Renal Disease in Cystic Fibrosis
More than meets the eye…

International Nurse Specialist Group/CF Meeting June 2012

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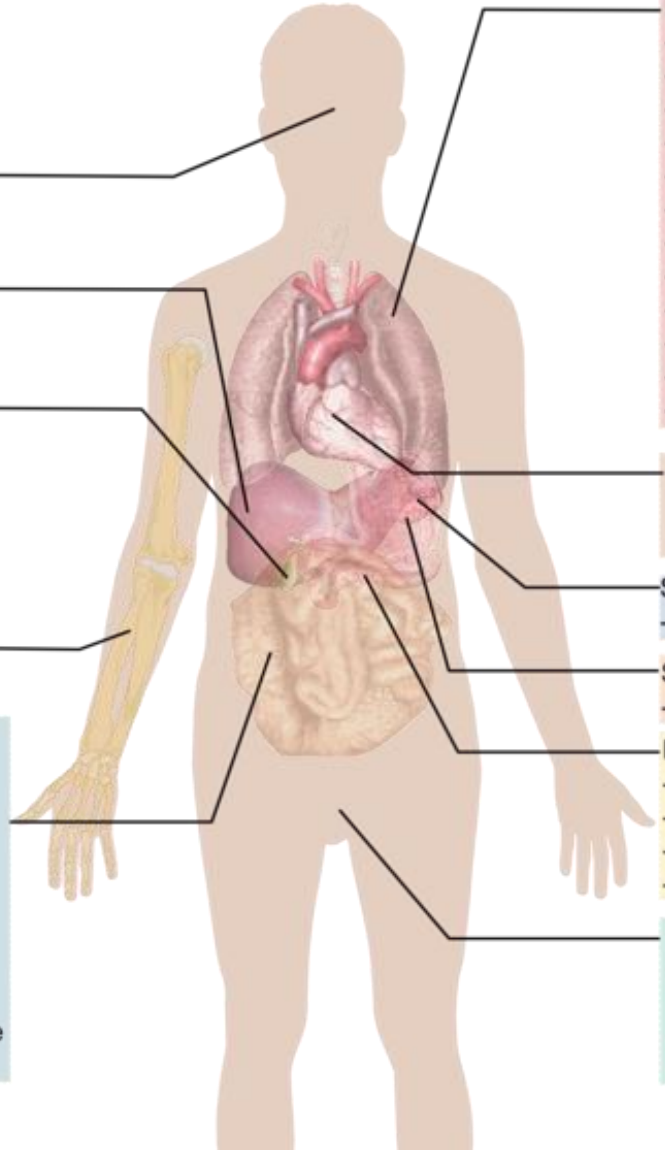
Manifestations of

Cystic Fibrosis



General
- Growth failure (malabsorption)
- Vitamin deficiency states (vitamins A, D, E, K)

Nose and sinuses
- Nasal polyps
- Sinusitis

Liver
- Hepatic steatosis
- Portal hypertension

Gallbladder
- Biliary cirrhosis
- Neonatal obstructive jaundice
- Cholelithiasis

Bone
- Hypertrophic osteoarthropathy
  - Clubbing
- Arthritis
- Osteoporosis

Intestines
- Meconium ileus
- Meconium peritonitis
- Rectal prolapse
- Intussusception
- Volvulus
- Fibrosing colonopathy (strictures)
- Appendicitis
- Intestinal atresia
- Distal intestinal obstruction syndrome
- Inguinal hernia

Lungs
- Bronchiectasis
- Bronchitis
- Bronchiolitis
- Pneumonia
- Atelectasis
- Hemoptysis
- Pneumothorax
- Reactive airway disease
- Cor pulmonale
- Respiratory failure
- Mucoid impaction of the bronchi
- Allergic bronchopulmonary aspergillosis

