

INFEZIONE URINARIA

DEFINIZIONE

Presenza di batteri nelle urine

Localizzazione

Severità
dell'invasione
tissutale

- **Batteriuria asintomatica**: presenza di urine infette in assenza di sintomatologia clinica.
- **Cistite acuta**: infezione in cui l'invasione batterica è limitata alla parete vescicale.
- **Pielonefrite acuta**: infezione in cui l'invasione batterica coinvolge il parenchima renale.

EPIDEMIOLOGIA

- Risk before puberty:

- 3-5% in ♀: 3.600.000/b.ne → 110.000 – 180.000
- 1-2% in ♂: 3.800.000/b.ni → 38.000 – 76.000

- Prevalenza:

- ♂ >1 anno: 2%
- ♂ <1 anno: 3%
- ♀ <1 anno: 7%
- ♀ >1 anno: 8%

- IVU nei bambini: marker di anomalie funzionali o strutturali a carico dell'apparato urinario (RVU, uropatia ostruttiva, disfunzione vescicale).

GESTIONE CLINICA

- 1. Patogenesi**
- 2. Problema clinico**
- 3. Diagnosi di IVU**
- 4. Diagnosi di sede**
- 5. Ricerca di causa/fattori di rischio**
- 6. Terapia**

GESTIONE CLINICA

- 1. Patogenesi**
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GESTIONE CLINICA

1. Patogenesi

UTI ascending infection from the fecal flora, colonize the perineum and enter the bladder via the urethra

Host factors favoring UTI

Female gender

Vesico-ureteral reflux

Obstructive uropathy

Neuropathic bladder – Voiding dysfunction

Costipation

Pregnancy

Sexual activity

GESTIONE CLINICA

1. Patogenesi e agenti etiologici

- ✓ **Echerichia Coli (75%-90% nelle femmine)**
- ✓ **Klebsiella**
- ✓ **Proteus (simil frequenza dell'EC nel maschio > 1 anno)**
- ✓ **Staphilococcus saprophyticus**

2. Problema clinico

- ✓ **Infezione ascendente, pielonefrite**
- ✓ **Cicatrici renali («renal scars»)**
- ✓ **Insufficienza renale**



GESTIONE CLINICA

- 1. Diagnosi di IVU**
2. Diagnosi di sede
3. Ricerca di causa/fattori di rischio
4. Terapia

DIAGNOSI DI IVU

- **Premesse:**

- Diagnosi errate (FP) sono molto frequenti nei lattanti poiché una raccolta delle urine affidabile, senza contaminazioni, è spesso difficile.
- **Diagnosi FP** possono portare a terapie e ad esami invasivi e costosi non necessari.

DIAGNOSI DI IVU

- **Premesse:** quadro clinico
 - Nel neonato e nel lattante
febbre senza segni di localizzazione;
turbe della crescita
 - Nel bambino più grande
sintomi soggettivi più frequenti al crescere dell'età;
 - Il neonato febbrile ha un'infezione urinaria fino a prova contraria

DIAGNOSI DI IVU: stick urine – valore diagnostico

Esterasi leucocitaria: *ruling out*

Nitriti: *ruling in*



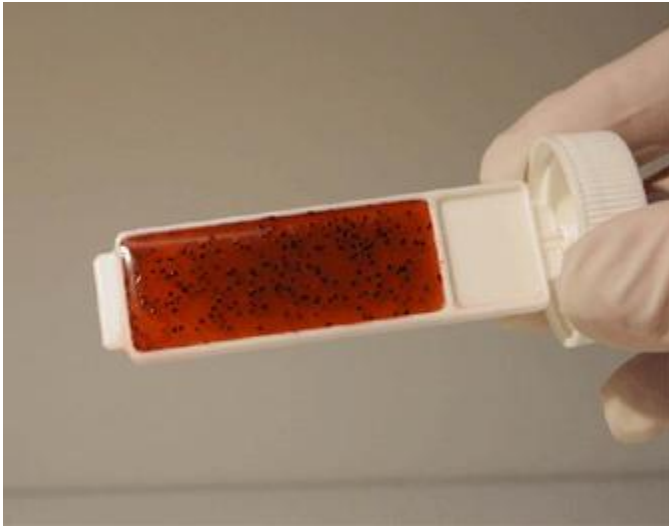
Valore diagnostico delle indagini urinarie

Sensibilità (%)

Specificità (%)

	Letteratura*	<i>Vidal E, Pecile P – SINP 2005</i>		Letteratura*	<i>Vidal E, Pecile P – SINP 2005</i>	VPN (Vidal E, Pecile P)
Stick						
Esterasi	83 (67-94)	80		78 (64-92)	80	92
Nitriti	53 (15-82)	15		98 (90-100)	99	73
Microscopio						
GB ($\geq 10\text{mm}^3$)	73 (32-100)	82		81 (45-98)	76	93
Batteri	81 (16-99)	95		83 (11-100)	38	95
GB+batteri		96			64	97

DIAGNOSI DI IVU: uricult/urocoltura



DIAGNOSI DI IVU

UTI

UFC > 100.000 di un singolo patogeno

UFC < 100.000 + sintomi



DIAGNOSI DI IVU: raccolta delle urine

- **Puntura sovrapubica** (gold standard)
- **Cateterizzazione urinaria**
- **Mitto intermedio**
- **Sacchettino**

INFEZIONE URINARIA

basse/alte vie

- La distinzione tra infezione delle alte e basse vie urinarie è importante a fini:
 - Terapeutici (durata della terapia)
 - Diagnostici (indagini e follow-up)
 - Prognostici (*renal scarring*)
- **La diagnosi di sede dell'IVU si basa sulla combinazione di dati clinici, di laboratorio e di *imaging*.**

IVU alte/pielonefrite

segni clinici

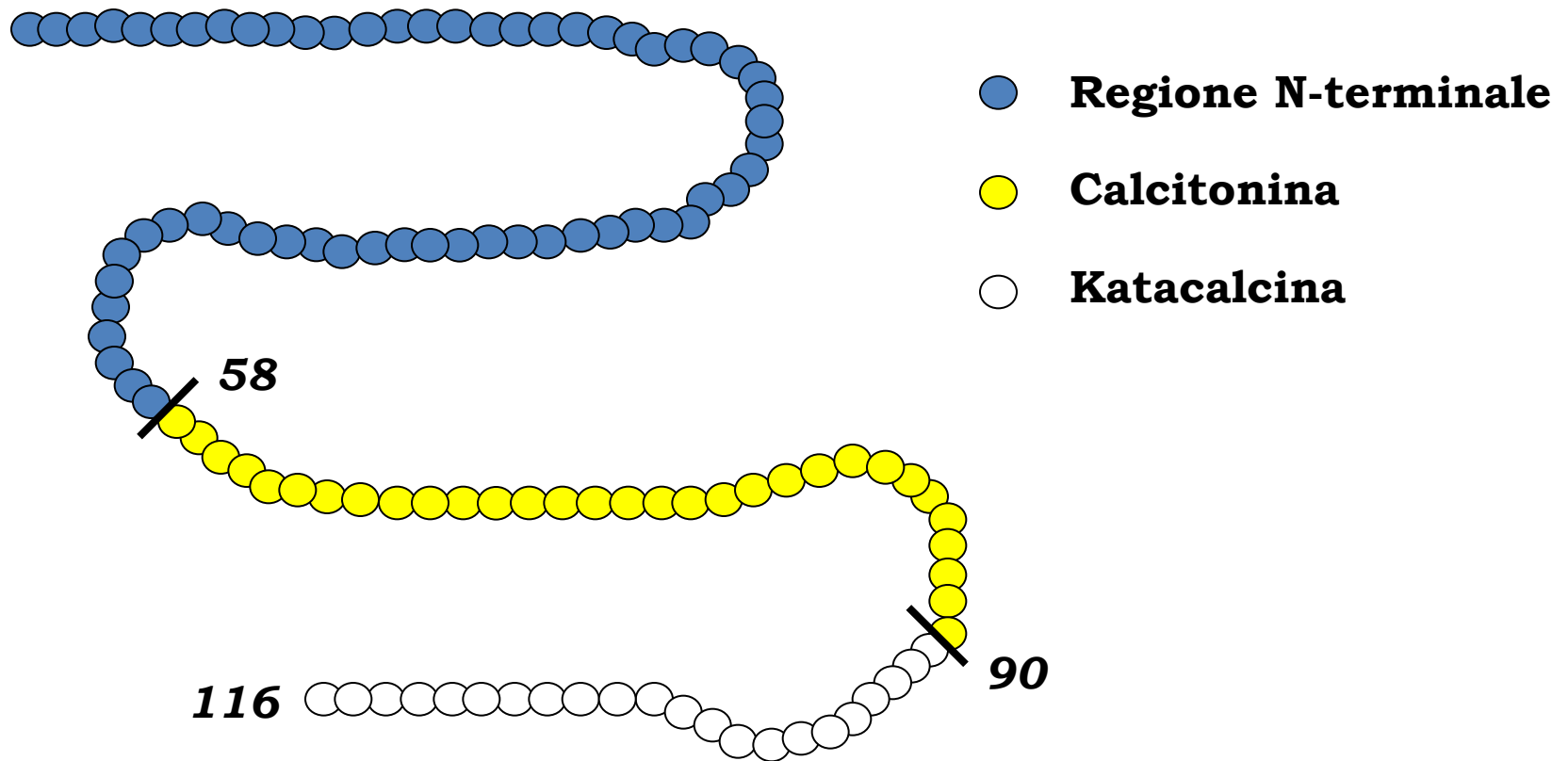
- In età pediatrica le infezioni delle vie urinarie si associano a sintomi aspecifici:
 - Febbre senza sintomi: *UTI should be considered in any infant aged less than 2 years with unexplained fever. AAP, Pediatrics 1999*);
 - diarrea, vomito, nausea;
 - irritabilità, crisi convulsive febbrili;
 - ittero;
 - ipoalimentazione, scarsa crescita.
- **Ad eccezione dell'età neonatale, l'assenza di febbre** porta ad escludere un interessamento parenchimale renale.

IVU alte/pielonefrite: parametri di laboratorio

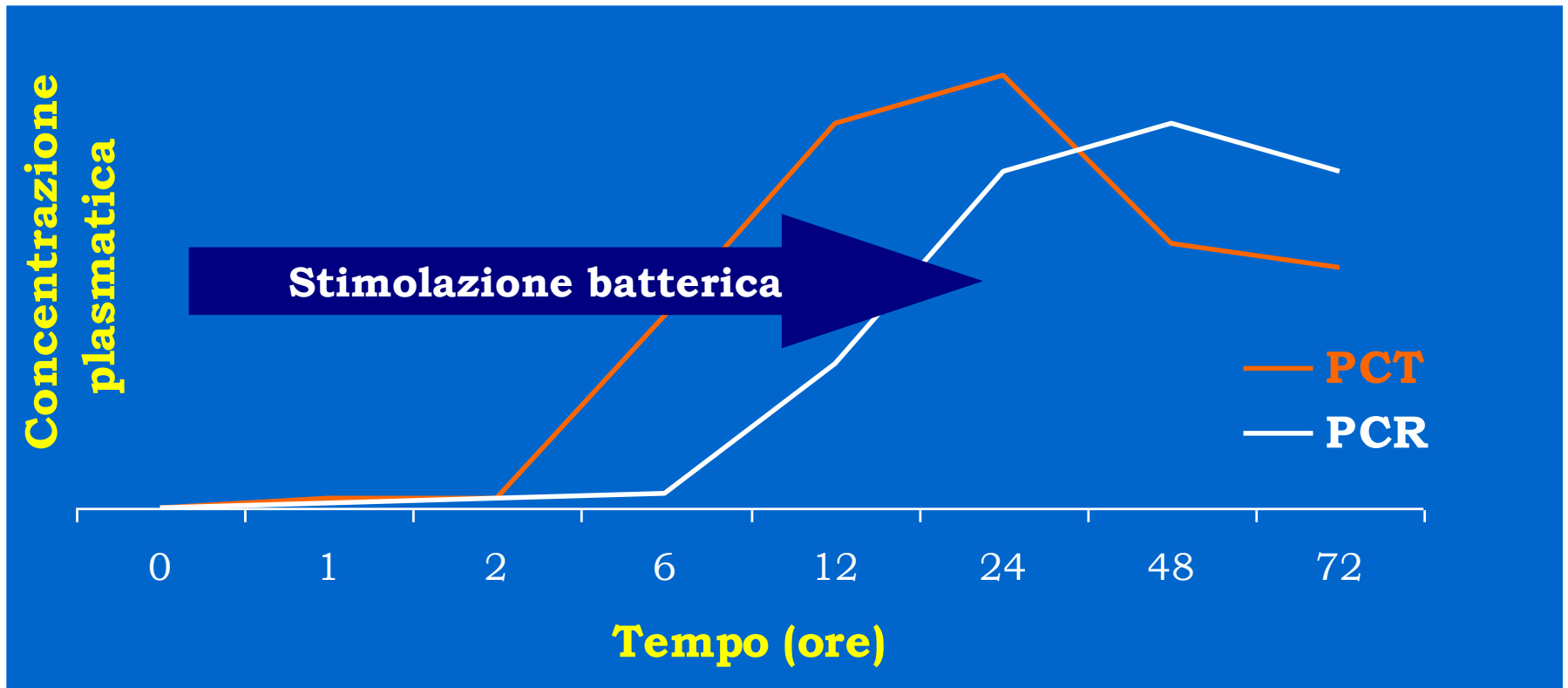
DMSA

	Positivo		Negativo		ORs	p
	N	%	N	%		
VES (mm/I^h)						
• <45	31	46	37	54	1	
• 45-57	42	53	37	47	1.36	0.3601
• 68-94	52	65	28	35	2.22	0.0185
• <u>≥95</u>	60	71	25	29	2.86	0.0020
PCR (mg/L)						
• <24	23	34	45	66	1	
• 24-54	42	49	43	51	1.91	0.0538
• 55-101	52	66	27	34	3.77	0.0001
• <u>≥102</u>	69	85	12	15	11.25	<.0001
WBC/mm³						
• <11000	14	38	23	62	1	
• 11000-15000	38	49	39	51	1.60	0.2495
• >15000	135	67	67	33	3.31	0.0012

IVU alte/pielonefrite: parametri di laboratorio - PCT



IVU alte/Pielonefrite: parametri di laboratorio - PCT



DIAGNOSI DI SEDE: tecniche di imaging

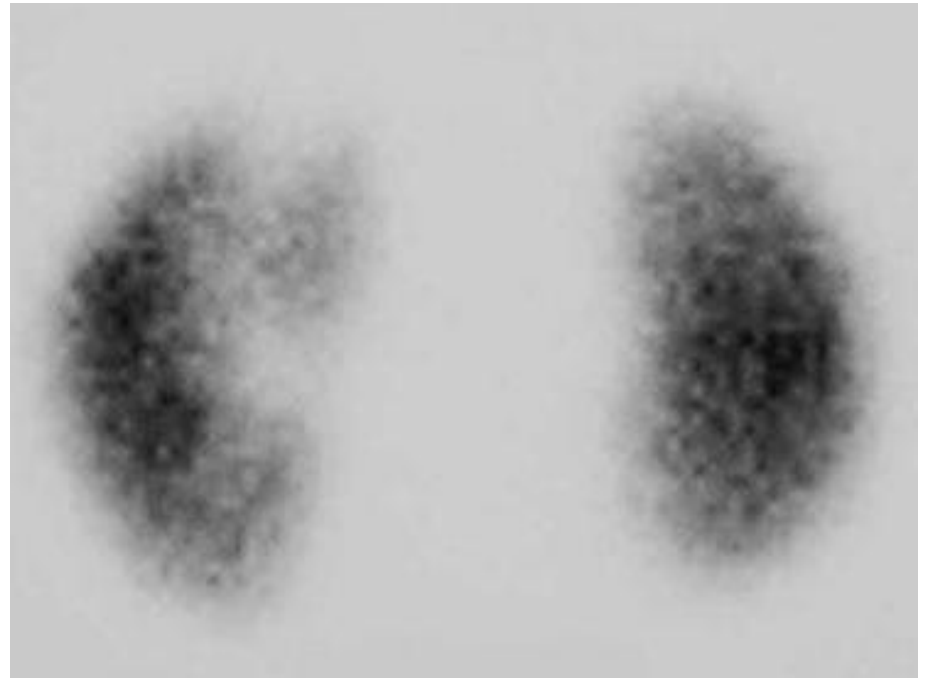
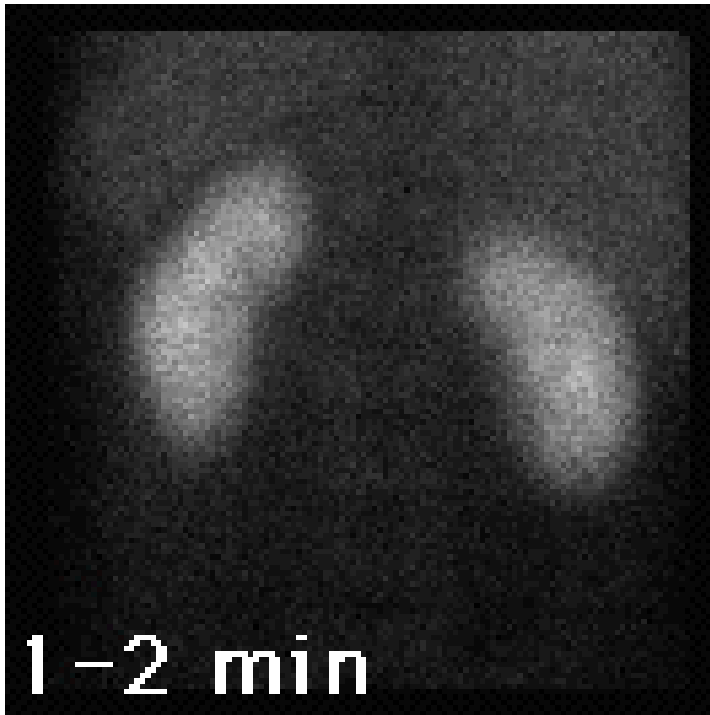
- **Razionale per procedere con studi di imaging:**
 - **Individuare anomalie congenite (e.g. reflusso vescico-ureterale; idronefrosi) – ECOgrafie**
 - **Studiare la presenza di «renal scars», in caso di sospetta infezione delle alte vie – Technetium labeled Dimercaptosuccinic Acid (DMSA) scan**

DIAGNOSI DI SEDE: tecniche di imaging

- **Ecografia reno-vescicale:**
 - Da eseguire sempre al I episodio.
 - Morfologia renale.
 - Stato vie escretrici.
 - Vescica (ureteri distali, spessore parietale, residuo post-minzionale).
 - Possibile ruolo diagnostico per IVU alta/bassa.

