ΙΕΕΟΥ
ινστιτούτο έρευνας & εφαρμογών ουροποιογεννητικού συστήματος
3η Επιστημονική Διημερίδα Νεφρολογικού Τμήματος ΓΝΘεσσαλονίκης "Παπαγεωργίου"
Λειτουργικές Διαταραχές της Ούρησης και Χρόνια Νεφρική Νόσος
15-16 Δεκεμβρίου 2017
Ξενοδοχείο Electra Palace Θεσσαλονίκη

ΚΥΣΤΕΟΟΥΡΗΤΗΡΙΚΗ ΠΑΛΙΝΔΡΟΜΗΣΗ ΚΑΙ ΧΡΟΝΙΑ ΝΕΦΡΙΚΗ ΝΟΣΟΣ

ΠΑΘΟΓΕΝΕΙΑ ΤΗΣ ΠΡΟΟΔΕΥΤΙΚΗΣ ΕΚΠΤΩΣΗΣ ΤΗΣ ΝΕΦΡΙΚΗΣ ΛΕΙΤΟΥΡΓΙΑΣ

Π. Κυρικλίδου
Νεφρολόγος
Γ.Ν «Παπαγεωργίου», Θεσ/νίκη

Η Κυστεοουρητηρική Παλινδρόμηση είναι συνήθως:

- ΠΡΩΤΟΠΑΘΗΣ
  οφείλεται σε συγγενή ανεπάρκεια του αντιπαλινδρομικού μηχανισμού που φυσιολογικά υπάρχει στην κυστεοουρητηρική συμβολή
- ΔΕΥΤΕΡΟΠΑΘΗΣ
  α) συγγενής ανωμαλίες της κυστεοουρητηρικής συμβολής π.χ. παραουρητιρικό εκκόλπωμα
  β) αυξημένη ενδοκυστική πίεση π.χ βαλβίδες οπίσθιας ουρήθρας, νευρογενή κύστη
  γ) φλεγμονώδη εξεργασία της ουροδόχου κύστης και
  δ) ιατρογενή βλάβη της κυστεοουρητηρικής συμβολής

Η ΚΟΠ μπορεί να είναι αμφοτερόπλευρη ή ετερόπλευρη, συνεχής ή διαλείπουσα

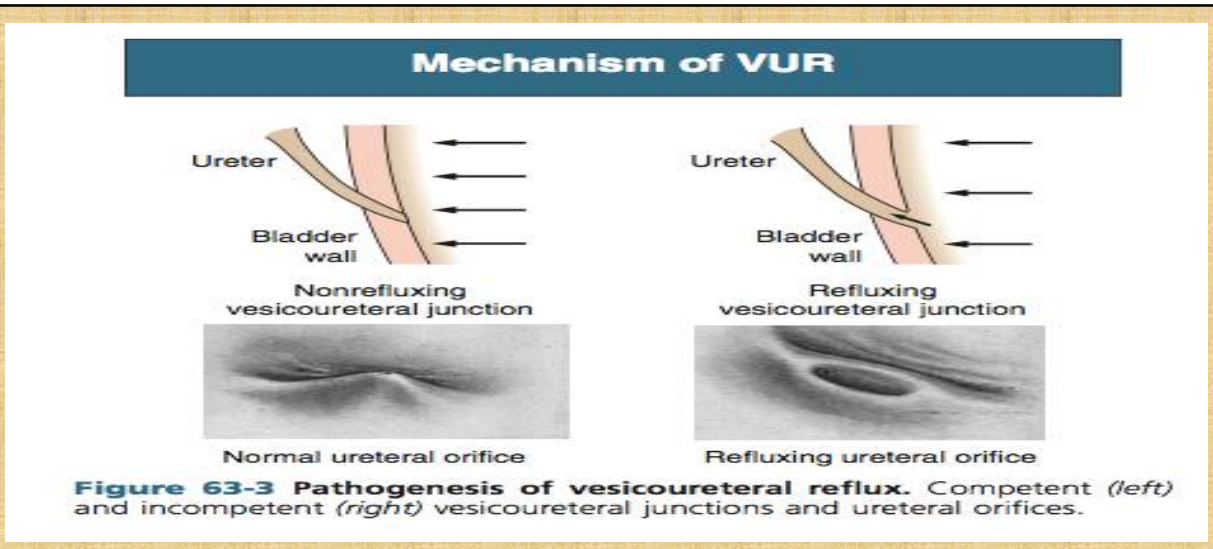
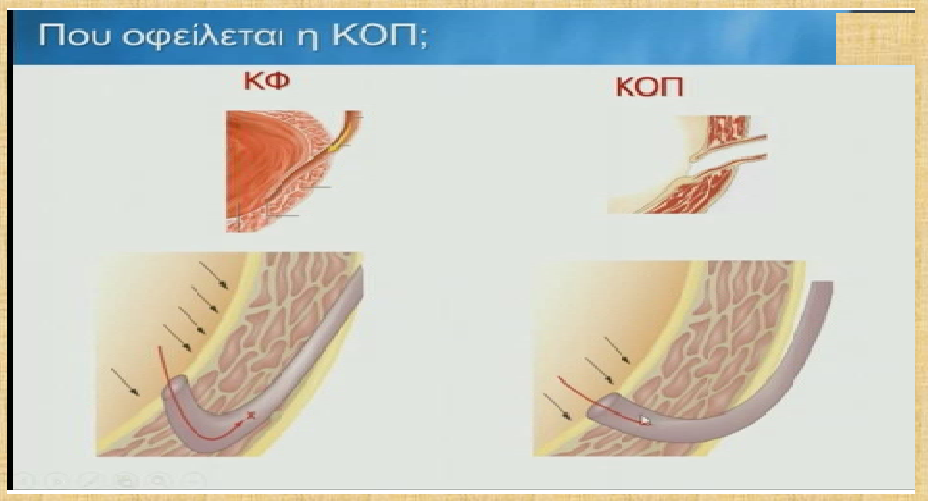


Figure 63-3 Pathogenesis of vesicoureteral reflux. Competent *(left)* and incompetent *(right)* vesicoureteral junctions and ureteral orifices.

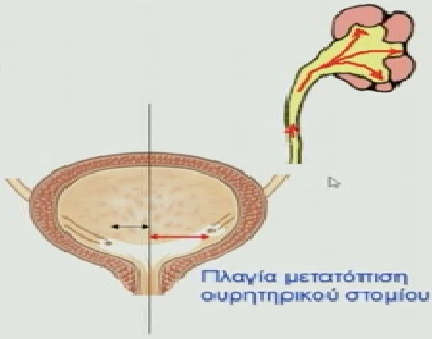
The normal ureter enters the urinary bladder obliquely and extends into the submucosa at a length that in adults averages 1.3 cm and in children 0.5cm (273). Physiologic VUJ function requires coordination of multiple factors, including correct insertion of the ureter into the bladder, an adequately long intramural ureteral segment, appropriate width of the ureteric opening, and muscle contraction at the trigone. Galen and Leonardo da Vinci were the first to describe the importance of the UVJ as a one-way valve that prevents backflow of urine



1)ΒΡΑΧΥ ΕΝΔΟΚΥΣΤΙΚΟ ΤΜΗΜΑ ΤΟΥ ΟΥΡΗΤΗΡΑ
2)ΠΛΑΓΙΑ ΜΕΤΑΤΟΠΙΣΗ ΟΥΡΗΤΗΡΙΚΟΥ ΣΤΟΜΙΟΥ

Συγγενείς νεφρικές βλάβες και ΚΟΠ

Όσο πιο βραχύ είναι το ενδοκυστικό τμήμα του ουρητήρα τόσο πιο συχνές οι συγγενείς νεφρικές βλάβες



