The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Renal biopsy – what a general paediatrician needs to know

MPGN – new classification

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THE great north CHILDREN'S HOSPITAL

Too many names….

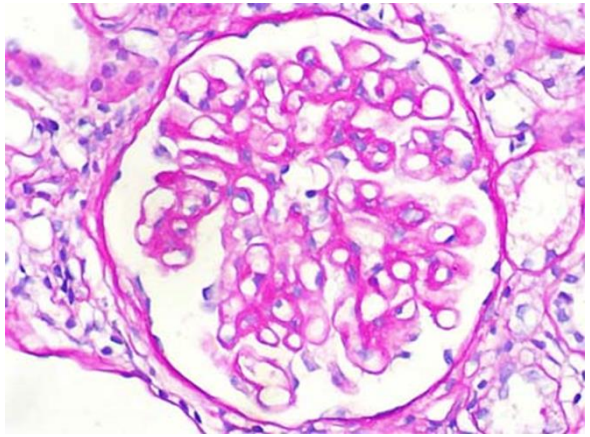
- Membranoproliferative glomerulonephritis
- Mesangiocapillary glomerulonephritis
- Dense Deposit Disease
- C3 Glomerulonephritis
- C3 Glomerulopathy

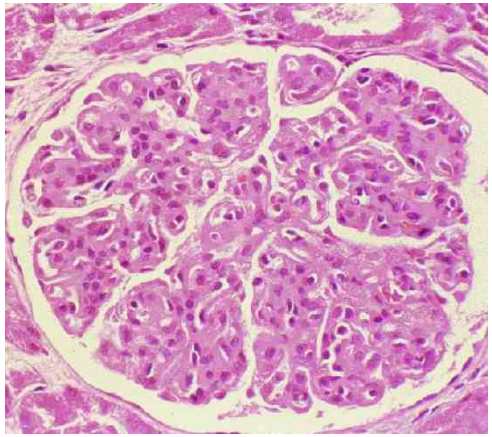
What is the clinical problem?

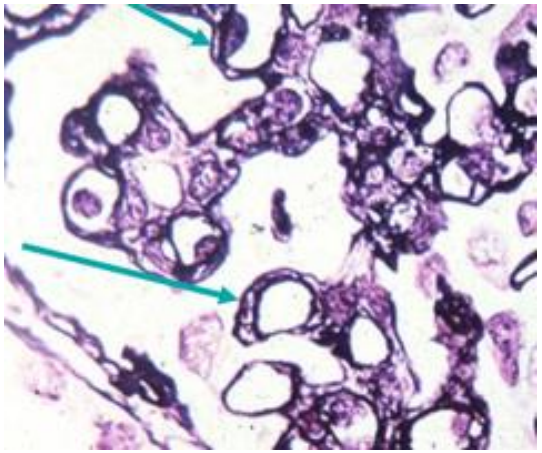
- Ben
  - 8 years old
    - Facial swelling
    - +++ protein in urine
    - Albumin 17g/l, normal creatinine
  - Diagnosis nephrotic syndrome
  - Commenced standard treatment
    - No remission at 28 days
  - Auto-antibody screen negative, C3/C4 normal
  - Renal biopsy

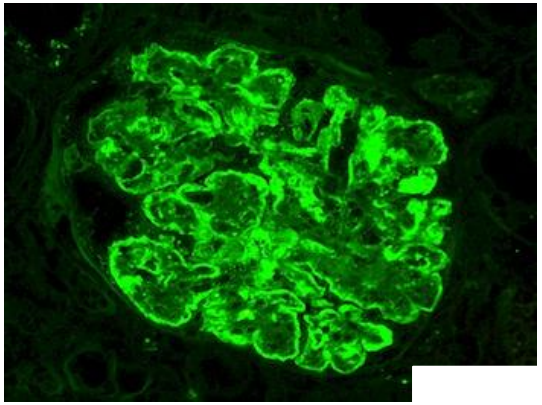
What we saw on the biopsy

Normal glomerulus



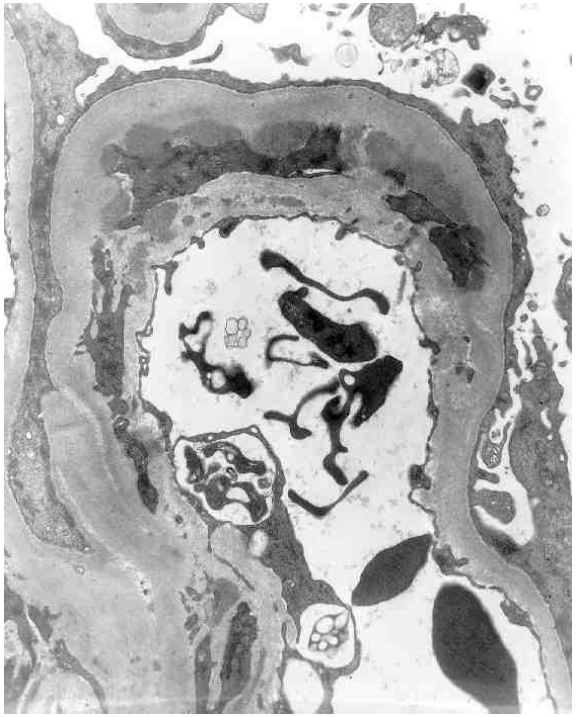




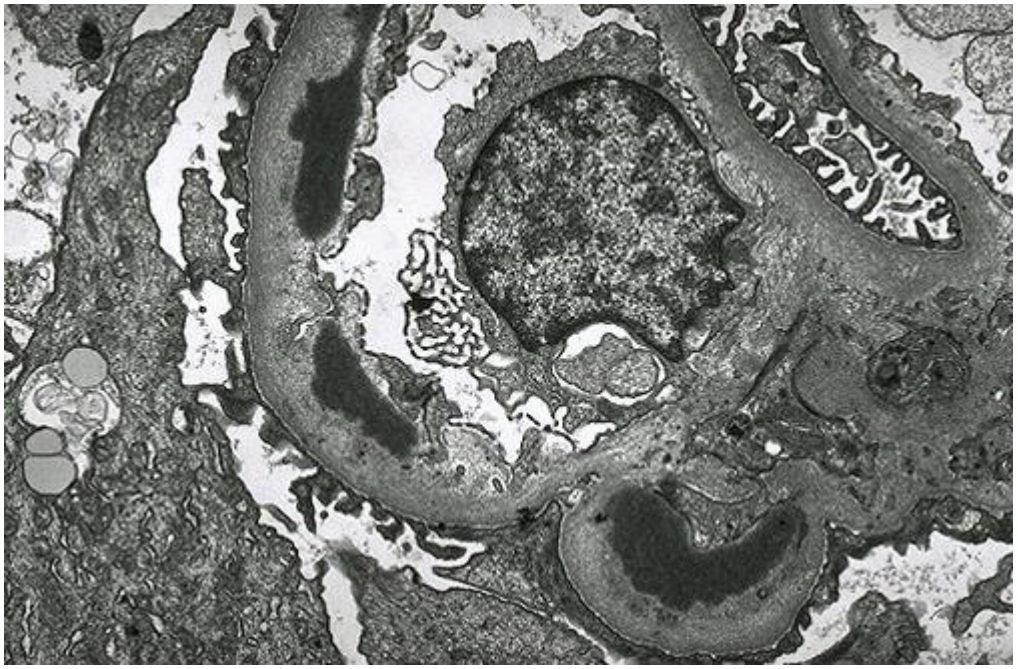


“Membranoproliferative glomerulonephritis”