Heart
- Right ventricular hypertrophy
- Pulmonary artery dilation

Spleen
- Hypersplenism

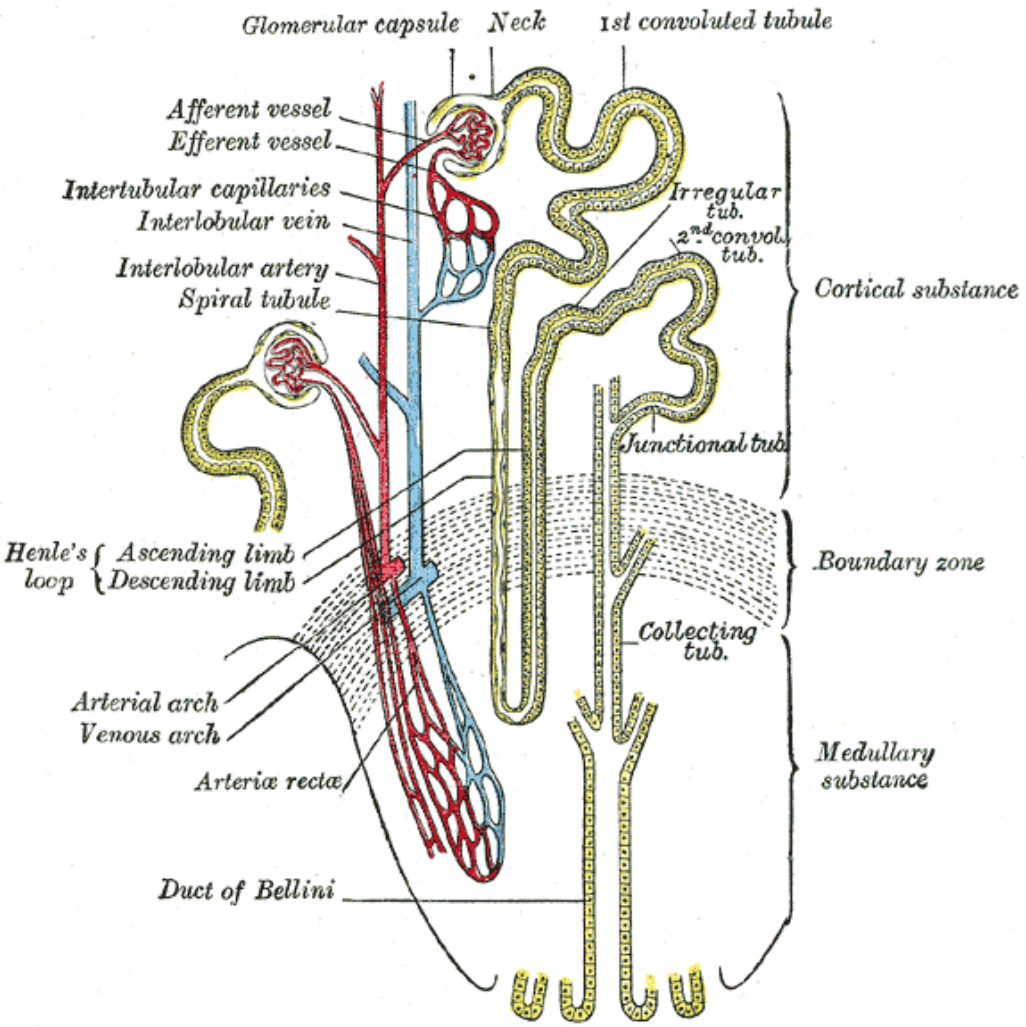
Stomach
- GERD

Pancreas
- Pancreatitis
- Insulin deficiency
- Symptomatic hyperglycemia
- Diabetes

Reproductive
- Infertility (aspermia, Absence of vas deferens)
- Amenorrhea
- Delayed puberty

What?

No Renal Involvement?



