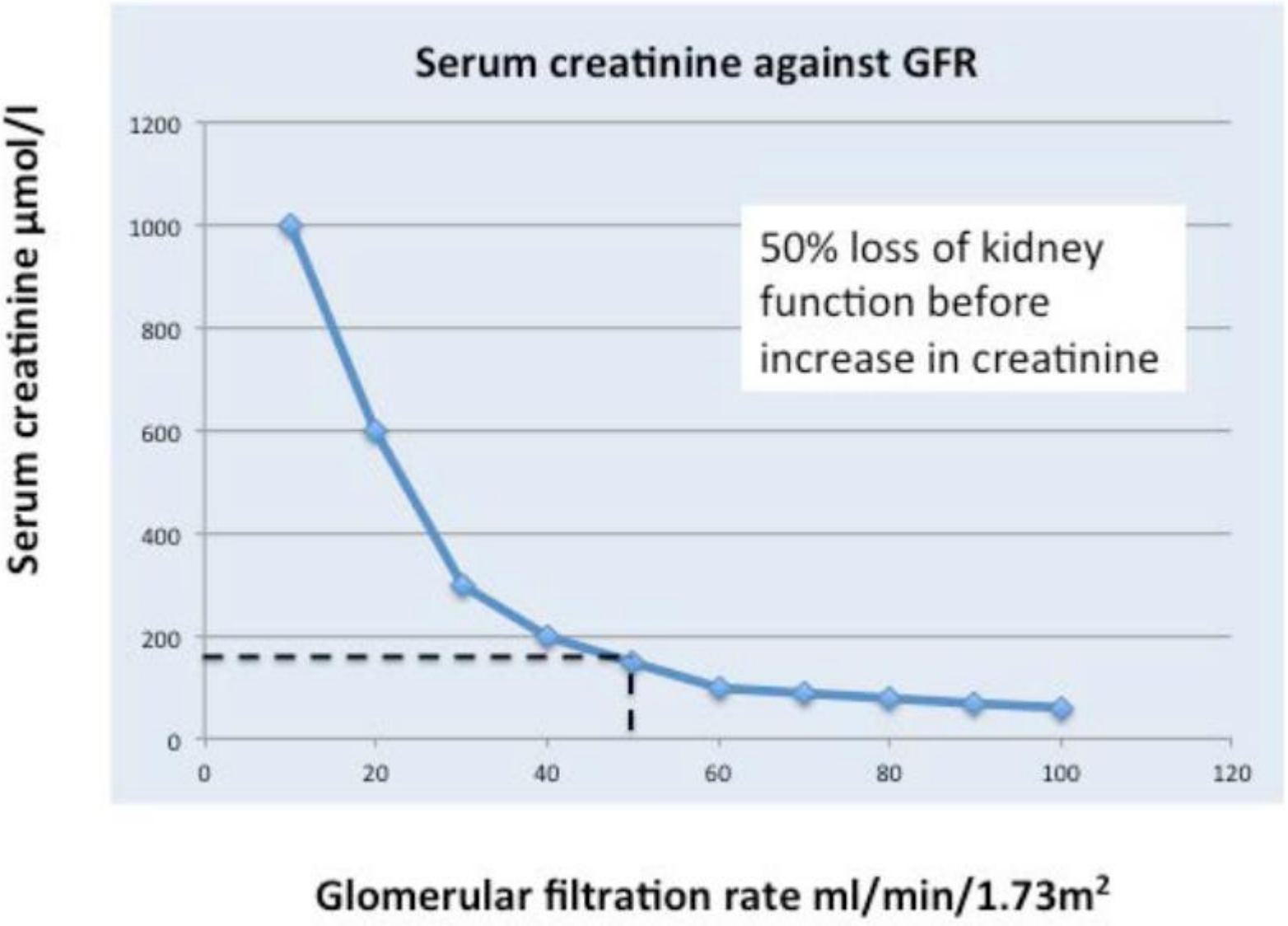
creatinine

- may take 24–36 h to rise after a definite renal insult, influenced by rate of creatinine generation
- creatinine affected by sepsis, liver disease, muscle wasting, drugs, diet

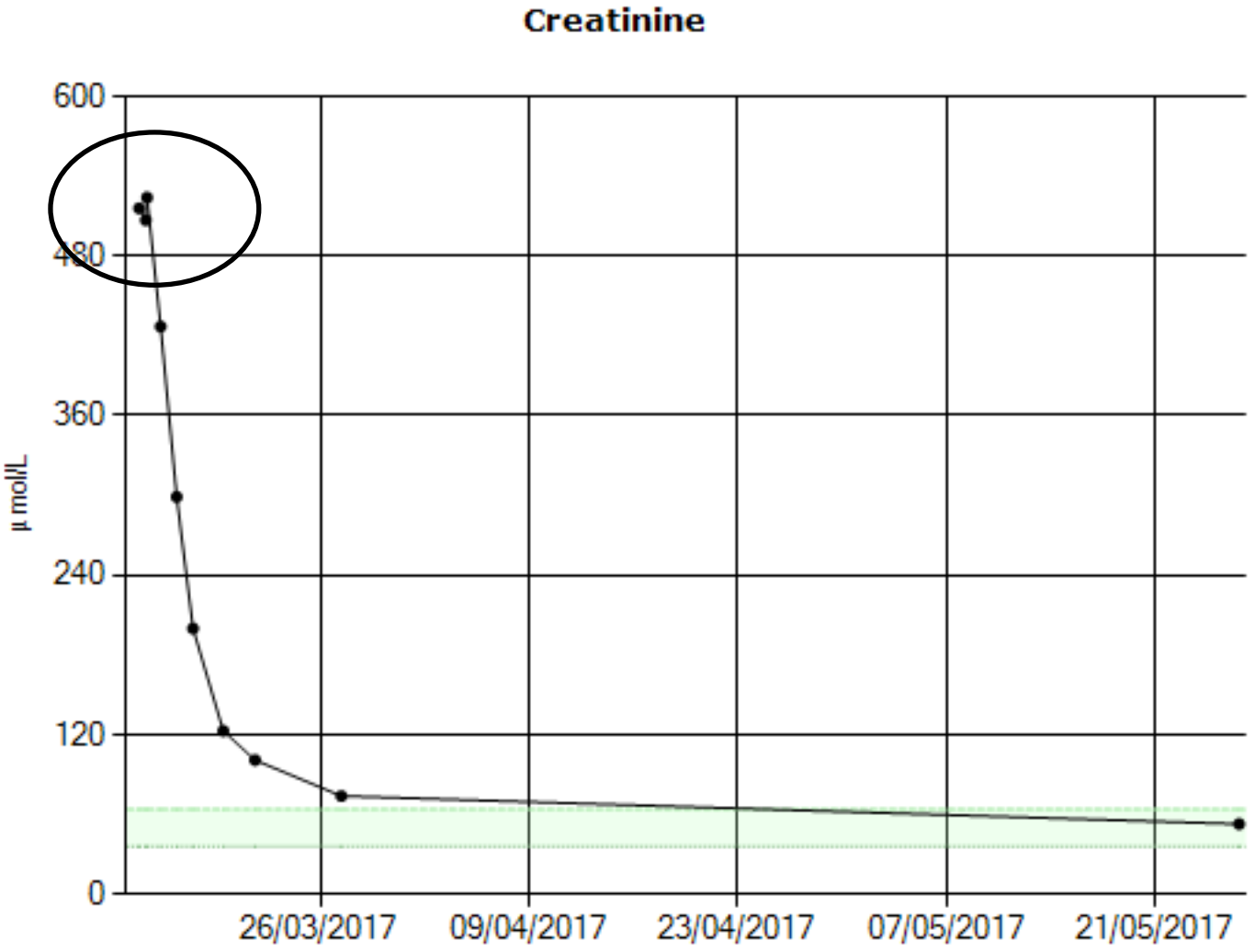
urine output

- may be an earlier marker but can be more difficult to monitor in children

Creatinine is a late marker of AKI



AKI or ACKD?


Creatinine
600
480
360
240
120
0
µ mol/L
26/03/2017
09/04/2017
23/04/2017
07/05/2017
21/05/2017

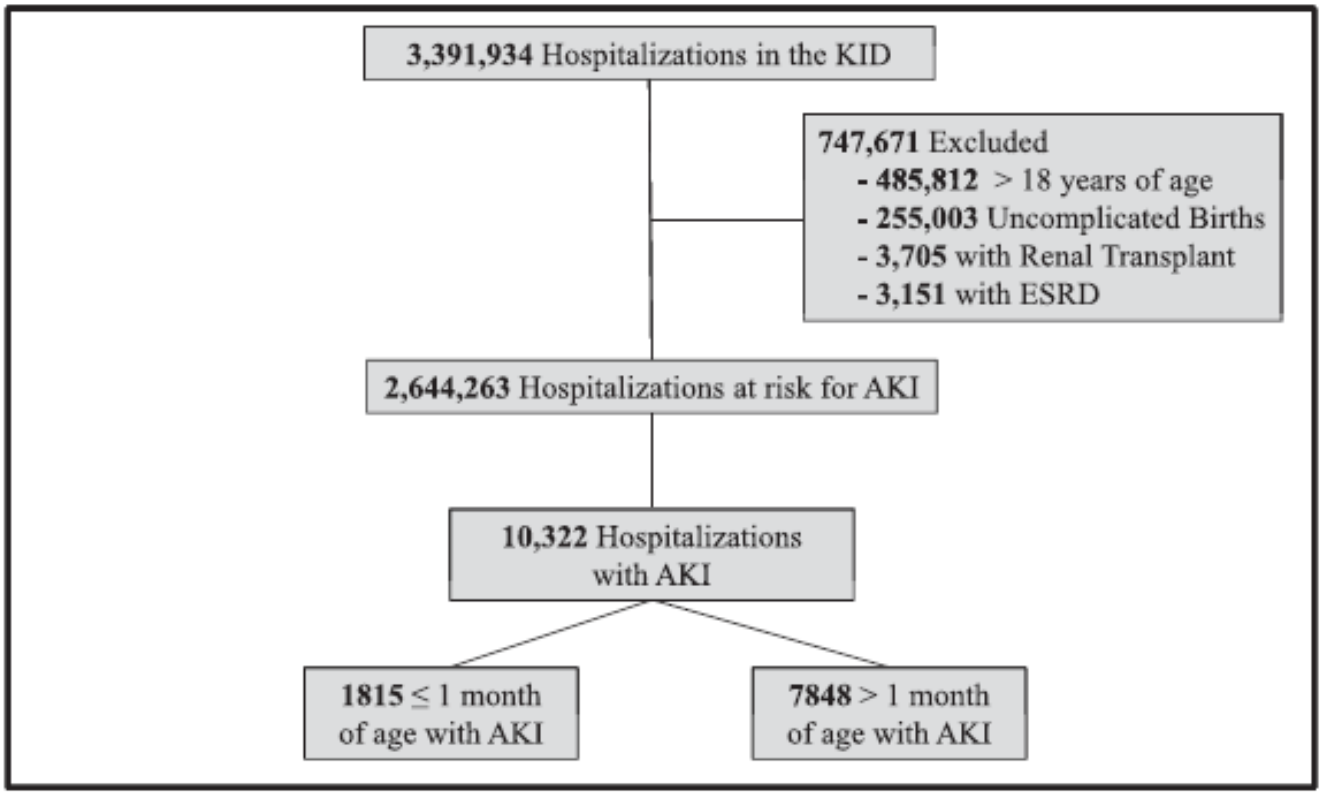
Incidence

(very little epidemiological data in children)

AKI in Hospitalized Children: Epidemiology and Clinical Associations in a National Cohort

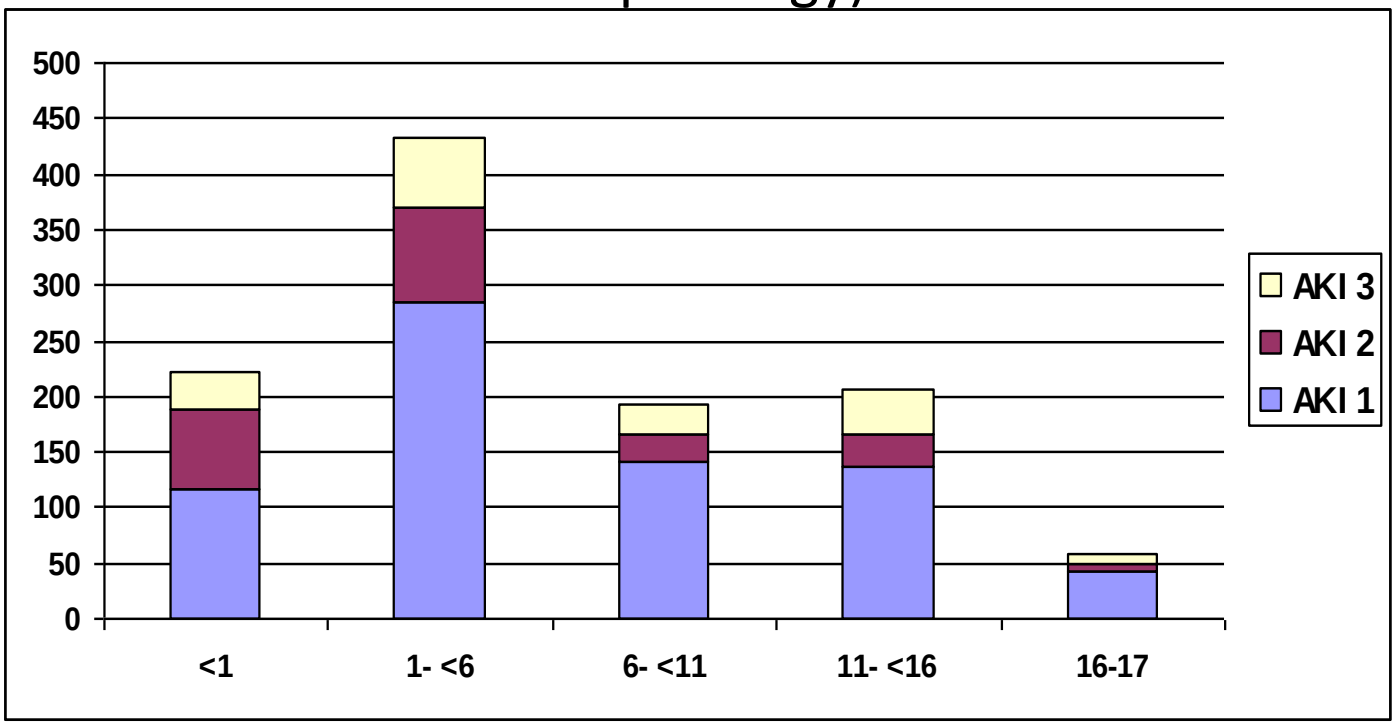
Scott M. Sutherland, Jun Ji,† Famoosh H. Sheikhi,‡ Eric Widen,‡ Lu Tian,§ Steven R. Alexander,* and Xuefeng B. Ling†*

C JASN 2013; 8: 1661-1669



Conclusions AKI occurs in 3.9/1000 at-risk US pediatric hospitalizations.

Recognition of AKI in children (6 centre audit on behalf of the British Association for Paediatric Nephrology)

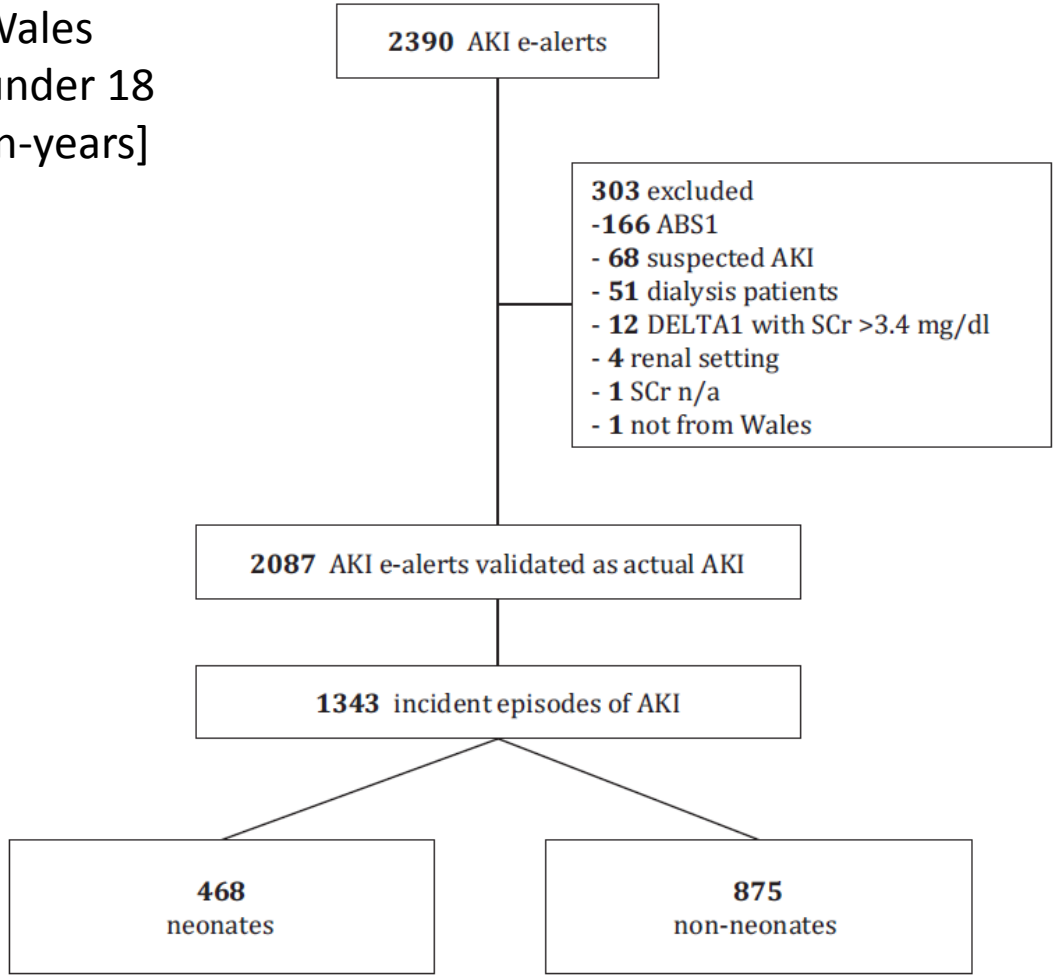


N=1112

- **60% of all patients with AKI were <6 years old**
- **In those aged <6years, worst stage in 2/3rd was of AKI 1**

The incidence of pediatric acute kidney injury is increased when identified by a change in a creatinine-based electronic alert

30 months surveillance across Wales
1.37 cases per 1000 person-years under 18
[Adults: 5.77 cases per 1000 person-years]



J Holmes et al, Welsh Renal Clinical Network
Kidney International 2017; 92 : 432–439

Causes and pathophysiology

Acute Kidney Injury

Pre-renal - normal tubular and glomerular function; GFR is depressed by compromised renal perfusion (potentially reversible/transient).