MPGN describes what it looks like



Type 1 – sub-endothelial deposits



Type 2 – intra-membranous dense deposits “Dense Deposit Disease”

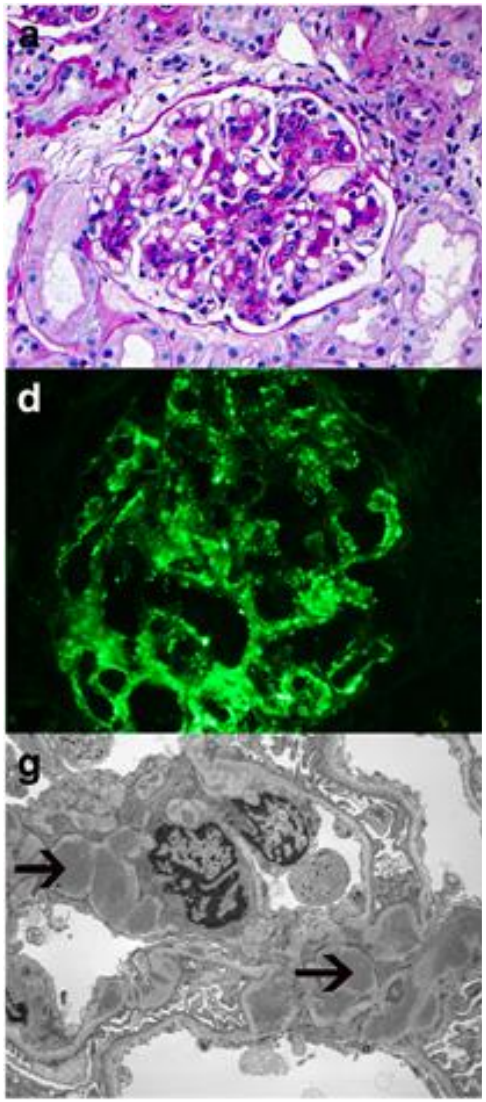
What happened next?

- Relentless nephrotic state
- Rapid decline in renal function
- Immunosuppression
  - More prednisolone
  - Cyclophoshamide
  - No effect
- Developed end stage renal disease within 6 months of presentation
- Peritoneal dialysis for 2 years
- Successful kidney transplant….so far

A different presentation

- Kia
  - 6 years old
    - Frank haematuria, urine protein ++
    - Preceding sore throat
    - Complement C3 0.09g/l
    - Normal BP and renal function
    - ASOT borderline
    - Auto-antibody screen negative
  - Presumed post-infectious glomerulonephritis
  - 3 months later
    - C3 0.06g/l
    - Persistent proteinuria
  - Renal biopsy consistent with post-infectious GN
  - 6 months later
    - C3 0.07g/l
    - Persistent proteinuria
  - Repeat renal biospy