Current perceptions

- Care Pathway dominated (appropriately) by pulmonary/microbiological issues

- CFRD a common complication (30%): *managed*

- Hazards of aminoglycosides/AKI: *acknowledged*
- Increased incidence of stone disease: *acknowledged*

- *'Renal disease'* felt to be *'uncommon'*

CF patients in Cork

- ~140 attend Adult CF Service
- ~ 80 attend Paediatric CF Service
- ~ 25% of national prevalence

- Renal Service Consultations
- 10-20% of adult cohort

- AKI
- CFRD
- CNi toxicity
- Urolithiasis
- ESKD/Dialysis
- Progressive CKD
- ESKD/Renal Transplant
- Other glomerular disease
- Electrolyte & Acid-Base problems

CF (E84)

- Cystic fibrosis transmembrane regulator (CFTR)

- ATP-responsive chloride channel - apical membrane epithelial cells
- Chromosome 7q31.2
- >1400 mutations
- ΔF508 in ~70%

- >50% will survive into 30's
- 2000 birth cohort (UK) projected life expectancy of up to 50yrs

- 1 in 19 Irish carry CF genetic mutation (1 in 25)
- >1100 patients (3666 patients had ESKD on 31/12/11)

CFTR mutations

- Class I: disruption of CFTR synthesis
- Class II: defective protein processing (ΔF508)
- Class III: defective regulation, not activated
- Class IV: conductance deficient
- Class V: normal but less

CFTR in the kidney
(an apical membrane ATP-responsive Cl-channel)

- Multifunctional integral membrane protein (ABC family)

- CFTR mRNA in all segments of the nephron
- Protein more selectively expressed
- Chloride secretion in distal tubule, principal cells
- Secretes ATP – effects on ENaC and ROMK2 (CCD)

- Contributes to cyst enlargement in ADPKD

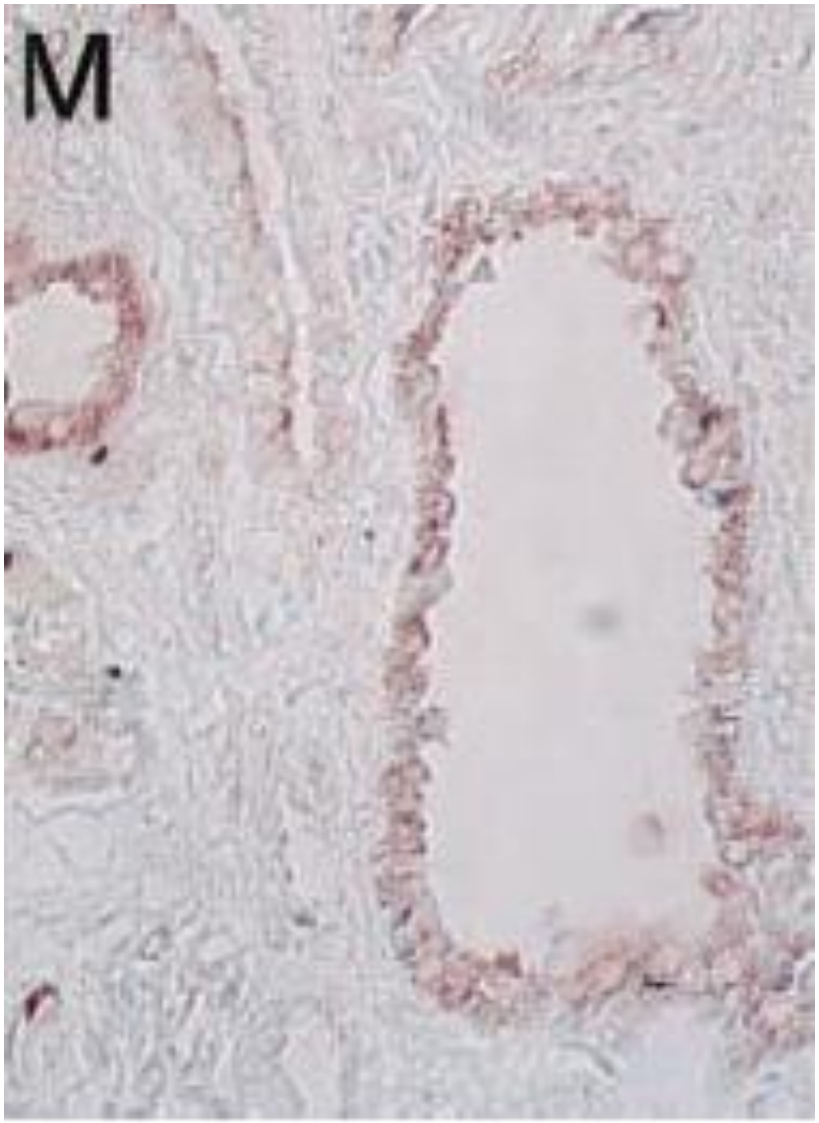
- Difficult to disentangle ECFV depletion effect/CFTR effect
- Abnormalities of drug excretion
- Abnormalities of urinary concentration/dilution