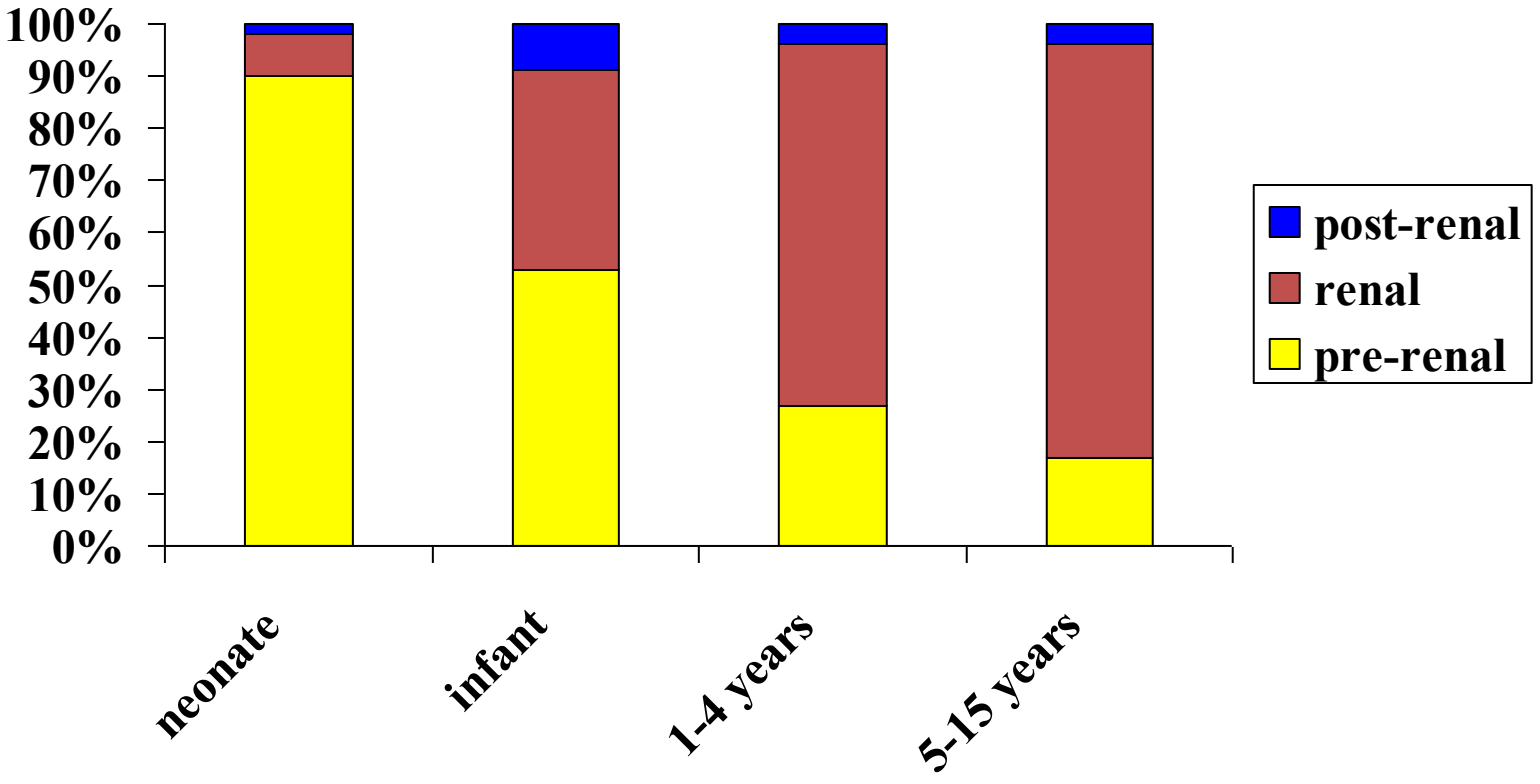
Intrinsic - diseases of the glomerulus or tubule; secondary to tubular ischaemia or toxic agents/drugs (may be treatable)

Post(obstructive) - increase in tubular pressure decreases filtration driving force (potentially reversible/transient).

Acute on chronic – acute decline in function superimposed on pre-existing CKD, may or may not be reversible

Cause of AKI

Aetiology of AKI 3 in children by age - Leeds



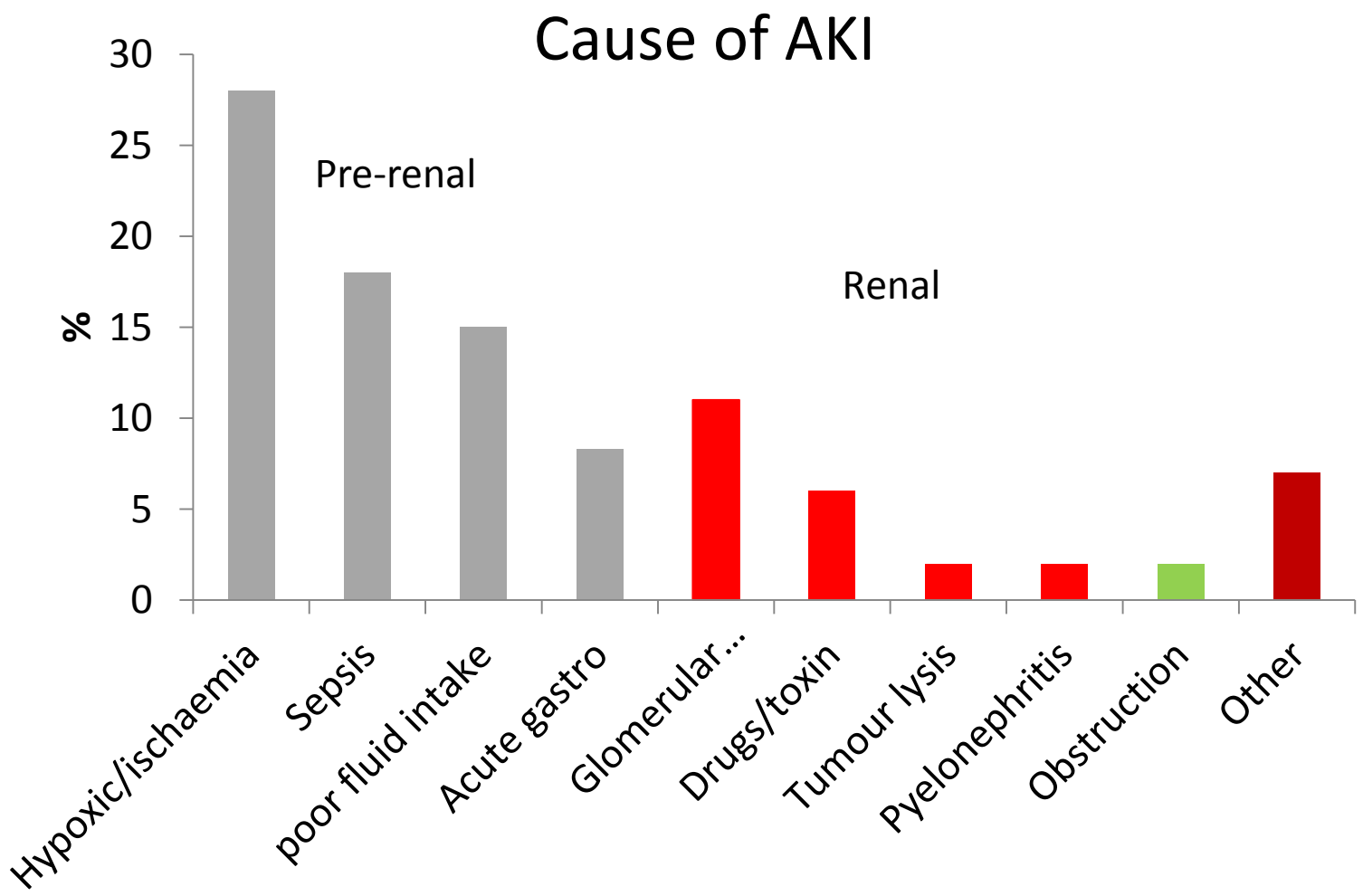
Moghal et al. Clin Nephrol 1998; 49:91

Pediatr Nephrol (2010) 25:1453–1461
DOI 10.1007/s00467-010-1541-y

ORIGINAL ARTICLE

Etiology and outcome of acute kidney injury in children

Ali Duzova · Aysin Bakkaloglu · Mukaddes Kalyoncu · Hakan Poyrazoglu ·



Pathophysiology

- kidneys account for 0.5% body weight
- renal blood flow 20-25% of cardiac output
- high oxygen consumption but high blood flow

$pO_{2art} = 95$

$pO_{2vein} = 70$

Why do the kidneys readily incur ischaemic damage in the face of an excellent blood supply?

Renal haemodynamics

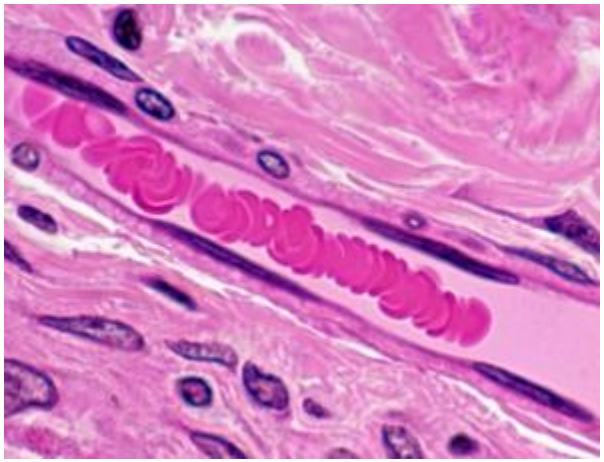
the renal response to hypotension - shunting mediated by vasoconstriction through the action of

- sympathetic nerve stimulation
- renin-angiotensin system
- endothelin
- adenosine, thromboxane A2