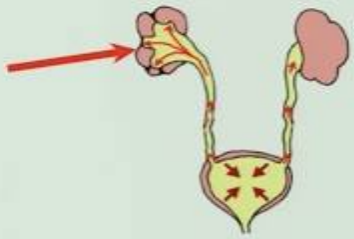
Mackie and Stephens (1975)

Reflux Nephropathy: Historical Perspective

Year	Investigator	Advance
100 AD	Galen of Pergamon and Asclepiades	Discovered they could not induce reflux in live or dead animals suggesting that VUJ is a one-way valve
1487-1513	Leonardo da Vinci	Reflux is accompanied by scarred kidneys.
1812	Charles Bell	Oblique course of the ureter
1893	Pozzi	Reflux in humans
1903	Samson and Young	Normal obliqueness of the ureter prevents reflux.
1913	Legueu and Papin	Hydronephrosis and hydroureter with urine reflux caused by a widely patent ureteral orifice
1914	Kretschmer	Familial reflux
1929	Gruber	Incidence of VUR varied based on the length of the intravesical ureter and muscularity of the detrusor muscle.
1950	Hutch	Pathophysiology of reflux in paraplegic patients and use of VCUG in patients with unexplained hydronephrosis
1960	Hodson	Radiologic diagnosis of VUR
1965	Tanagho	Incision in the trigone distal to the ureteral in dogs induced reflux.
1975	Ransley and Risdon	Resection of the roof of the subcostal ureteral tunnel in piglets induced reflux.
1985		The International Reflux Grading System established
2000s		Mouse models and genetic studies

From Refs. (273,274,275).

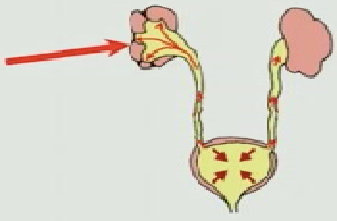
Δεκαετία 1960



Σχέση εμπύρετης ουρολοίμωξης – ΚΟΠ
με μόνιμες νεφρικές βλάβες.

Hodson CJ, Edwards D Chronic pyelonephritis and vesicoureteric reflux. Clin Radiol 1960; 11:219-231

Δεκαετία 1960



Μόνιμες νεφρικές βλάβες στο 36% των παιδιών
με υποτροπιάζουσες ουρολοιμώξεις

Steele RE Jr, Leadbetter GW Jr, Crawford JD. Prognosis of childhood urinary tract infection N Engl J Med 1963;269:883-9.

Η εκτεταμένη νεφρική ουλοποίηση που μπορεί να προκύψει
ως αποτέλεσμα της ταυτόχρονης παρουσίας ΚΟΠ και ουρολοιμώξεων
ονομάζεται **Νεφροπάθεια από Παλινδρόμηση (reflux nephropathy)**
και αποτελεί συχνή αιτία υπέρτασης και Νεφρικής Ανεπάρκειας Τελικού Σταδίου
στα παιδιά και σε νεαρούς ενήλικες

Clin Nephrol. 1973 May-Jun;1(3):132-41.

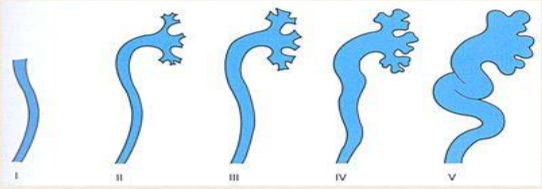
The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy.

Bailey RR.

HODSON CJ. The radiological contribution toward the diagnosis of chronic pyelonephritis. Radiology 1967, 88:857□871

ΚΟΠ και ουρολοιμώξεις

- Συχνότητα της ΚΟΠ: στο **2%** του γενικού πληθυσμού
- Στο **30-40%** των παιδιών με ουρολοίμωξη
  - Από αυτά περίπου 30% έχουν νεφροπάθεια από παλινδρόμηση (ακτινολογικά ευρήματα νεφρικών ουλών)

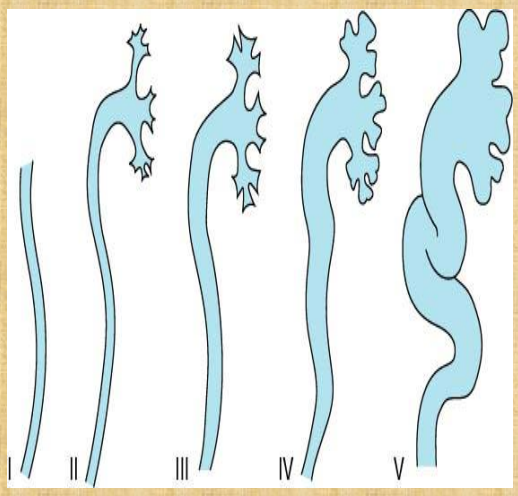


Σύμφωνα με το Διεθνές Σύστημα Ταξινόμησης διακρίνονται Πέντε βαθμοί ΚΟΠ

International Reflux Study in Children Classification of Vesicoureteral Reflux (VUR)

Grade	Degree of VUR
I	Ureter only
II	Reflux into ureter, pelvis, and calyces with no dilation and with normal calyceal fornices
III	Mild or moderate dilation and/or tortuosity of the ureter and mild or moderate dilation of the pelvis; no or slight blunting of the fornices
IV	Moderate dilation and/or tortuosity of the ureter, and moderate dilation of the pelvis and calyces; complete obliteration of the pelvis and calyces; complete obliteration of the sharp angles of the fornices but maintenance of the papillary impressions in the majority of the calyces (see Fig. 63-7C)
V	Gross dilation and tortuosity of the ureter, pelvis, and calyces; the papillary impressions are no longer visible in the majority of calyces (see Fig. 63-2)

Table 63-1 Classification of VUR. The International Reflux Study in Children classification.



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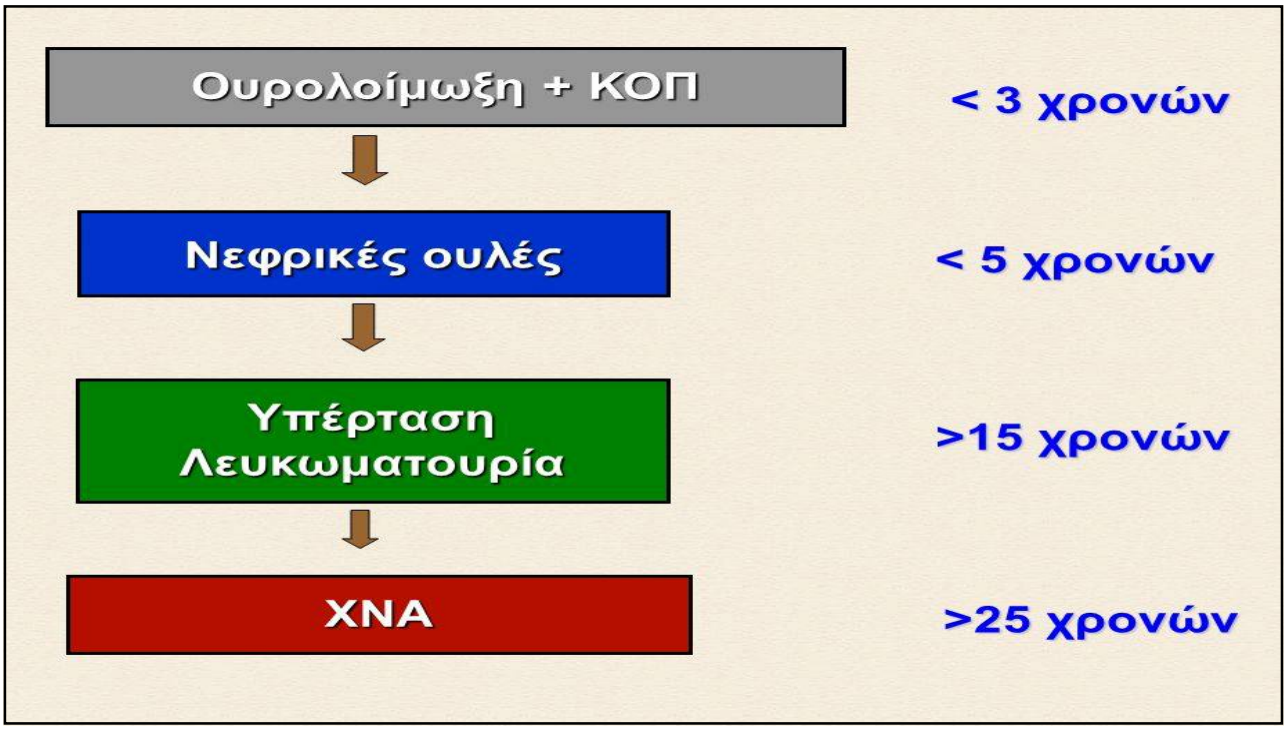
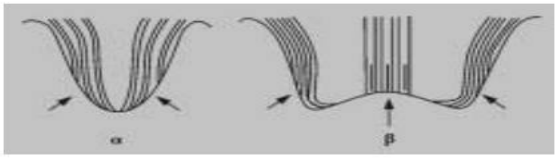