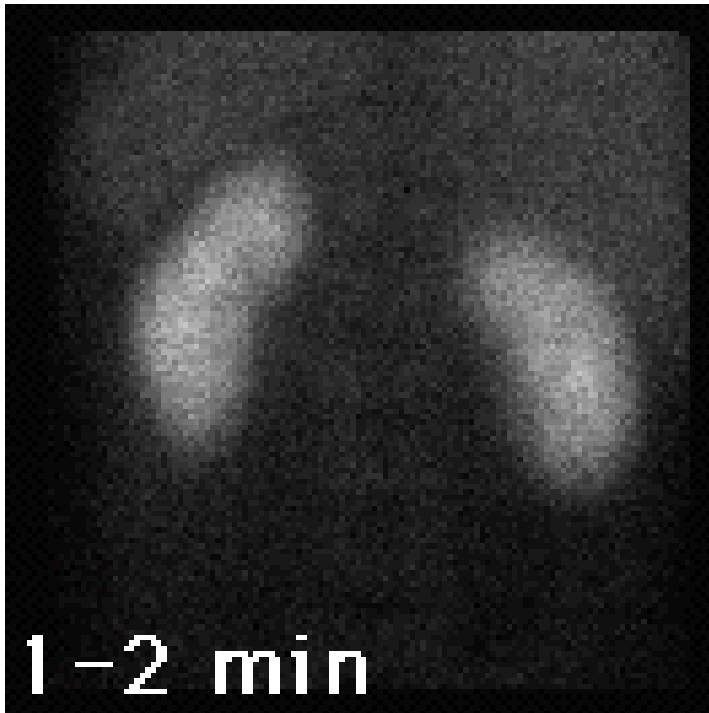
IVU / pielonefrite

- Scintigrafia renale statica (DMSA)
 - Ruolo in acuto

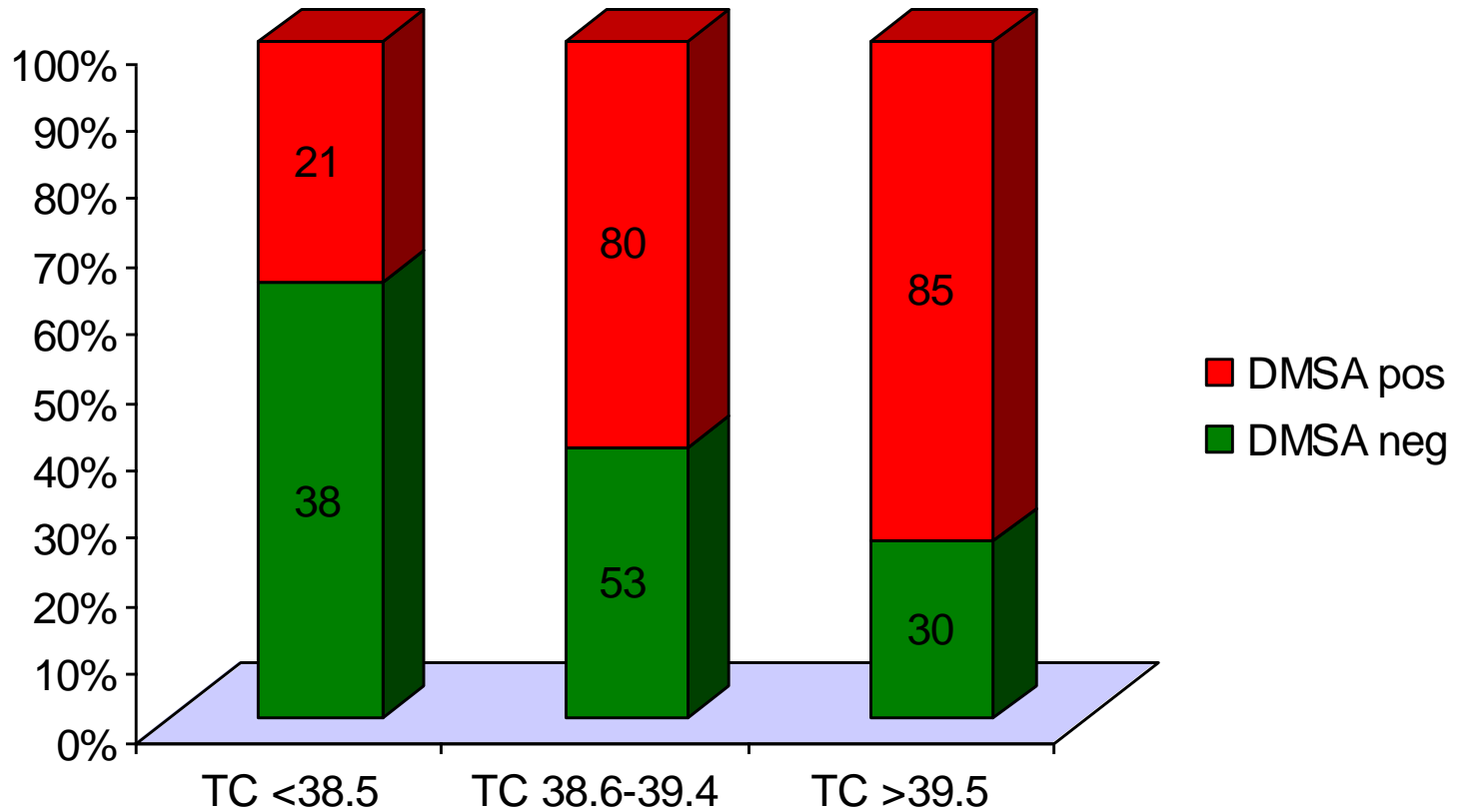


Pielonefrite/**scar**: tecniche di imaging

- Scintigrafia renale statica (DMSA)
 - Ruolo “a distanza” (scars)

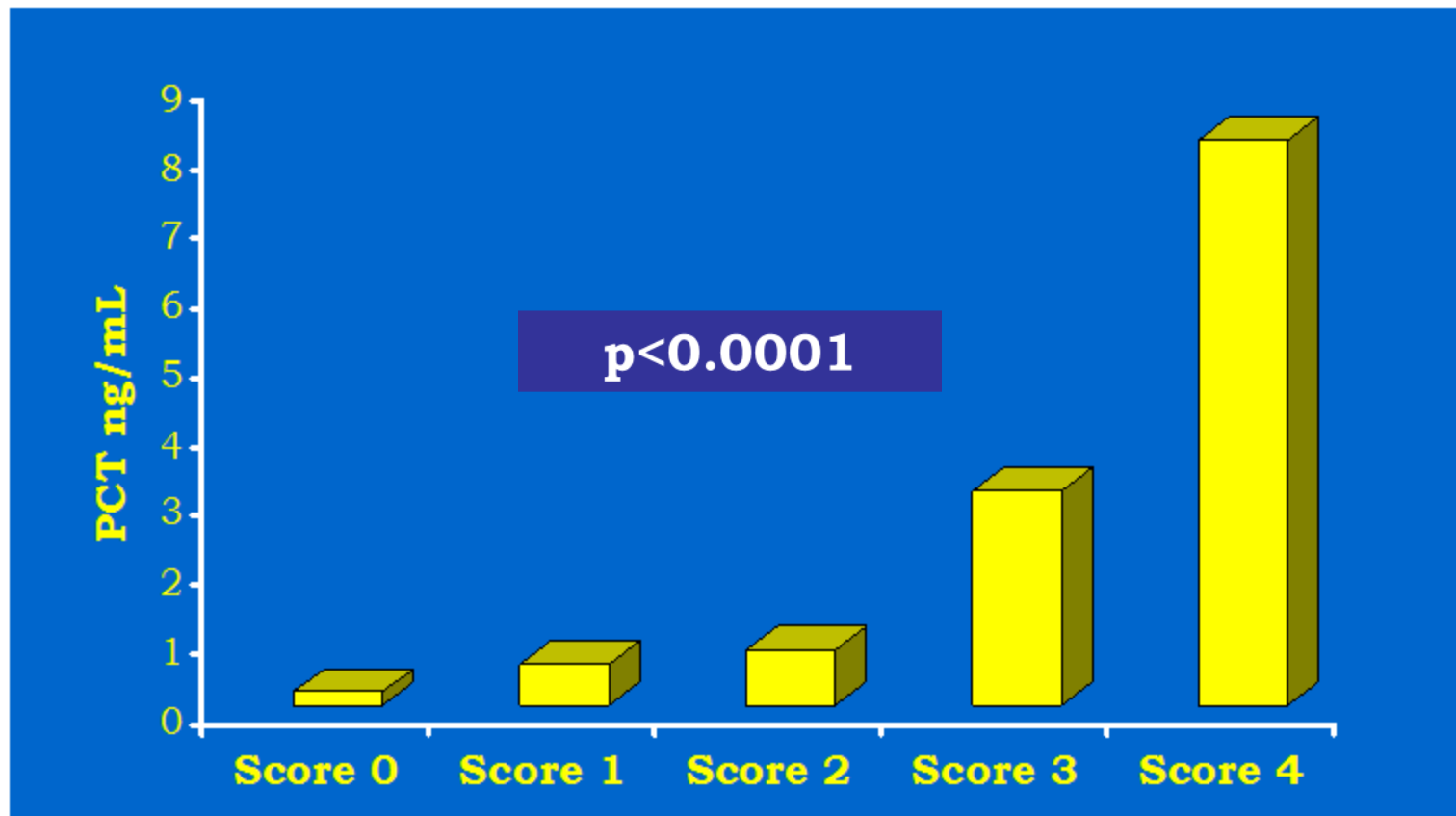


IVU alte/pielonefrite: segni clinici - febbre



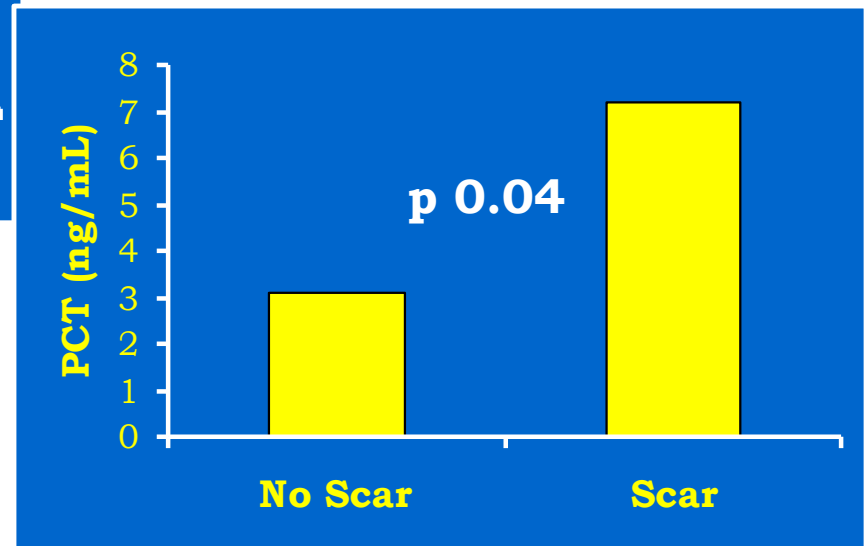
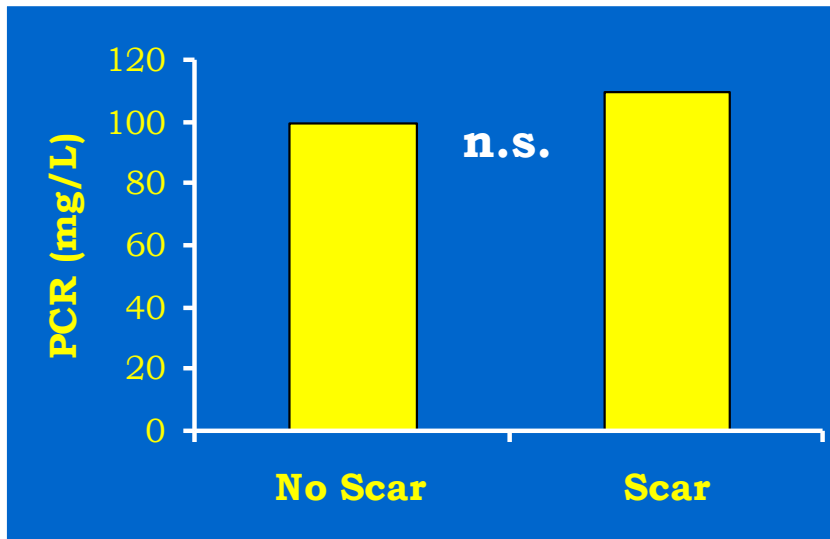
Procalcitonin: A Marker of Severity of Acute Pyelonephritis Among Children

Entità interessamento renale (in acuto)

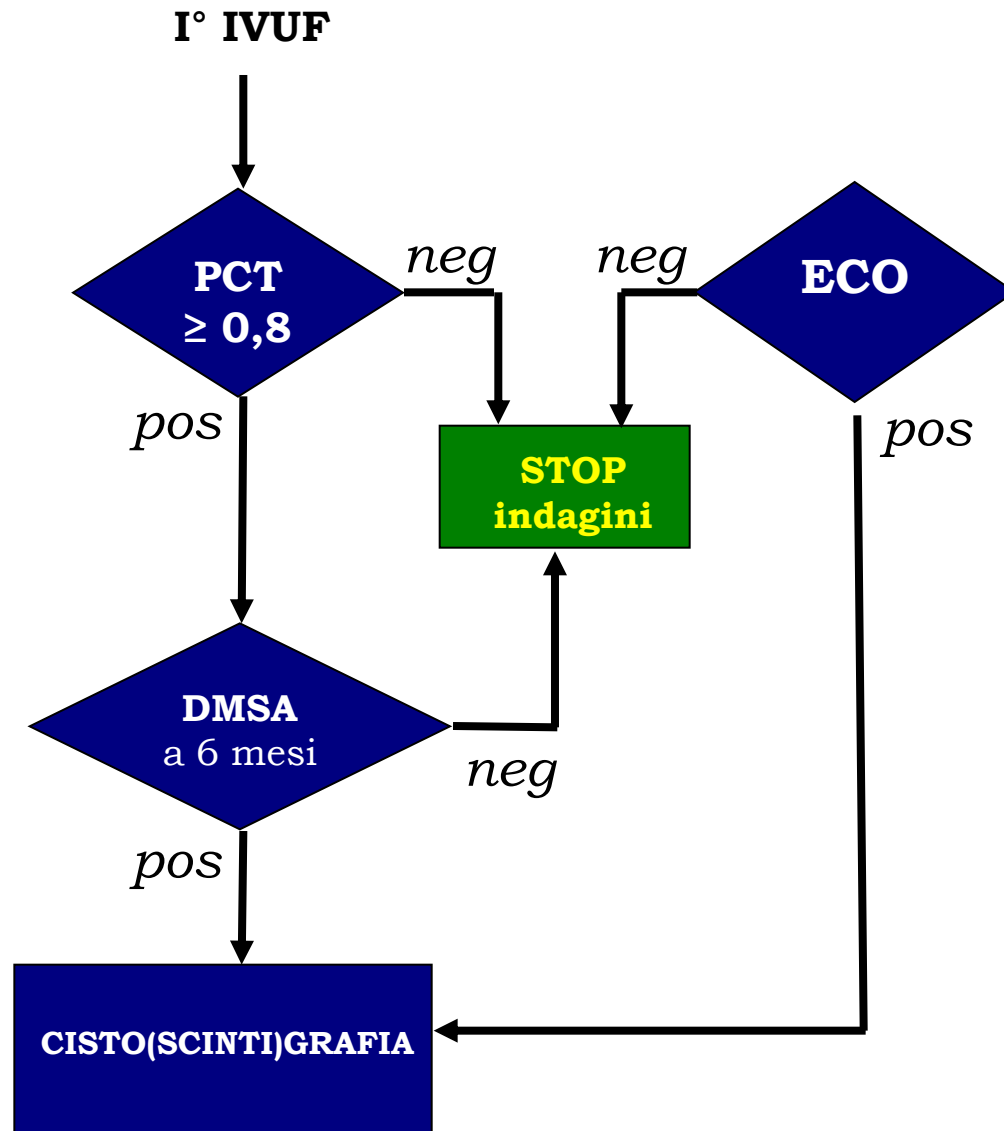


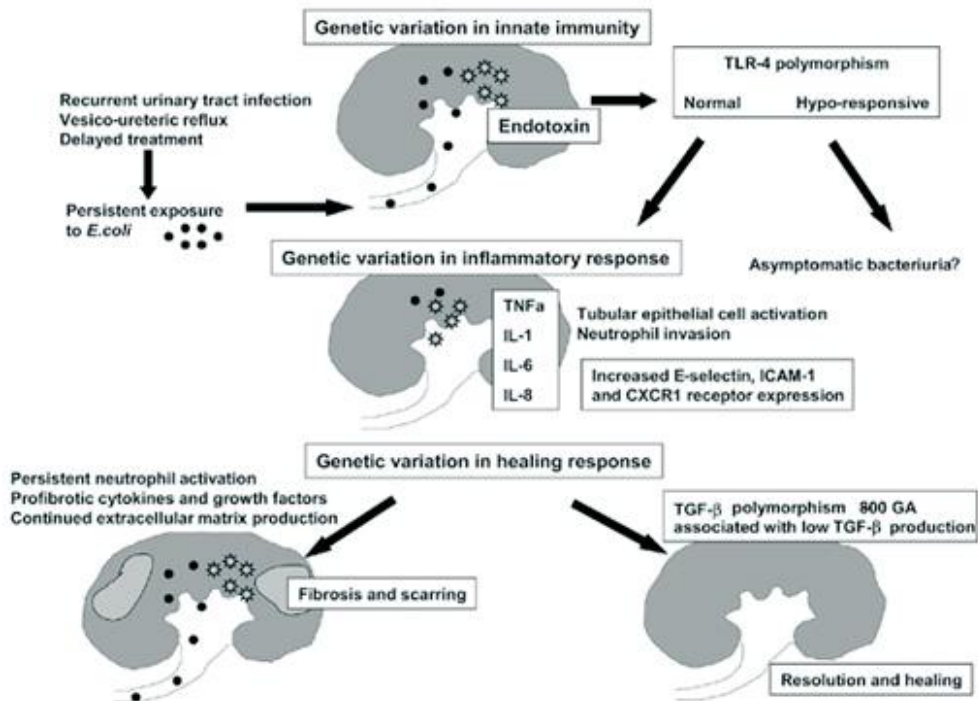
Procalcitonin: A Marker of Severity of Acute Pyelonephritis Among Children

Rischio di sviluppare scar



PCT-based selective approach





Webb JN 2004

Renin-angiotensin system polymorphisms and renal scarring

Pardo R et al Ped Nephrol 2003

Renin-angiotensin system polymorphisms: a risk factor for progression to end-stage renal disease in vesicoureteral reflux patients

Akman B Renal Fail 2009

Genetic control of VEGF and TGF-beta1 gene polymorphisms in childhood urinary tract infection and vesicoureteral reflux

Yim HE et al Pediatr Res 2007

Interleukin-8 and CXCR1 Receptor Functional Polymorphisms and Susceptibility to Acute Pyelonephritis

Lina Artifoni, Susanna Negrisola, Giovanni Montini, Pietro Zucchetta, Pier Paolo Molinari, Walburga Cassar, Roberta Destro, Franca Anglani, Waifro Rigamonti, Graziella Zacchello and Luisa Murer

From the University of Padova, Padova, Italy

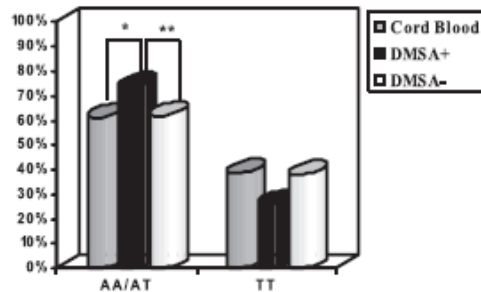


FIG. 1. Genotype distribution of -251 A>T IL-8 polymorphism in different groups. Single asterisk indicates cord blood vs DMSA positive (+) $p = 0.032$. Double asterisks indicate DMSA positive vs negative (-) $p = 0.049$.

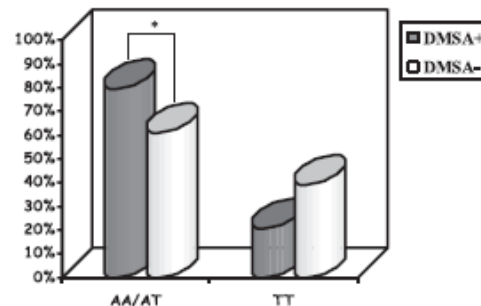


FIG. 2. Genotype distribution of IL-8 -251A>T polymorphism in children without VUR. Asterisk indicates DMSA positive (+) vs negative (-) $p = 0.018$.

CLINICAL AND LABORATORY OBSERVATIONS

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Upper Urinary Tract Infections Are Associated with *RANTES* Promoter Polymorphism

Sonia Centi, MS, PhD, Susanna Negrisola, MS, Alejandra Stefanic, MS, Elisa Benetti, MD, Walburga Cassar, MD, Liviana Da Dalt, MD, Waifro Rigamonti, MD, Pietro Zucchetta, MD, Giovanni Montini, MD, Luisa Murer, MD, PhD, and Lina Artifoni, MS, ScD

Table. Genotype frequencies of *RANTES*, *CCR5*, *MCP-1*, and *CCR2* polymorphisms in 273 children with UTI and 326 cord blood samples

Polymorphism	Genotype	UTI		Control population		P
		n	%	n	%	
<i>RANTES</i> -403G>A	GG	195	71.4	193	59.2	.007
	GA	69	25.3	116	35.6	
	AA	9	3.3	17	5.2	
<i>CCR5</i> Δ32	Wild-type	228	83.5	283	86.8	.452
	Wild-type/Δ32	43	15.7	42	12.9	
	Δ32/Δ32	2	0.7	1	0.3	
<i>MCP-1</i> -2518A>G	AA	151	55.7	202	62	.067
	AG	111	41	107	32.8	
	GG	9	3.3	17	5.2	
<i>CCR2</i> 190G>A	GG	221	81	254	77.9	.658
	GA	49	17.9	68	20.9	
	AA	3	1.1	4	1.2	

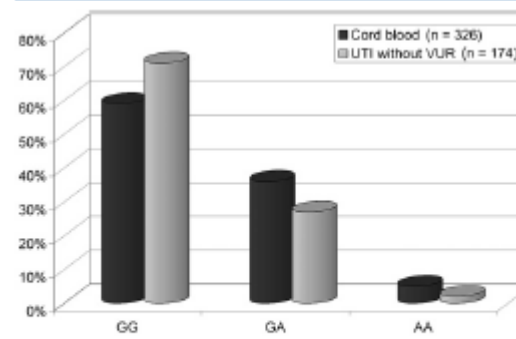


Figure. Genotype distribution of the -403G>A *RANTES* polymorphism in children without VUR and the control population ($P = .020$).