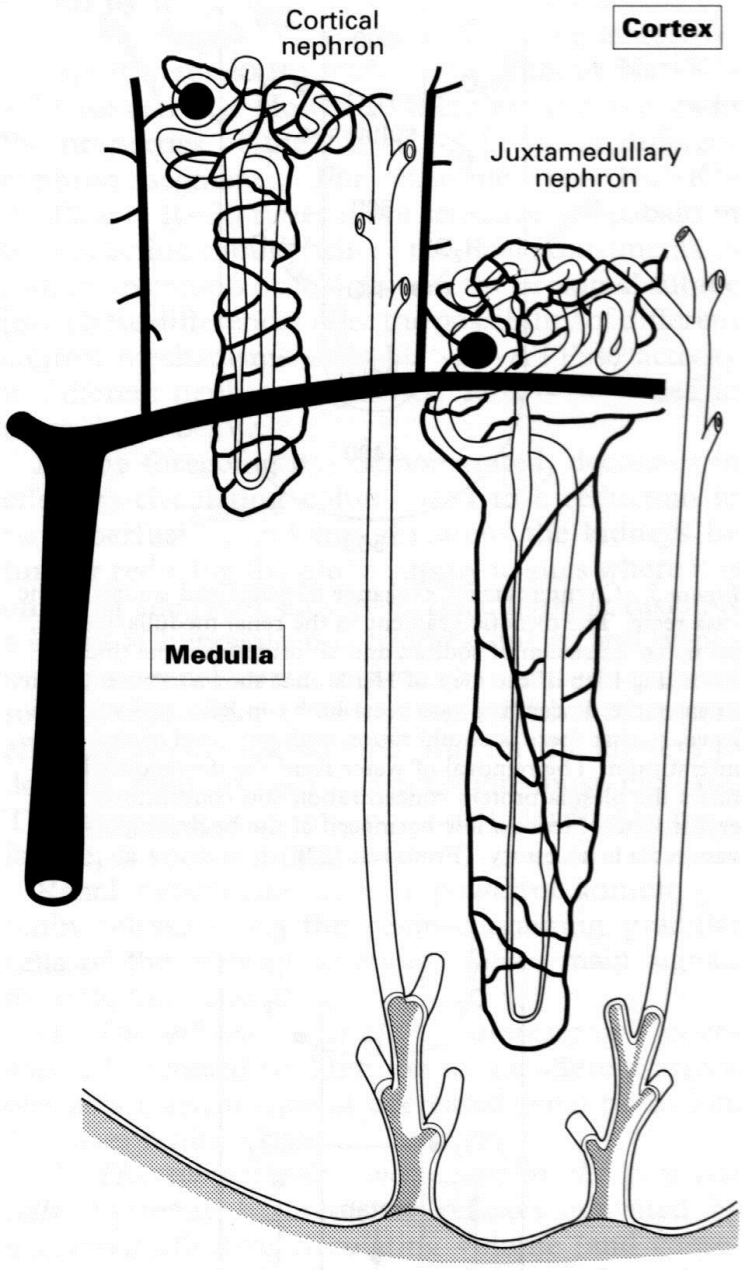
to support systemic BP

→ systemic BP may not be a good guide to the adequacy of renal perfusion

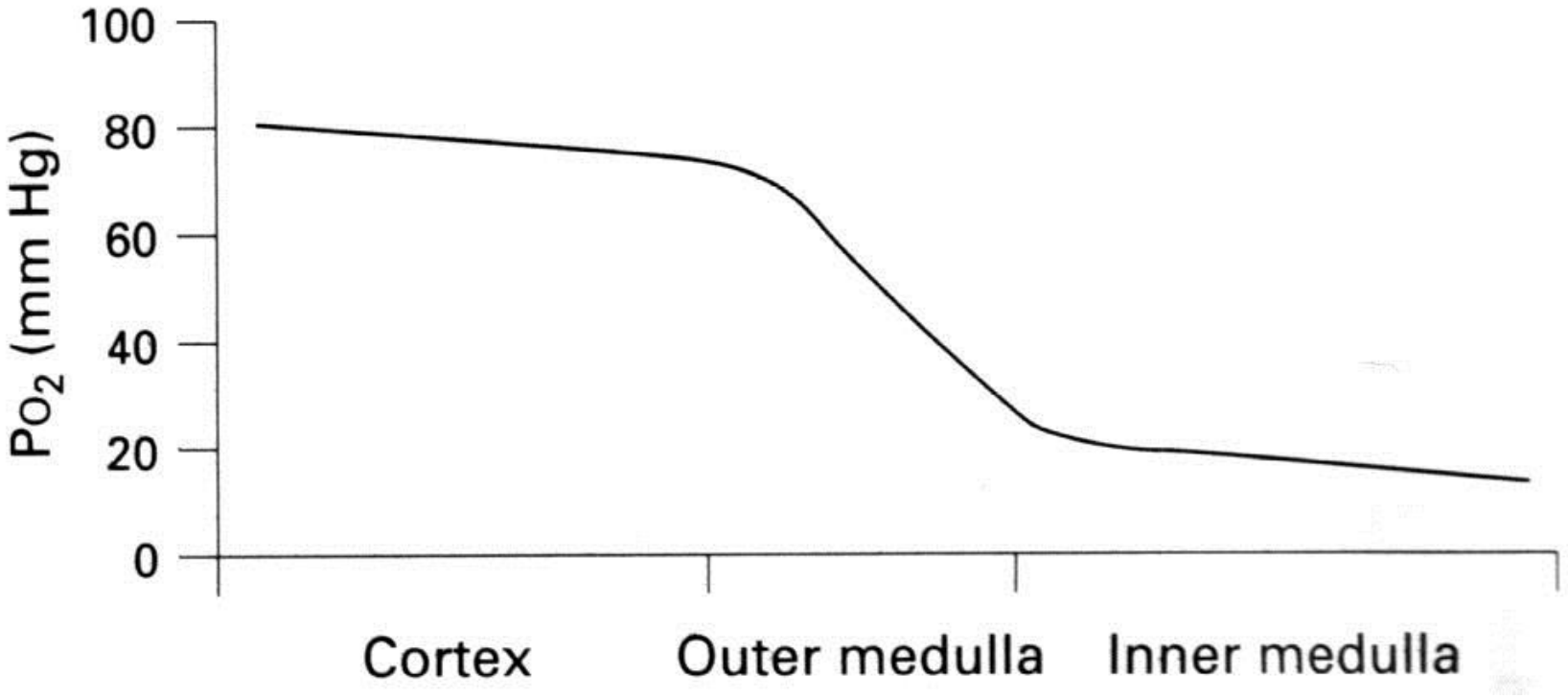
Oxygen delivery



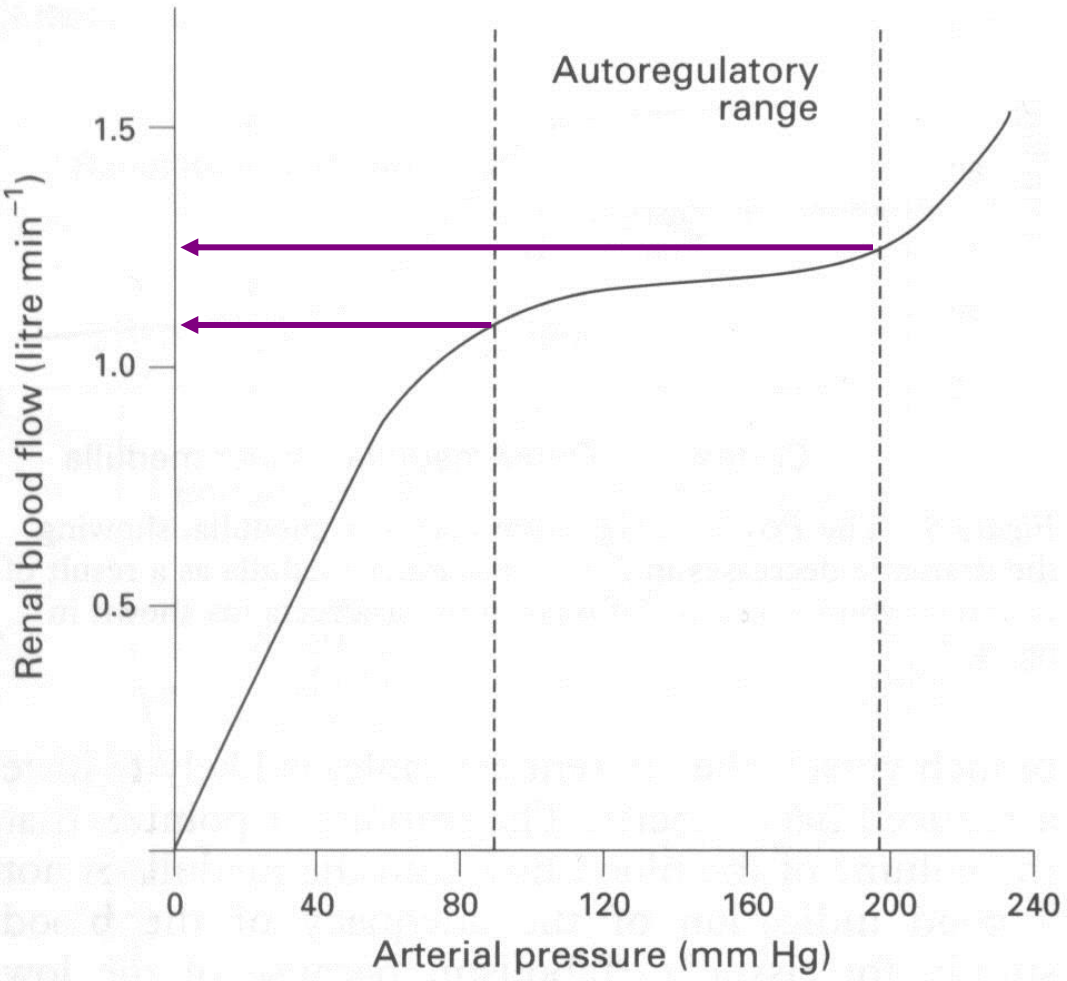
- plasma skimming ensures low haematocrit (10%)
- O_2 undergoes countercurrent exchange
- consequence is low O_2 delivery to medulla



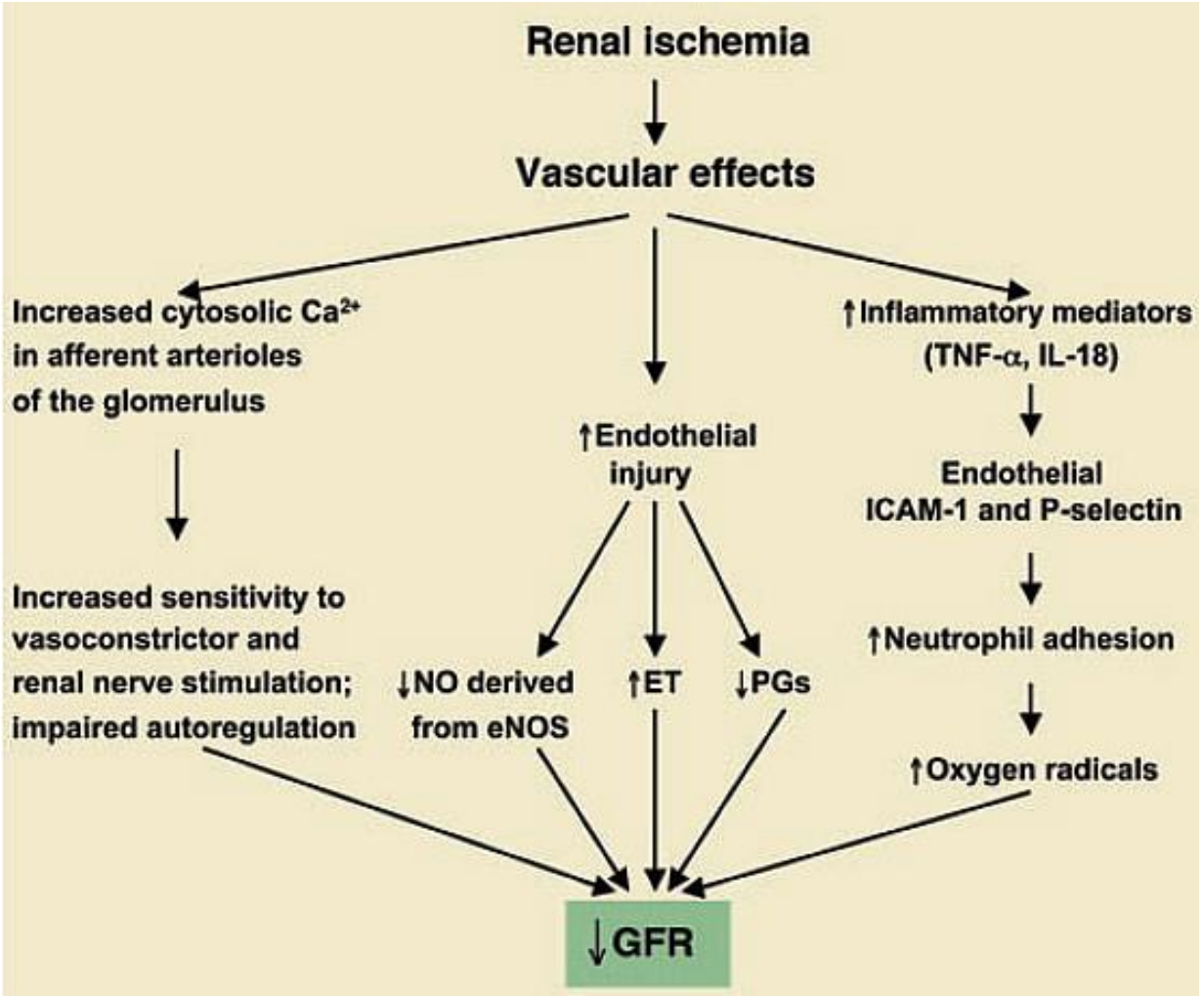
Oxygen delivery - pO_2 from cortex to medulla



Renal autoregulation

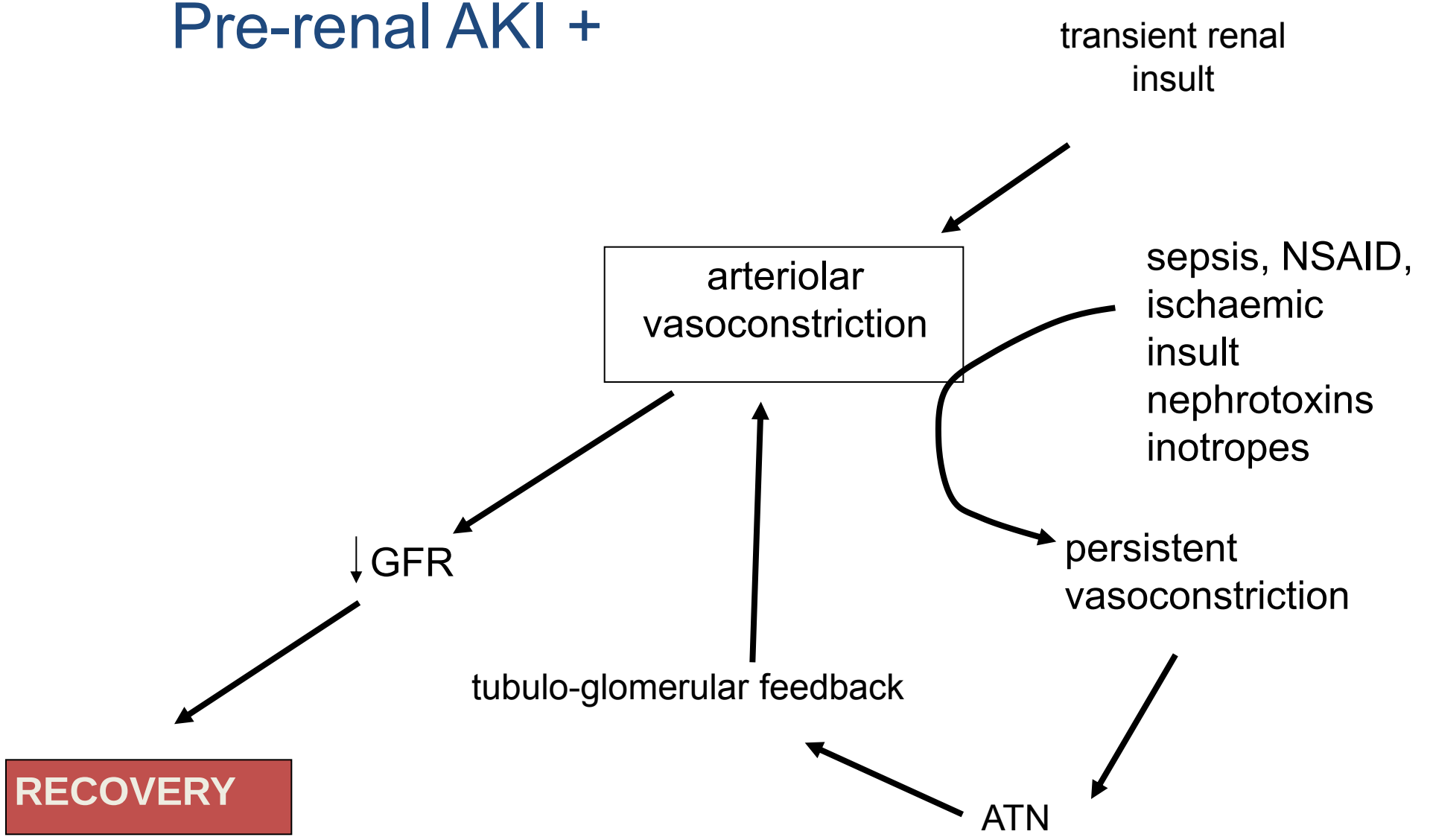


Genesis of AKI



Schrier et al. J. Clin. Invest. **114**:5–14 (2004)

Pre-renal AKI +



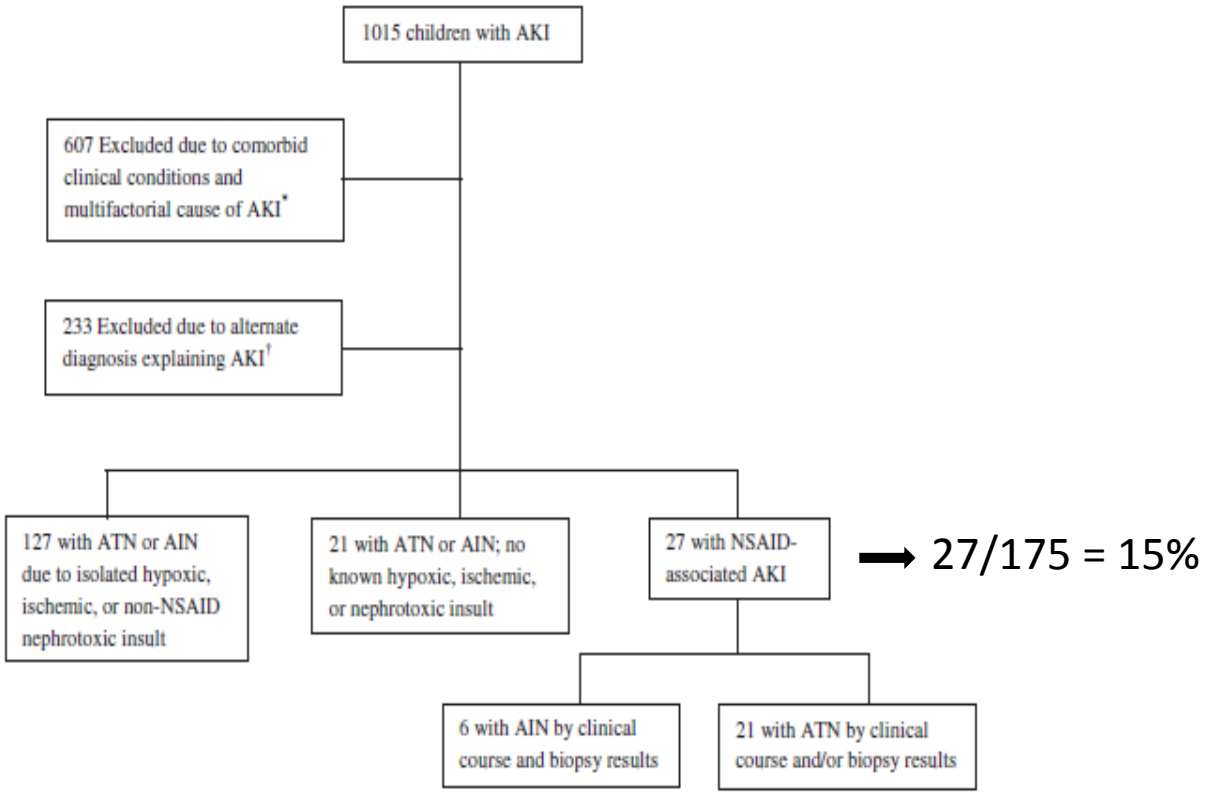
Still under-recognised…..

Clinical Nephrology, Vol. 49 No. 5 – 1998 (293–295)

Care in the use of ibuprofen as an antipyretic in children

N. E. MOGHAL, S. A. HULTON and D. V. MILFORD

Nonsteroidal Anti-Inflammatory Drugs Are an Important Cause of Acute Kidney Injury in Children



→ 27/175 = 15%

Figure. Classification of patients with AKI. *Malignancy, complex congenital heart disease, sickle cell disease, etc. †Obstruction, hemolytic uremic syndrome, pyelonephritis, sepsis, transplant rejection, or glomerulonephritis.

JM Misurac *et al*. J Pediatrics 2013;162:1153-9

Case 15 yr old male

- Attends ED 3 day h/o abdominal pain & loose stools
- **PEWS = 4 (no BP measured initially)**
  - Weight 47 Kg (51.1 kg 4 weeks before)
- at triage given
  - paracetamol 700 mg
  - ibuprofen 400mg
- Urine
  - bld/prot +

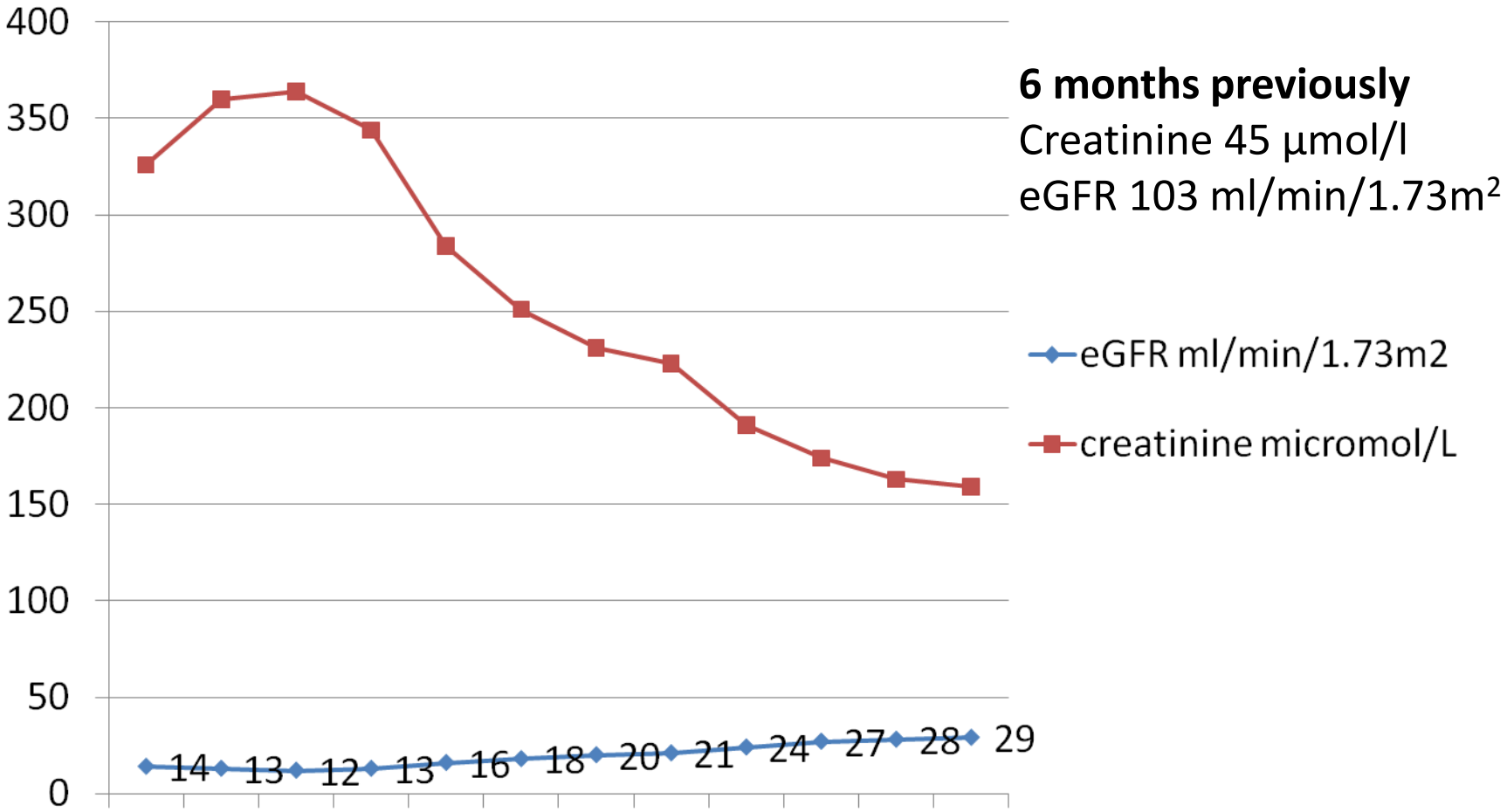
Progress …….