What we saw on the biopsy



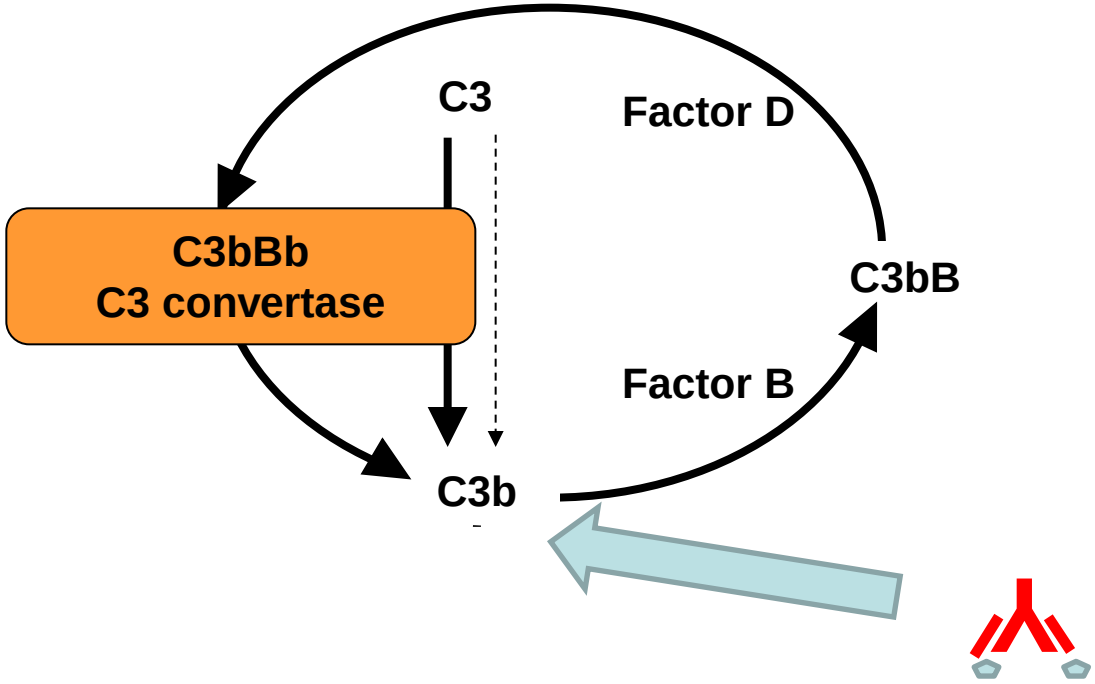
C3 glomerulonephritis

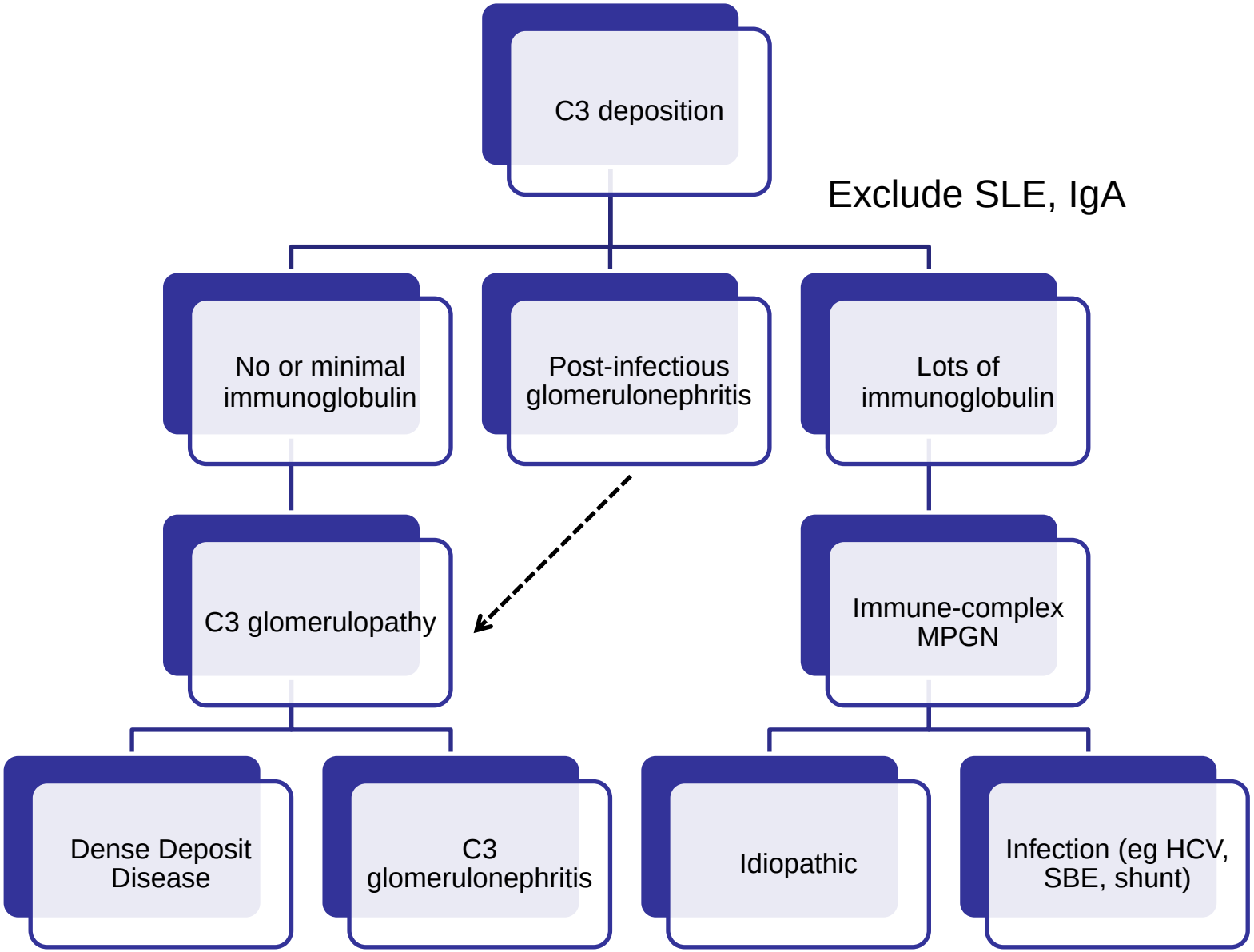
And another presentation

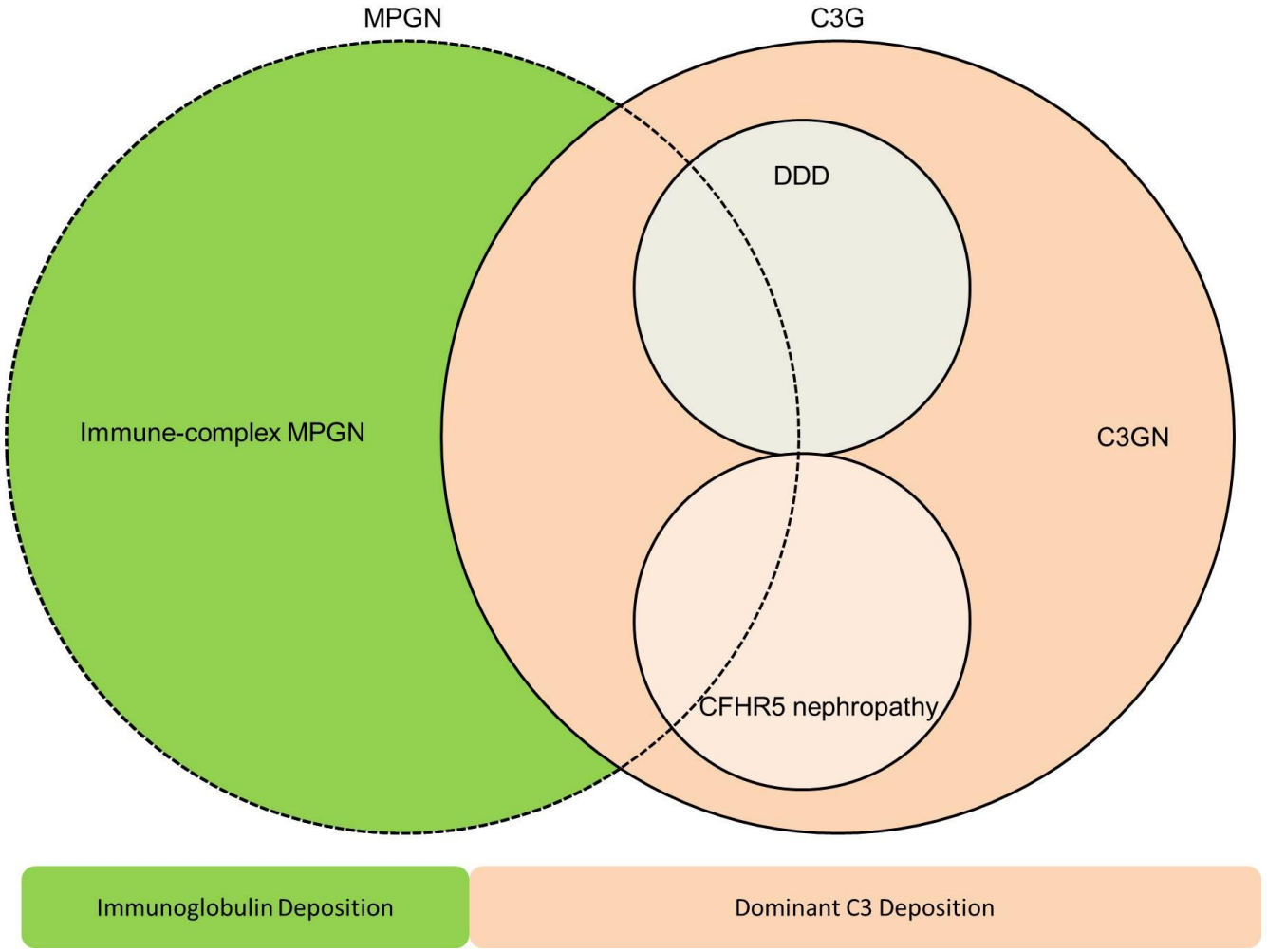
- Aaron
  - 10 years old
  - Incidental haematuria and proteinuria
    - Persistent
  - Normal renal function and albumin
  - Borderline C3
  - Urine protein:creatinine ratio ~100
  - Renal biopsy
    - MPGN pattern with C3 and IgG in capillary walls
    - Sub-endothelial deposits
    - MPGN type 1