GESTIONE CLINICA

1. Diagnosi di IVU
2. Diagnosi di sede
3. Ricerca di causa/fattori di rischio
4. **Terapia**

TERAPIA (I episodio di IVU)

- **Il bambino con presunta IVU deve essere trattato empiricamente con terapia antibiotica, in attesa dei risultati dell'urocoltura.**
- **La via di somministrazione viene scelta sulla base della clinica:**

IVU "NON COMPLICATA"

- **Paziente febbrile ma in buone condizioni generali**
- **Assume liquidi/farmaci per os**
- **Disidratato in modo lieve**
- **Previsione di buona compliance**

ANTIBIOTICO PER OS

IVU "COMPLICATA"

- **Paziente settico, TC >40°**
- **Vomito persistente**
- **Moderatam/severam. disidratato**
- **Previsione di scarsa compliance**

ANTIBIOTICO PARENTERALE

TERAPIA (I episodio di IVU)

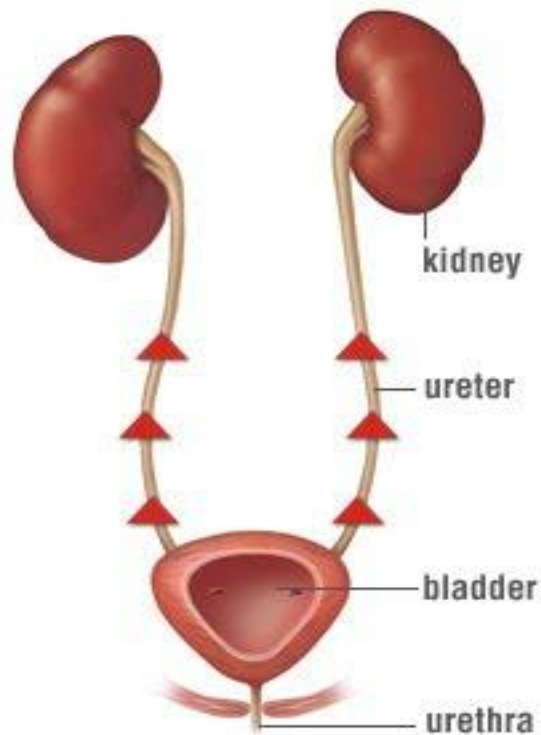
- La durata dipende dalla sede (cistite Vs. pielonefrite acuta).
- La terapia della IVU febbrile prevede comunque 10 gg di terapia antibiotica.
- Evitare cefalosporine nel trattamento della cistite (rischio ESBL).
- Antibiotico profilassi.

NEFROPATIA DA REFLUSSO ACQUISITA

Infezioni urinarie ricorrenti

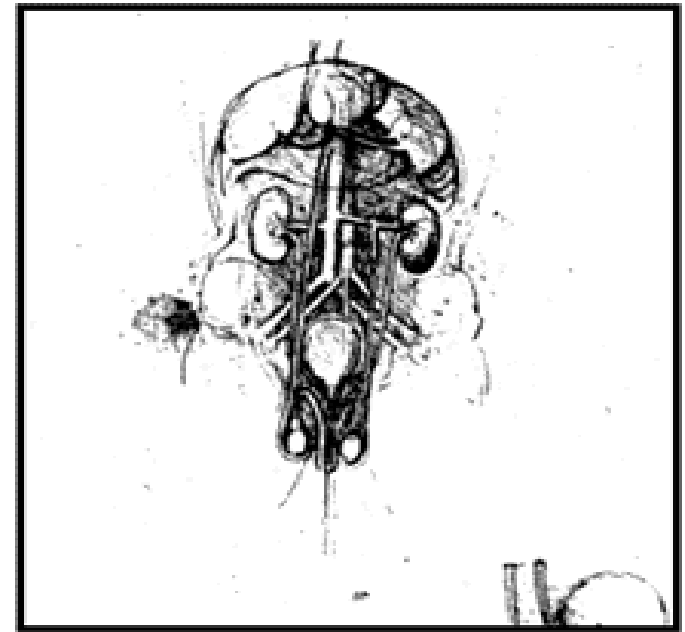
- ✓ Sesso femminile :brevità uretra
- ✓ Età : brevità dell'uretra
minore immunità innata
papille convesse reflusso intrarenale
- ✓ Suscettibilità individuale

VUR primitivo





Leonardo da Vinci
(1452-1519)

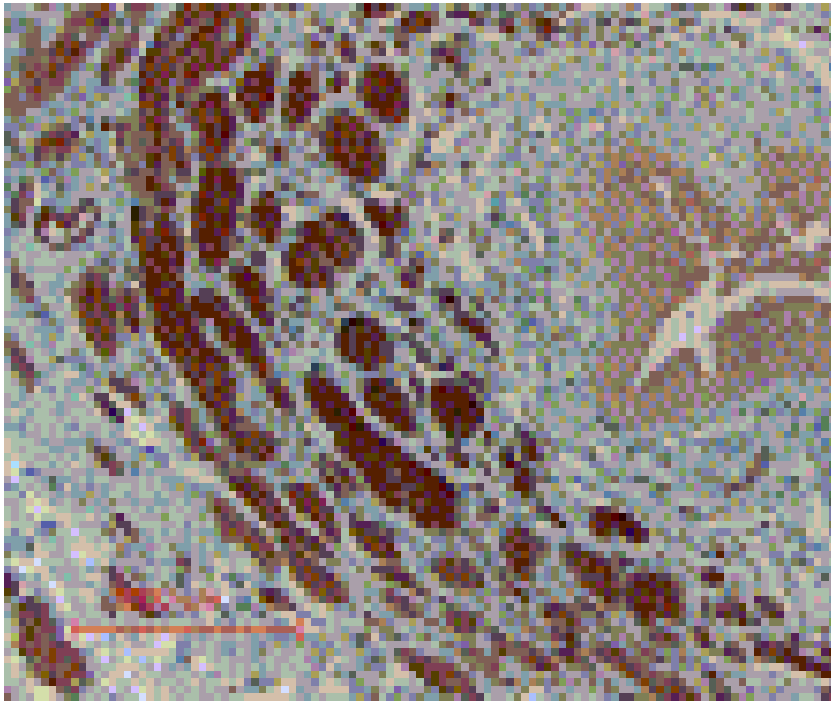


Il Reflusso Vescico Ureterale primitivo (VUR) è un difetto congenito dell'uretere che causa un flusso retrogrado dell'urina dalla vescica verso la pelvi e il rene in assenza di patologie neuromuscolari e di patologie ostruttive o malformative complesse delle basse vie urinarie



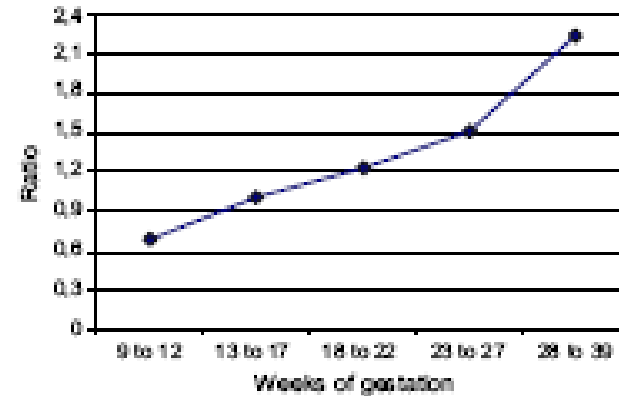
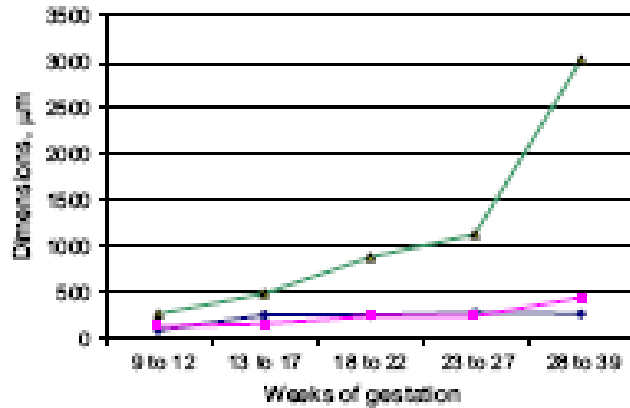
- ✓ **Anamnesi minzionale e controllo sfinteri**
- ✓ **Encompresi, stipsi**
- ✓ **Esame obiettivo (masse add, anomalie genitali est, disrafismo spinale)**
- ✓ **Valutazione urodinamica**

La base anatomica della giunzione uretero-vescicale continente è data dal corretto sviluppo del trigono vescicale che deriva dalla fusione dei prolungamenti della tonaca muscolare degli ureteri intravesicali con l'estensione dorsale dell' anello muscolare dello sfintere vescicale interno.



Tra la 8° e la 12° SG la parete esterna del dotto metanefrico pre ed intravesicale è costituita da mesenchima indifferenziato che, in seguito all'interazione con l'epitelio, si differenzia progressivamente in tonaca muscolare. Contemporaneamente l'uretere in corso di differenziazione si allunga, migra, si canalizza e si apre in vescica.

*Schwentenner JO et al J Urology 2006
Radmayr C et al J Ped Urology 2005*

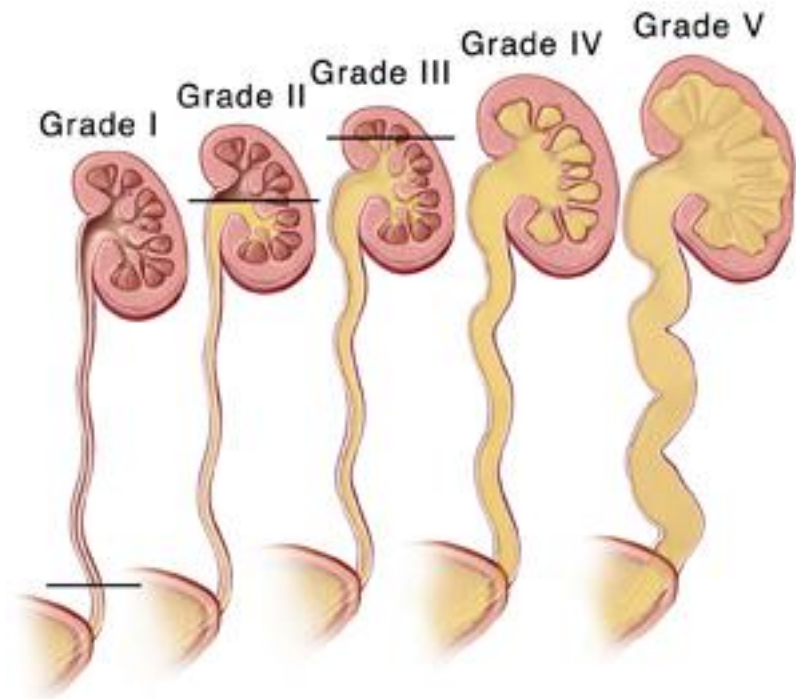


Il normale rapporto tra la lunghezza del tunnel ureterale e il suo diametro permette la continenza della giunzione uretero-vescicale. Tale rapporto aumenta nel feto con l'età gestazionale e all'età di 1-3 anni nei bambini con VUJ continente il rapporto **LTU/DU arriva a 5:1**. Nei neonati e nei feti il reflusso è più frequente per una immaturità della VUJ, ma tende a risolversi spontaneamente nei primi anni di vita.

Nei bambini con reflusso persistente il rapporto LTU/DU è in media 1.4:1

VUR primitivo

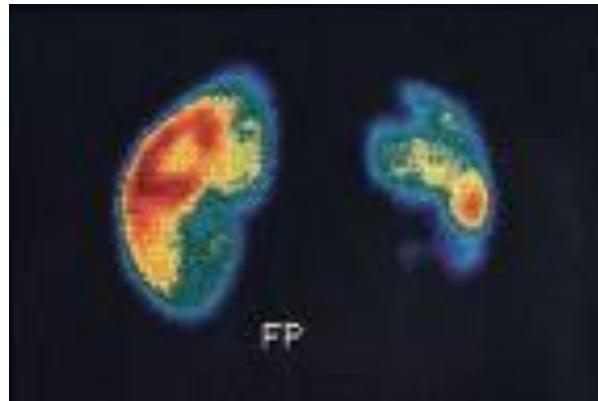
Diversi gradi – in base alla morfologia del tratto urinario come visualizzato alle cisto.-uretrografia retrograda minzionale con contrasto



NEFROPATIA ASSOCIATA A REFLUSSO “REFLUX NEPHROPATHY”

“Reflux nephropathy” è un termine coniato da Bailey nel 1973 per descrivere delle alterazioni renali osservate in pazienti con VUR.

Si associa generalmente a reflussi di IV-V grado e l'unità renale associata mostra ipofunzione severa alla scintigrafia con DMSA



Le forme bilaterali associate a VUR primitivo sono responsabili del 25% delle IRC in età pediatrica.

NEFROPATIA DA REFLUSSO CONGENITA

Sesso maschile

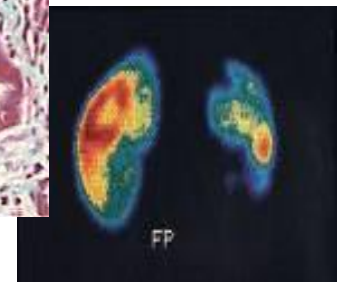
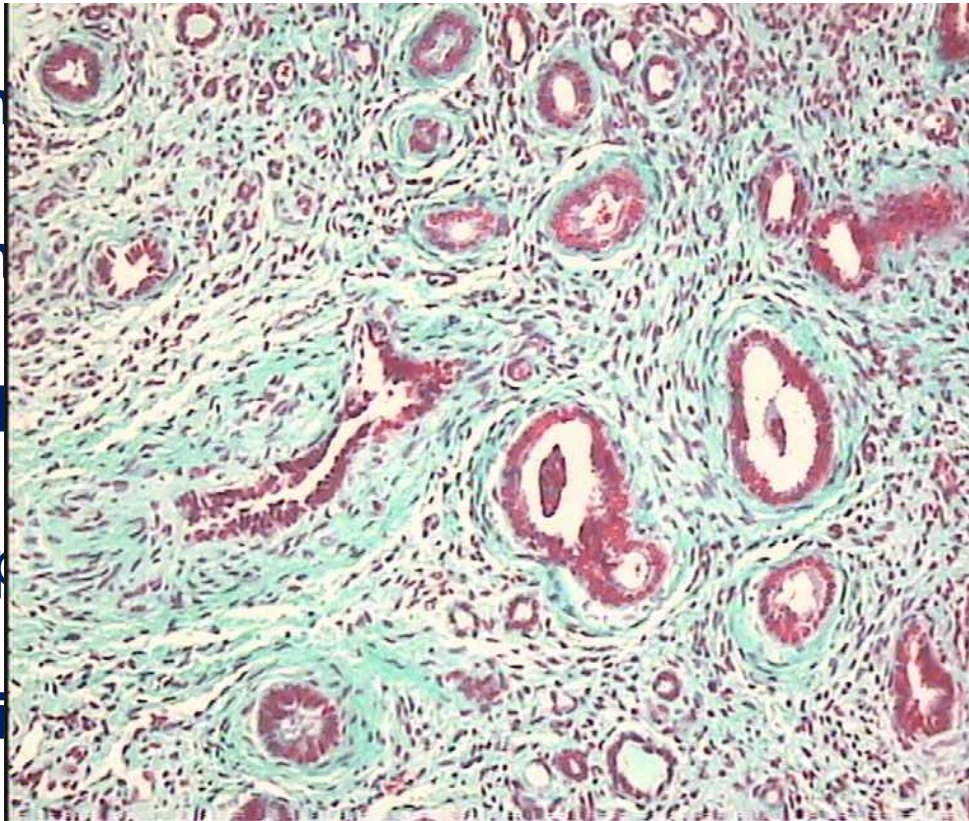
IRC nell'infanzia