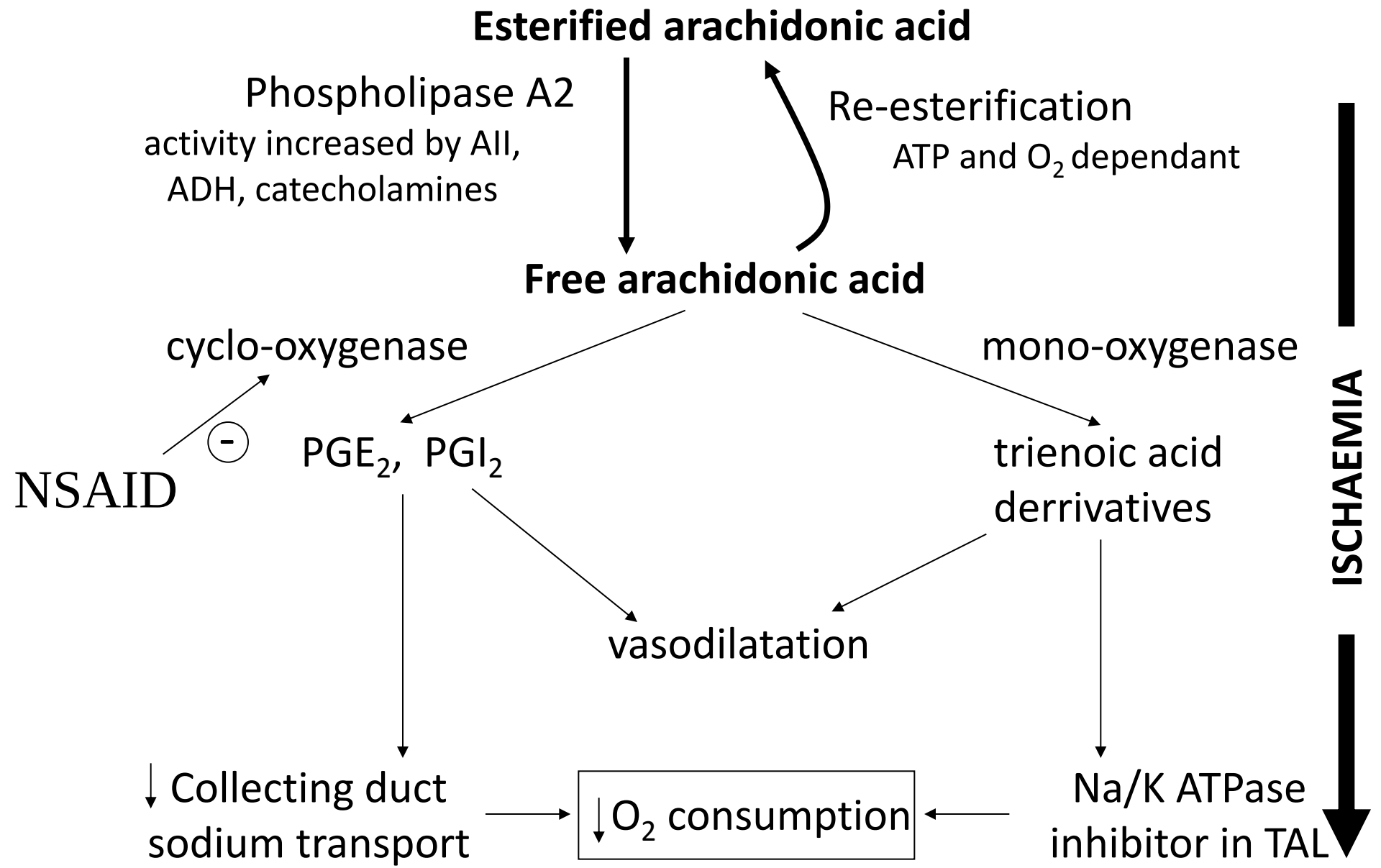
- Examination:
  - poor volume peripheral pulses, cool peripheries, sunken eyes, RIF pain
  - BP 100/60

- Impression:
  - unwell, dehydrated ?appendicitis +/- perforation

- Plan :
  - IV access and bloods,
  - 1000ml fluid bolus, reviewed by ED consultant

AKI progression over 2 weeks following admission




Esterified arachidonic acid
Phospholipase A2
activity increased by AII,
ADH, catecholamines
Re-esterification
ATP and O_2 dependant
Free arachidonic acid
cyclo-oxygenase
mono-oxygenase
NSAID
PGE2, PGI2
trienoic acid
derrivatives
vasodilatation
↓ Collecting duct
sodium transport
↓O_2 consumption
Na/K ATPase
inhibitor in TAL
ISCHAEMIA

Is your child unwell?

A child with diarrhoea and vomiting often can't take enough fluid to maintain hydration. This puts their kidneys at risk.

Speak to your doctor or pharmacist before giving them ibuprofen.

Keep their kidneys safe

'THINK KIDNEYS'

Visit www.thinkkidneys.nhs.uk
Or talk to your GP or pharmacist to find out more

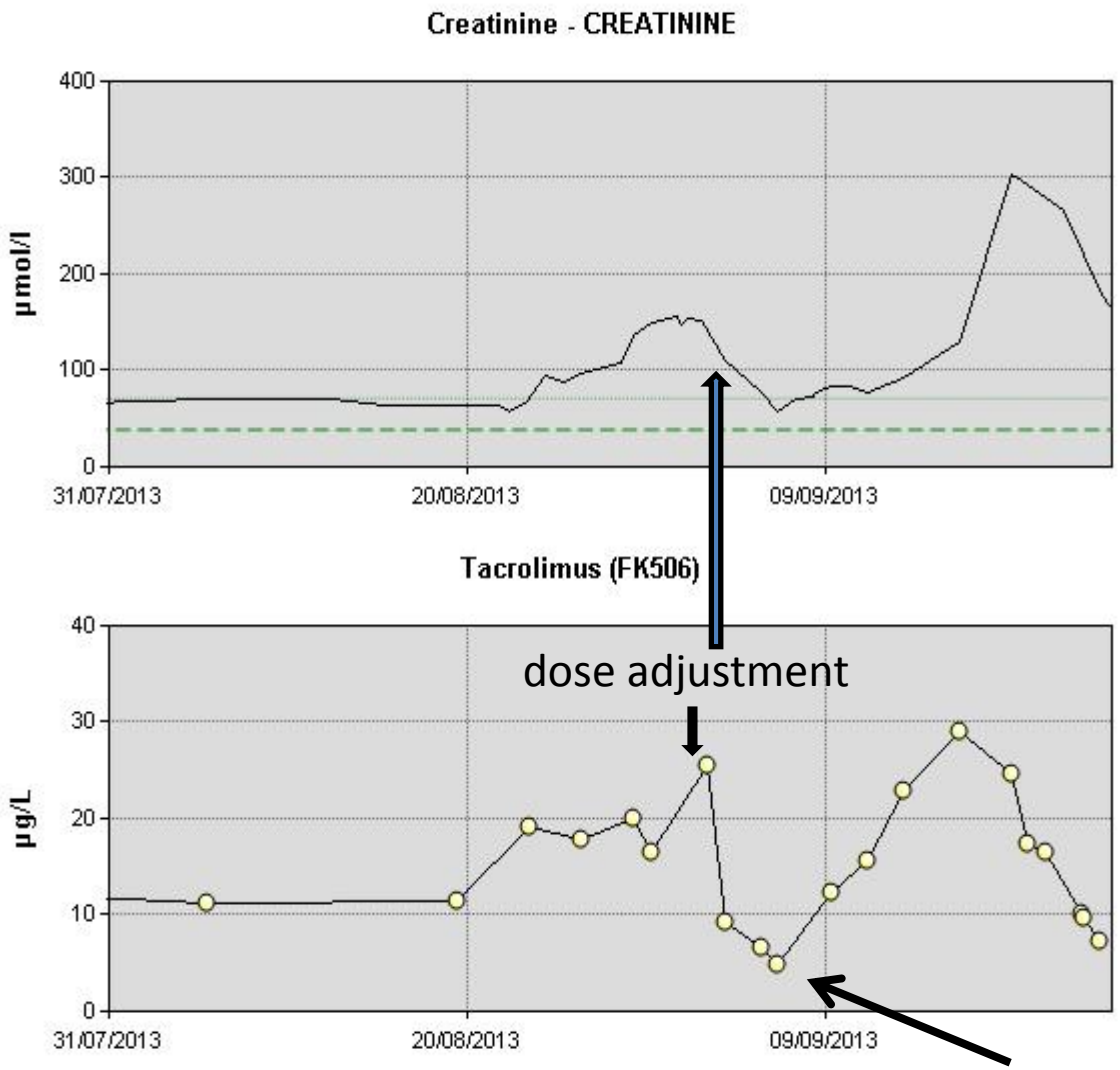
Endorsed by the Royal Pharmaceutical Society

'THINK KIDNEYS' NHS

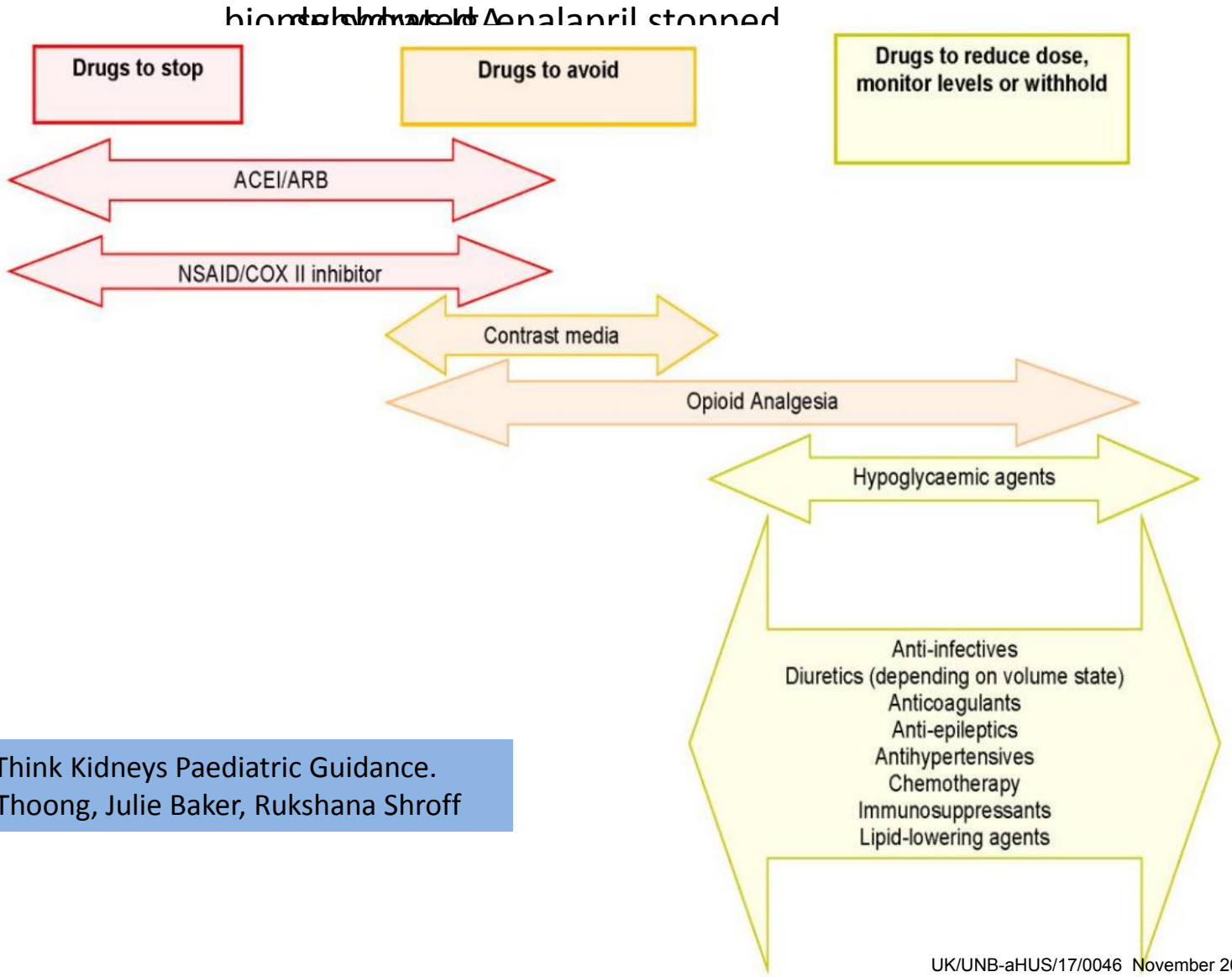
Think Kidneys is a national programme led by NHS England in partnership with UK Renal Registry

Drug interactions

stem cell transplant patient

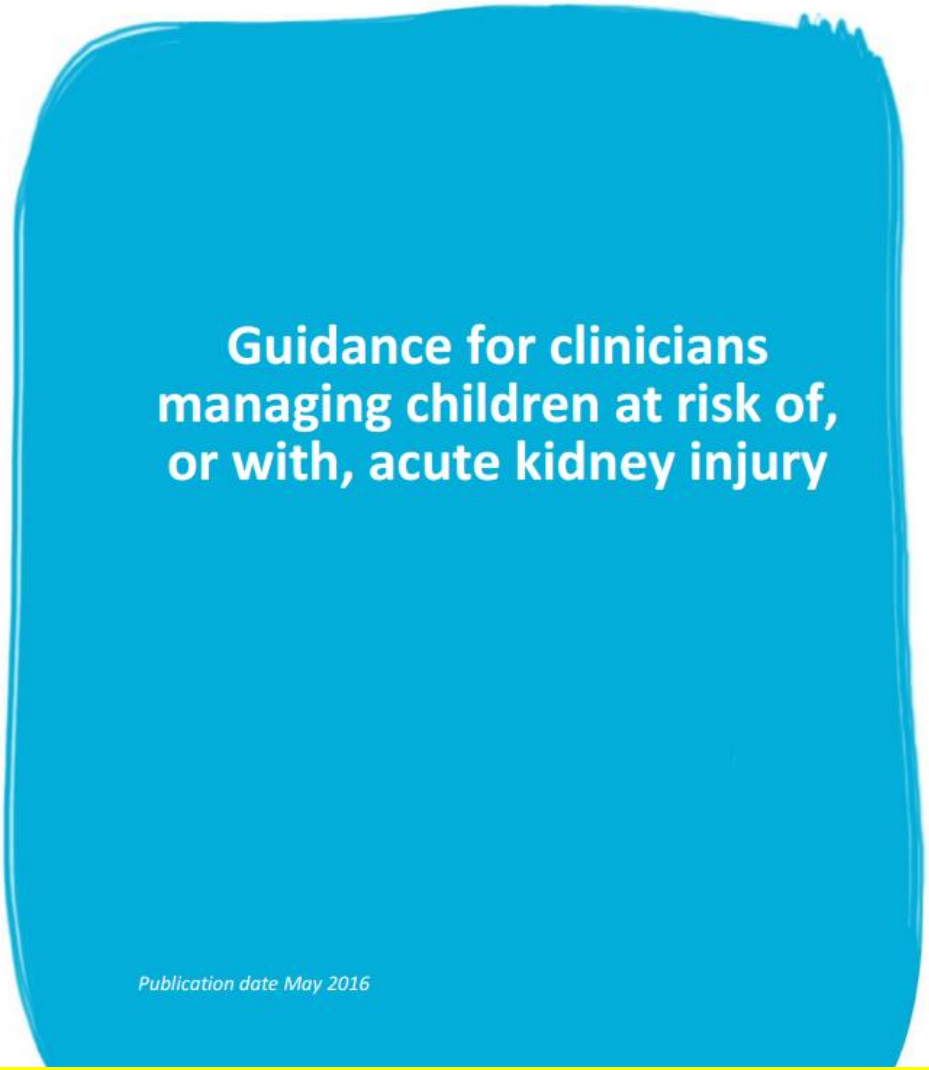


Drugs and the kidneys



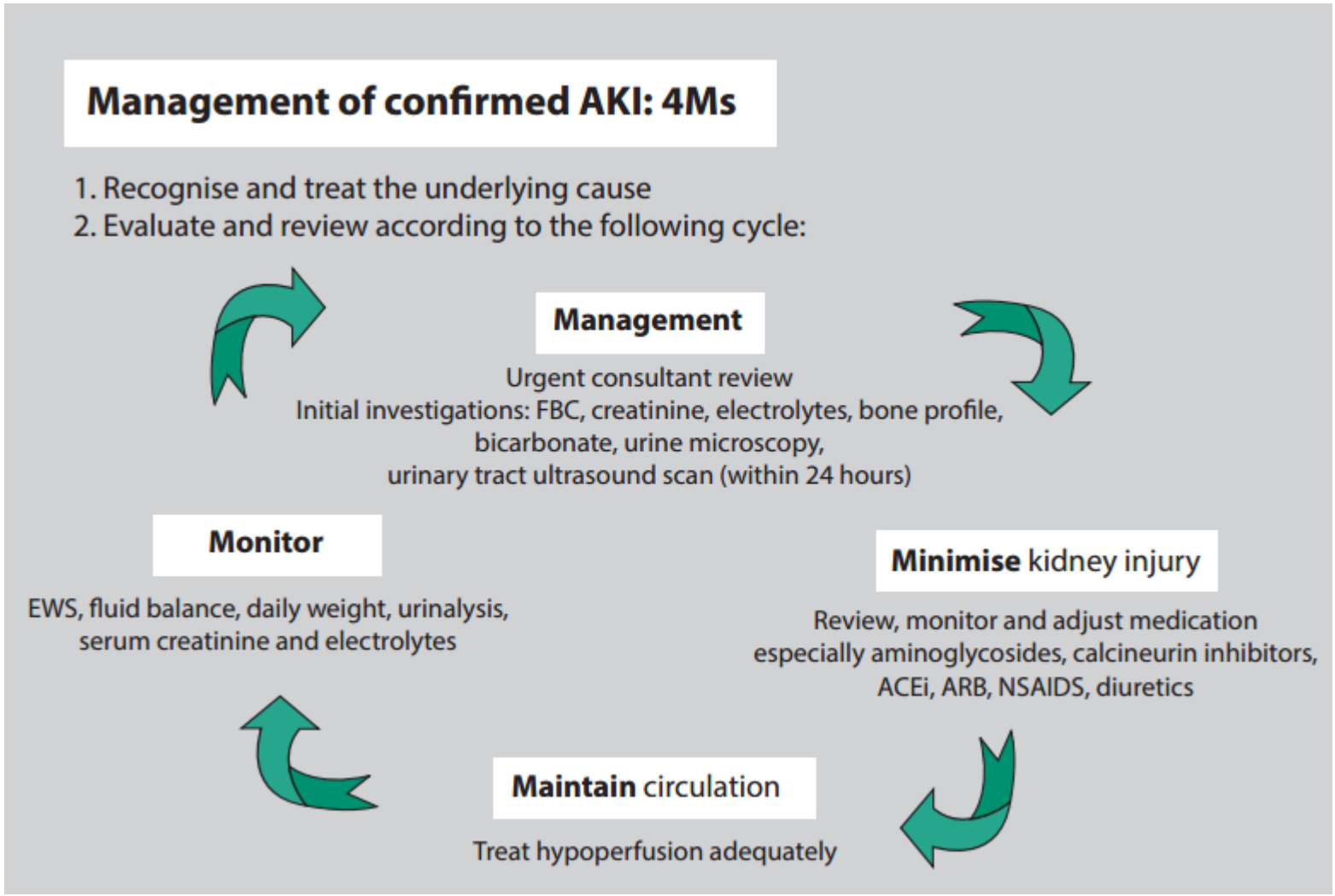
From Think Kidneys Paediatric Guidance.
Hong Thoong, Julie Baker, Rukshana Shroff