Παθογένεση των νεφρικών ουλών

- ✓ **Σημαντικός ο ρόλος της ανατομικής κατασκευής των νεφρικών θηλών (απλές, σύνθετες),** (Williams, 1970)
- ✓ Η ενδονεφρική βλάβη εμφανίζεται στα σημεία του νεφρού που υπάρχει **ενδονεφρική παλινδρόμηση** (Bailey,1973)
- ✓ Η εστιακή φύση της νεφρικής βλάβης (νεφρική ουλή) στη νεφροπάθεια από παλινδρόμηση μπορεί να εξηγηθεί από την παρουσία ενδονεφρικής παλινδρόμησης όρος που χρησιμοποιήθηκε το 1965 (Brodeur, Goyer και Melick)
- ✓ Οι Ransley, Risdon (1978) θεωρία του «μεγάλου πλήγματος» (big bag theory)



Εικόνα 1. Μορφολογία των νεφρικών θηλών και η σχέση τους με την ενδονεφρική παλινδρόμηση: (α) Κυρτή, μη παλινδρομούσα νεφρική θηλή, (β) κοίλη ή επίπεδη (παλινδρομούσα) νεφρική θηλή.[13]

BRODEUR AE, GOYER RA, MELLICK W. A potential hazard of barium cystography. Radiology 1965, 85:1080–1084
WILLIAMS DI. The ureter, the urologist and the paediatrician. Proc R Soc Med 1970, 63:595–602

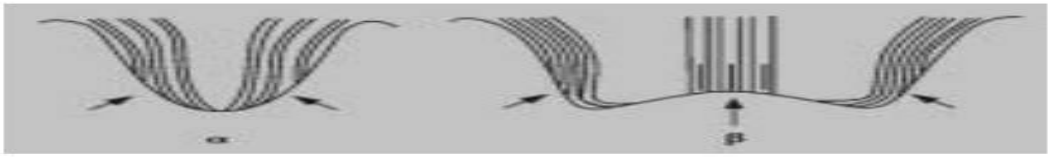
RANSLEY PG, RISDON RA. The renal papilla, intrarenal reflux and chronic pyelonephritis. In: Hodson CJ, Kincaid-Smith P (eds) Re- flux nephropathy. Masson Publ, New York, 1979:126–133

the "big bang" effect.

- One episode of pyelonephritis produce Scarring, especially in very young.
- Ransley and Risdon named this condition the "big bang" effect.

Intrarenal Reflux

- Most scarring tends to occur at the renal poles,
- Where the anatomy of the renal papillae permits backflow of urine into the collecting ducts.
- This phenomenon is referred to as intrarenal reflux
- & gives pathogenic bacteria access



Εικόνα 1. Μορφολογία των νεφρικών θηλών και η σχέση τους με την ενδονεφρική παλινδρόμηση: (α) Κυρτή, μη παλινδρομούσα νεφρική θηλή, (β) κοίλη ή επίπεδη (παλινδρομούσα) νεφρική θηλή.[13]

Σύμφωνα με τη θεωρία αυτή, η νεφρική ουλή που θα δημιουργηθεί, περιορίζεται μόνο στην περιοχή του νεφρού που περιέχει τις σύνθετες θηλές, ενώ περιοχές με απλές θηλές παραμένουν άθικτες ακόμη και σε επαναλαμβανόμενα επεισόδια ουρολοίμωξης (φαινόμενο του όλου ή ουδέν).

Η παραπάνω θεωρία αρχικά υποστήριζε την άποψη ότι η νεφρική βλάβη εγκαθίσταται μόνο μετά από το πρώτο επεισόδιο ουρολοίμωξης. Στη συνέχεια όμως τροποποιήθηκε, με βάση τα ευρήματα μελετών σε πειραματόζωα με ουρολοιμώξεις, στα οποία είχε γίνει έγκαιρη χορήγηση αντιβιοτικών.[15] Έτσι, οι ίδιοι ερευνητές πρότειναν ότι η νεφρική βλάβη είναι δυνατό να αναπτυχθεί και μετά από άλλα επεισόδια ουρολοίμωξης και, επιπρόσθετα, ότι οι βλάβες αυτές μπορεί να μην εγκαθίστανται ταυτόχρονα ακόμη και στο ίδιο επεισόδιο ουρολοίμωξης ("little bangs"). Επιπλέον, πρόσθεσαν στη θεωρία τους την πιθανότητα ότι, με την πάροδο του χρόνου, μπορεί να παρατηρηθεί μεταβολή μιας απλής θηλής σε σύνθετη θηλή,[13] με αποτέλεσμα την εμφάνιση ενδονεφρικής παλινδρόμησης και την επέκταση ή την εξέλιξη της αρχικής νεφρικής βλάβης. Με τα παραπάνω πειράματα, οι Ransley και Risdon κατέληξαν στο συμπέρασμα ότι η έγκαιρη και αποτελεσματική θεραπεία της ουρολοίμωξης μπορεί να περιορίσει την έκταση της αρχικής βλάβης καθώς και την εξέλιξή της σε μόνιμη ουλή.[15]

ΑΝΙΧΝΕΥΣΗ ΤΩΝ ΝΕΦΡΙΚΩΝ ΟΥΛΩΝ

✓ Οι νεφρικές ουλές εντοπίζονται κυρίως στους πόλους των νεφρών, λόγω της υπεροχής των κοίλων ή σύνθετων θηλών σ' αυτές τις περιοχές