Anamnesi: Id

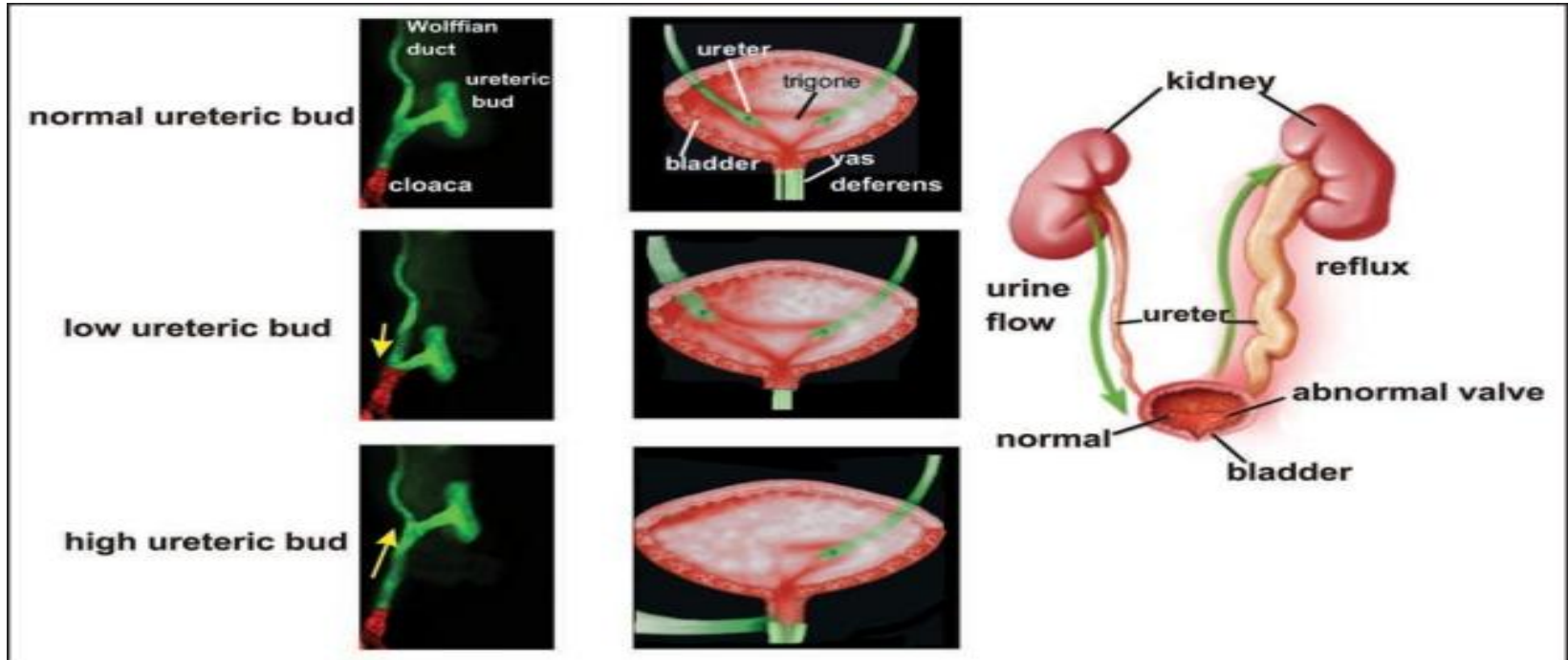
CUMS: VUR p

Eco:rene ± pi

DMSA: rene piccolo ipocaptante in toto

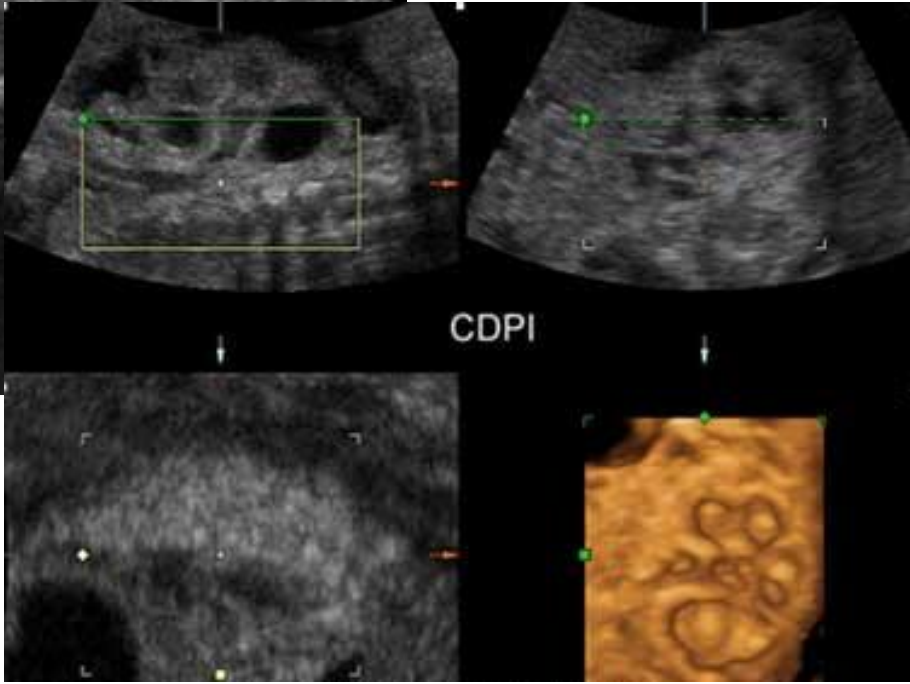
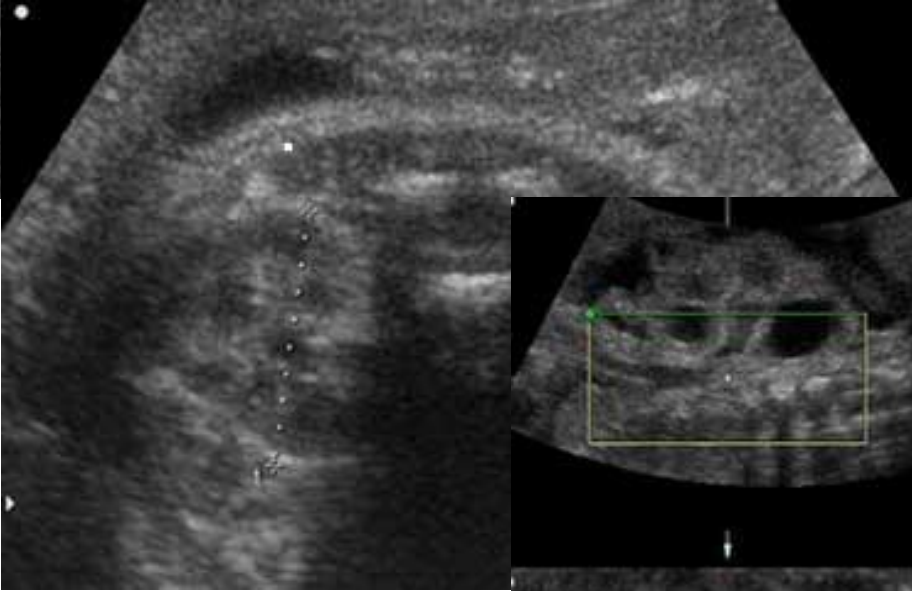


VUR ectopico-lateralizzato



Una induzione della bozza ureterale craniale o caudale con il mesenchima metanefrico causa un difetto di migrazione dell'uretere e con orifizio ectopico-lateralizzato in vescica e conseguente VUR di grado severo. Inoltre il non corretto contatto spazio temporale con il metanefrico sovrverte la crescita e differenziazione del rene con conseguente ipo/displasia renale

VUR e Nefropatia da Reflusso



NEFROPATIA DA REFLUSSO ACQUISITA

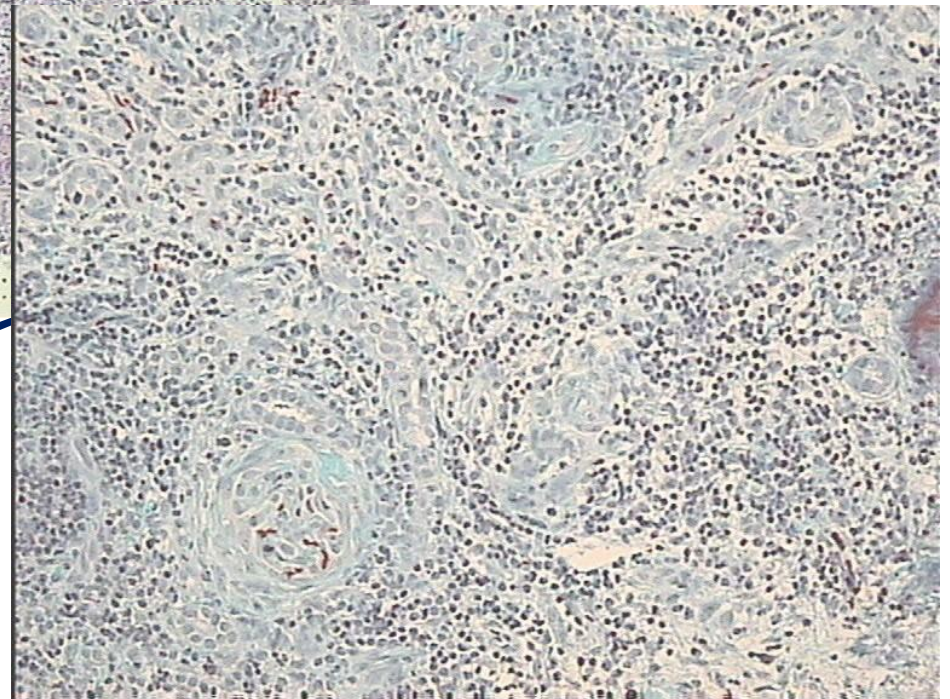
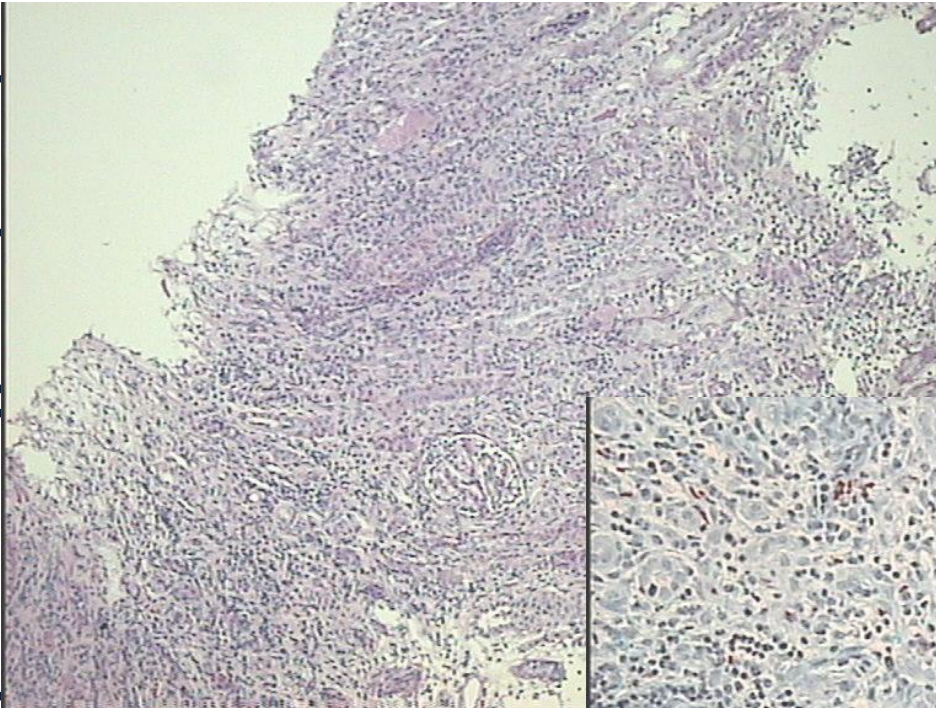
Giovan

Anamr

CUMS:

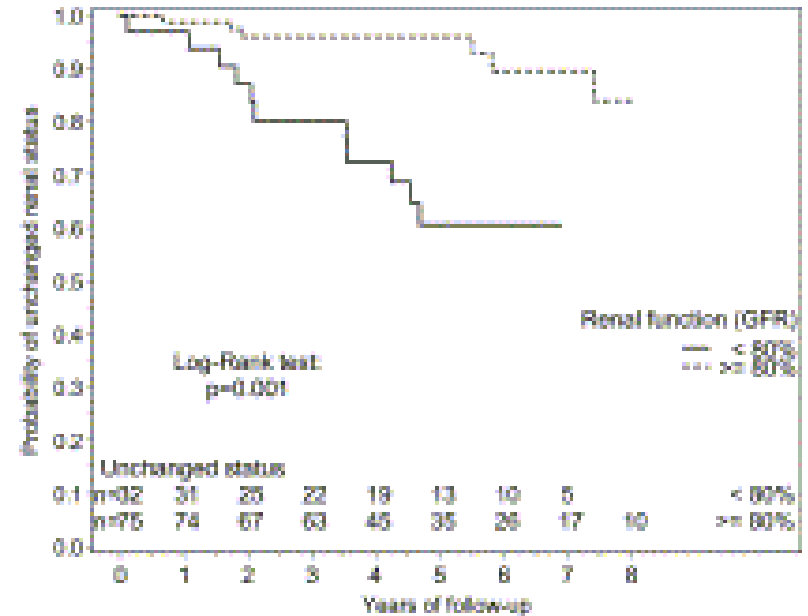
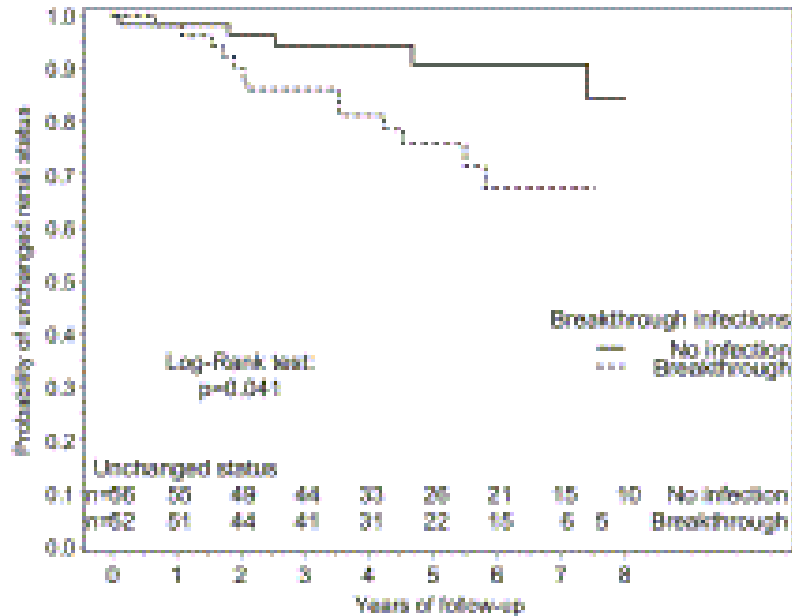
Eco:re

DMSA: scars segmentar



NEFROPATIA DA REFLUSSO ACQUISITA

Infezioni urinarie ricorrenti





VUR e infezioni

- VUR è presente in 1% della popolazione pediatrica
- VUR di I-II grado si risolvono spontaneamente entro i 2-3 anni
- VUR senza infezioni non provoca un danno renale acquisito
- VUR è presente nel 30-40% della popolazione con IVU
- Lo scar è più frequente nei pazienti con UTI e VUR di III-V grado
- I pazienti con scar al DMSA hanno maggiore rischio di avere nuove infezioni e un danno renale. Tale rischio è maggiore nel bambino piccolo ed è in relazione ad una suscettibilità individuale

Nel bambino di età inferiore ai 2 anni.....

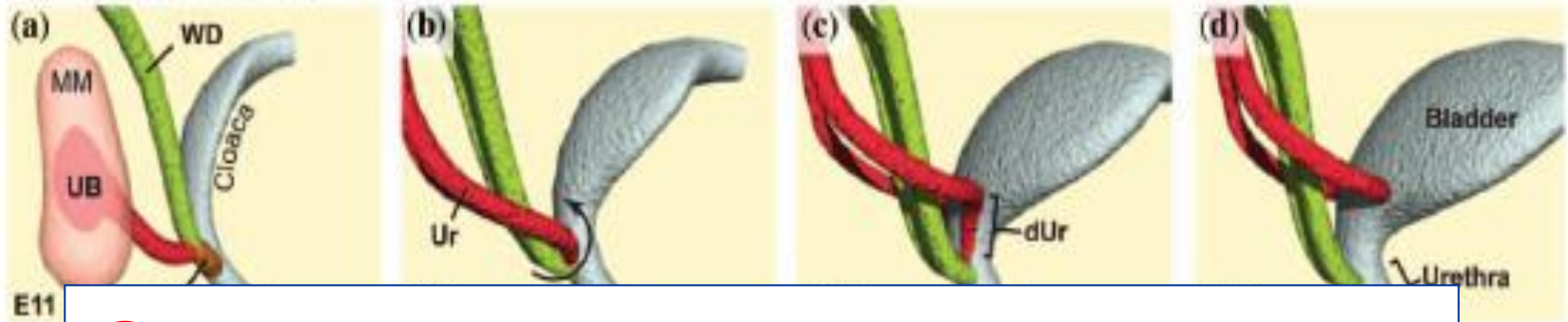
VUR I e III grado sorveglianza ed eventuale profilassi antibiotica se UTI con DMSA positivo per 1 anno (?)

Lo studio svedese (bambini di 12-23 mesi con follow-up di 2 anni e VUR di III-IV grado) ha dimostrato parità di efficacia della profilassi e del trattamento endoscopico nella prevenzione di UTI rispetto alla sorveglianza senza alcun trattamento preventivo e maggiore efficacia nella prevenzione del danno renale nelle bambine della profilassi rispetto alla sorveglianza

**VUR di IV-V grado profilassi antibiotica, ma trattamento endoscopico se se ricorrenza di IVU
ATTENZIONE: disfunzioni vescicali**

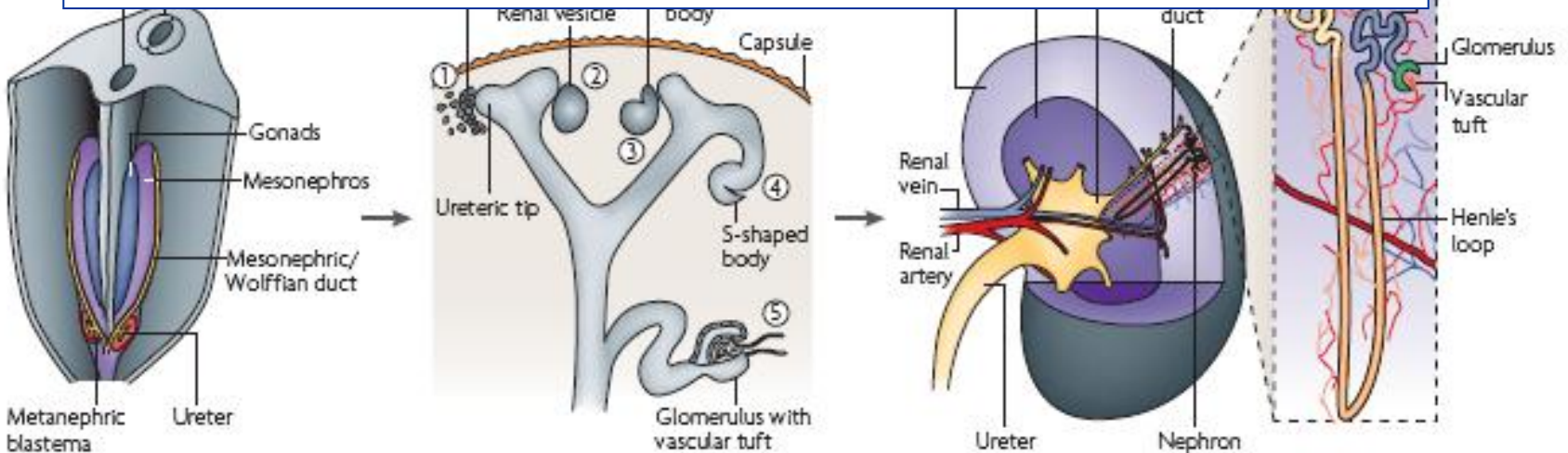
NEFROUROGENESI

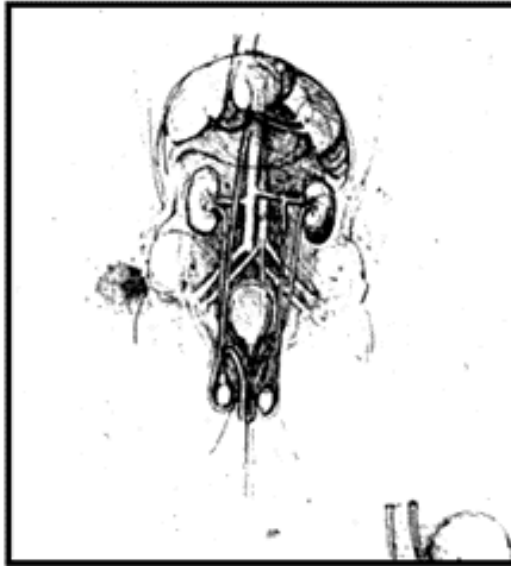
Normal ureter maturation



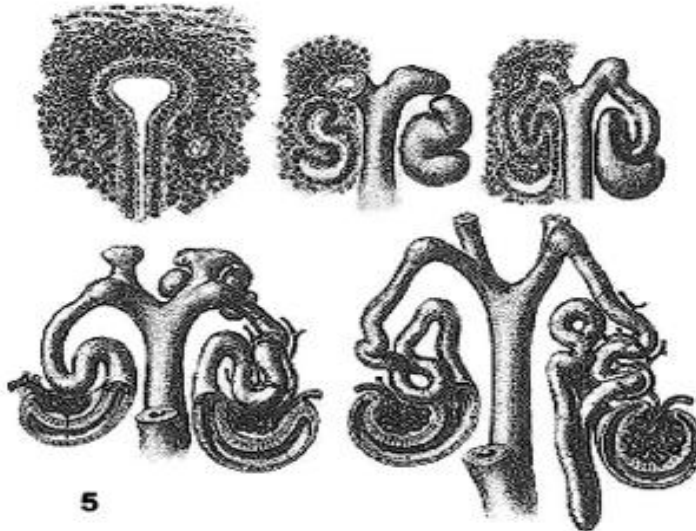
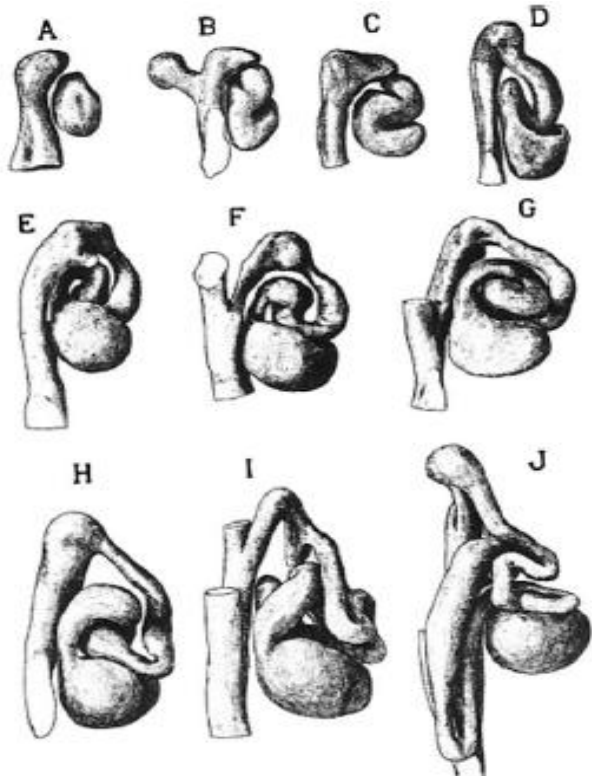
Congenital Anomalies of Kidney and Urinary Tract

a E11
Dors





*Leonardo da Vinci
1452-1519*



*Huber GC Am J Anat 1905; 4:1-98
Brodel M in Diseases of Kidney, Ureter and
Bladder Vol.2, 1914*