Heterogeneity

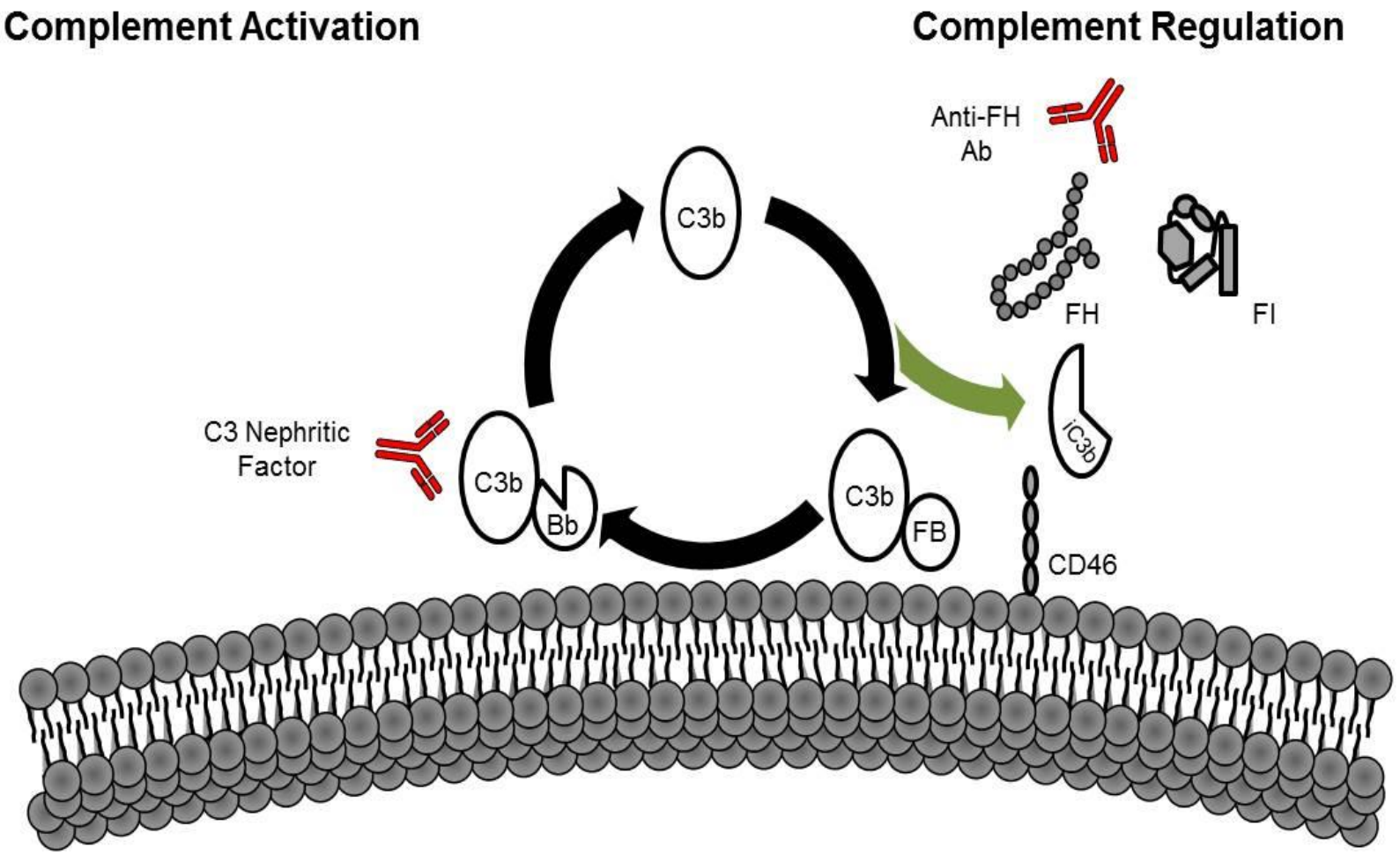
- A variety of presentations
  - Nephrotic syndrome
  - Nephritic picture
  - Asymptomatic dipstick haematuria and proteinuria
- A variety of outcomes
  - ESRD
  - Significant proteinuria
  - Minor urinary abnormalities
- Unifying feature is glomerular complement C3 deposition