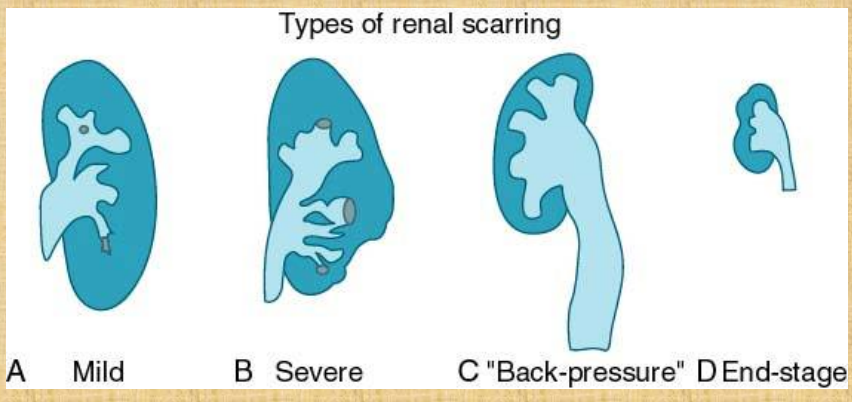
✓ Ωστόσο, η έκταση των νεφρικών ουλών ποικίλλει, σε βαθμό που μια ουλή μπορεί να περιορίζεται στην περιοχή μόνο μίας θηλής ενός πόλου του νεφρού ή να εκτείνεται σε μεγαλύτερη έκταση (**εστιακή βλάβη**), ενώ στις πιο σοβαρές περιπτώσεις οι νεφρικές ουλές μπορεί να είναι γενικευμένες και διάσπαρτες, ώστε να οδηγήσουν στη δημιουργία του ***μικρού-ρικνού νεφρού,*** με αποτέλεσμα την εγκατάσταση ***τελικού σταδίου χρόνιας νεφρικής ανεπάρκειας***

✓ Ενδοφλέβια πυελογραφία

✓ DMSA-σπινθηρογράφημα βασίζεται στην ιδιότητα μιας ουσίας(διμερκαπτοσουκινικό οξύ) να προσλαμβάνεται από τα υγιή επιθηλιακά κύτταρα του εγγύς εσπειραμένου σωληναρίου του νεφρού, καθώς και από το ανιόν σκέλος της αγκύλης του Henle

Η Goldraich(1983) ταξινόμησε τη βαρύτητα της νεφροπάθειας από παλινδρόμηση σε 4 βαθμούς

GOLDRAICH NP, GOLDRAICH IH. Update on dimercaptosuccinic acid renal scanning in children with urinary tract infection. Pedi- atr Nephrol 1995, 9:221□226
GOLDRAICH IH, GOLDRAICH NP, RAMOS OL. Classification of reflux nephropathy according to findings at DMSA renal scan. Eur J Pe- diatr 1983, 140:212 (Abstract)
SMELLIE JM, EDWARDS D, HUNTER N, NORMAND ICS, PRASCOD N. Vesi- co-ureteric reflux and renal scarring. Kidney Int 1975, 8(Suppl 4):65□72



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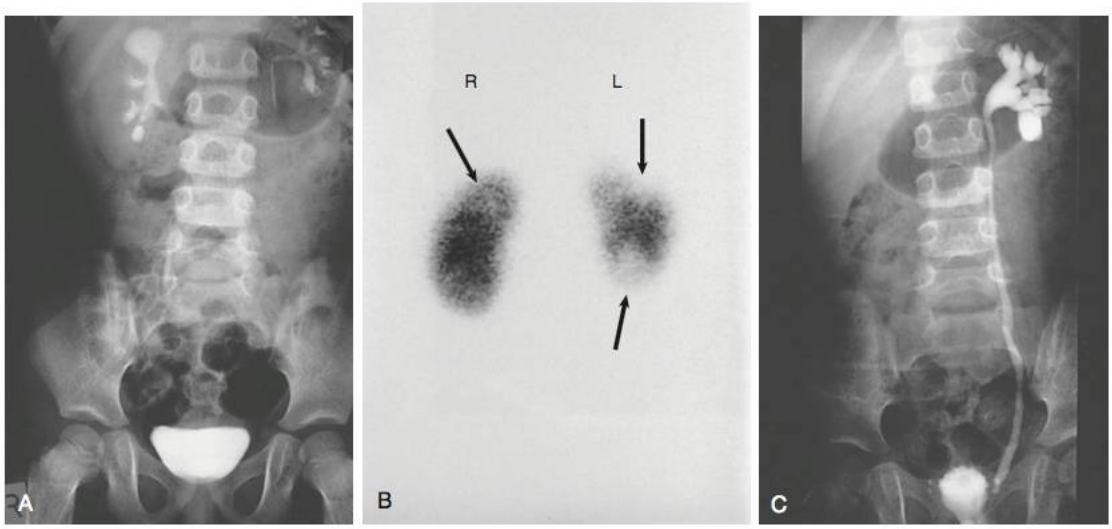


Figure 63-7 Investigation of reflux nephropathy. Investigation of a 3-year-old child with urinary tract infection. **A,** Intravenous urogram showing calyceal diverticulum in the upper pole of the right kidney and renal scarring in the upper pole and, probably, the lower pole of the left kidney. **B,** DMSA scintigraphy (posterior view) demonstrating upper and lower pole scarring *(arrows)* in the left kidney and scarring of the right upper kidney in association with the calyceal diverticulum *(arrowhead)*. **C,** Voiding cystourethrogram showing grade IV vesicoureteral reflux on the left.

Συνέπειες των νεφρικών ουλών

Οι συνέπειες που προκύπτουν από την παρουσία των νεφρικών ουλών (νεφροπάθεια από παλινδρόμηση) έχουν μελετηθεί εκτενώς και μπορεί να διακριθούν στις παρακάτω κατηγορίες:

(1) ***ιστοπαθολογικές αλλοιώσεις***, με κύριο εύρημα την εστιακή και τμηματική σπειραματοσκληρυνση

(2) ***μορφολογικές και λειτουργικές επιπτώσεις***, με συνέπεια την καθυστέρηση στην αύξηση του νεφρού, την εμφάνιση λευκωματουρίας και τη μείωση της νεφρικής λειτουργίας

(3) ***κλινικές επιπλοκές*** που περιλαμβάνουν την υπέρταση και τη χρόνια νεφρική ανεπάρκεια

ΜΗΧΑΝΙΣΜΟΙ ΑΝΑΠΤΥΞΗΣ ΛΕΥΚΩΜΑΤΟΥΡΙΑΣ

1) Ανοσολογική βλάβη του σπειράματος με σχηματισμό *in situ* ανοσοσυμπλεγμάτων, στα οποία το αντιγόνο μπορεί να είναι βακτηριακή πρωτεΐνη ή πρωτεΐνη Tamm- Horsfall

2) Αγγειακές μεταβολές

3) Μεσαγειακή δυσλειτουργία με παγίδευση μακρομορίων (IgM, C3)

4) Σπειραματική υπερδιήθηση

Solari et al., 2004; Strutz et al., 1995,1996,1999, 2003; Weiss et al., 1994). The process of renal scarring may be divided into four phases: induction, fibrogenic signaling, fibrogenic, and destructive phases (Eddy, 2000). Induction phase is also known as cellular activation and injury phase. The interstitial space is infiltrated by both neutrophils and monocytes. In acute

Eddy A.A. (2000): Molecular basis of renal fibrosis, *Pediatr Nephrol* 15:290-301.