Management



https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/05/Guidance_for_paediatric_patients_FINAL.pdf

British Association for Paediatric Nephrology management recommendations



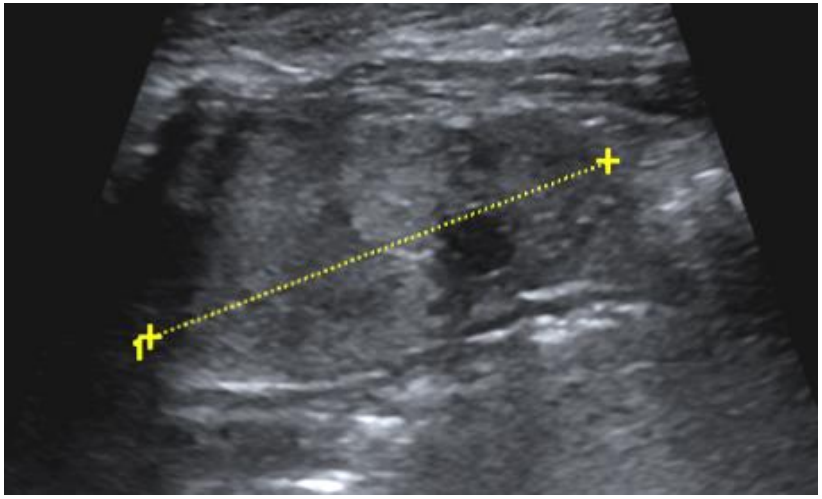
The 4 'Ms' was adopted from the London AKI Network

Initial management

- clinical examination especially BP/perfusion and volume status
- bloods
  - full blood count
  - creatinine, electrolytes, bone profile, bicarbonate
- urinalysis, urine microscopy
- renal ultrasound scan (NICE - within 24 hours)
- other investigations
  - LFT's, clotting, C3/C4, ASOT, immunoglobulins, ANA, ANCA, anti-GBM antibodies, CK, LDH, blood film

Recognition – role of imaging

- NICE recommends USS <24 hours
  - obstruction (rare in children)
  - CKD: small, loss of CMD, scarred kidneys, cysts
  - AKI: big, bright kidneys



What can be done for the child with AKI…

actively manage

- volume status
- hyperkalaemia
- acidosis
- hyponatraemia

optimise bladder drainage (monitor UO/relieve obstruction)

drug therapy

- nephrotoxic drugs/dose correction for GFR
- treat sepsis
- steroids for immunological conditions

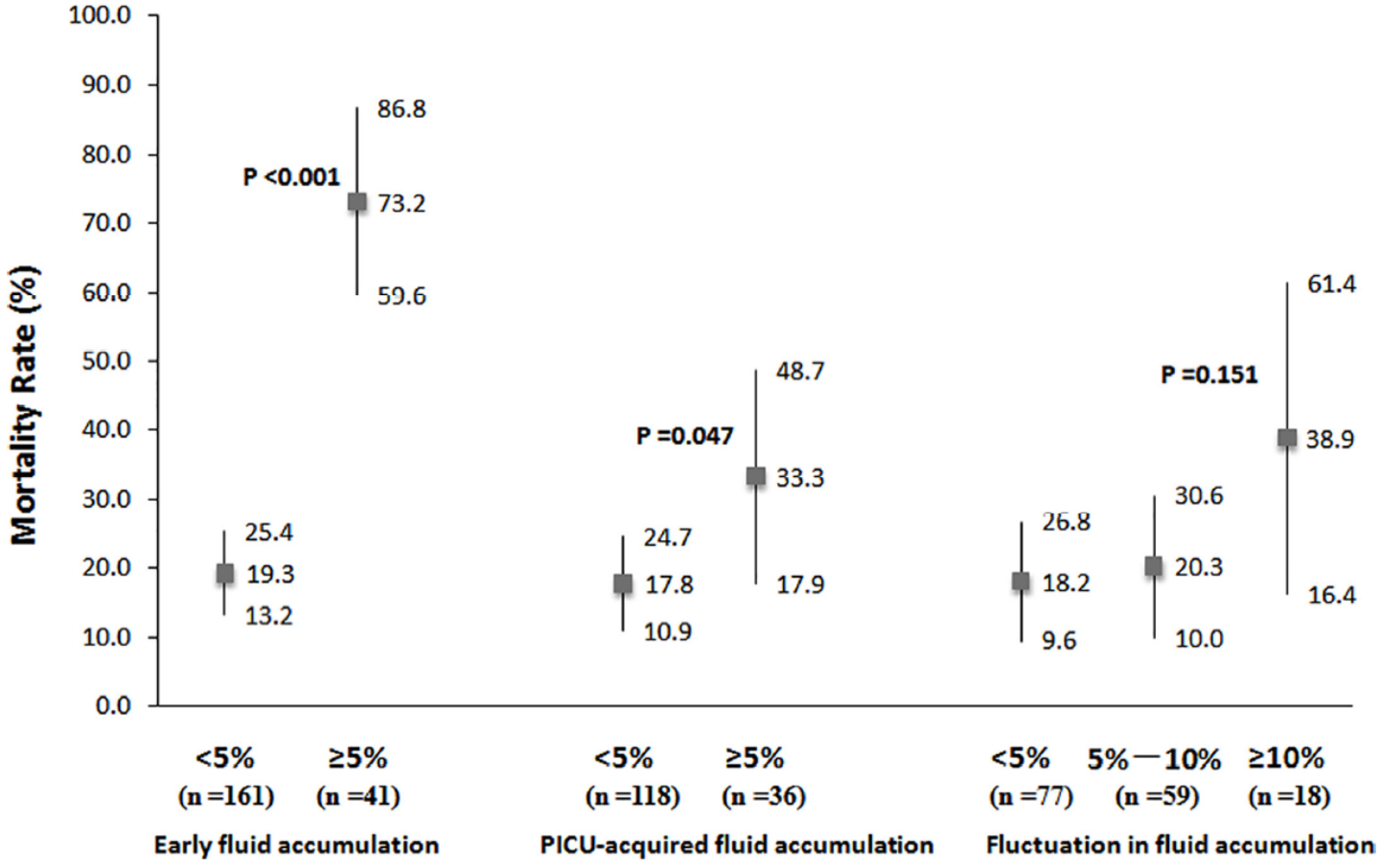
Don’t make it worse…..

PLOS ONE | DOI:10.1371/journal.pone.0172137 February 14, 2017

RESEARCH ARTICLE

Association of Fluid Accumulation with Clinical Outcomes in Critically Ill Children with Severe Sepsis

Jiao Chen[1,2], Xiaozhong Li[2], Zhenjiang Bai[1], Fang Fang[3], Jun Hua[1], Ying Li[1], Jian Pan[3], Jian Wang[3], Xing Feng[4], Yanhong Li[2,3]*



Comparison of mortality rates between severe septic patients with and without fluid overload.

Diuretic Effects in AKI

- diuretics are not recommended for AKI by NICE (CG169)
- diuretics commonly used to enhance urine output, and convert ‘oliguric’ to ‘non-oliguric AKI’
- no evidence diuretics shorten the duration of AKI, reduce the need for dialysis or improve outcomes in AKI
- loop diuretics might even be deleterious for the kidney because they disturb the protective corticomedullary redistribution of blood flow

Indications for RRT

- fluid overload with oligo/anuria
- severe or persistent hyperkalaemia
- severe and uncorrectable acidosis
- control of urea, creatinine = ‘uraemia’
- removal of toxins
  - metabolic eg ammonia
  - drugs, myoglobin, cytokines

Choice of RRT

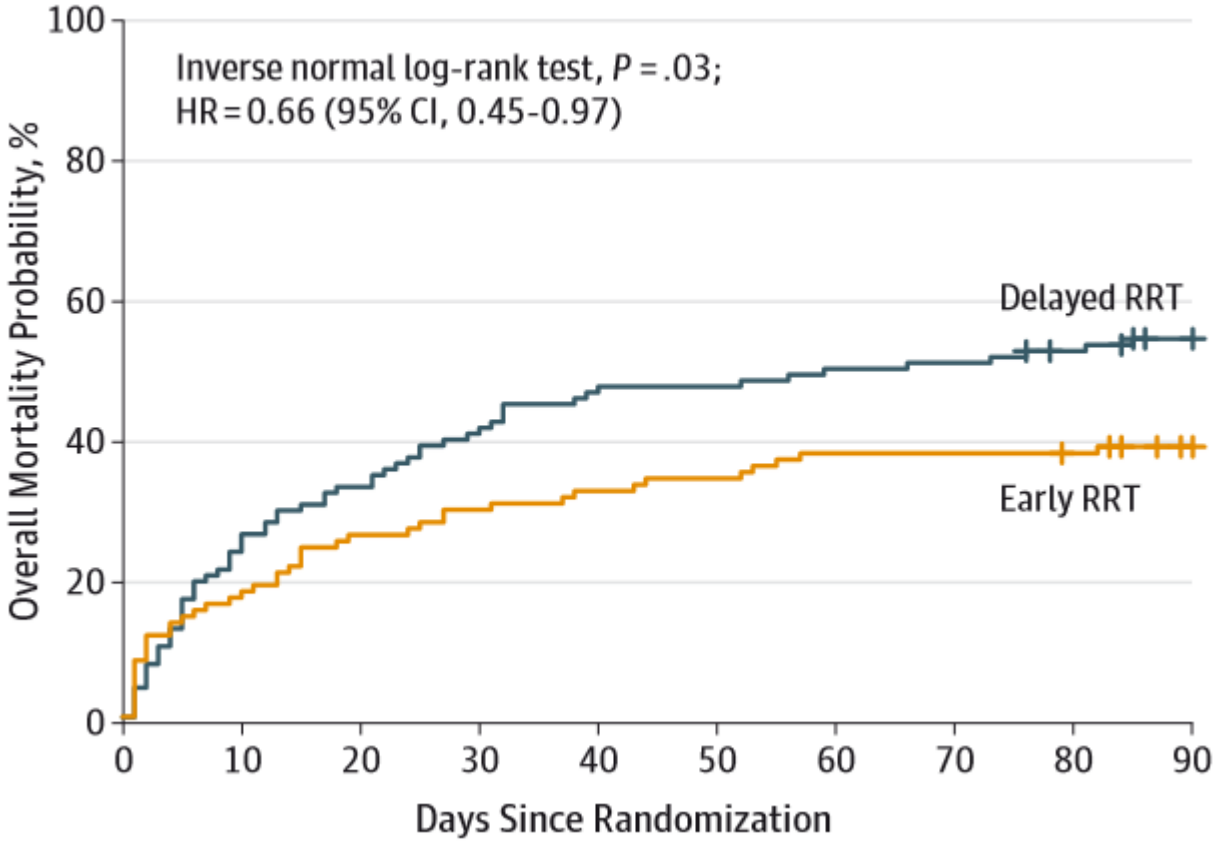
- Renal unit
  - peritoneal dialysis
  - haemodialysis
- PICU
  - peritoneal dialysis
  - various forms of CRRT

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury

The ELAIN Randomized Clinical Trial

Alexander Zarbock, MD; John A. Kellum, MD; Christoph Schmidt, MD; Hugo Van Aken, MD; Carola Wempe, PhD; Hermann Pavenstädt, MD; Andreea Boanta, MD; Joachim Gerß, PhD; Melanie Meersch, MD

JAMA. 2016;315(20):2190-2199. doi:10.1001/jama.2016.5828



Wierstra *et al. Critical Care* (2016) 20:122
DOI 10.1186/s13054-016-1291-8

Critical Care

RESEARCH Open Access

The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis

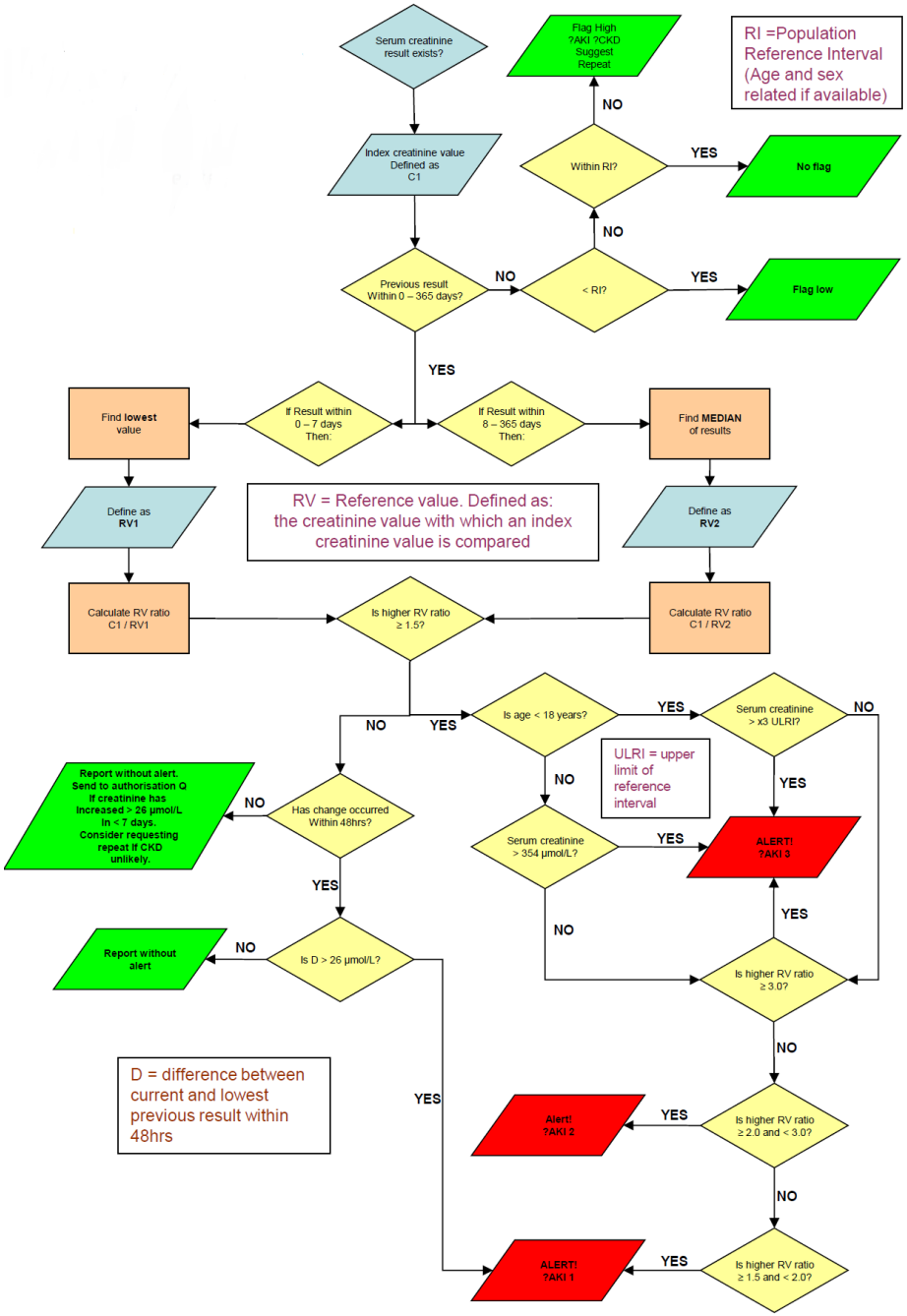
Benjamin T. Wierstra[1], Sameer Kadri[2], Soha Alomar[2], Ximena Burbano[2], Glen W. Barrisford[2] and Raymond L. C. Kao[2,3*]

Conclusions: Our conclusion based on this evidence synthesis is that "early" initiation of RRT in critical illness complicated by AKI does not improve patient survival or confer reductions in ICU or hospital LOS.

Prevention/ameliorate

Be aware of high risk groups…..