C3
Factor D
C3bBb
C3 convertase
C3bB
Factor B
C3b

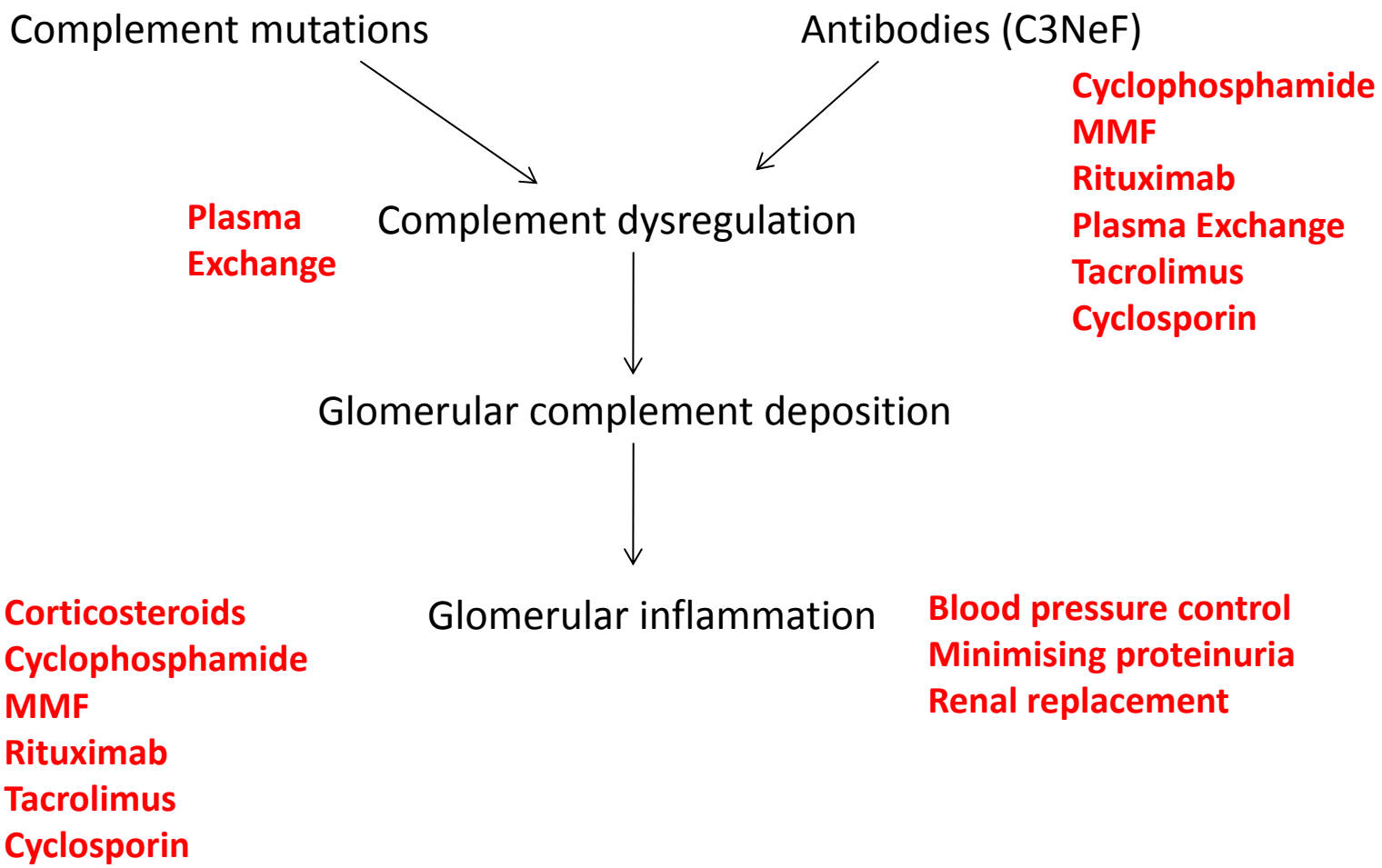

C3 deposition
Exclude SLE, IgA
No or minimal immunoglobulin
Post-infectious glomerulonephritis
Lots of immunoglobulin
C3 glomerulopathy
Immune-complex MPGN
Dense Deposit Disease
C3 glomerulonephritis
Idiopathic
Infection (eg HCV, SBE, shunt)


MPGN
C3G
DDD
Immune-complex MPGN
C3GN
CFHR5 nephropathy
Immunoglobulin Deposition
Dominant C3 Deposition

What causes it?



Treatment of MPGN/C3G



National Study of MPGN and C3 glomerulopathy

Sally Johnson
David Kavanagh
Tim Goodship
Kevin Marchbank
Newcastle upon Tyne

Roger Malcomson
Leicester

Mark Taylor
Birmingham

Claire Harris
Paul Morgan
Cardiff

Terry Cook
Daniel Gale
Stephen Marks
Matthew Pickering
London

MRC Medical Research Council

wellcome trust

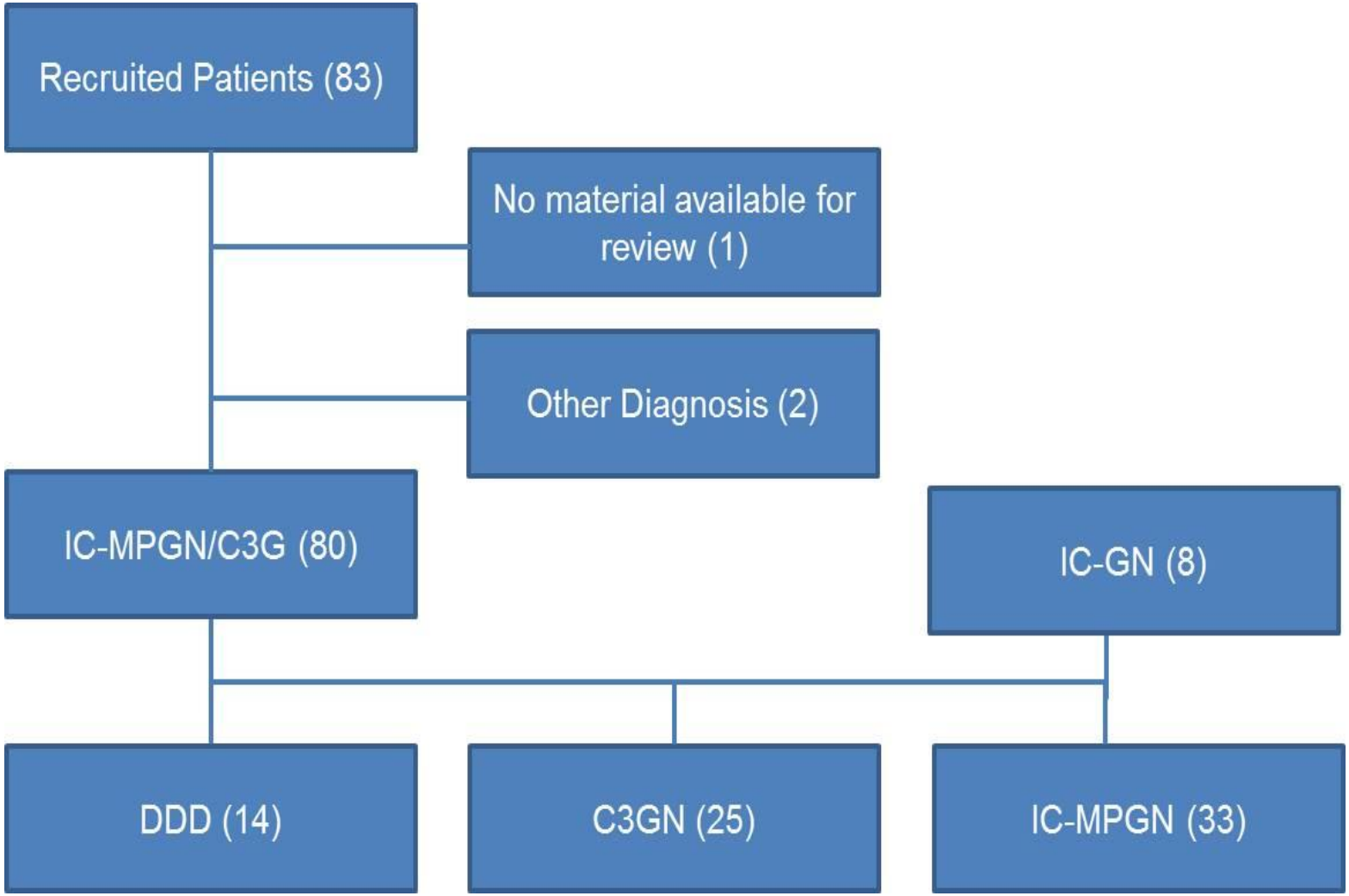
Kidney Research UK
Funding research to save lives