COTRAN RS. Glomerulosclerosis in reflux nephropathy. *Kidney Int* 1982, 21:528–534

BRENNER BM, MEYER TW, HOSTETER TH. Dietary protein intake and the progressive nature of kidney disease. The role of hemodynamically mediated glomerular injury in the pathogenesis of glomerulosclerosis in aging, renal ablation and intrinsic renal disease. *N Engl J Med* 1982, 307:52–59

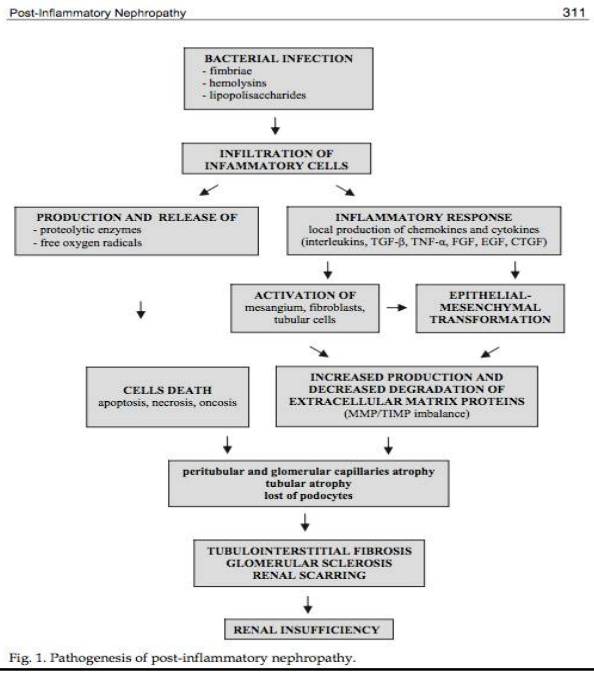


Fig. 1. Pathogenesis of post-inflammatory nephropathy.

Ιστοπαθολογικές αλλοιώσεις

The injury results from the local infiammatory response that may persist with chronic inflammation, tubular injury, local fibrobroblast activation, and interstitial collagen deposition. The loss of nephrons is associated with hyperfiltration and hypertension that result in proteinuria and progressive loss of renal function. This can also lead to the development of FSGS

The histologic findings of this form of reflux nephropathy are: interstitial infiltration with chronic inflammatory cells, tubular basement membrane thickening, epithelial cell atrophy, collapse of tubular lumen, dilation of other tububes with atrophic epithelium, eosinophilic casts, medial and intimab thickening of arteries and arterioles, perigbomerular fibrosis, collapse and hyalinization of glomerular tufts, and compensatory hypertrophy in adjacent unscarred renal tissue
It is important to emphasize here that the histopathobogic profile of this type of scarring contains **no dysplastic features** that are characteristic of the **"congenital" reflux nephropathy** hat would appear to have a different etiopathogenesis

Proteinuria

Patients may also present with microalbuminuria, persistent proteinuria, or rarely nephrotic-range proteinuria. e presence of proteinuria may suggest a histologic diagnosis of secondary FSGS, which can be confirmed by renal biopsy if kidney size is normal and diagnosis is uncertain
Proteinuria is usually modest (0.5 to 4 g/day) and is commonly associated with hypertension and renal dysfunction. CKD progression o en occurs gradually over 5 to 10 years

End-Stage Renal Disease

According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) annual report of 2008, 3.5% of the 6491 children on dialysis had RN, which makes it the fourth most common cause of ESRD a er FSGS; renal aplasia, hypoplasia, or dysplasia; and obstructive uropathy
The number of pediatric patients with RN who present with ESRD as adults is not clear. According to one study of 123 adults with VUR diagnosed in childhood, the eGFR in those with non dilating VUR averaged 75 ml/1.73 m2 and that in the dilating group was 72 ml/1.73 m^2; four patients (9%) in the non dilating group and 13 (17%) in the dilating group had eGFR below 60 ml/ 1.73 $m^{2.30}$

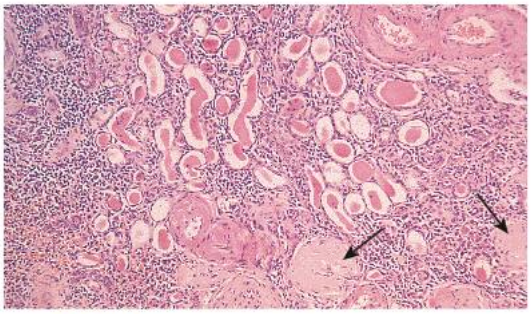


Figure 63-4 Histologic changes in reflux nephropathy. Sclerosed glomeruli *(arrows)*, chronic inflammatory cell infiltration, and atrophic tubules with eosinophilic casts are present. (Hematoxylin-eosin; original magnification ×40.)

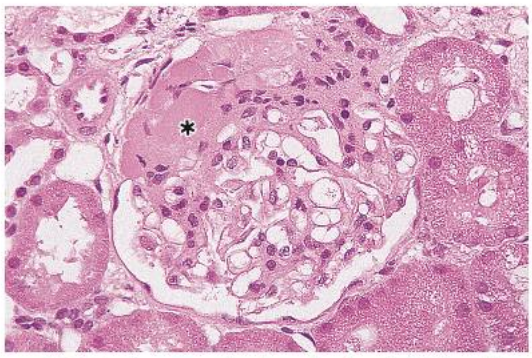


Figure 63-5 Focal segmental glomerulosclerosis (*) in reflux nephropathy. Light microscopy of a glomerulus from a patient with reflux nephropathy shows FSGS. (Hematoxylin-eosin; original magnification ×400.)

HYPERTENSION

- ✓ Hypertension affects approximately 10% of children with renal scans, although vary (5 to 27%) from series to series
- ✓ It is the most common cause of severe hypertension in childhood
- ✓ Gender has some role in the development of hypertension. However, in addition, there was in a spite of the higher incidence of reflux nephropathy in females, males, proportionally, have a higher risk of hypertension as well as other complications such as proteinuria and renal failure
- ✓ Histologically, the finding of focal segmental gbomerulosclerosis is significantly associated with hypertension
- ✓ No direct correlation between PRA and blood pressure could be demostrated, but the findings suggest a dissociation between blood pressure and renin in reflux nephropathy with age
- ✓ **The renin-angiotensin system** has for many years been implicated in the genesis of hypertension in reflux nephropathy
- ✓ Histopathologically, the scarred areas of kidney are associated a with **arterial damage** and it would not be unlikely that this might lead to segmental ischemia with resulting renin-driven hypertension

Savage IM, Dillon MI, Shah V. Barratt TM, Williams DI: Renin and blood-pressure in children with renal scanning and vesico- uretenic reflux. *Lancet* ii: 441-444, 1978
Zucchelli F, Gaggi R, Zuccala224}A: The natural history of refiux nephropathy. In: *The Progressive Nature of Renal Disease: Myths and Facts*, edited by Oldnizzi L, Maschio G, Rugiu C, Basel, Karger, 1989, pp 90-99
Reflux Nephropathy MICHAEL J. DILLON and CHULANANDA D. A. GOONASEKERA
Renal Unit, Great Ormond Street Hospitalfor Children and Department of Nephrourology, Institute of Child Health, London, United Kingdom. J Am Soc Nephrol 9: 2377-2383, 1998

Proteinuria as a Marker for Reflux Nephropathy

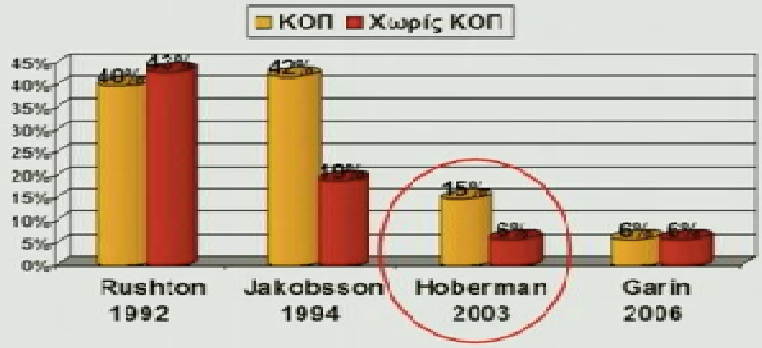
Proteinuria predicts CKD progression due to RN. Persistent micro- albuminuria is helpful in diagnosis of glomerular damage at a very early stage. Microalbuminuria increases with increasing severity of VUR and renal scarring. In children with bilateral VUR with renal scarring and normal creatinine clearance, microalbuminuria was detected in 54% of the cases. Microalbuminuria screening offers the possibility of early intervention, such as the use of ACE inhibitors, aimed at retarding CKD progress. Proteinuria, when it is severe, is usually associated with FSGS

Torres VE, Velosa JA, Holley KE, et al. e progression of vesicoureteral re ux nephropathy. *Ann Intern Med*. 1980;92:776.
Quattrin T, Waz WR, Du y LC, et al. Microalbuminuria in an adolescent cohort with insulin-dependent diabetes mellitus. *Clin Pediatr (Phila)*. 1995; 34:12.
Bell FG, Wilkin TJ, Atwell JD. Microproteinuria in children with vesicoure- teric re ux. *Br J Urol*. 1986;58:605.