JASN 2000; 11: 2285-96

CFTR Staining

(Antibody 169)

ADPKD Cysts



What is the Evidence for Clinical Kidney Disease?

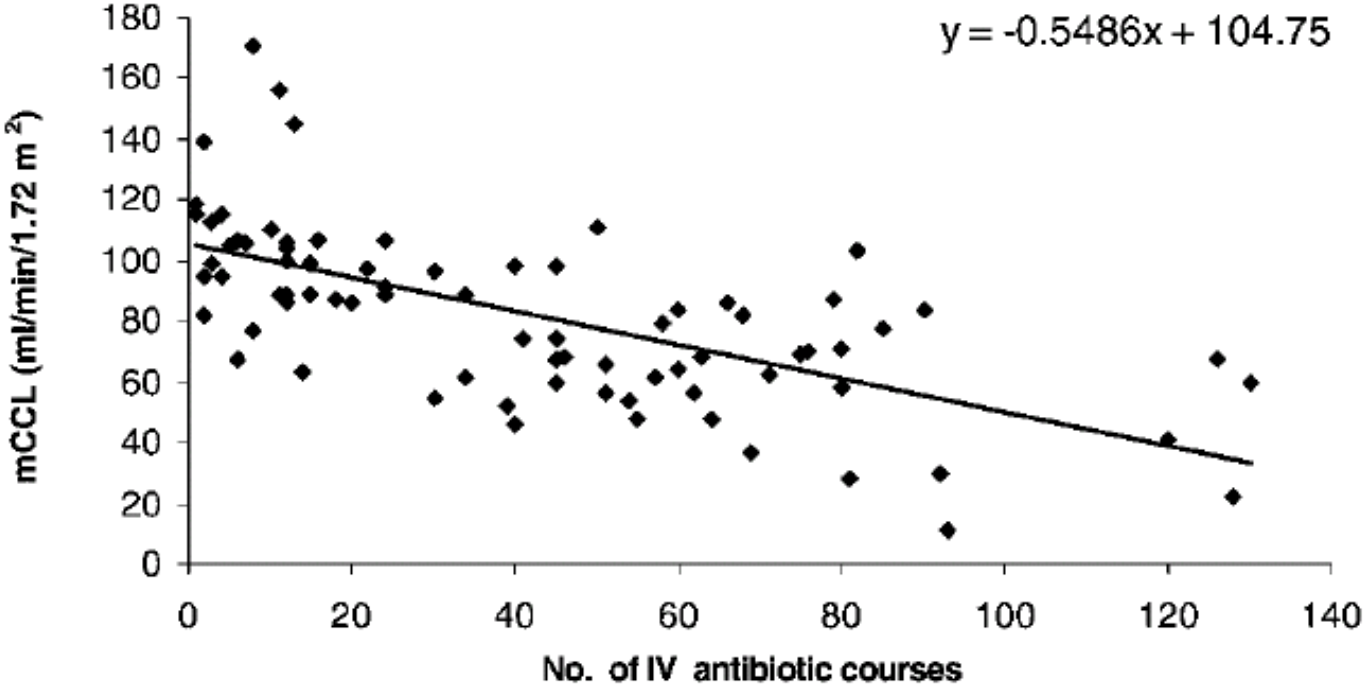


Fig. 2. Correlation between renal function (mCCL) and lifetime use of IV nephrotoxic antibiotics (courses containing aminoglycosides and/or colistin). r = 0.65, $P < 0.00001$.