Kidneeds

Site Name	Recruited
NEWCASTLE UPON TYNE HOSPITALs	21
NOTTINGHAM - QUEEN'S MEDICAL CENTRE CAMPUS	18
ROYAL FREE HOSPITAL	17
NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST - CITY CAMPUS	16
ROYAL HOSPITAL FOR SICK CHILDREN (GLASGOW)	13
CITY GENERAL HOSPITAL	12
THE ROYAL VICTORIA INFIRMARY	11
BIRMINGHAM CHILDREN'S HOSPITAL	10
ST THOMAS' HOSPITAL	9
ALDER HEY CHILDREN'S NHS FOUNDATION TRUST	8
GREAT ORMOND STREET HOSPITAL CENTRAL LONDON SITE	8
ROYAL DEVON & EXETER HOSPITAL (WONFORD)	7
ROYAL MANCHESTER CHILDREN'S HOSPITAL	7
ST JAMES'S UNIVERSITY HOSPITAL	7
LEEDS GENERAL INFIRMARY	6
LEICESTER GENERAL HOSPITAL	5
SUNDERLAND ROYAL HOSPITAL	5
UNIVERSITY HOSPITAL OF WALES	5
ROYAL SUSSEX COUNTY HOSPITAL	4
NORFOLK & NORWICH UNIVERSITY HOSPITAL	3
NORTHERN GENERAL HOSPITAL	3
SOUTHERN GENERAL HOSPITAL (GLASGOW)	3
BRISTOL ROYAL HOSPITAL FOR CHILDREN	1
SOUTHAMPTON GENERAL HOSPITAL	1
COVENTRY	0

Pending Sites
LISTER (STEVENAGE)
BIRMINGHAM ADULTS
WOLVEHAMPTON
CAMBRIDGE

The National study of MPGN/C3G

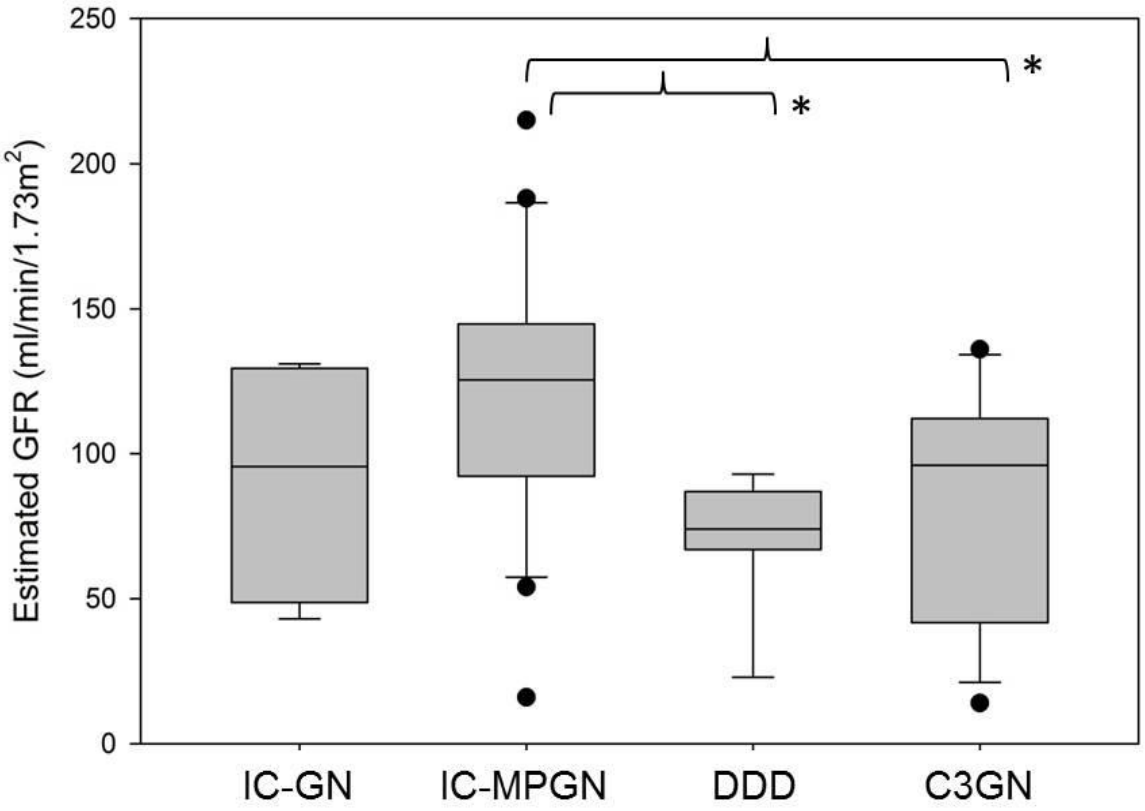


Central Pathology review by Professor Terry Cook

Clinical characteristics at presentation

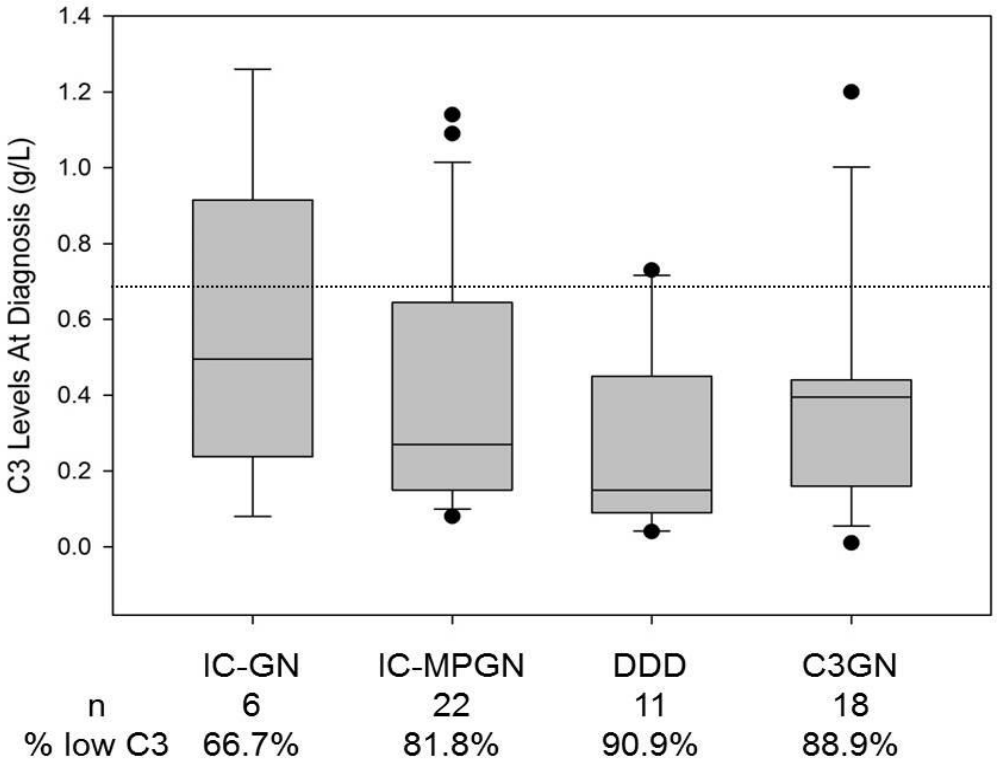
	IC-GN	IC-MPGN	DDD	C3GN
Number of patients	8	33	14	25
Median age at presentation (range)	8 (2-10)	9 (2-15)	9.5 (4-15)	9 (4-15)
Median albumin at presentation (n)(g/L)	34 (7)	25 (31)	30 (14)	26 (22)
Median P:Cr (n) (mg / mmol creatinine)	332.3 (5)	546.9 (18)	775.5 (8)	402.0 (17)