Congenital Anomalies of Kidney and Urinary Tract



20-30% anomalie malformative prenatali

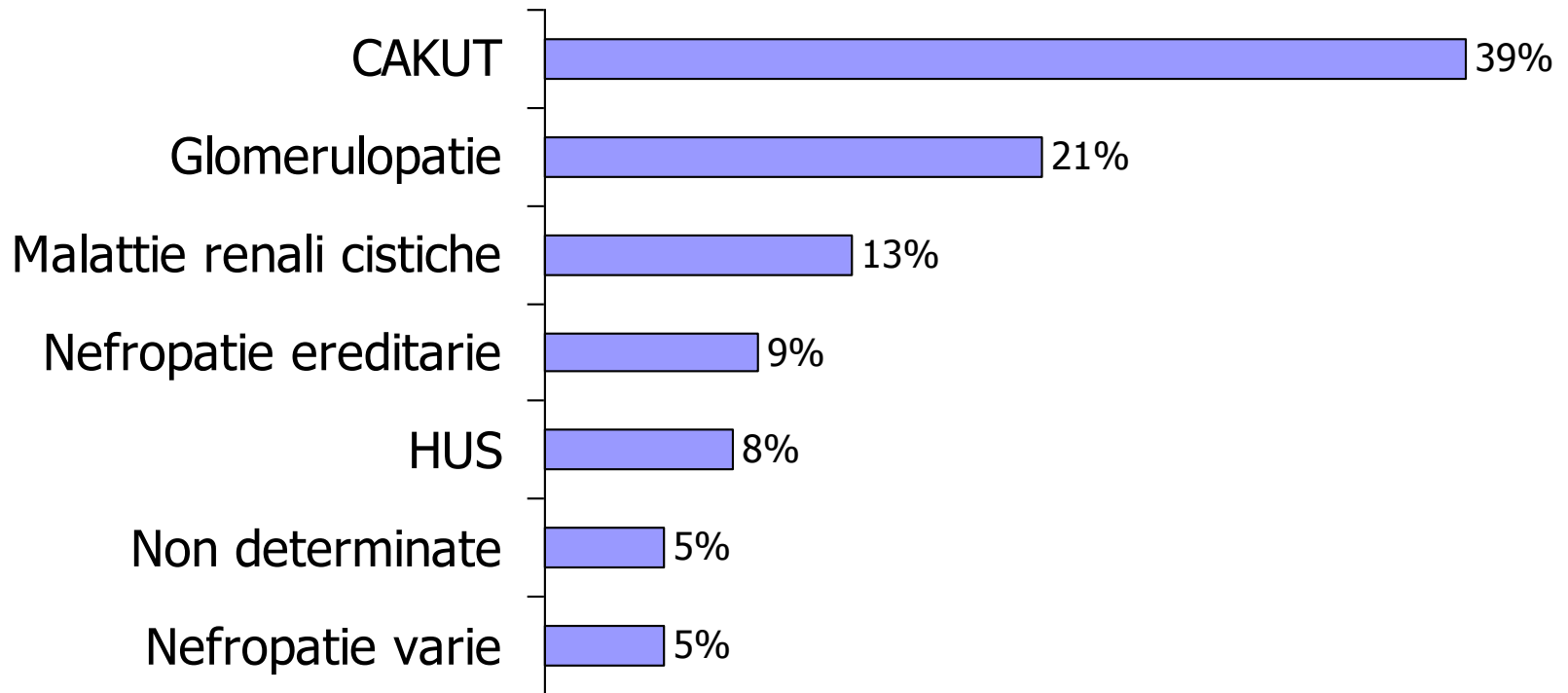
Prevalenza ????? 2-6 per 1000 nati vivi

Wiesel A et al. Eur J Med Gen 2005

Loan M et al Birth Defects Res A Clin Mol Teratol 2011

Malattie Renali Primitive

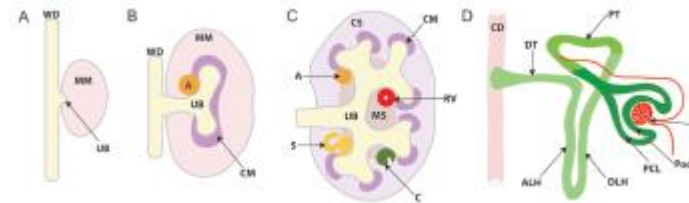
Registro Italiano Dialisi Pediatrica – *Report 2008*



Ramificazione dotti collettori
Allungamento e canalizzazione uretere
Trigono vescicale

bud ureterale

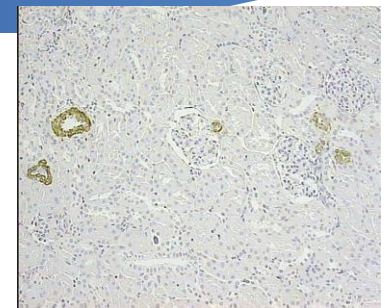
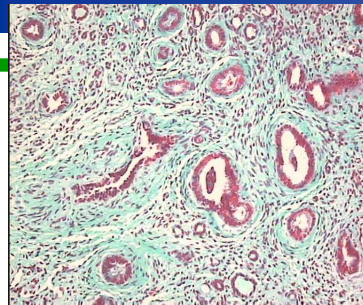
metanefro



5°

16°

34°



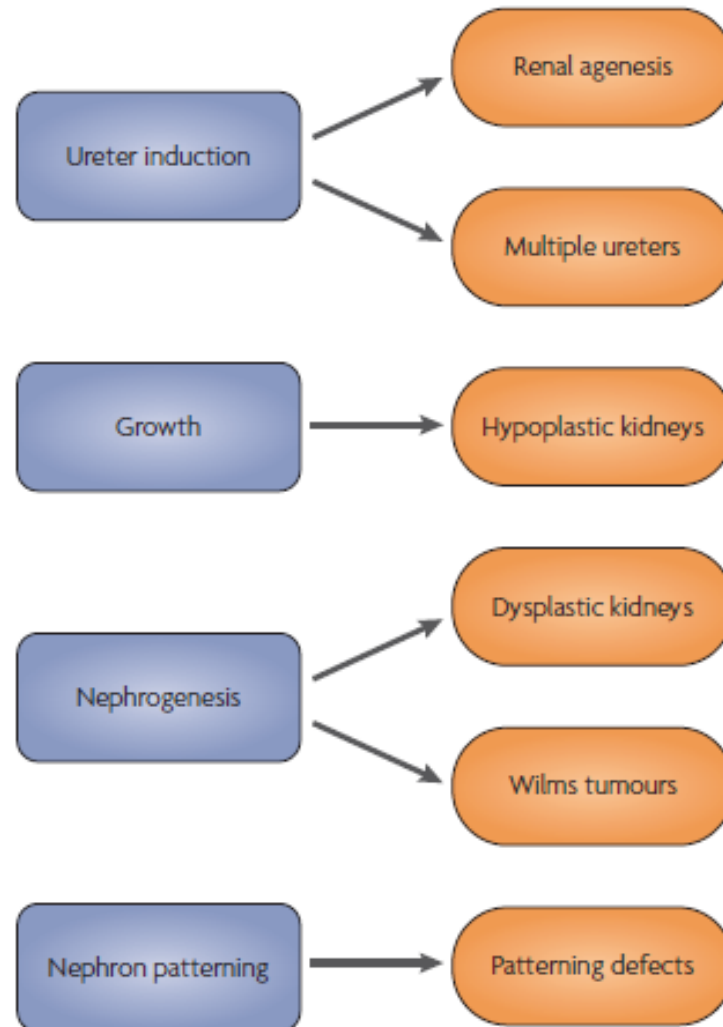
Proliferazione, condensazione, vescicolazione, segmentazione (tubuli e glomeruli) nefrone maturo

NEFROUROGENESI e CAKUT

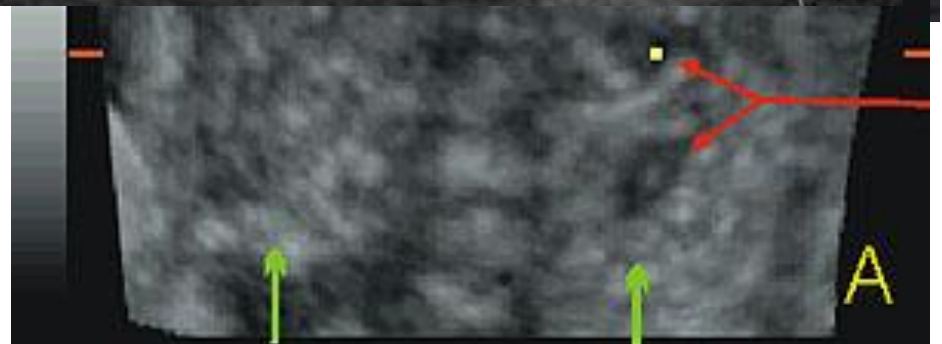


-  **Induzione**
-  **Crescita**
-  **Differenziazione**

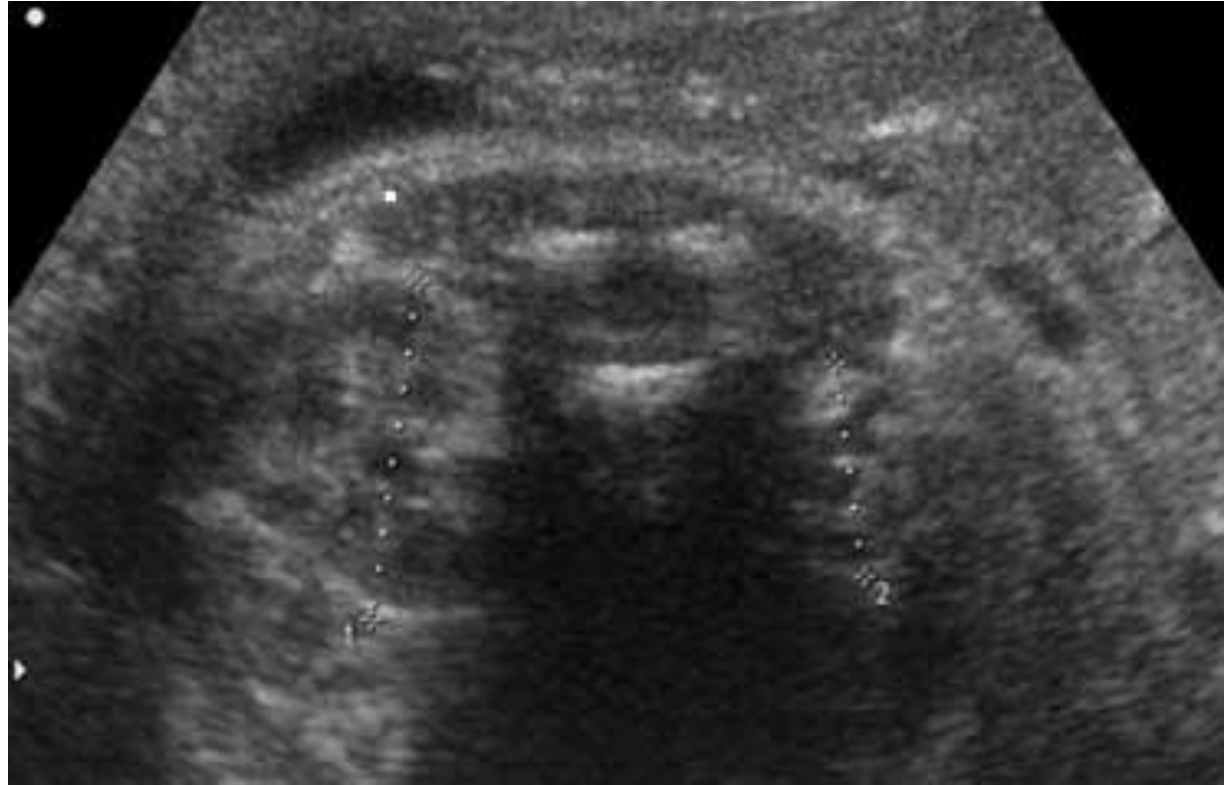
NEFROUROGENESI e CAKUT



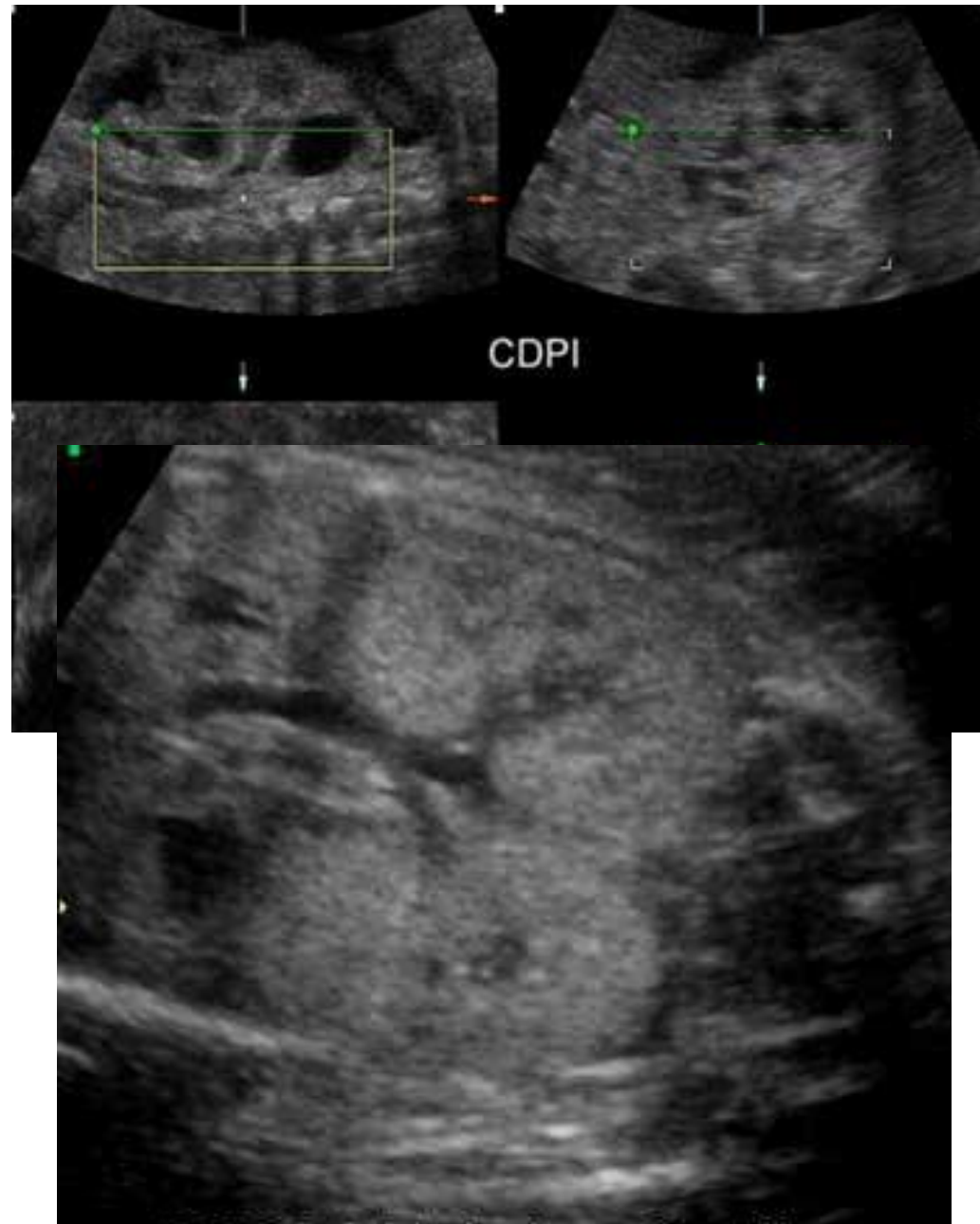
**ERRORI FASE
INDUZIONE**
(bud ureterale/metanefro)



ERRORI FASE
CRESCITA
(branching)



**ERRORI FASE
DIFFERENZIAZIONE
E PATTERNING**



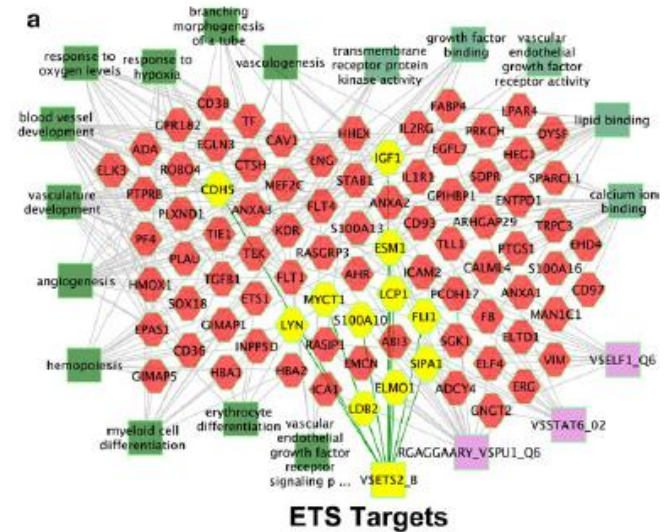
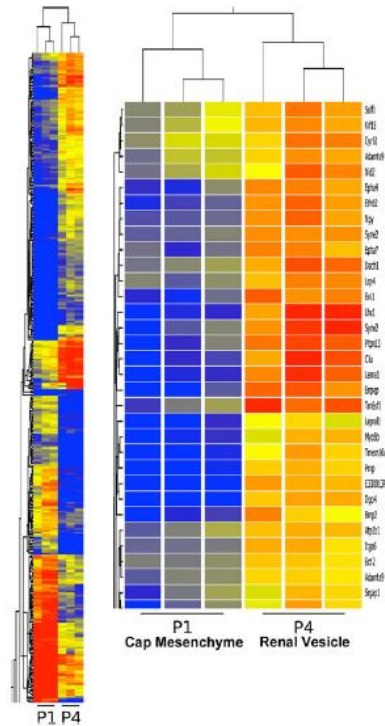
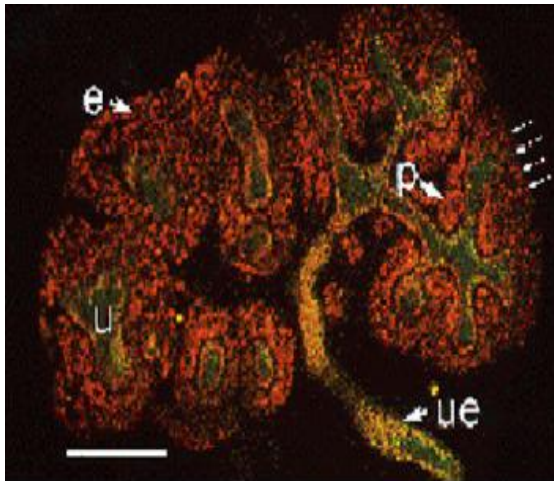
Transgenic mouse models