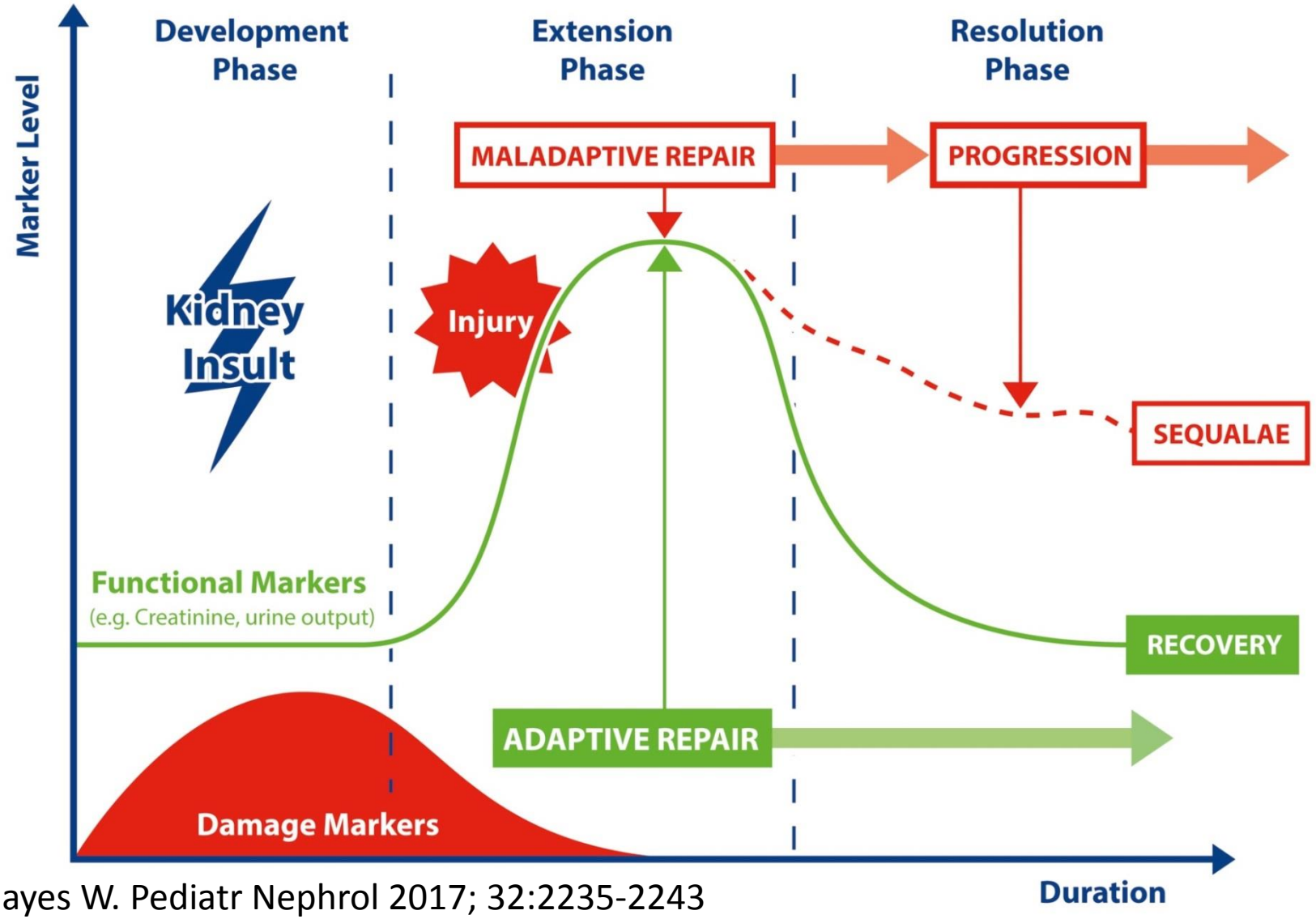
- CKD, heart failure, liver disease
- Previous AKI
- Oliguria (<0.5 ml/kg/hr)
- Neuro/developmental delay
- Hypovolaemia, hypotension
- Nephrotoxic drugs
- Urological obstruction
- Sepsis
- Deteriorating PEWS
- Severe diarrhoea/bloody diarrhoea
- Symptoms/signs of nephritis
- Haematological malignancy



….prevention not cure

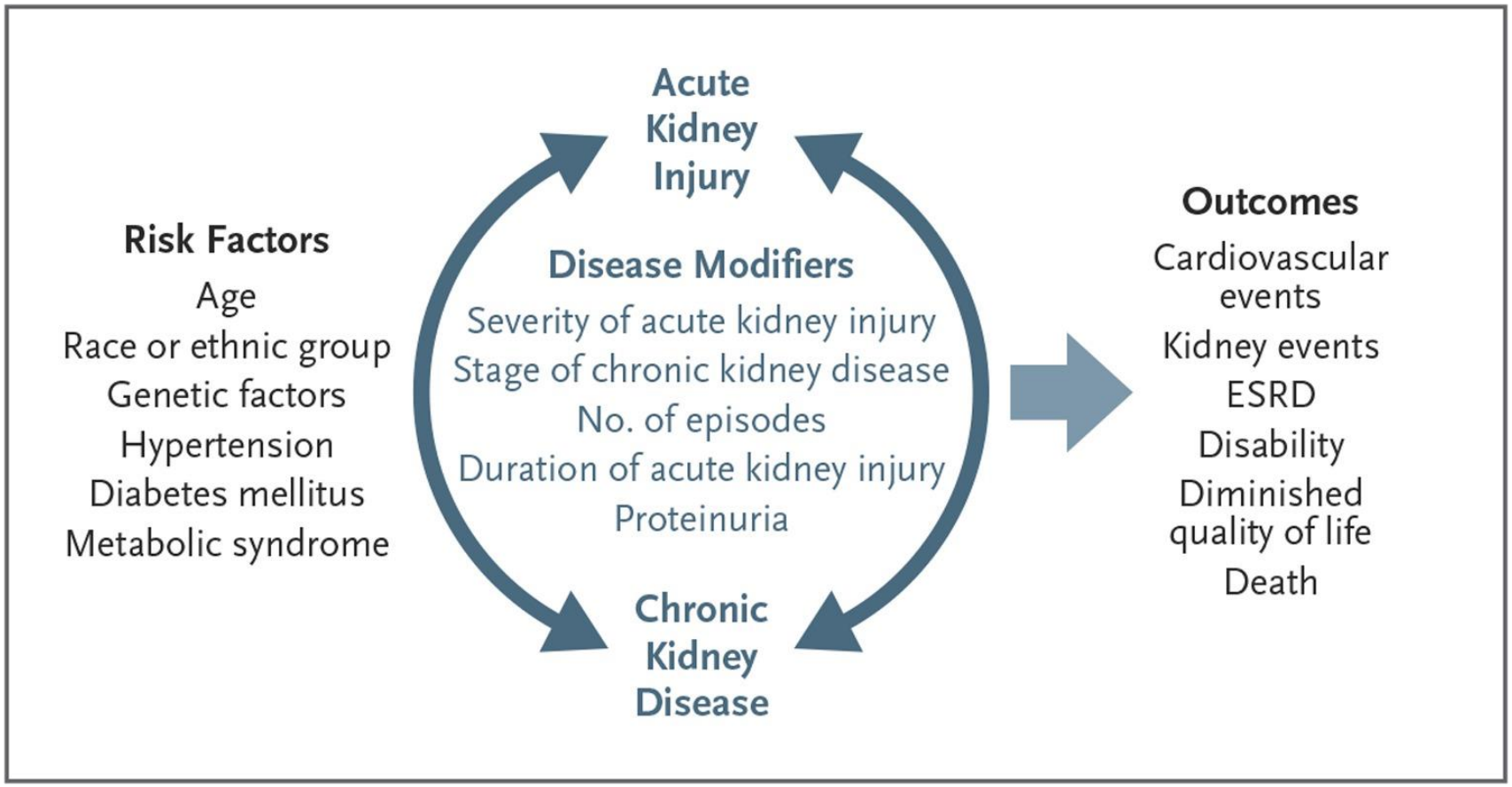
Potassium				
	Potassium		4.9	mmol/L
Urea				
	Urea	*	32.8	mmol/L
Creatinine				
	Creatinine	*	253	µmol/L
AKI Warning Stage 3 Note significant increase in Urea and Creatinine concentration				
Calcium				
	Calcium	*	2.09	mmol/L
	Adjusted Calcium		2.33	mmol/L

AKI and beyond….



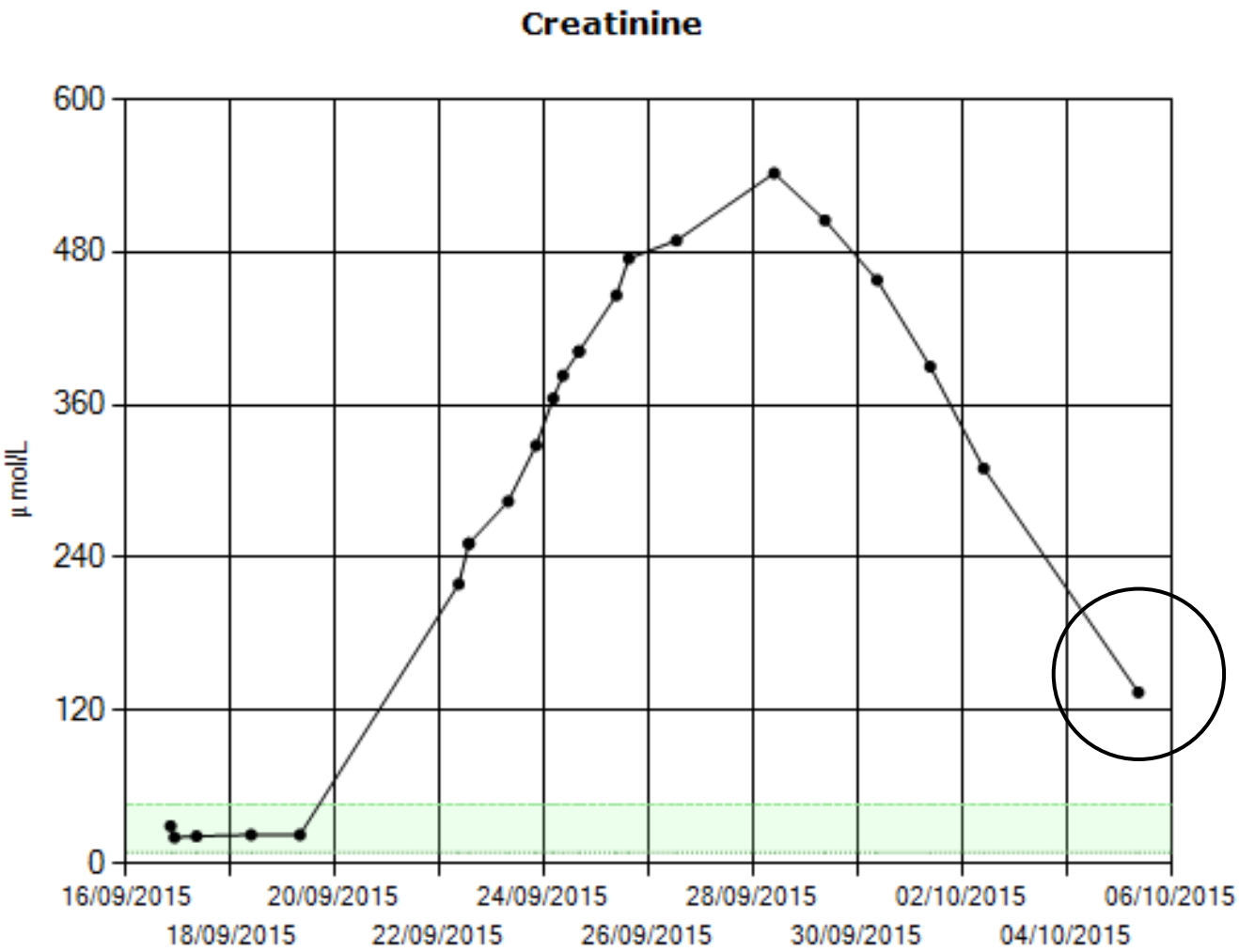
Hayes W. Pediatr Nephrol 2017; 32:2235-2243

Acute Kidney Injury and Chronic Kidney Disease as an Interconnected Syndrome

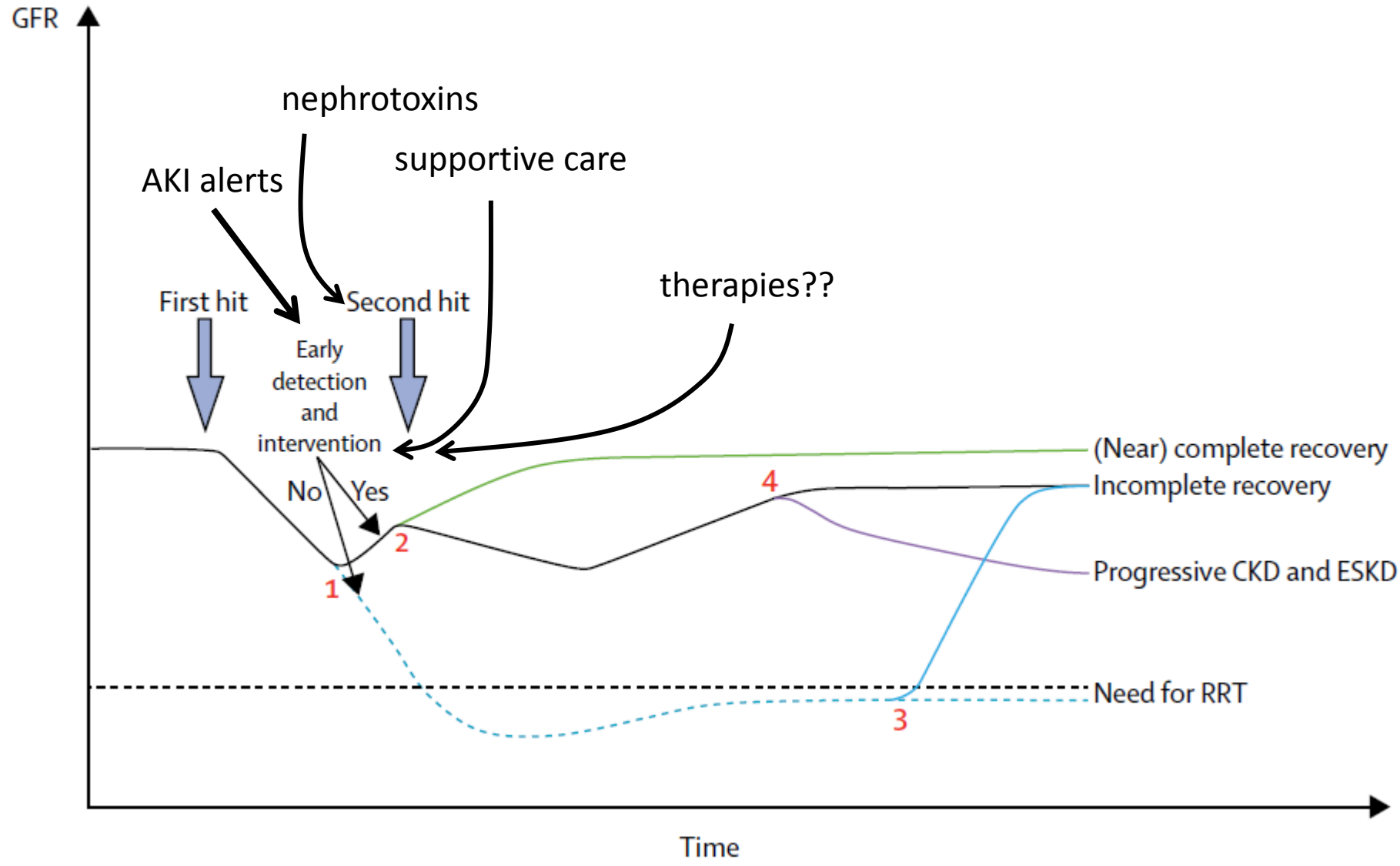


Chawla LS et al. N Engl J Med 2014;371:58-66

AKI


Creatinine
600
480
360
240
120
0
µ mol/L
16/09/2015
18/09/2015
20/09/2015
22/09/2015
24/09/2015
26/09/2015
28/09/2015
30/09/2015
02/10/2015
04/10/2015
06/10/2015

Influencing outcome?



Lancet Vol 389 May 27, 2017

Therapies in AKI

- **Tubular obstruction**
- rasburicase (synthetic urate oxidase)
- synthetic RDG peptides (anti-integrin therapy)

- **Tubular cell regeneration/protection**
- IGF-1
- apoptosis reduction
- stem cell transfusion

- **Blood flow**
- vasodilating prostaglandins (PGE2, PGI)
- synthetic ANP (anaritide)
- anti-endothelin
- ROS/peroxynitrile scavengers
- iNOS inhibitor
- theophylline (may block adenosine receptor)
- fenoldopam (DA-1 receptor agonist)

Atypical HUS a treatable AKI?