Presentation of Vesicoureteral Reflux in the Mother During Pregnancy

Vesicoureteral reflux may also first be manifested in the mother during pregnancy, when it can be associated with asymptomatic bacteriuria or symptomatic UTI, hypertension, preeclampsia, low- birth-weight babies, or miscarriage. VUR is present in approximately 5% of women with UTI in pregnancy and 4% to 5% of women with preeclampsia. VUR can be distinguished from the normal ureteral dilation that occurs in pregnancy, which preferentially affects the midportion of the ureter, and lack of involvement of the renal parenchyma

Μόνιμες νεφρικές βλάβες στο DMSA

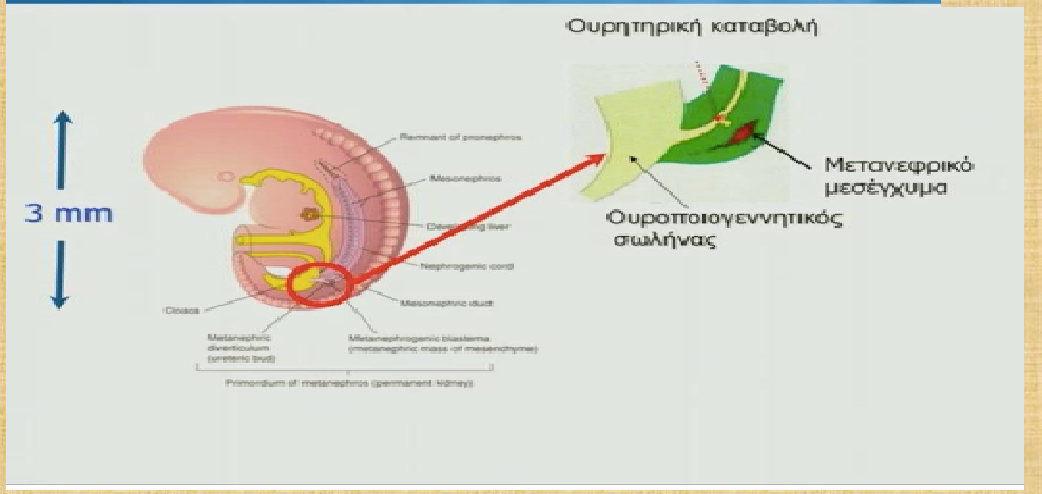


Ron Keren, MD, MPH

CPCE

The Children's Hospital of Philadelphia

5η εμβρυϊκή βδομάδα



Συγγενείς νεφρικές βλάβες και ΚΟΠ

- ✓ **Study of VUR pathogenesis has shifted from clinical and experimentally induced VUR in animals to genetically** engineered mice and cocultures of metanephric mesenchyme with ureteral bud tissue. This discussion will focus on the development of the ureter, its orifice, and the detrusor muscle at the trigone
- ✓ VUR is a congenital urinary track anomaly with **high frequency of reflux in siblings**; twin concordance and **parent-child transmission provide strong evidence that VUR is at least in part a heritable disease**. **Autosomal dominant, autosomal ecessive, X-Linked, and polygenetic inheritance are reported**. Four different strategies are employed to search for genes involved in human VUR: (a) screening for **mutations** in candidate genes known from mouse VUR models, (b) genetically characterize **chromosomal** abnormalities found in patients with VUR to identify new genes, (c) **genes known to cause multiple organ malformations** in syndromic VUR in patients with nonsyndromic VUR, and (d) **whole genome mapping**

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Partial list of genes involved in human VUR

Gene	Mutations in humans
Pax2	Optic nerve colobomas and familial renal anomalies, 30% of which have VUR.

775

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AGTR2	VUR and CAKUT
ACE	VUR alone
SOX17	VUR
ROBO2/SLIT2	High-grade VUR + other renal anomalies
RET/GDNF	Primary reflux, duplicate ureters, megaureter, and CAKUT
BMP4	CAKUT including VUR
Eya1	VUR, duplex ureters, CAKUT, renal agenesis
FOXC1	CAKUT with VUR
TGF-β	High-grade VUR

From Refs. (292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326).

VUR is also associated with heritable syndromes such as Hirschsprung disease, Apert syndrome, branchiootorenal syndrome, Townes-Brocks, and renal-coloboma syndrome

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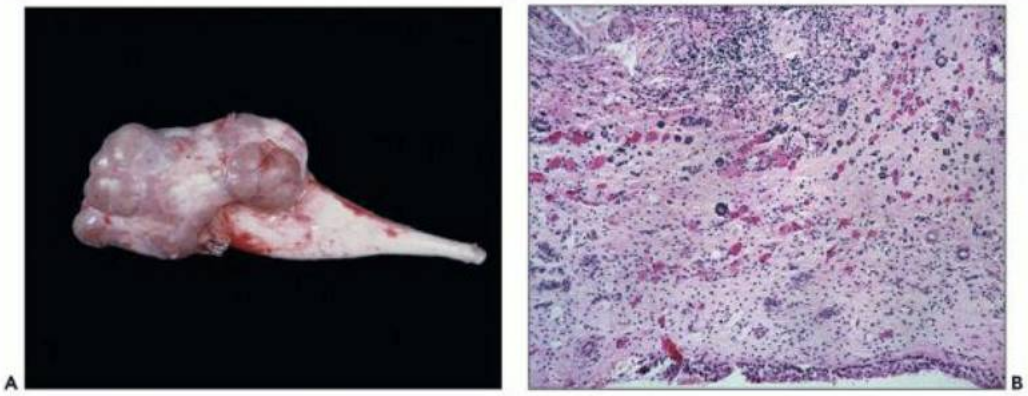
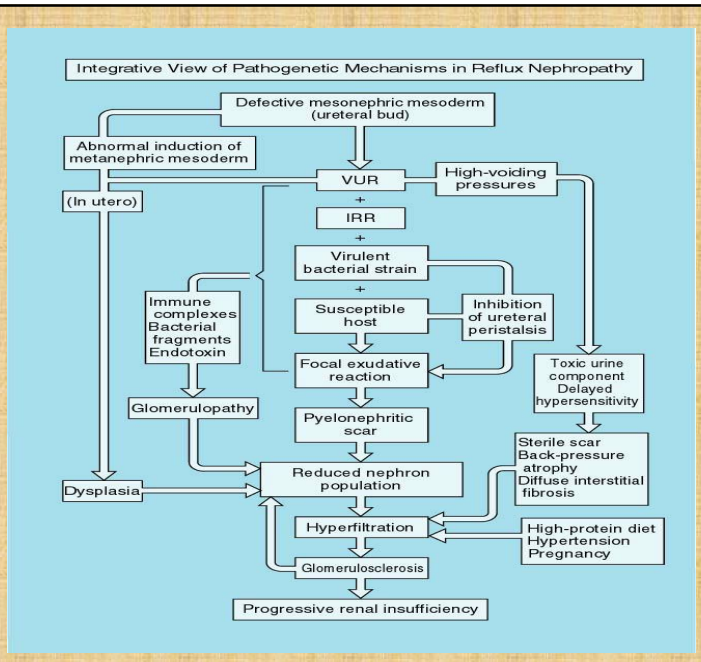
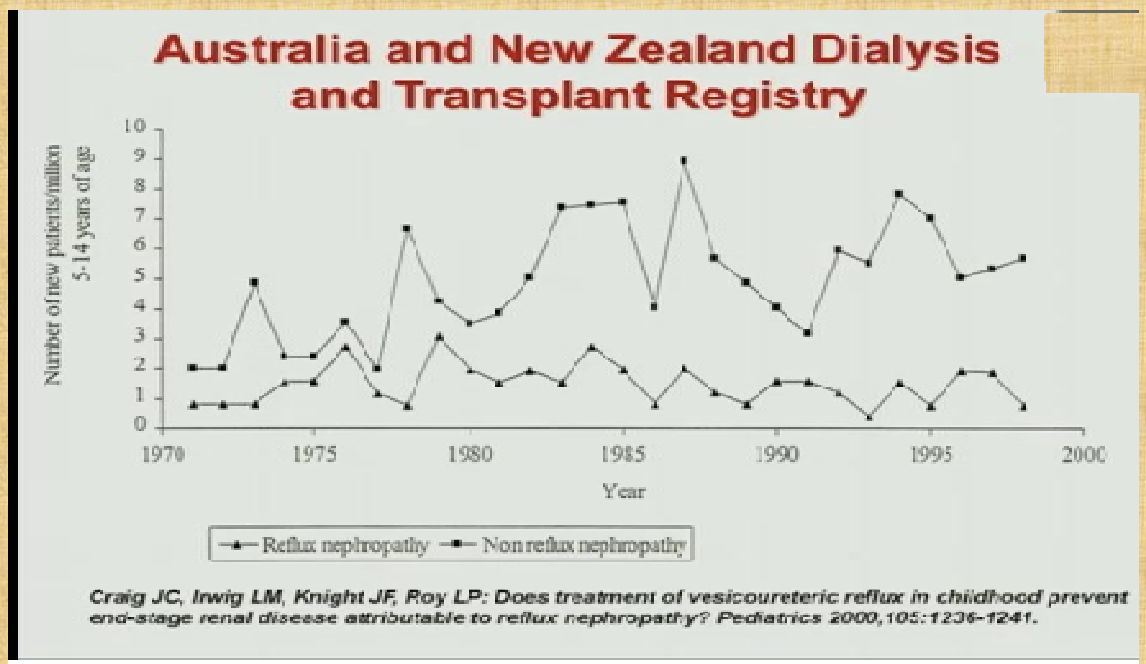