Genomwide **linkage analysis** in spontaneously affected mouse strains

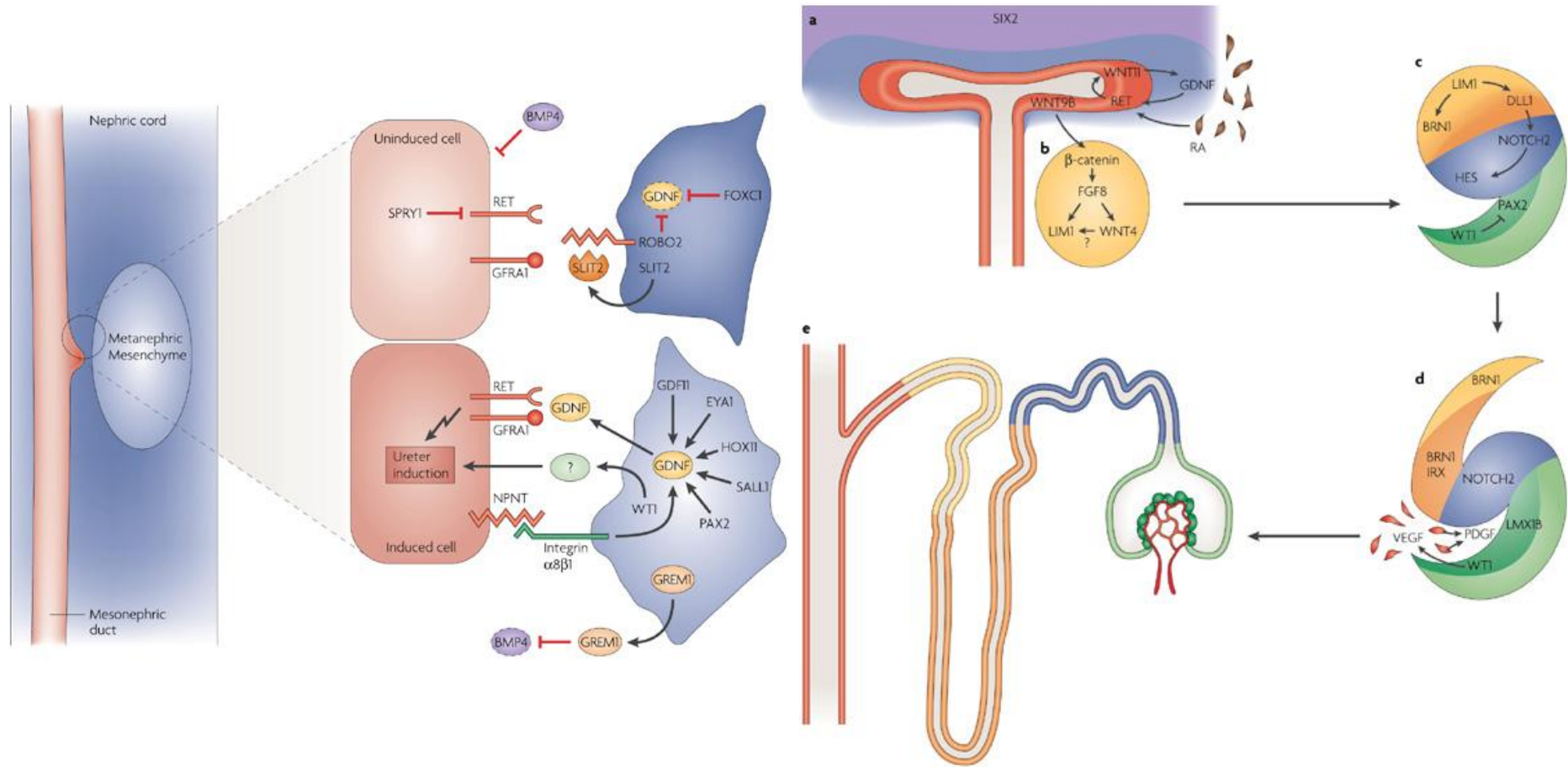
Gene expression profile in **wild type** and **spontaneously affected** mouse strains

Gene expression and functional genomics



Rumballe B et al *Pediatr Nephrol* 2010; 25:1005-16
 Potter SS et al *Pediatr Nephrol* 2011; 26:1469-78
 Weber S et al *Nephrol Dial Transpl* 2011; 26:136-43

[http:// GUDMAP.org](http://GUDMAP.org)
<http://golgi.ana.an.ed.ac.uk/kidhome.html>



**Sindromi complesse con pattern
ereditarietà mendeliana**



**Diversa incidenza
≠
Diversa etnia**

**Concordanza 80-100% gemelli omozigoti
35-50% gemelli eterozigoti**

Human syndromes with CAKUT

Syndrome	Kidney and urinary tract phenotype	Other associated abnormalities	Inheritance pattern	Disrupted gene product
Bardet-Biedl	renal cysts/dysplasia, duplicity, HN, VUR, nephritis/sclerosis	Obesity, polysyndactyly, MR, retinopathy, hypogonadism	AR	<i>BBS 1-10</i>
Branchio-oto-renal	renal agenesis, hypoplasia/dysplasia, duplicity, obstruction,	Branchial remnant, preauricular pit/tag, microtia, deafness	AD	<i>EYA1 or SIX1</i>
Epstein	PAX 2 ➔ 46,XX,del(10)(q23.2q24.3)			<i>MYH9</i>
<i>Benetti E & Murer L. Nephrol Dial Transpl 2007</i>				
Hypoparathyroidism-deafness-renal dysplasia	VUR, renal hypoplasia, renal aplasia	Hypoparathyroidism, deafness	AD	<i>GATA3</i>
Kallmann	ROBO2 ➔ 46,X,t(Y;3)(p11;p12)			<i>ANOSMIN-1</i>
Nager acrofacial dysostosis	renal agenesis, HN, VUR, duplicity	Facial b eyelid, radial ray defect	<i>Lu W et al. Am J Hum Genet 2007</i>	
Renal-coloboma	renal hypoplasia/dysplasia, renal agenesis, VUR	Optic nerve coloboma, nerve deafness	AD	<i>PAX2</i>
Townes-Brocks	VUR, renal agenesis, renal dysplasia, duplicity, ureteral/urethra diverticulae	Triphalangeal thumb, imperforate anus, skin tag, deafness	AD	<i>SALL1</i>
Wolfram	VUR, HN	Diabetes mellitus/insipidus, optic atrophy, nerve deafness	M	<i>WFS1-2</i>

CAKUT isolate (non sindromiche)



NIH Public Access

Author Manuscript

Published in: *Pediatr Nephrol*. Author manuscript; available in PMC 2012 June 1

Published in final edited form as:
Pediatr Nephrol. 2011 June ; 26(6): 897–903. doi:10.1007/s00467-011-1826-9

HNF1B and *PAX2* mutations are a Common Cause of Renal Hypodysplasia in the CKiD Cohort

Rosemary Thomas, MD¹, Simone Sanna-Cherchi, MD², Bradley A. Warady, MD³, Susan L. Furth, MD⁴, Frederick J. Kaskel, MD, PhD, FASN¹, and Ali G. Gharavi, MD²

In this study, we identified pathogenic *HNF1B* or *PAX2* mutations in 14% of Caucasian individuals in a North American cohort of children with RHD. The mutation prevalence is consistent with previous studies of European and Japanese children with RHD [8–10, 27,

original article

<http://www.kidney-international.org>

© 2012 International Society of Nephrology

Identification of two novel CAKUT-causing genes by massively parallel exon resequencing of candidate genes in patients with unilateral renal agenesis

Pawaree Saisawat¹, Velibor Tasic², Virginia Vega-Warner¹, Elijah O. Kehinde³, Barbara Günther⁴, Rannar Airik¹, Jeffrey W. Innis¹, Bethan E. Hoskins¹, Julia Hoefele¹, Edgar A. Otto¹ and Friedhelm Hildebrandt^{1,5,6}

We here identified seven different mutations of four different genes in 7 out of 40 patients with CAKUT, using massively parallel exon resequencing. Two heterozygous mutations were novel mutations in known human CAKUT-causing genes: *BMP4* and *RET*. Five heterozygous mutations were in two candidate genes that have never been reported in non-syndromic CAKUT: *FRAS1* and *FREM2*. McGregor *et al.*¹¹

Hum Genet (2012) 131:1725–1738
DOI 10.1007/s00439-012-1181-3

ORIGINAL INVESTIGATION

Traditional and targeted exome sequencing reveals common, rare and novel functional deleterious variants in *RET*-signaling complex in a cohort of living US patients with urinary tract malformations

Rajshekhhar Chatterjee · Enrique Ramos · Mary Hoffman · Jessica VanWinkle · Daniel R. Martin · Thomas K. Davis · Masato Hoshi · Stanley P. Hmiel · Anne Beck · Keith Hruska · Doug Copen · Helen Liapis · Robi Mitra · Todd Druley · Paul Austin · Sanjay Jain

We sequenced *GDNF*, *SPRY1* and *RET* in 122 unrelated living CAKUT patients to discover deleterious mutations that cause CAKUT. Novel or rare deleterious mutations in *GDNF* or *RET* were found in six unrelated patients. A ndividuals. Our study supports 5 % CAKUT are due to mutations in either *GDNF*/*RET*/*GFR α 1*. Since there are

TABLE 2: Single-gene mutations associated with nonsyndromic human CAKUT.

Gene	Disease OMIM	Chromosome	Renal phenotype	Extra-renal phenotype	References
<i>AGT</i>	RTD	1p42	Reduced number of proximal tubules, short proximal tubules without brush border, atrophic loops of Henle and collecting ducts, closely packed glomeruli, marked thickening and disorganization of interlobular and perglomerular arteries	Large low-set ears, limb-positioning defects, arthrogryposis, lung hypoplasia, skull ossification defects	[29, 45]
<i>AGTR1</i>	RTD	3p24	Similar to <i>AGT</i> phenotype, PUV	Similar to <i>AGT</i> phenotype	[29, 45, 46]
<i>AGTR2</i>	—	Xq22-q23	UPJ obstruction, megaureter, MCCK, hydronephrosis, PUV	—	[38–41, 47]
<i>ACE</i>	RTD	17q25.3	Similar to <i>AGT</i> phenotype renal hypodysplasia, PUV	Similar to <i>AGT</i> phenotype	[29, 45, 46]
<i>BMP4</i>	—	14q22-q23	Renal hypodysplasia	Cleft lip, microphthalmia	[48]
<i>BMP7</i>	SHFM				
<i>Dbp5/Dlx6</i>	#603273	3q27	Urethral malformations	Split-hand/split-foot malformation	[49]
<i>p63</i>					

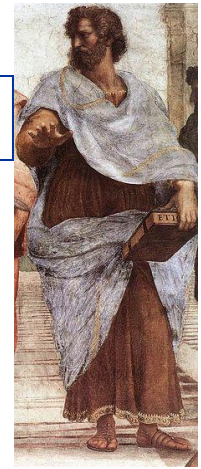
1.9-20% di pazienti con CAKUT isolate presentano mutazione in uno dei geni identificati come potenzialmente coinvolti nello sviluppo del rene e delle vie urinarie in modelli animali

<i>HNF1β/TCF2</i>	RCAD #137920 GCKD #609886	17q12	Renal hypodysplasia, cysts	Diabetes	[20, 55, 56]
<i>Pax2</i>	Renal-coloboma syndrome	10q24	Renal hypoplasia, VUR	Optic nerve coloboma branchial cysts	[34, 57, 58]
<i>Ren</i>	RTD Renal agenesis	17q23.3	Similar to <i>AGT</i> phenotype	Similar to <i>AGT</i> phenotype	[29, 45]
<i>Ret</i>	#191830	10q11.2	Absence of the kidney and ureter	Hirschsprung disease	[37]
<i>Robo2</i>	—	3p12.3	VUR	Limb and facial defects	[44, 59–61]
<i>Six2</i>	—	2p16-p15	Renal hypodysplasia	—	[48]
<i>Slt2</i>	—	4p15.2	Hydroureter, supernumerary UBs	—	[59]
<i>Umod</i>	MCCK2	16p12.3	Cysts in distal tubules and collecting ducts, renal dysplasia	—	[62, 63]
<i>Upk3A</i>	—	22q13.31	Renal agenesis/hypodysplasia	Facial and limb defects	[64, 65]
<i>Usf2</i>	—	46XX t(6;19) (p21;q13.1)	Multicystic kidney dysplasia	—	[66]
<i>XPNPEP3</i>	NPHP-like nephropathy	22q13.2	Renal cysts and dysplasia	—	[67]

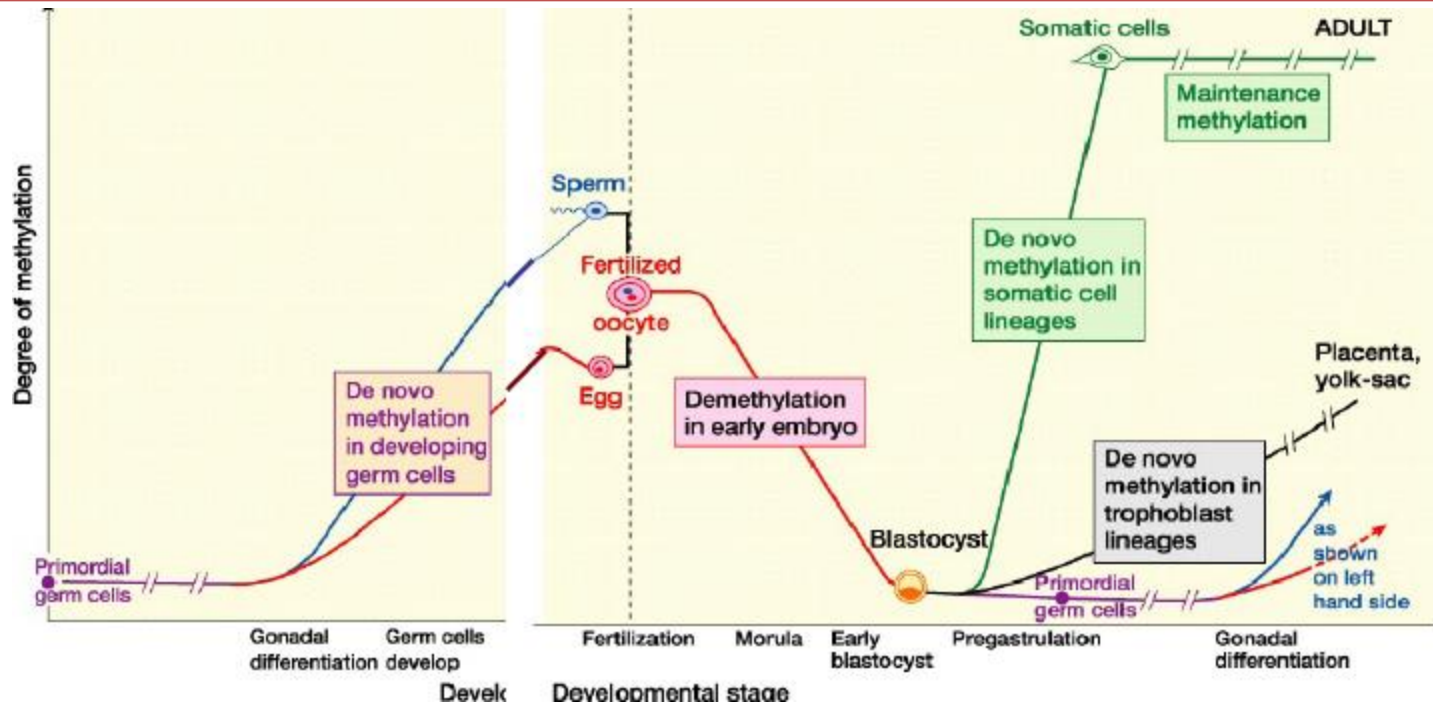
AGTR: angiotensin II receptor type 1, AGTR2: angiotensin II receptor type 2, ARPKD: autosomal-recessive polycystic kidney disease, ADPKD: autosomal-dominant polycystic kidney disease, UPJ: ureteropelvic junction, VUR: vesico ureteral reflux, PUV: posterior urethral valves, UPJ: ureteropelvic junction, MCCK: multicystic dysplastic kidney, PUV: posterior urethral valve, RTD: renal tubular dysgenesis, RCAD: renal cysts and diabetes, MODY: maturity-onset diabetes, GCKD: glomerulocystic kidney disease, and NPHP: nephronophthisis, X-prolyl aminopeptidase (aminopeptidase P) 3, putative.

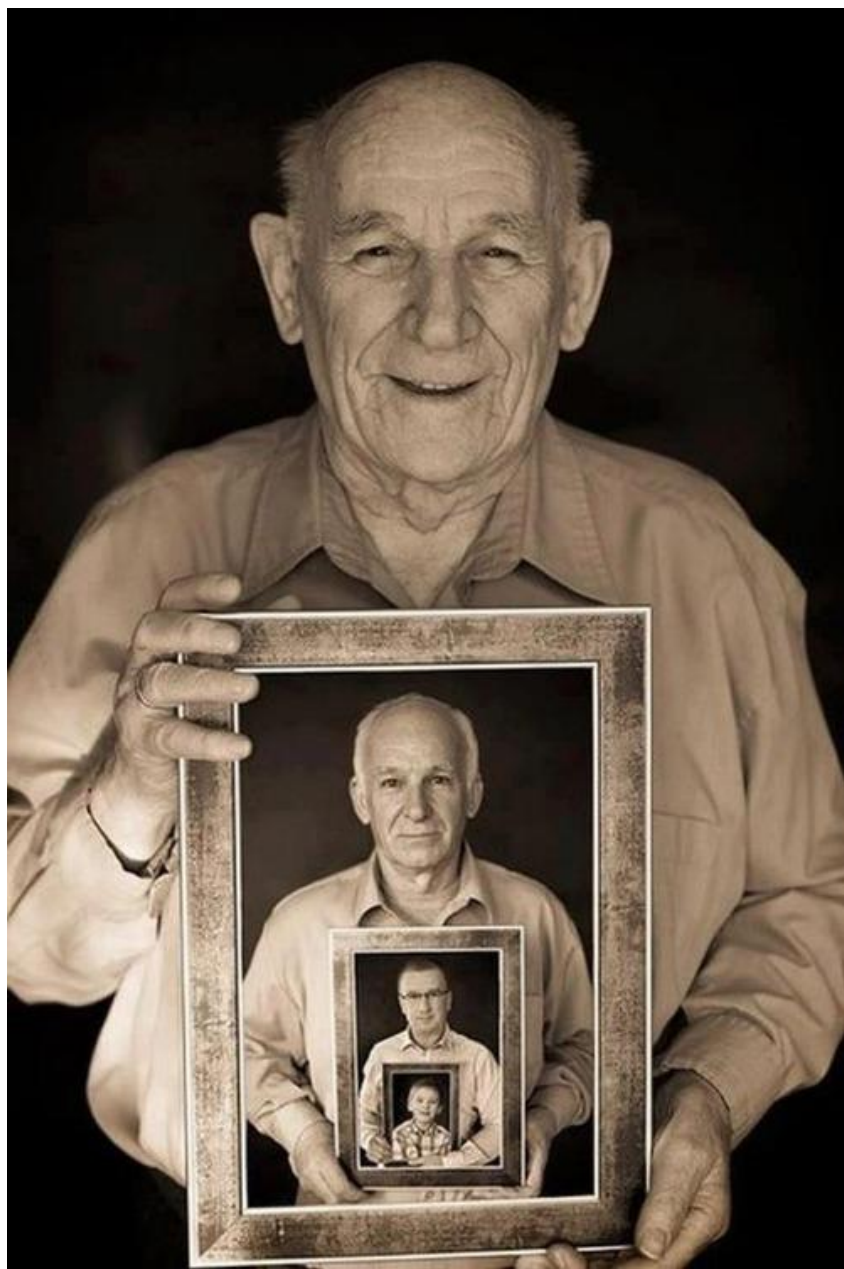
L'epigenetica επί "sopra" e γεννητικός = eredità familiare

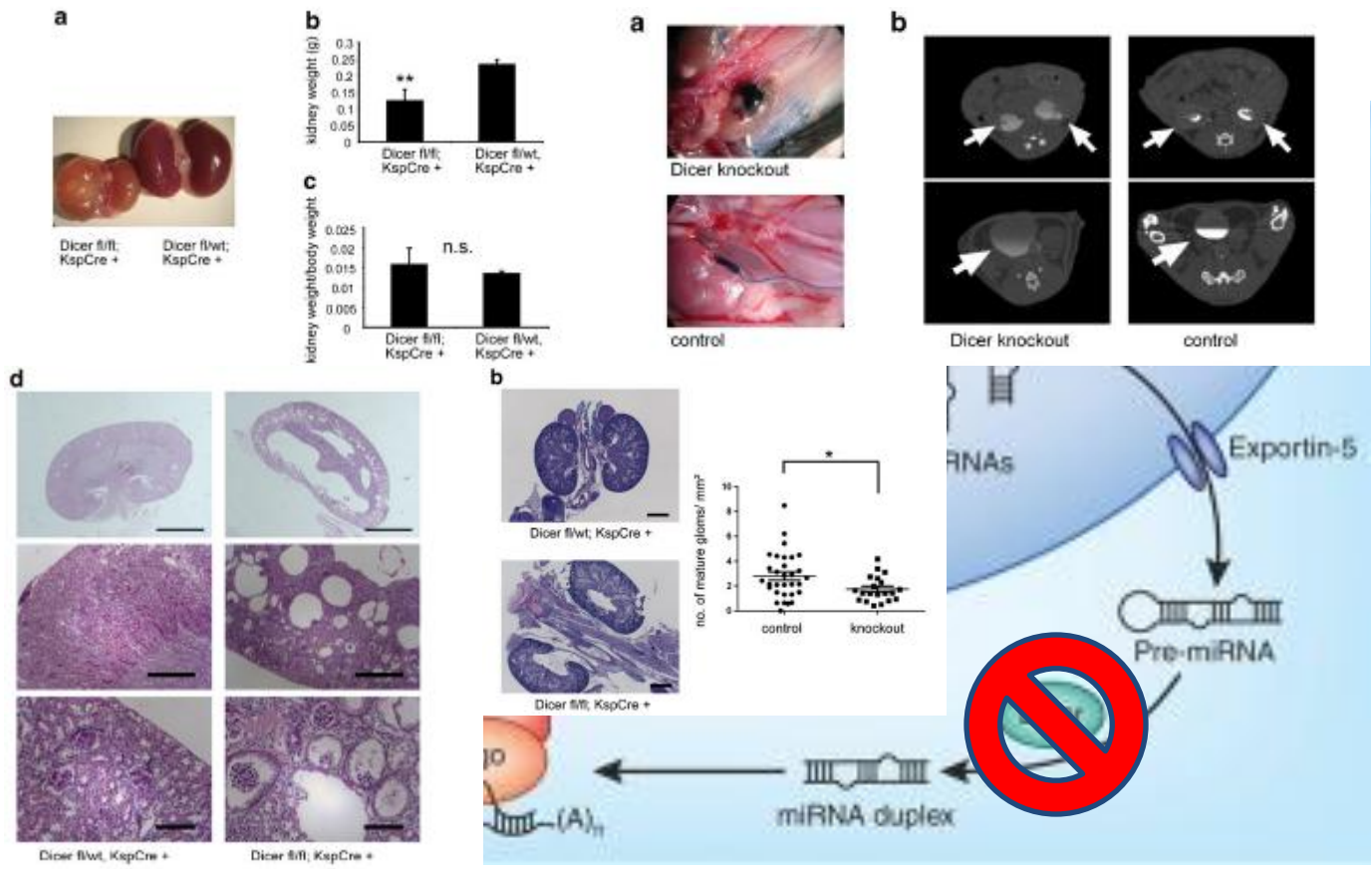
"la branca della biologia che studia le interazioni causali fra i geni e il loro prodotto cellulare e pone in essere il fenotipo" C. Waddington (1905-1975)



I meccanismi di regolazione epigenetica comprendono la metilazione del DNA a livello delle isole CpG nella regione del promotore del gene e le modifiche istoniche post-traduzionali, quali acetilazioni e metilazioni.