716 *Archives of Disease in Childhood* 1990; **65**: 716–721

ORIGINAL ARTICLES

Haemolytic uraemic syndromes in the British Isles 1985–8: association with Verocytotoxin producing Escherichia coli. Part 1: clinical and epidemiological aspects

D V Milford, C M Taylor, B Guttridge, S M Hall, B Rowe, H Kleanthous

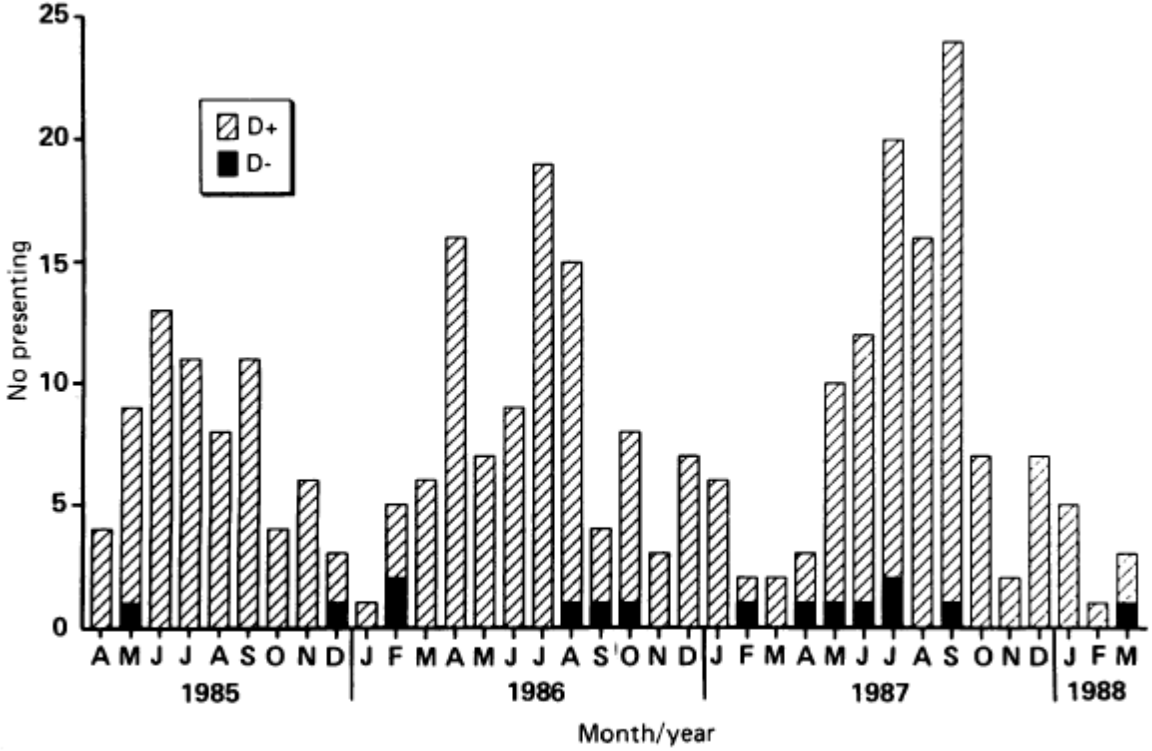
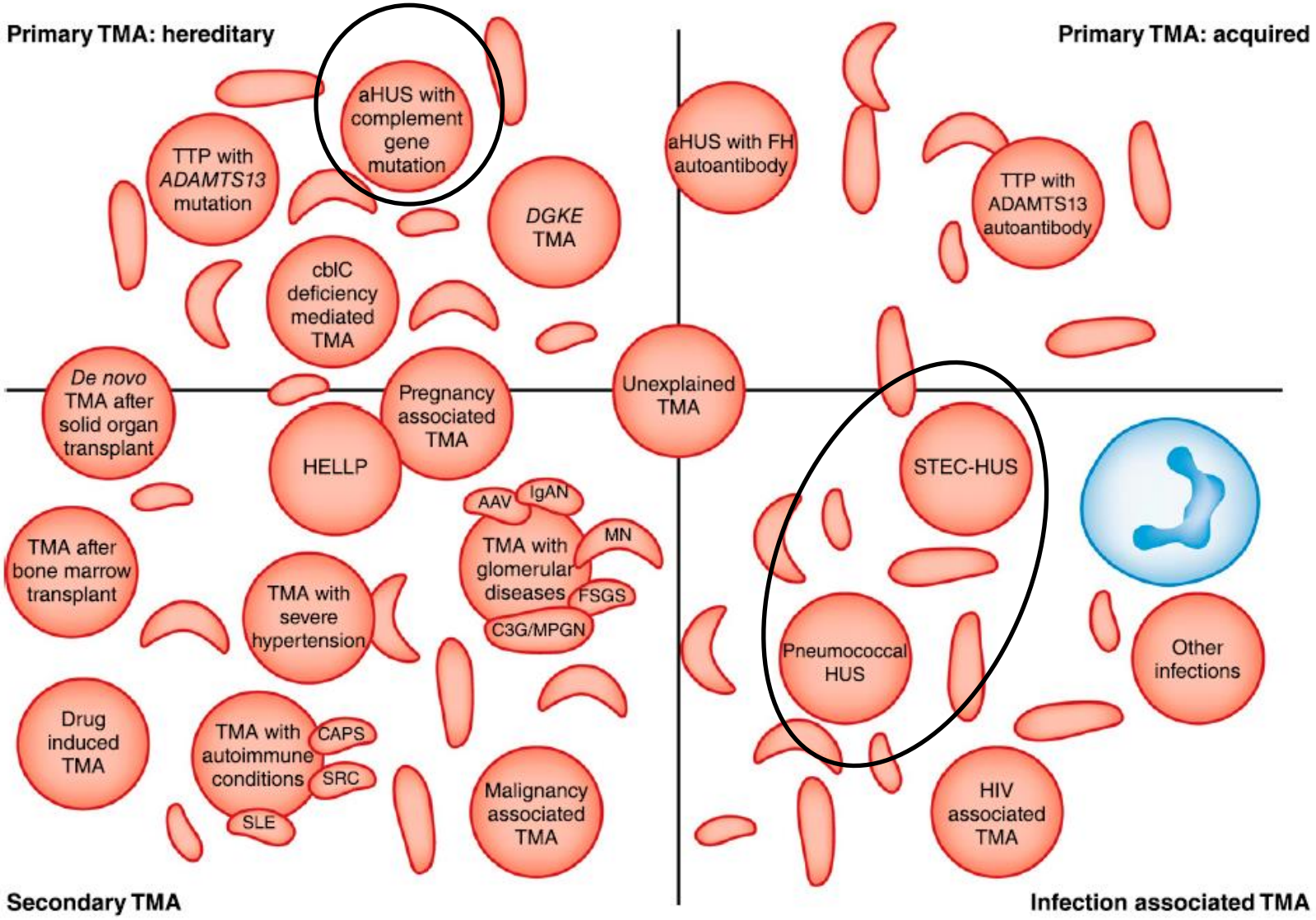


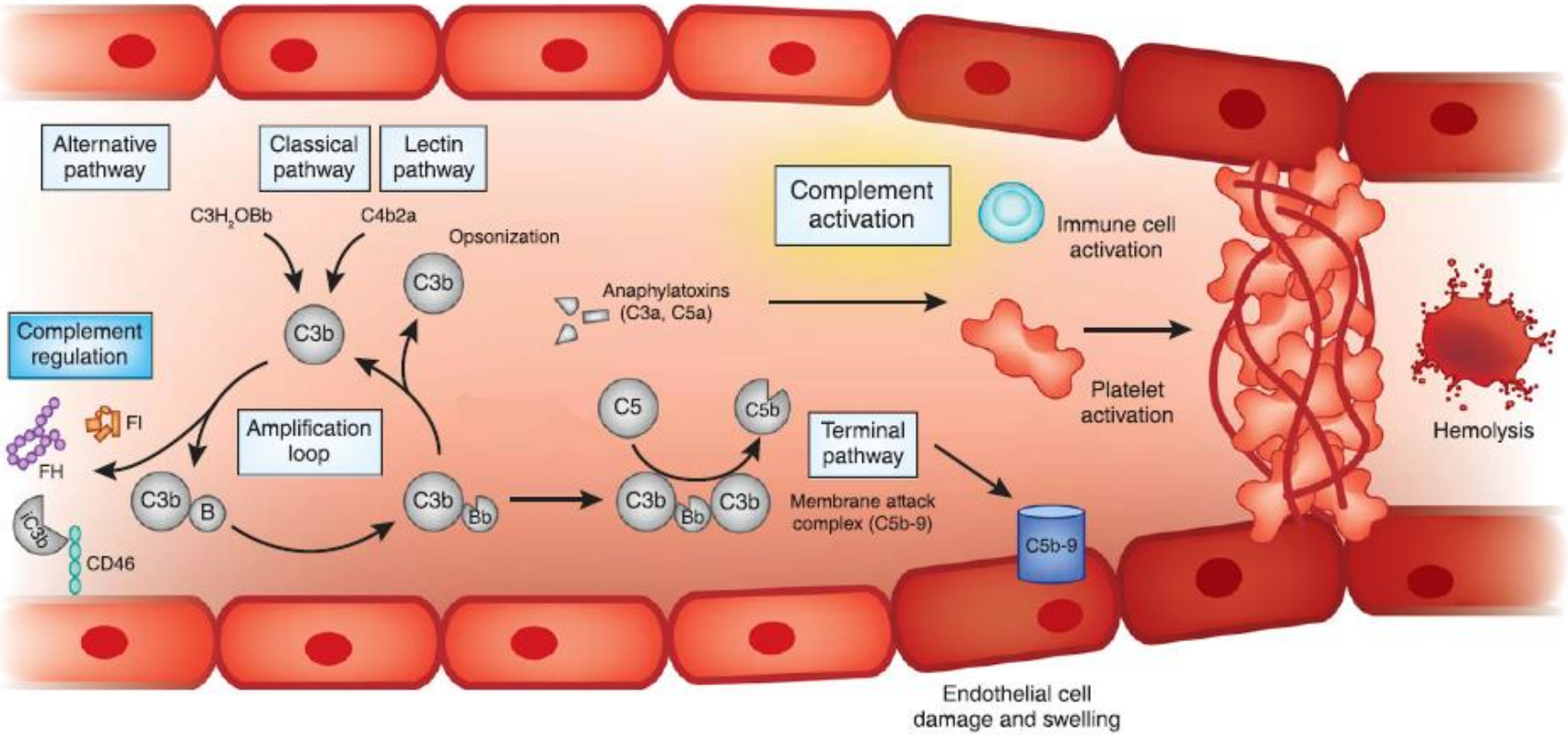
Figure 1 Distribution of cases of haemolytic uraemic syndrome by month showing seasonality confined to D+ patients.



Brocklebank et al CJASN 2018

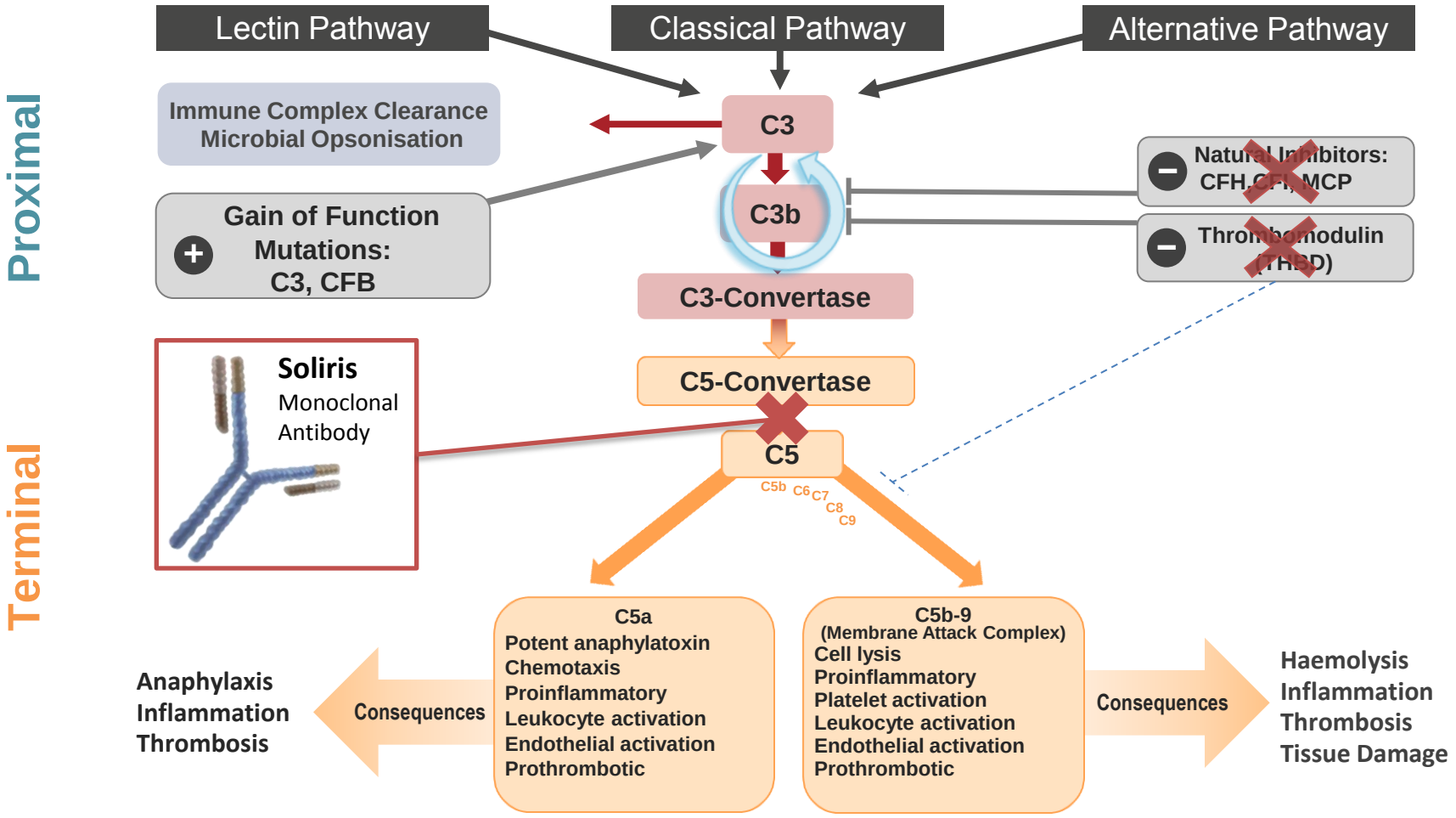
Unfettered complement activation

thrombus formation, platelet consumption, vascular occlusion and mechanical hemolysis



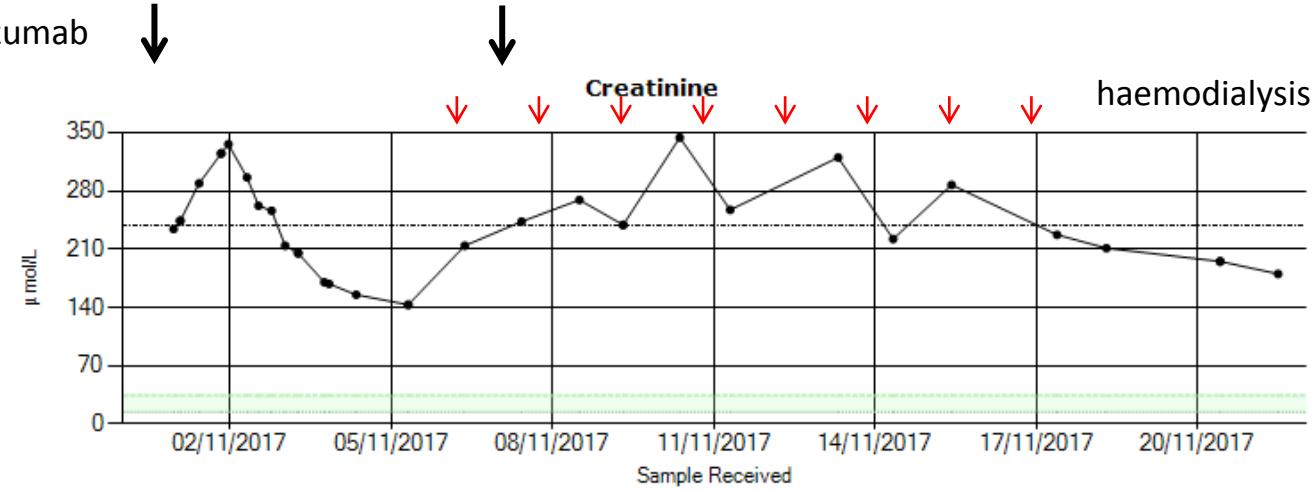
Brocklebank et al CJASN 2018

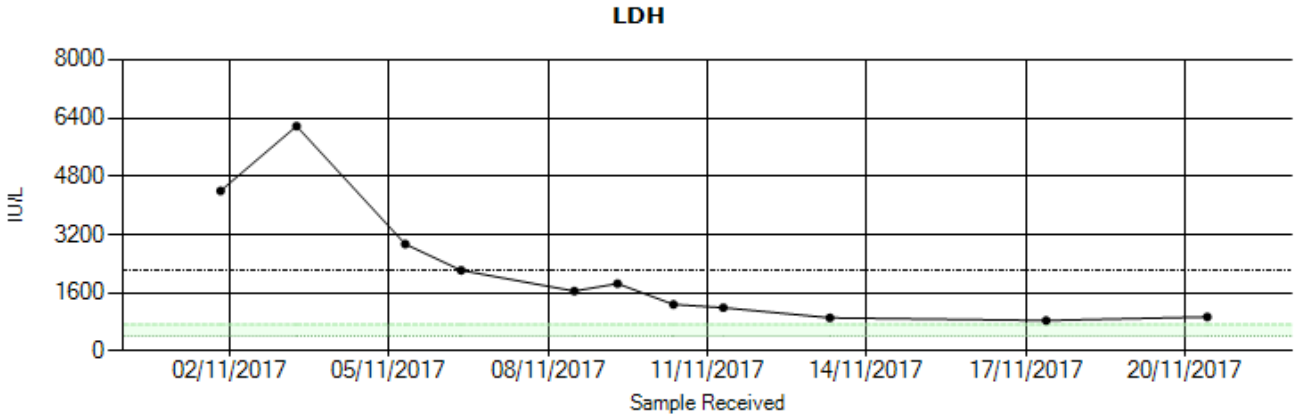
In aHUS, Constant Uncontrolled Complement Activity Leads to Progressive and Life-threatening Complications[1-7]