eGFR at presentation



* P<0.05

C3 Levels at Diagnosis

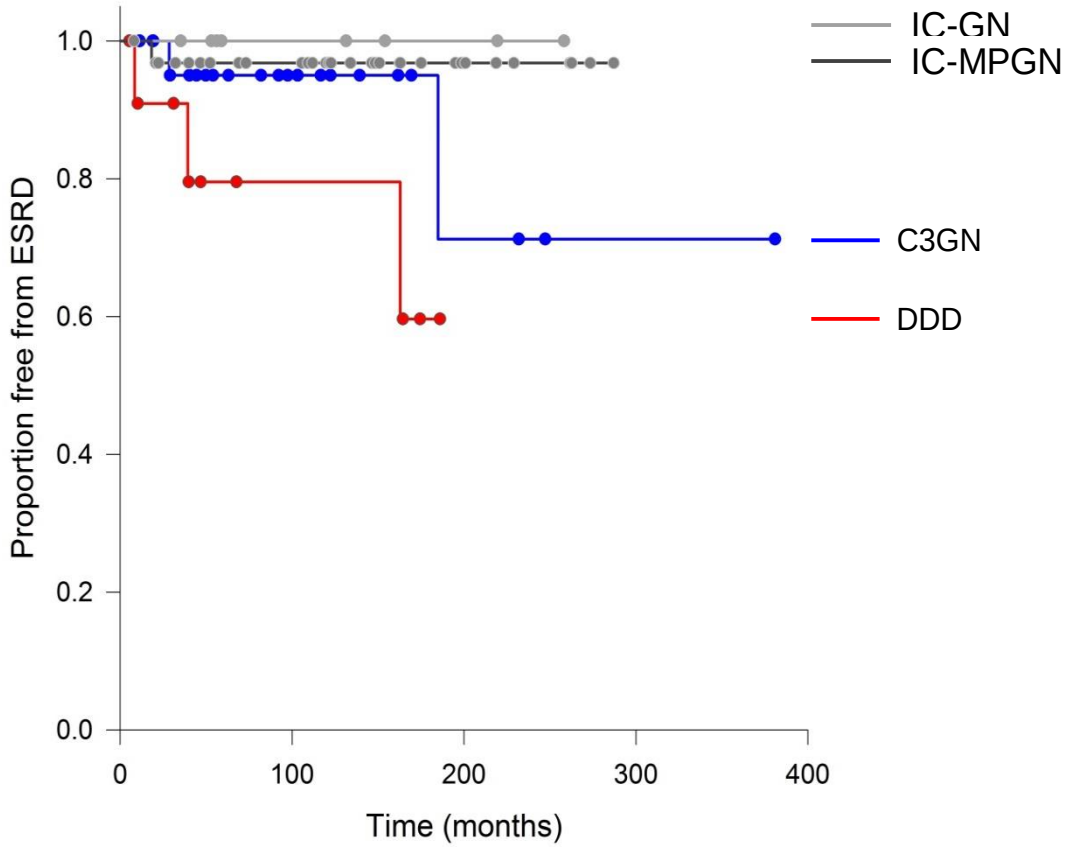


Complement abnormalities by disease

- Acquired abnormalities predominant in this cohort

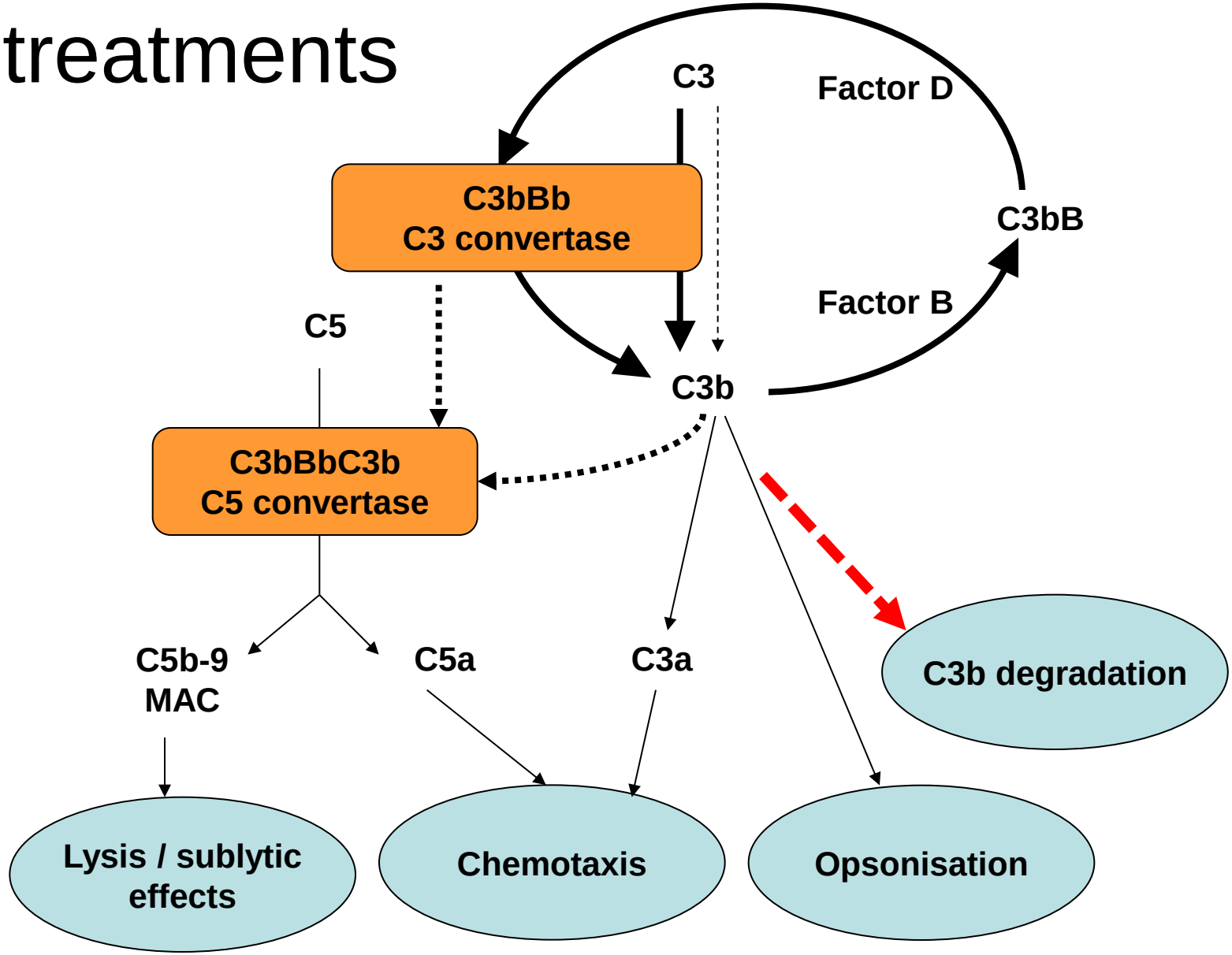
	Overall	ICGN	ICMPGN	C3GN	DDD
C3 Nephritic Factor	42.1%	0%	28.6%	33.3%	66.7%
Autoantibody to FH	16.7%	37.5%	12.5%	12.5%	21.4%
Rare Genetic Variant	8.3%	0%	14.3%	4.5%	8.3%