MicroRNAs in renal development

Jacqueline Ho • Jordan A. Kreidberg

Conditional loss of kidney microRNAs results in congenital anomalies of the kidney and urinary tract (CAKUT)

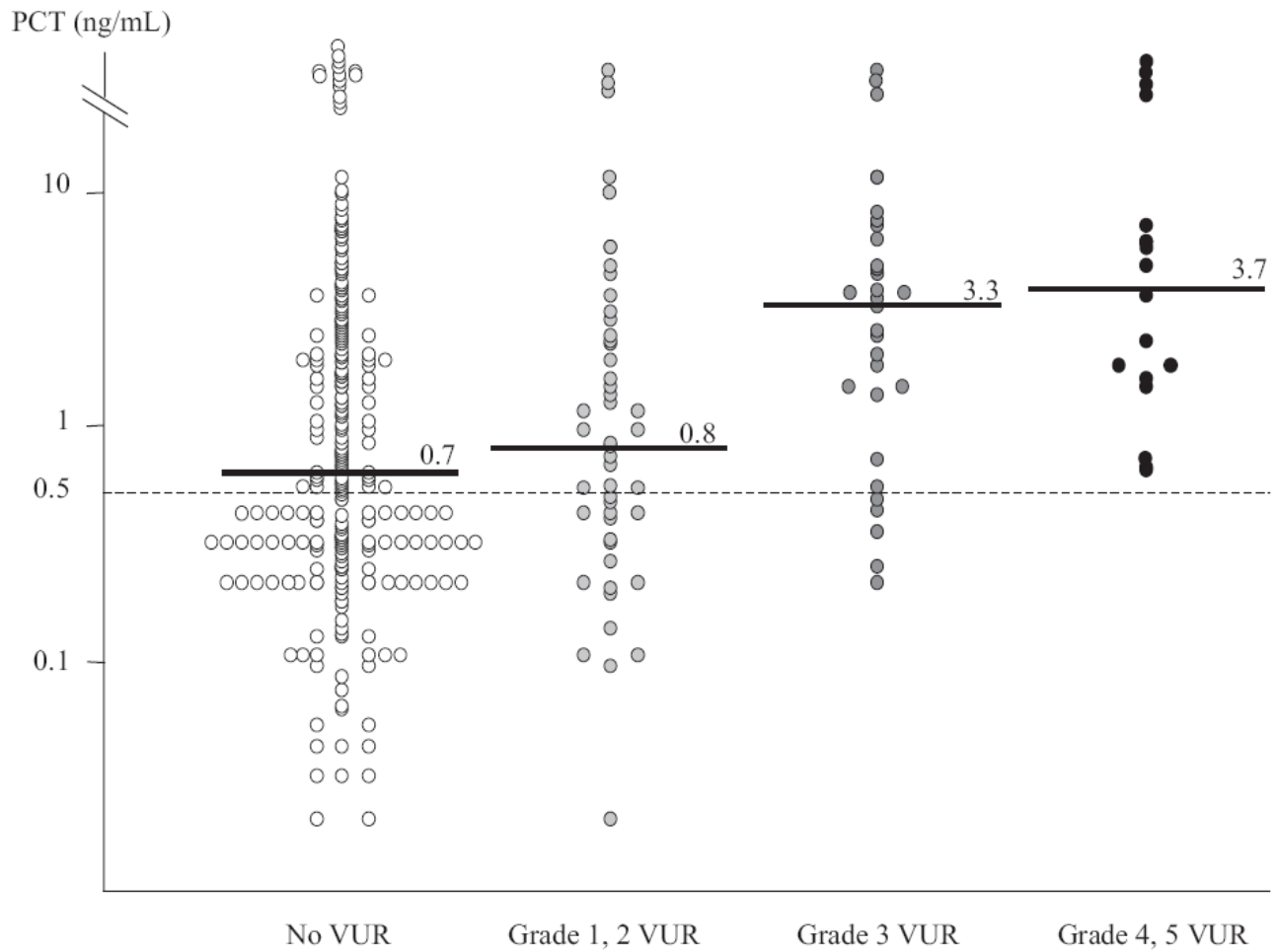
Malte P. Bartram • Martin Höhne • Claudia Dafinger • Linus A. Völker •

TABLE 1: Prevalence of CAKUT.

Type of malformation	Prevalence	References
Unilateral renal agenesis		
<i>Fetuses</i>	0.0089%	[8]
<i>Newborns</i>		[11]
Bilateral renal agenesis		
<i>Fetuses</i>	0.013%	[8]
<i>Newborns</i>	1 in 30,000	[11]
Congenital hydronephrosis	1 in 1,000 live births	[12]
Renal hypodysplasia		
<i>Fetuses</i>	0.027%	[8]
<i>Newborns</i>	1 in 400 live births	[8]
Horseshoe kidney	1 in 1,000 newborns	[13]
PUV		
<i>Fetuses</i>	0.003%	[8]
VUR		
<i>Infants with hydronephrosis on prenatal ultrasonography</i>	3–19%	[14]
<i>Well children</i>	1–2%	
<i>Children with UTI</i>	25–40%	
Unilateral duplex ureter	1–8%	[15]

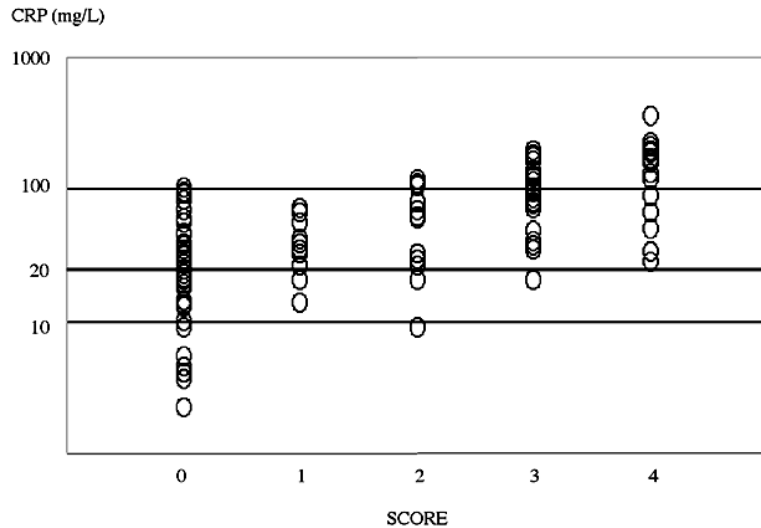


PCT and VUR



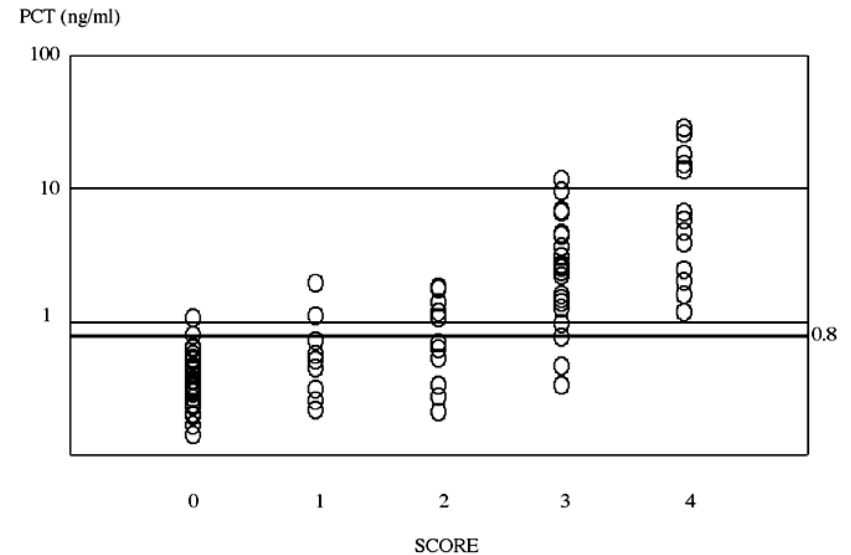
Procalcitonin: A Marker of Severity of Acute Pyelonephritis Among Children

Entità interessamento renale (in acuto)



Sensibilità: 94%

Specificità: 32%

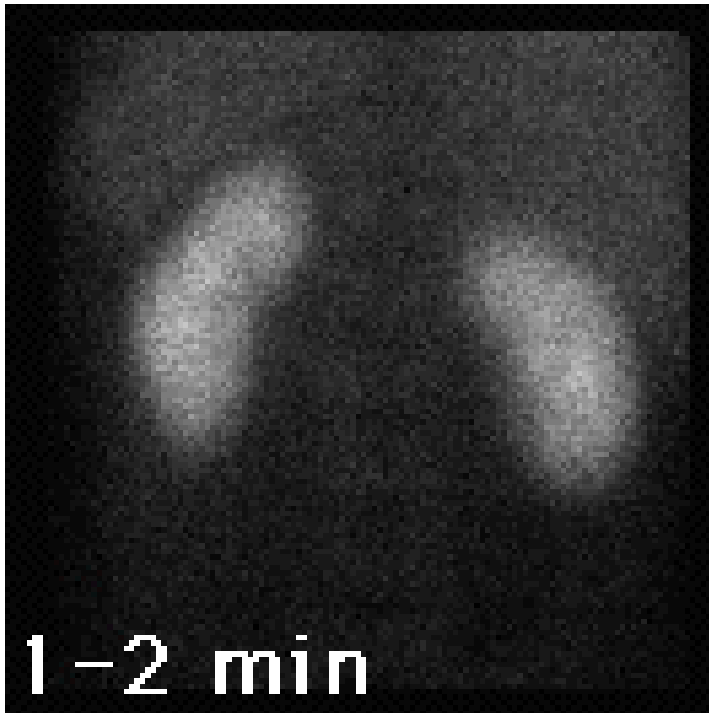


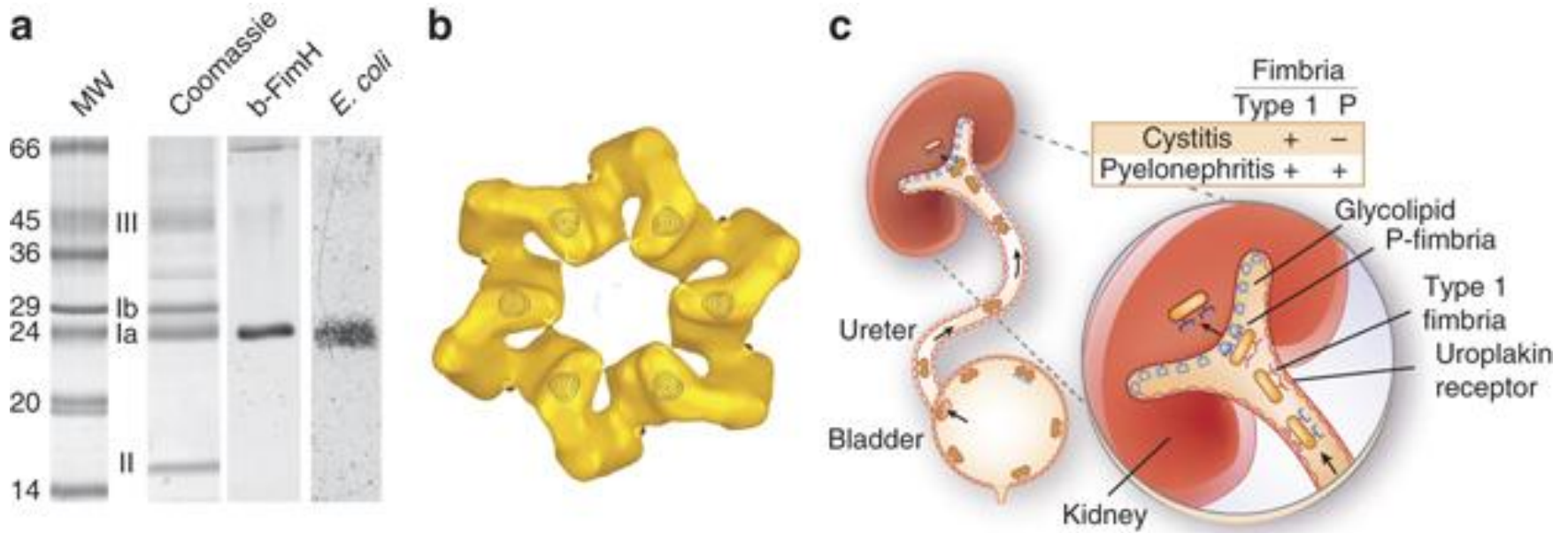
Sensibilità: 83.3%

Specificità: 93.6%

Pielonefrite/**scar**: tecniche di imaging

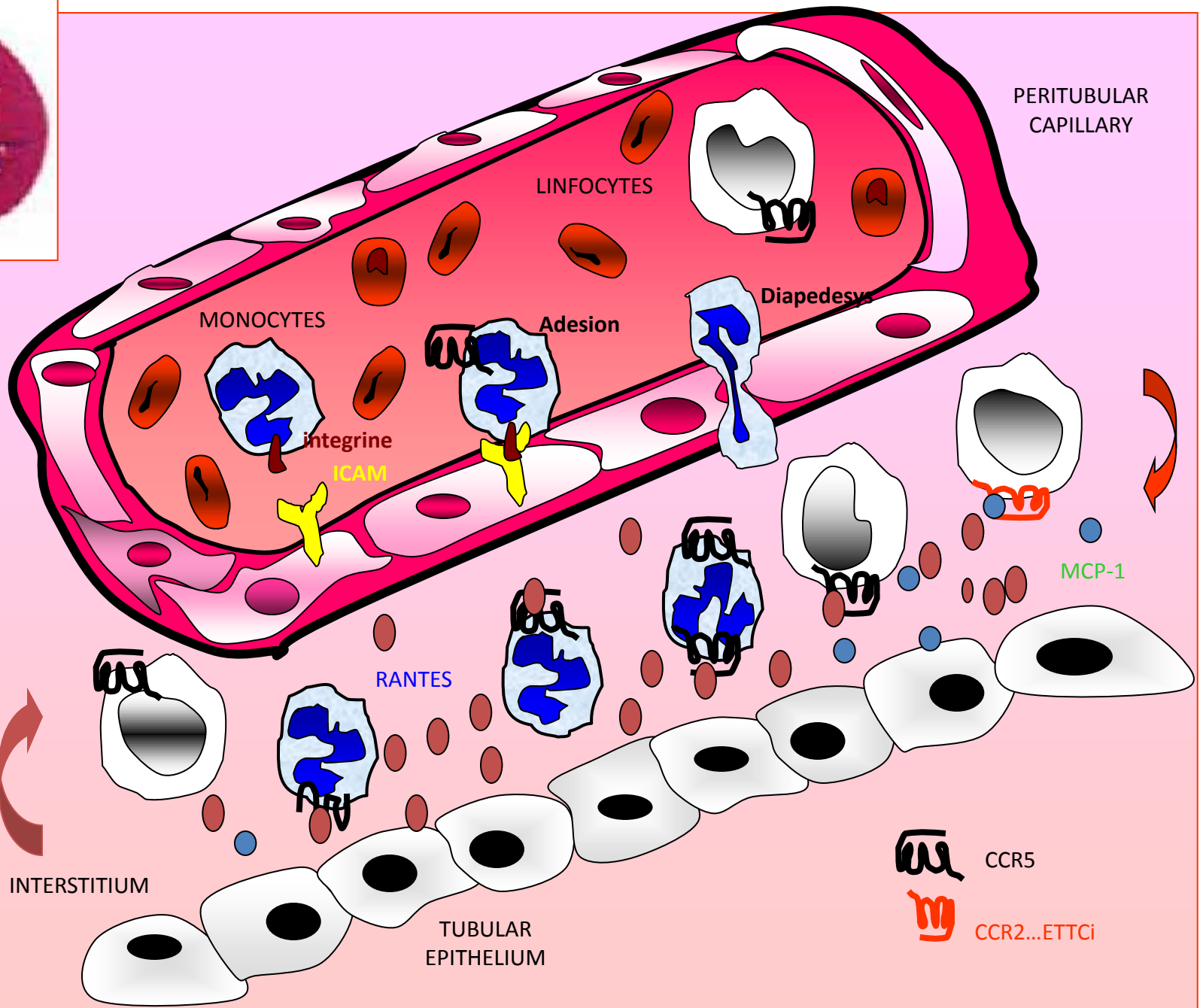
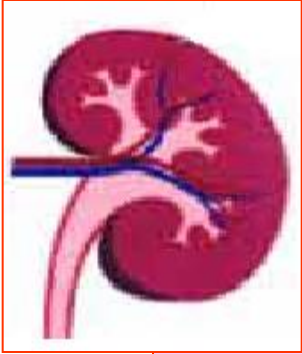
- Scintigrafia renale statica (DMSA)
 - Ruolo “a distanza” (scars)





Uroplakins in urothelial biology, function, and disease

Xue-Ru Wu et al Kidney Int 2009

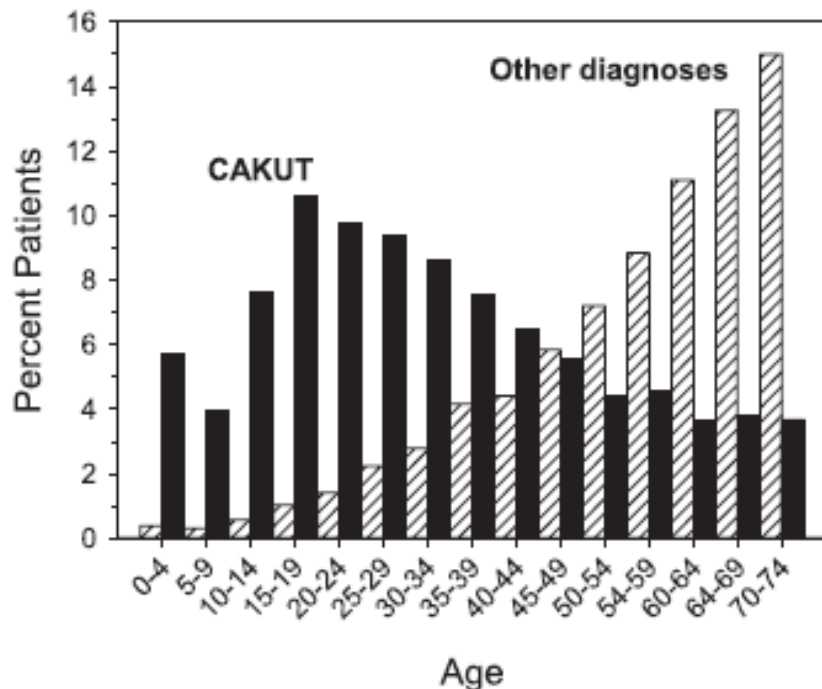


Timing and Outcome of Renal Replacement Therapy in Patients with Congenital Malformations of the Kidney and Urinary Tract