Risk Factors for Chronic Kidney Disease in Adults with Cystic Fibrosis

Am J Respir Crit Care Med 2011; 184: 1147-52

- Cohort of adults CF Foundation Registry ‘01-’08
- 11,912 - fu median 4yrs
- 204 had CKD (2.3%)
- Prevalence doubled with every 10yrs age
- CFRD-insulin 1-4yrs (2.4 1.74-3.32)

- 1-5 0.79 0.56-1.11
- 6-9 0.92 0.58-1.46
- >10 1.16 0.75-1.81

Proteinuria in cystic fibrosis: a possible correlation between genotype and renal phenotype
J Bras Pneumonol 2009; 35: 669-675.

	Proteinuria <150mg/d	Proteinuria >150mg/d
ΔF508/ΔF508	9	1
ΔF508/P2055	3	0
ΔF508/R334W	2	1
ΔF508/R1066C	1	0
ΔF508deL/N1M	1	0
A516E/A516E	0	1
R334W/R334W	0	3
	16	6

Renal impairment in children with cystic fibrosis
J Cystic Fibrosis 2010; 9: 263-8.

- Single centre 112 children
- Retrospective

- eGFR (Schwartz) median 123, 161, 155 ml/min
  (1,5,15 years)

- Microalbuminuria in 22/38.....
- Hyperoxaluria in 58/83.....
- Hypercalciuria in 16/87.....
- Hypocitraturia in 57/76.....

Microvascular complications in patients with CFRD

J Cystic Fibrosis 2008; 7: 515-9

- 79 CFRD matched with 79 T1DM patients
- Age, gender, duration of insulin use matched

- Microalbuminuria 22% v 4%
- Retinopathy 10% v 24%

- Lower BMI, better HbA1c, fewer smokers

- Lipid levels and BP levels the same

Microalbuminuria as a screening tool in cystic fibrosis-related disease.

Paediatric Pulmonology 2005; 39: 103-5

- 40 CF patients: CFND/CFRD
- 43 nonCF patients without diabetes
- Raised ACR in 67% CFRD; 32% CFND; 15% controls
- Persistent raised ACR in 17% CFRD; 12% CFND

Post Lung Transplant

Do patients with CF develop more severe renal dysfunction?