FIGURE 24.56 A: Atrophic kidney with cortical scars from a young boy with history of hypertension associated with nonfunctioning left kidney. B: Histologically, the scar consists of atrophic tubules, chronic inflammatory cells, and absent glomeruli. (H&E; ×400.)



James M. Gloor & Vicente E. Torres



vol 2 Table 7.1 Distribution of reported incident pediatric ESRD patients by primary cause of ESRD (aged 0-21 years), and by demographic characteristics

(a) 2006-2010 (period A)	Total Patients		Percent Incidence		Median Age		Percent Males		Percent White		Percent Black/ African American		Percent Other Race	
Primary Disease Groups	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
All ESRD, (reference)	8221	7340	100	100	16	16	56.6	56.5	66	66.3	24.8	23.9	9.2	9.9
CAKUT	1662	1617	20.2	22	12	11	69.9	68.7	76.4	74.2	17.1	19.5	6.6	6.2
Congenital obstructive uropathies	721	712	8.8	9.7	11	11	83.4	82.4	74.1	69.9	20.7	24.4	5.3	5.6
Renal hypoplasia, dysplasia, oligonephronia	745	737	9.1	10	10	10	63.8	59.6	75.8	75.2	16.8	17.9	7.4	6.9
Chronic pyelonephritis, reflux nephropathy	196	168	2.4	2.3	16	17	43.9	50.6	86.7	88.1	5.1	6	8.2	6
Cystic/Hereditary/Congenital Diseases	954	921	11.6	12.5	14	13	58.8	59.3	79.1	76.9	15.9	15.9	4.9	7.3
Polycystic kidneys, adult type (dominant)	46	48	0.6	0.7	18	18	47.8	39.6	78.3	83.3	19.6	14.6	2.2	2.1
Polycystic, infantile (recessive)	145	151	1.8	2.1	4	1	47.6	49	77.2	79.5	19.3	13.2	3.4	7.3
Medullary cystic disease, including nephronophthisis	113	112	1.4	1.5	13	12	40.7	42.9	89.4	77.7	5.3	12.5	5.3	9.8
Hereditary nephritis, Alports syndrome	186	162	2.3	2.2	17	17	86.6	87.7	73.1	75.9	20.4	17.3	6.5	6.8
Cystinosis	59	40	0.7	0.5	13	11	49.2	62.5	96.6	82.5	3.4	12.5	0	5
Primary oxalosis	19	17	0.2	0.2	6	11	52.6	70.6	78.9	70.6	5.3	11.8	15.8	17.6
Congenital nephrotic syndrome	124	135	1.5	1.8	2	3	58.1	49.6	78.2	82.2	15.3	11.9	6.5	5.9
Drash syndrome, mesangial sclerosis	29	21	0.4	0.3	1	1	55.2	52.4	79.3	81	17.2	14.3	3.4	4.8
Other (congenital malformation syndromes)	204	208	2.5	2.8	14	13	58.3	63	84.8	76.9	9.8	13.9	5.4	9.1
Sickle cell disease/anemia	22	15	0.3	0.2	20	20	63.6	73.3	9.1	0	90.9	100	0	0
Primary Glomerular Disease	1985	1603	24.1	21.8	18	18	55.1	55.5	61.1	65.4	31.4	26.9	7.5	7.6
Glomerulonephritis (GN) (histologically not examined)	399	290	4.9	4.0	19	19	61.2	58.3	66.2	72.1	24.3	19.3	9.5	8.6
Focal glomerulosclerosis, focal sclerosing GN	1017	849	12.4	11.6	17	17	55	56.8	53.3	59.4	41.5	34.9	5.2	5.8
Membranous nephropathy	48	39	0.6	0.5	18	19	45.8	69.2	54.2	61.5	39.6	33.3	6.3	5.1
Membranoproliferative GN type 1, diffuse MPGN	105	70	1.3	1.0	17	17	43.8	45.7	66.7	75.7	21.9	14.3	11.4	10
Dense deposit disease, MPGN type 2	33	26	0.4	0.4	16	16	54.5	53.8	90.9	84.6	3	7.7	6.1	7.7
IgA nephropathy	208	187	2.5	2.5	19	18	65.4	58.8	73.6	74.9	14.9	10.2	11.5	15
IgM nephropathy	19	15	0.2	0.2	19	19	63.2	60	63.2	66.7	36.8	26.7	0	6.7
With lesion of rapidly progressive GN	64	47	0.8	0.6	15	16	32.8	27.7	71.9	72.3	15.6	17	12.5	10.6
Other proliferative GN	92	80	1.1	1.1	16	17	39.1	41.3	76.1	66.3	15.2	30	8.7	3.8

Data Source: Special analyses, USRDS ESRD Database. Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; AIDS, acquired-immune deficiency syndrome; CAKUT, congenital anomalies of the kidney and urinary tract; congenital obstructive uropathy, combination of congenital ureteropelvic junction obstruction, congenital ureterovesical junction obstruction, and other congenital anomalies; ESRD, end-stage renal disease; GN glomerulonephritis; IgA immunoglobulin A; IgM, immunoglobulin M; incl., including; MPGN, membranoproliferative glomerulonephritis; SBE, sub-acute bacterial endocarditis. Diagnoses with 10 or fewer total patients for year categories are suppressed.