Outcomes by Disease



P= 0.04 – no significant differences between groups

Possible treatments



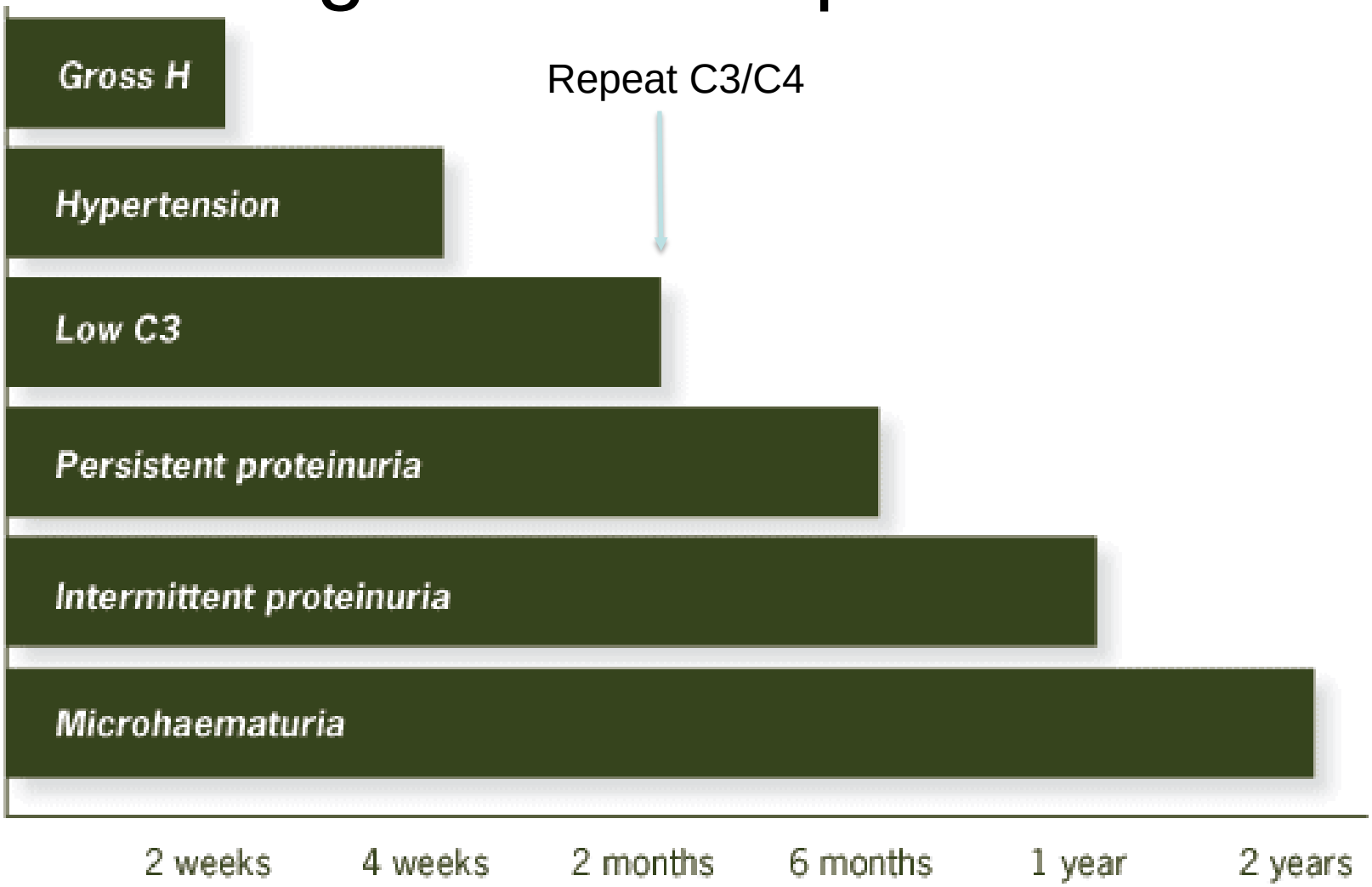
Take home messages

- MPGN and C3 glomerulopathy are rare kidney diseases with poor prognosis and no curative treatment
- The terminology needs to improve!
- They can present in a variety of ways
  - Nephrotic syndrome
  - Like post-infectious glomerulonephritis
  - Incidental urinary abnormalities
- The key defect is a failure to control complement activation
  - This will ultimately lead to targeted treatments

Red flags that may indicate MPGN/C3G

- Low C3 in a child with nephrotic syndrome
- Steroid resistant nephrotic syndrome
- Persistent low C3 and proteinuria in a child with apparent post-infectious glomerulonephritis
  - Even with barn-door evidence of streptococcal infection!

Evolution of post-infectious glomerulonephritis



Thank you!