Acute Kidney Injury

- ‘Usual’ causes of AKI in ill patients
- ‘Usual’ contributing factors

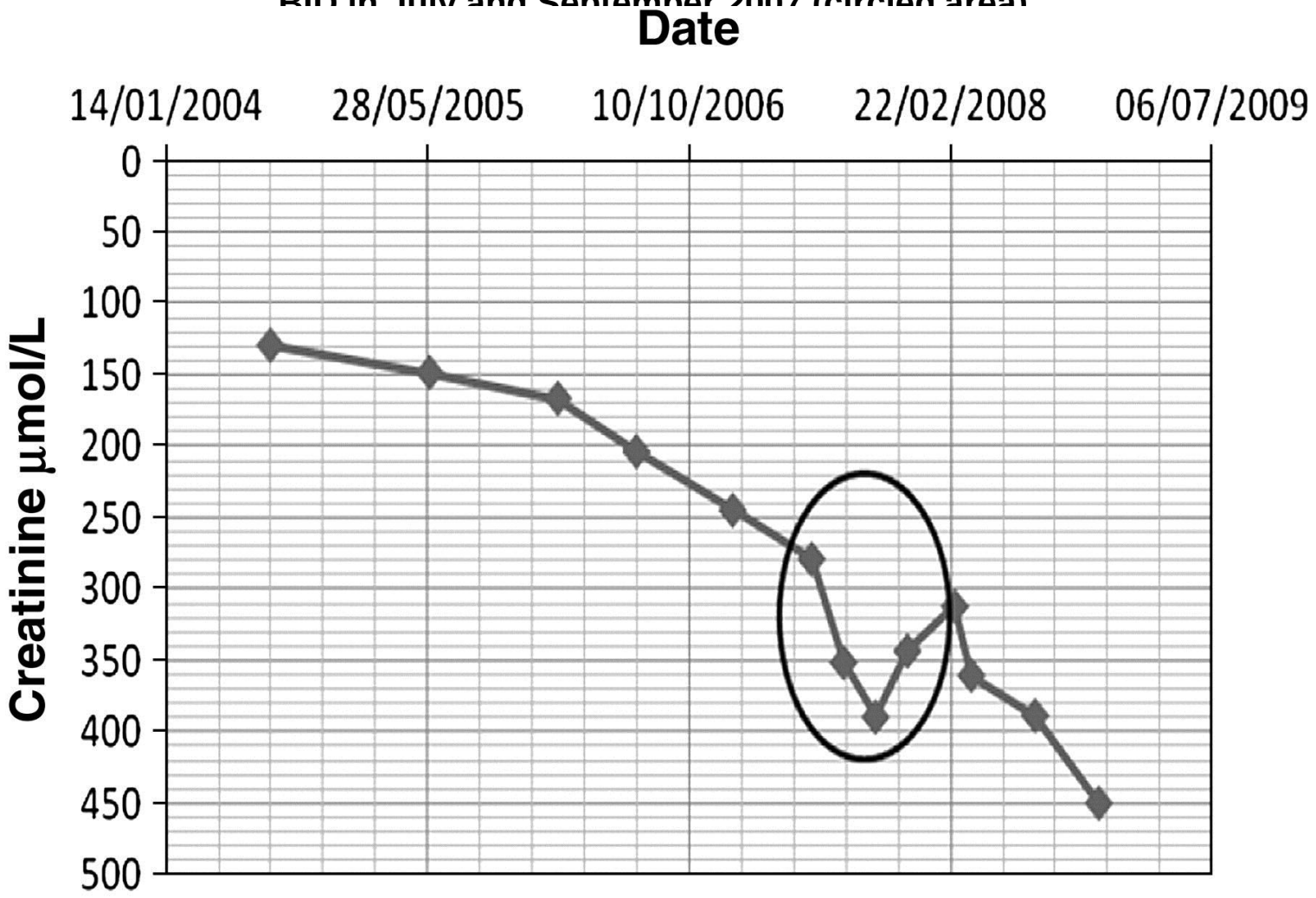
- Aminoglycosides and *Pseudomonas* infection

- Definition of AKI.....
  [Creat]; NAG appearance

- UK Survey (Thorax 2007; 62: 541-5):
  AKI 4.6-10.5/10 000 CF patients/year
  88% aminoglycoside (78% gentamicin)
  54% RRT; 88% full recovery
- TOPIC Study (Lancet 2005; 365: 573-8):
  Once daily tobramycin
  (Time of dose?!)

- Also seen with inhaled tobramycin; colistin

Creatinine over time plot demonstrating the progressive decline in renal function and intercurrent reversible dip following the temporary initiation of nebulized tobramycin 300 mg BID in July and September 2007 (circled area)



O'Connell O et al. NDT Plus 2010;3:354-356

NDT PLUS
Nephrology Dialysis Transplantation

Disorders of urinary oxalate excretion

- Kidney stones

  (Am J Kidney Dis 2003; 42: 1-11)

  3-6% v 1-2%

- Acute allograft dysfunction

  (Am J Transplant 2010; 10: 954)

Absence of Oxalobacter formigenes in cystic fibrosis patients: a risk factor for hyperoxaluria.

The Lancet 1998; 352: 1026-9.

- 43 paediatric CF patients; 21 healthy volunteers
- Stool culture and DNA

- 71% of healthy volunteers colonised
- 1 (6) of CF patients colonised
- What's it about the 1 patient who is colonised.....?