USRDS UNITED STATES RENAL DATA SYSTEM

2017 Annual Data Report
Volume 2, Chapter 7

9

Does Treatment of Vesicoureteric Reflux in Childhood Prevent End-Stage Renal Disease Attributable to Reflux Nephropathy?

Jonathan C. Craig, Epi), PhD, Les M. Irwig, FFAPHM, PhD, John F. Knight and L. Paul Roy

Pediatrics 2000;105;1236-1241
DOI: 10.1542/peds.105.6.1236

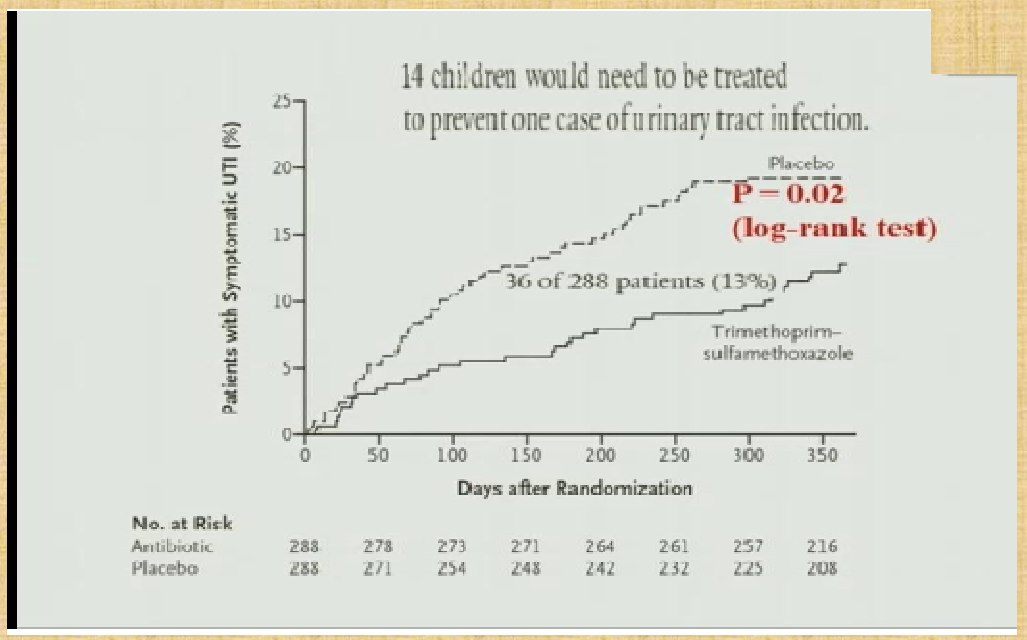
Conclusions. Treatment of children with vesicoureteric reflux has not been accompanied by the hoped-for reduction in the incidence of ESRD attributable to reflux nephropathy. A randomized trial with a control (no-treatment) arm is required to appropriately assess the medical belief that long-term antibiotics and surgery improve the natural history of vesicoureteric reflux. *Pediatrics* 2000; 105:1236–1241; *vesicoureteric reflux, end-stage renal disease, before–after study.*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

Jonathan C. Craig, M.B., Ch.B., Ph.D., Judy M. Simpson, Ph.D., Gabrielle J. Williams, Ph.D., M.P.H., Alison Lowe, B.Sc., Graham J. Reynolds, M.B., B.S., Steven J. McTaggart, M.B., B.S., Ph.D., Elisabeth M. Hodson, M.B., B.S., Jonathan R. Carapetis, M.B., B.S., Ph.D., Noel E. Cranswick, M.B., B.S., Grahame Smith, M.B., B.S., Les M. Irwig, M.B., B.Ch., Ph.D., Patrina H.Y. Caldwell, Ph.D., Sana Hamilton, M.P.H., and Leslie P. Roy, M.B., B.S., for the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) Investigators



RESEARCH ARTICLE

Disease Models & Mechanisms 6, 934-941 (2013) doi:10.1242/dmm.011650

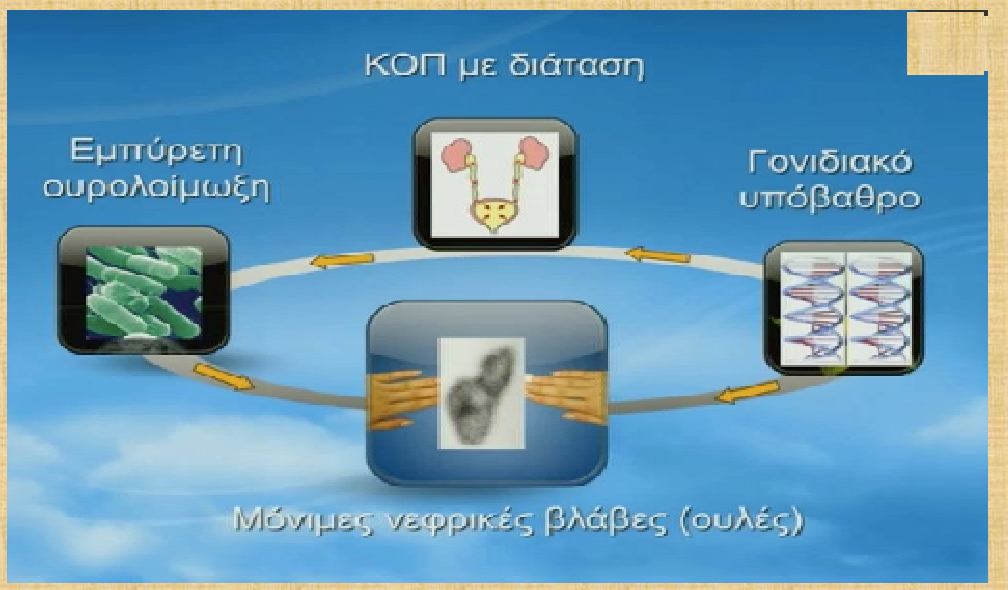
Interplay between vesicoureteric reflux and kidney infection in the development of reflux nephropathy in mice

Samantha E. Bowen[1,*], Christine L. Watt[2,*], Inga J. Murawski[2], Indra R. Gupta[2,3] and Soman N. Abraham[1,4,5,6,‡]

SUMMARY

Vesicoureteric reflux (VUR) is a common congenital defect of the urinary tract that is usually discovered after a child develops a urinary tract infection. It is associated with reflux nephropathy, a renal lesion characterized by the presence of chronic tubulointersitial inflammation and fibrosis. Most patients are diagnosed with reflux nephropathy after one or more febrile urinary tract infections, suggesting a potential role for infection in its development. We have recently shown that the C3H mouse has a 100% incidence of VUR. Here, we evaluate the roles of VUR and uropathogenic *Escherichia coli* infection in the development of reflux nephropathy in the C3H mouse. We find that VUR in combination with sustained kidney infection is crucial to the development of reflux nephropathy, whereas sterile reflux alone fails to induce reflux nephropathy. A single bout of kidney infection without reflux fails to induce reflux nephropathy. The host immune response to infection was examined in two refluxing C3H substrains, HeN and HeJ. HeJ mice, which have a defect in innate immunity and bacterial clearance, demonstrate more significant renal inflammation and reflux nephropathy compared with HeN mice. These studies demonstrate the crucial synergy between VUR, sustained kidney infection and the host immune response in the development of reflux nephropathy in a mouse model of VUR.

DMM



Εξέλιξη της ΚΟΠ σε 1.000.000 παιδιά