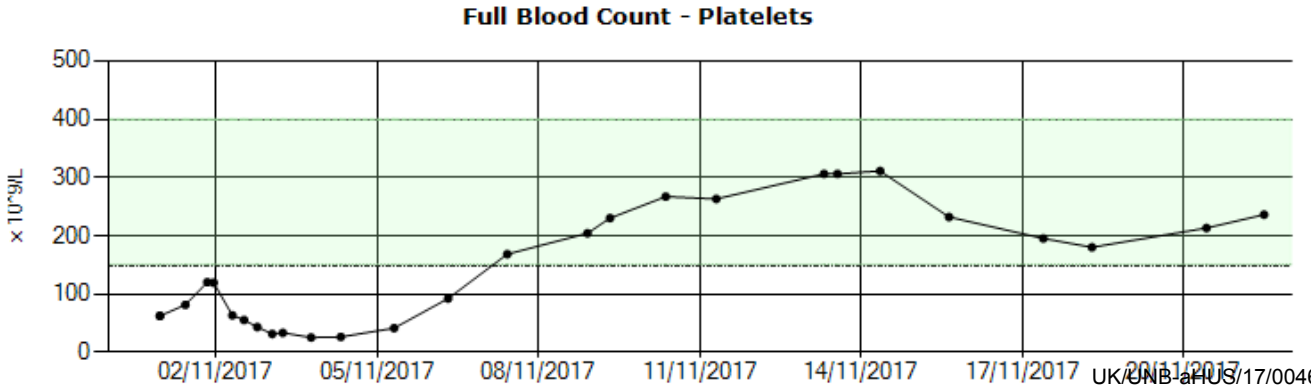


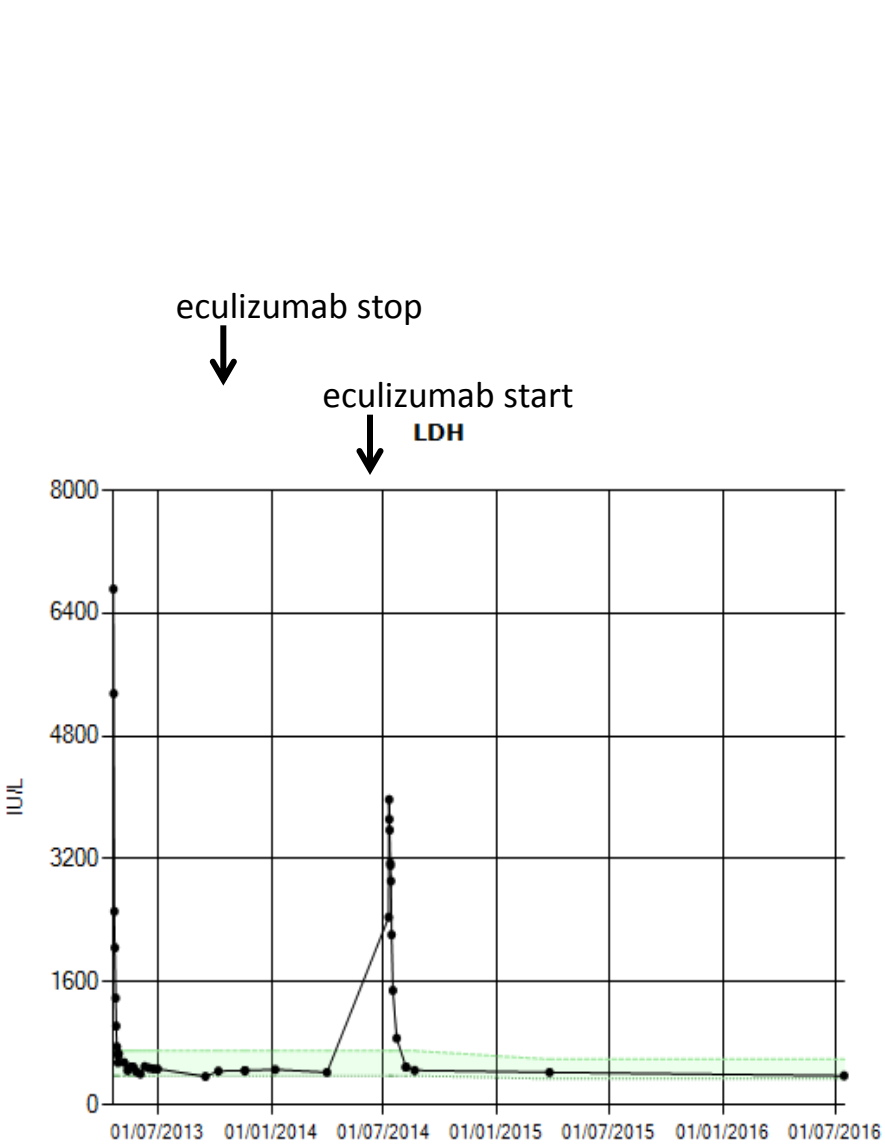
References: 1. Soliris® SmPC: Soliris® (eculizumab) summary of product characteristics. Alexion Pharmaceuticals, Inc.; 2014. **2.** Laurence J. Clin Adv Hematol Oncol. 2012;10(suppl 17):1-12. **3.** Legendre CM, et al. N Engl J Med. 2013;368:2169-2181. **4.** Sellier-Leclerc A-L, et al; French Society of Pediatric Nephrology. J Am Soc Nephrol. 2007;18:2392-2400. **5.** Noris M, et al. Nat Rev Nephrol. 2012;8:622-633. **6.** Kelly R, et al. Ther Clin Risk Manag. 2009;5:911-921. **7.** Rother RP, et al. Nat Biotechnol. 2007;25:1256-1264. [Published correction appears in Nat Biotechnol. 2007;25:1488].

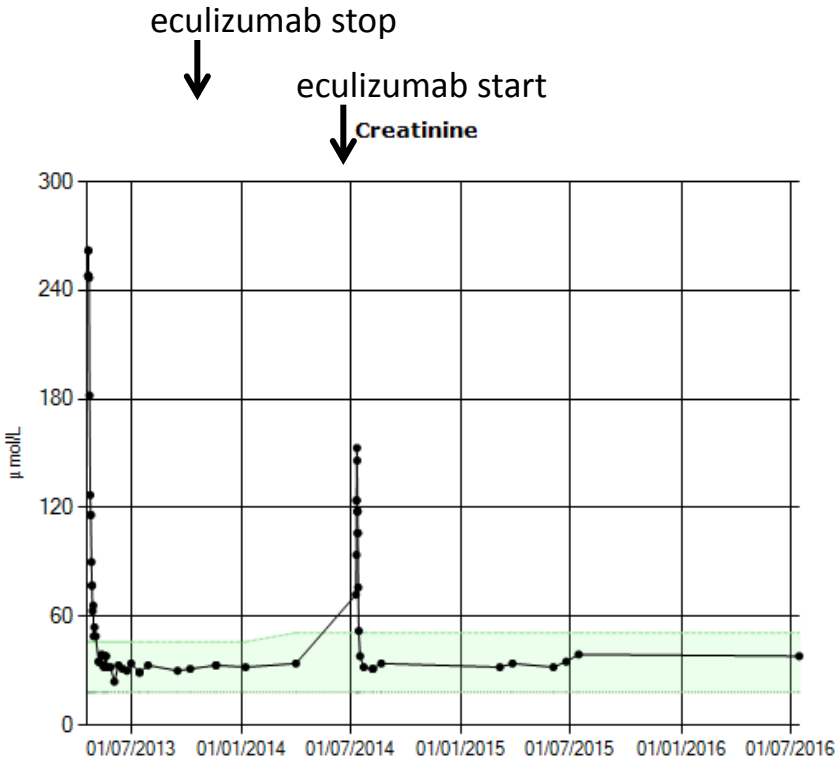
eculizumab


Creatinine
haemodialysis
350
280
210
140
70
0
µ mol/L
02/11/2017
05/11/2017
08/11/2017
11/11/2017
14/11/2017
17/11/2017
20/11/2017
Sample Received

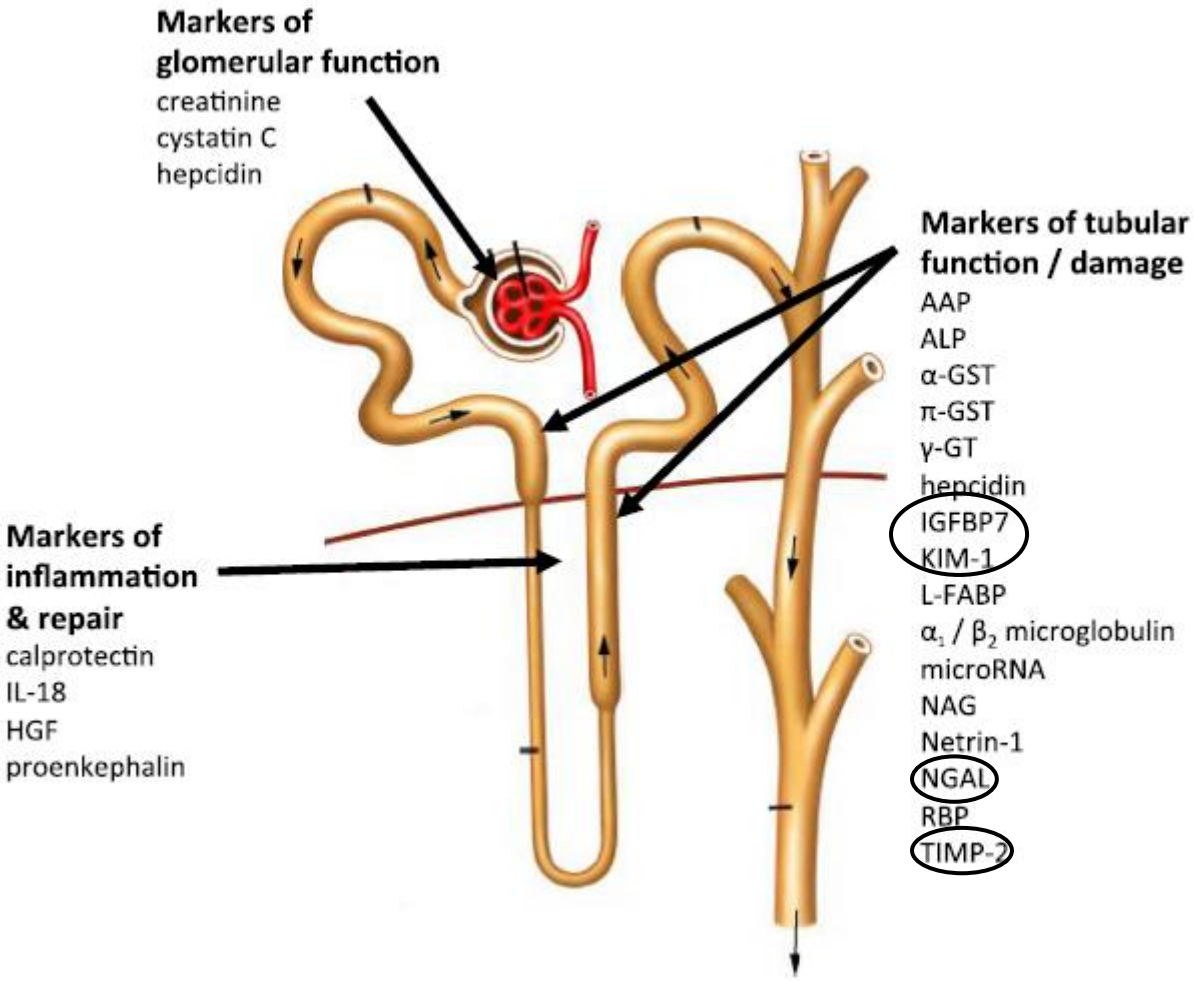

LDH
8000
6400
4800
3200
1600
0
IU/L
02/11/2017
05/11/2017
08/11/2017
11/11/2017
14/11/2017
17/11/2017
20/11/2017
Sample Received

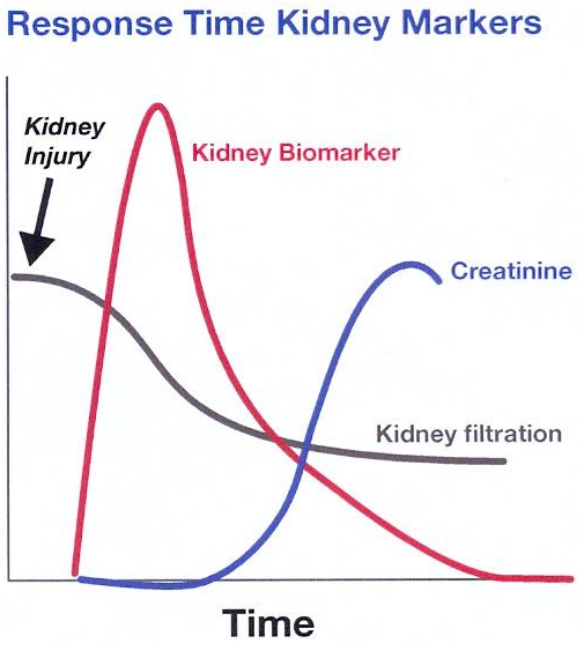

Full Blood Count - Platelets
500
400
300
200
100
0
x 10^9/L
02/11/2017
05/11/2017
08/11/2017
11/11/2017
14/11/2017
17/11/2017
20/11/2017


eculizumab stop
eculizumab start
LDH
IU/L
8000
6400
4800
3200
1600
0
01/07/2013
01/01/2014
01/07/2014
01/01/2015
01/07/2015
01/01/2016
01/07/2016


eculizumab stop
eculizumab start
Creatinine
µ mol/L
300
240
180
120
60
0
01/07/2013
01/01/2014
01/07/2014
01/01/2015
01/07/2015
01/01/2016
01/07/2016

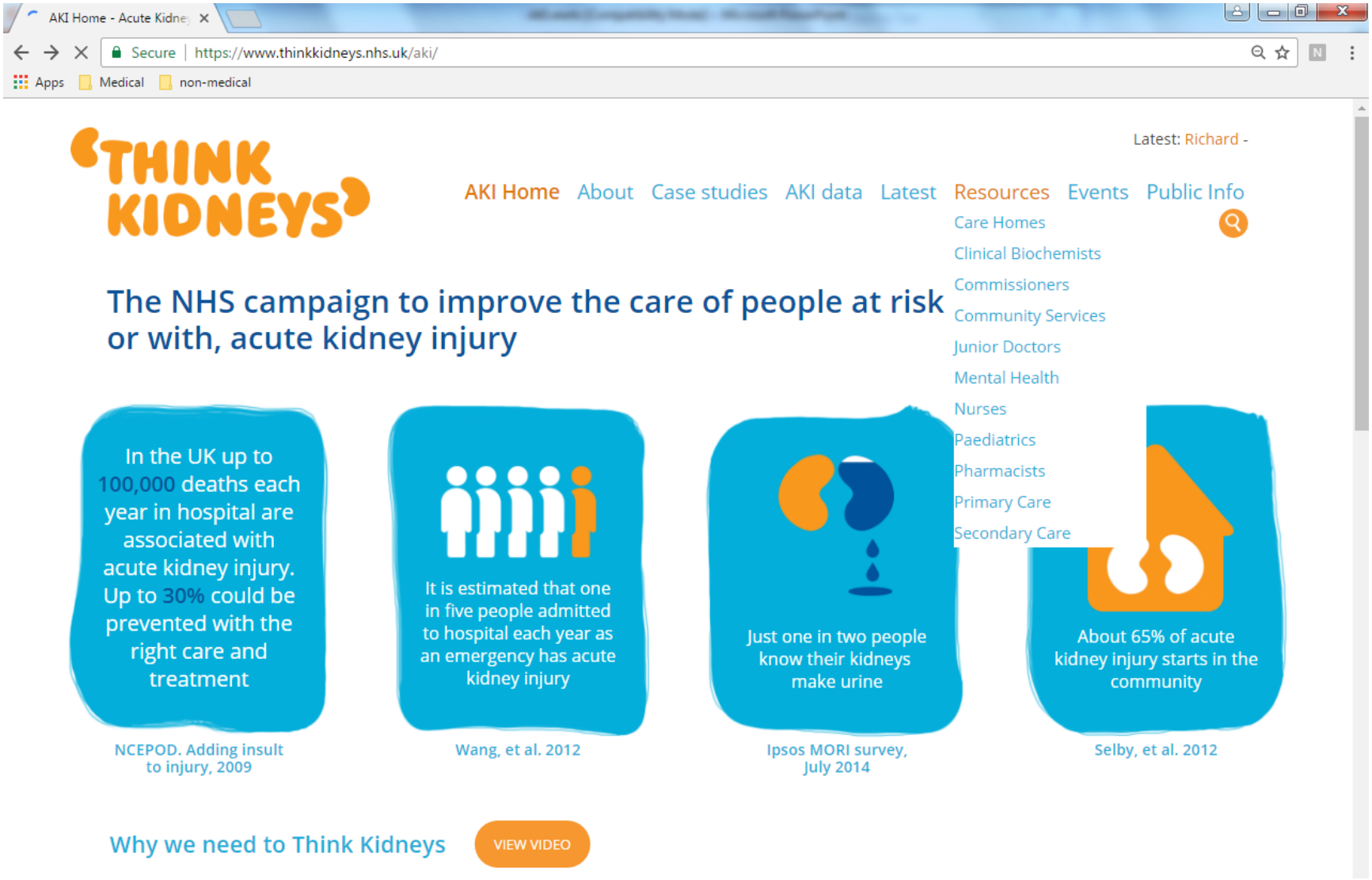
….prevention not cure…. biomarkers





Summary

- no proven therapy for established AKI
- early detection and appropriate management is still the mainstay – promote this to colleagues!
- promote use of the ‘Think Kidneys’ website
- biomarkers – no clarity with regard to clinical utility


AKI Home - Acute Kidne
Secure | https://www.thinkkidneys.nhs.uk/aki/
Apps
Medical
non-medical
THINK KIDNEYS
Latest: Richard -
AKI Home
About
Case studies
AKI data
Latest
Resources
Events
Public Info
Care Homes
Clinical Biochemists
Commissioners
Community Services
Junior Doctors
Mental Health
Nurses
Paediatrics
Pharmacists
Primary Care
Secondary Care
The NHS campaign to improve the care of people at risk or with, acute kidney injury
In the UK up to 100,000 deaths each year in hospital are associated with acute kidney injury. Up to 30% could be prevented with the right care and treatment
NCEPOD. Adding insult to injury, 2009
It is estimated that one in five people admitted to hospital each year as an emergency has acute kidney injury
Wang, et al. 2012
Just one in two people know their kidneys make urine
Ipsos MORI survey, July 2014
About 65% of acute kidney injury starts in the community
Selby, et al. 2012
Why we need to Think Kidneys
VIEW VIDEO