- Colonised had normal oxalate excretion
- 56% of non-colonised patients hyperoxaluric

Progressive CKD

- Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use.

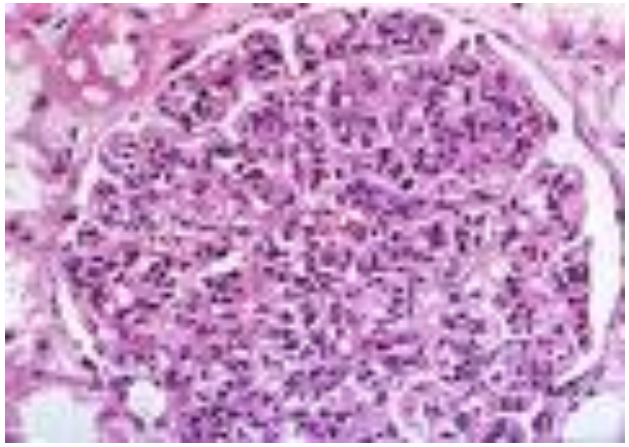
  Paediatr Pulmonol 2005; 39: 15-20.

- 80 CF patients (Pseudomonas colonised)
- Median of 80 courses of antibiotics
- 42% had CrCl <80ml/min
- Aminoglycoside + colistin associated with lower values

- Other diseases: DN, CNi toxicity in LT, other GN

Renal pathology

‘Madamina, il catalogo e questo’



Leperello

Act 1, Scene 5
‘Don Giovanni’
Mozart

Renal Involvement in Cystic Fibrosis: Diseases Spectrum and Clinical Relevance

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Background and objectives: Clinically relevant kidney involvement is uncommonly described in adult patients with cystic fibrosis (CF). We sought to report on a series of patients with CF and kidney biopsy–documented renal involvement.

Design, setting, participants, & measurements: A retrospective study was undertaken in two referral centers for adult patients with CF in Paris, France. Patients who had undergone a biopsy of native kidneys between 1992 and 2008 were identified, and their medical records were reviewed.

Results: We identified 13 adult patients with CF and renal disease. Proteinuria was present in all but two cases and was associated with progressive renal impairment in four patients (median serum creatinine 85 μmol/L; range 53 to 144 μmol/L). Renal biopsy disclosed a heterogeneous spectrum of nephropathies including AA amyloidosis ($n = 3$), diabetic glomerulopathy ($n = 3$), FSGS ($n = 2$), minimal-change disease ($n = 1$), postinfectious glomerulonephritis ($n = 1$), IgA nephropathy related to Henoch-Schönlein purpura ($n = 1$), membranous nephropathy ($n = 1$), and chronic interstitial nephropathy ($n = 1$). Chronic renal failure occurred in five patients, and one patient reached ESRD.

Conclusions: Although rare, clinically significant renal disease may arise in young adult patients with CF. Given the wide spectrum of diseases that may be encountered, definite diagnosis by kidney biopsy is mandatory to optimize clinical treatment of these complex patients, particularly in the perspective of organ transplantation.

Clin J Am Soc Nephrol 4: 921–928, 2009. doi: 10.2215/CJN.00750209

NDT Plus (2010) 3: 354–356
doi: 10.1093/ndtplus/sfq054
Advance Access publication 9 April 2010

Case Report

NDT PLUS
Nephrology Dialysis Transplantation

A CF patient with progressive proteinuric renal disease: a CF-specific nodular glomerulosclerosis?

Oisin O'Connell[1], Ciara N. Magee[2], Brendan Fitzgerald[3], Louise Burke[3], William D. Plant[2] and Barry J. Plant[1]

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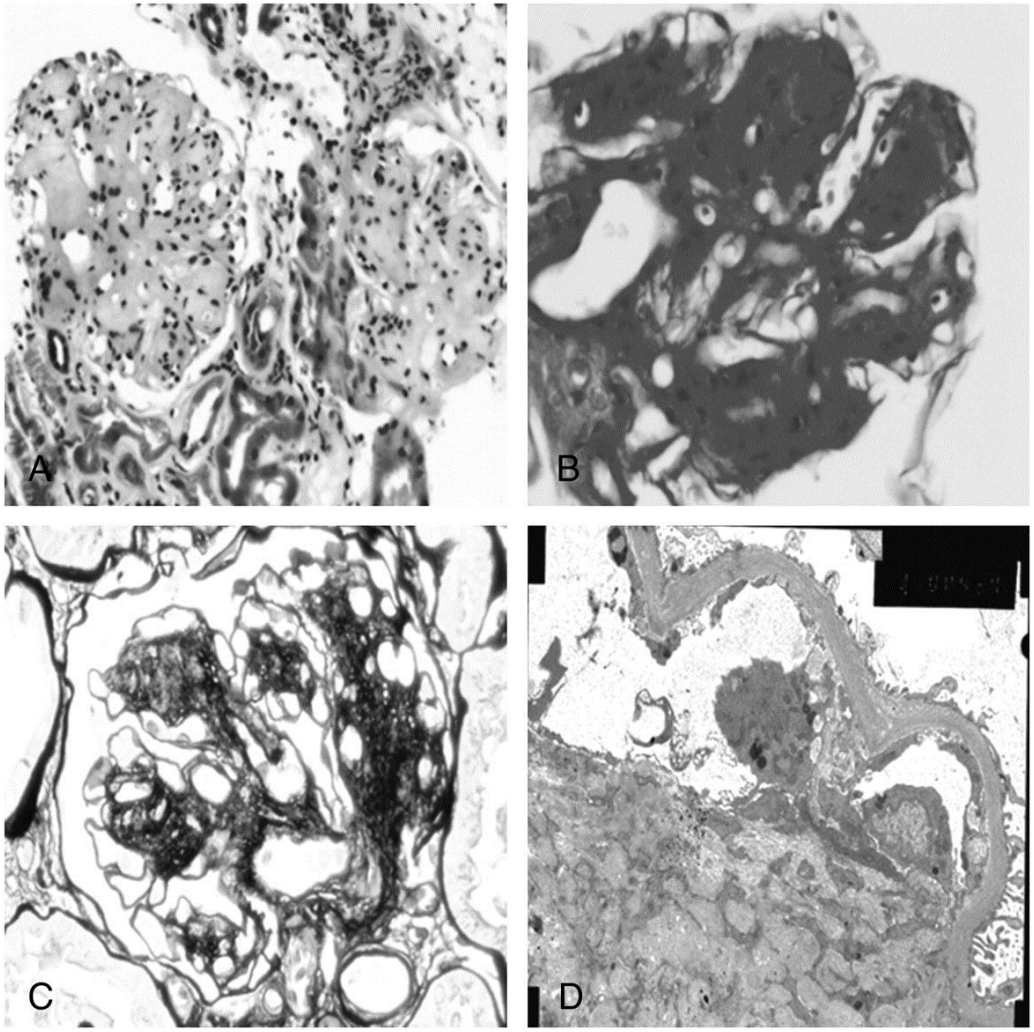
(A) Haematoxylin and eosin-stained section demonstrating increased mesangial matrix with Kimmelstiel–Wilson-like mesangial nodules.



O'Connell O et al. NDT Plus 2010;3:354-356

NDT PLUS
Nephrology Dialysis Transplantation

RAGE

Receptor for advanced glycosylation end-products

- CF patients have:
  chronic pulmonary infection/inflammation
  lower gluthathione levels
  →oxidative state→?AGE in normoglycaemics
- CF patients have:
  increased serum S100/calgranulin cytokines
  →RAGE activation
- CF patients have:
  elevated HMBG-1
  →renal matrix protein accumulation

A Challenge.....?

- Patients will survive longer
- Renal complications will become more prevalent
- Renal complications will be better understood
- Renal services will become more involved

A Manifesto for the Future

- Integrate this potential within Care Pathway

- Prospective epidemiological studies
- Prospective clinical studies

- Focus as well as acknowledge