Elke Wühl, Karlijn J. van Stralen, Enrico Verrina, Anna Bjerre, Christoph Wanner, James Goya Heaf, Oscar Zurriaga, Andries Hoitsma, Patrick Niaudet, Runolfur Palsson, Pietro Ravani, Kitty J. Jager, and Franz Schaefer

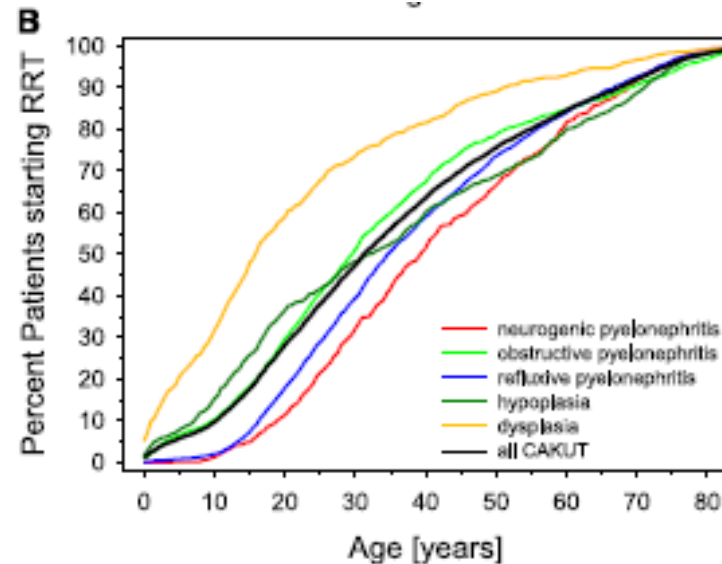
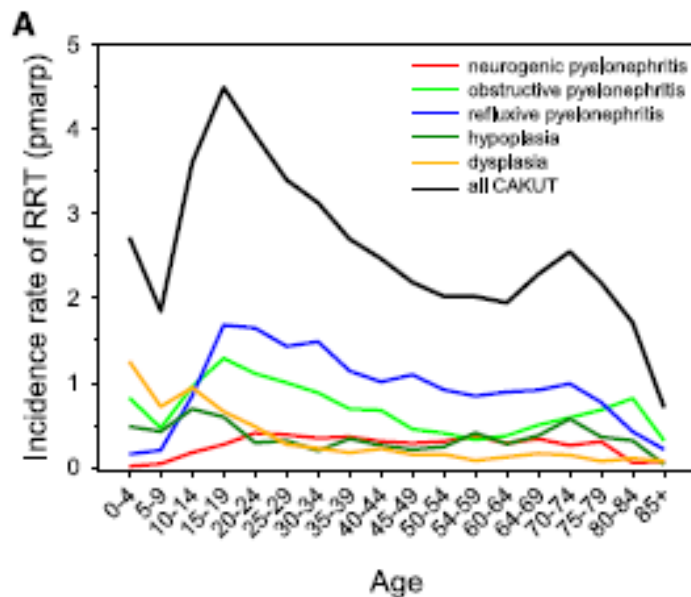
Diagnosis of CAKUT comprised ERA-EDTA primary renal disease codes:

1. Congenital hypoplasia *code 60*
2. Oligomeganephronic hypoplasia *code 61*
3. Congenital dysplasia± urinary tract malfor. *code 63*
4. Prune belly Syndrome *code 66*
5. Obstructive pyelonephritis *code 22*
6. Reflux Pyelonephritis *code 24*



European Dialysis and Transplant Association Registry between January 1, 1990, and December 31, 2009

Characteristic	All Patients	Patients with CAKUT
Prevalence 2009 (pmp)	947.5	44.9
Incidence (n)	212,930	4,765
Male patients (%)	61.5	61.5
Renal diagnoses (%)		
Hypertensive or diabetic nephropathy	46.9	
Unknown/unspecified	19.4	
Glomerulonephritis	14.4	
Cystic kidney diseases	7.1	
Vasculitis	2.0	
Other	8.0	
CAKUT		
Total	2.2	100
Neurogenic PN		5.6
Obstructive PN		22.9
Reflux PN		41.9
Hypoplasia		17.3
Dysplasia		12.3
RRT modality (%)		
Hemodialysis	80.2	61.5
Peritoneal dialysis	17.2	26.1
Pre-emptive transplantation	2.6	12.4
Mean age at start RRT (yr)		
All	61.4±16.6	35.1±21.0
Male patients	61.2±16.5	33.1±21.3
Female patients	61.7±16.8	38.3±20.1 ^a
1990-1999	58.4±16.7	32.9±19.7
2000-2009	62.9±16.3 ^a	36.6±21.5 ^a
Neurogenic PN		41.8±18.4 ^{b,c}
Obstructive PN		34.1±21.4 ^d
Reflux PN		38.5±18.7 ^{c,e}
Hypoplasia		35.7±23.9 ^{c,e}
Dysplasia		22.1±19.7^f



Incidenza di RRT per displasia renale ha il picco nella prima decade di vita , per nefropatia da reflusso nelle prime due decadi e per pileonefrite ostruttiva nella terza e quarta decade con un secondo picco nell'anziano.

L'età media di inizio di RRT è:

- 16 anni nel gruppo "dysplasia"
- 32 anni nel gruppo "hypoplasia"
- 29.5 anni nel gruppo "obstructive pyelonephritis"
- 35 anni nel gruppo "reflux pyelonephritis"
- 39.5 nel gruppo "neurogenic pyelonephritis"



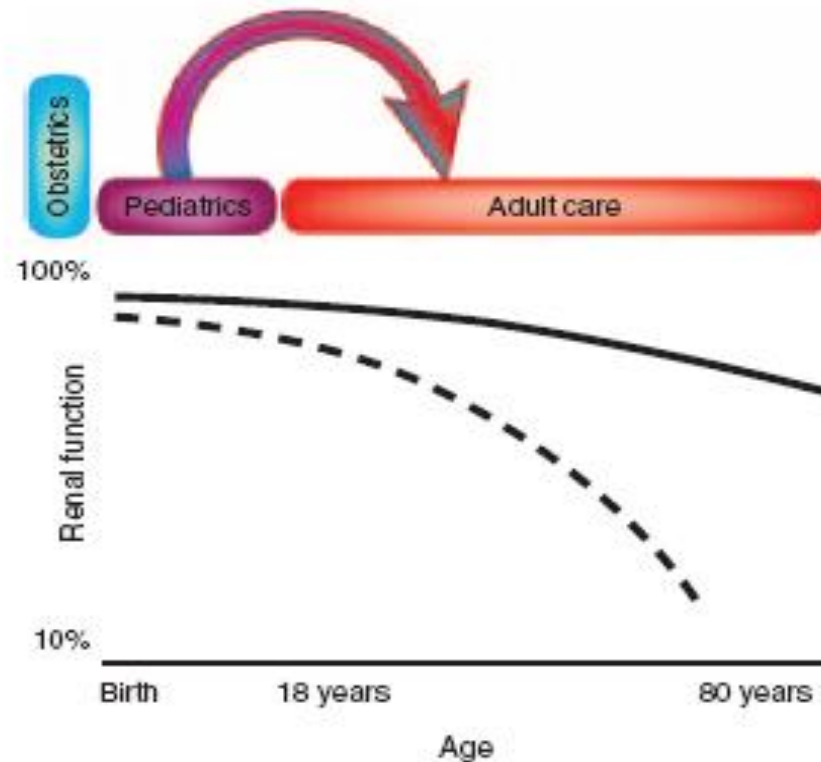
2/3 dei pazienti con CAKUT progrediscono in ESRD in età adulta e il 50% non necessita RRT prima della quarta decade di vita

cJASN 2013; 8: 67-75

Follow-up in età adulta di paziente pediatrico paziente con diagnosi di CAKUT con o senza proteinuria, ipertensione o IRC

- Es urine ed urocoltura se sospetto IVU (attenzione gravidanza!)
- Controllo PAO
- Esami urinari (proteinuria tubulare e FeNa, proteinuria 24 H)
- Esami ematochimici (cistatina C)
- Esami strumentali: ecodoppler renale, eco vescicale pre /post minzi., urodinamica
quale frequenza controlli?
- Terapia e prevenzione delle infezioni
- Terapia e prevenzione di ipertensione e proteinuria: ACE inibitori

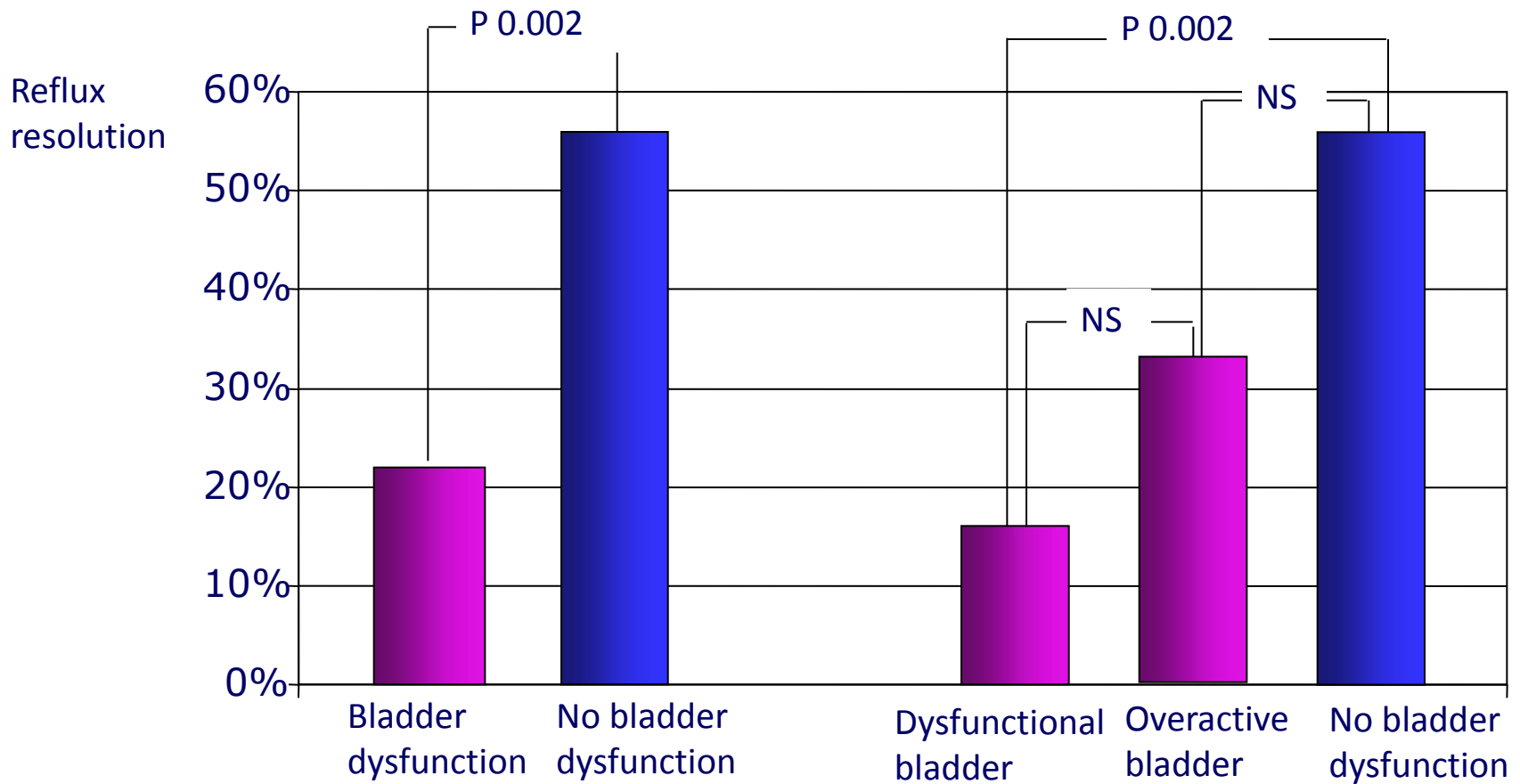
Nefrologo



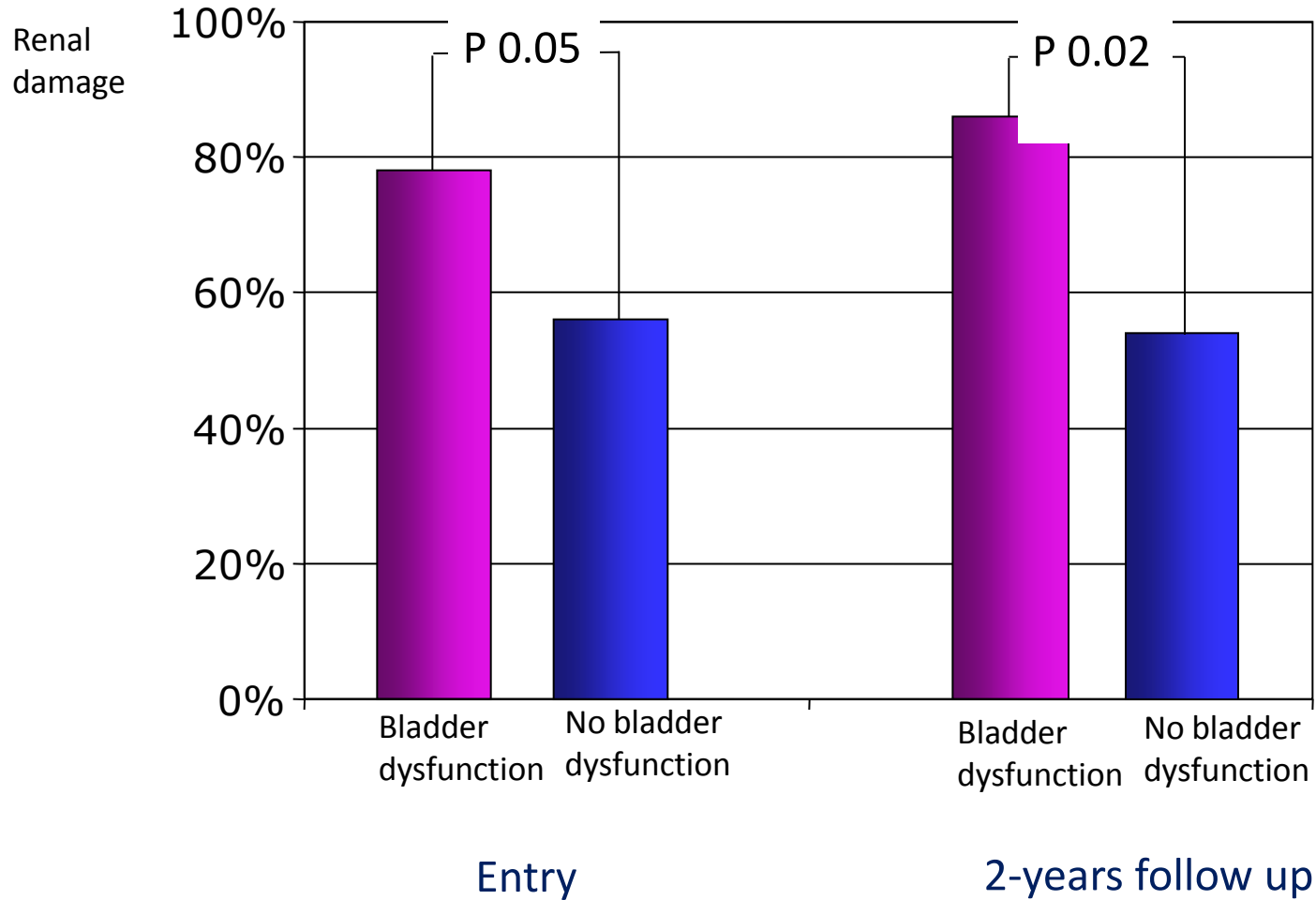
Urologo

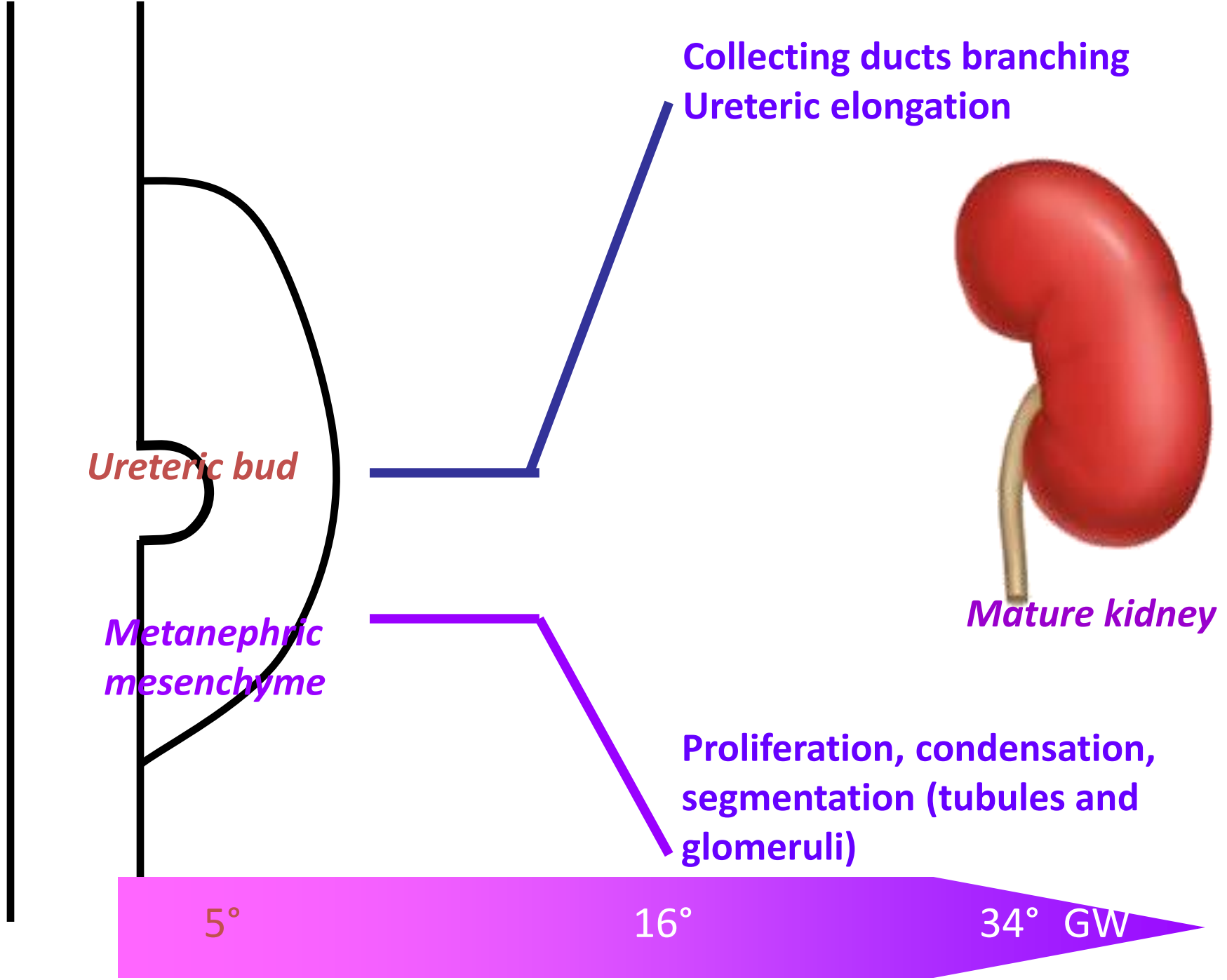
Handover of care from pediatric to adult health providers is a critical transition in the life of the child with CAKUTs (curved arrow): many patients experience accelerated deterioration in renal function in late adolescence (dashed line). With adherence to quality initiatives,¹⁴ renal function may be maintained (solid line).

Reflux resolution vs bladder dysfunction

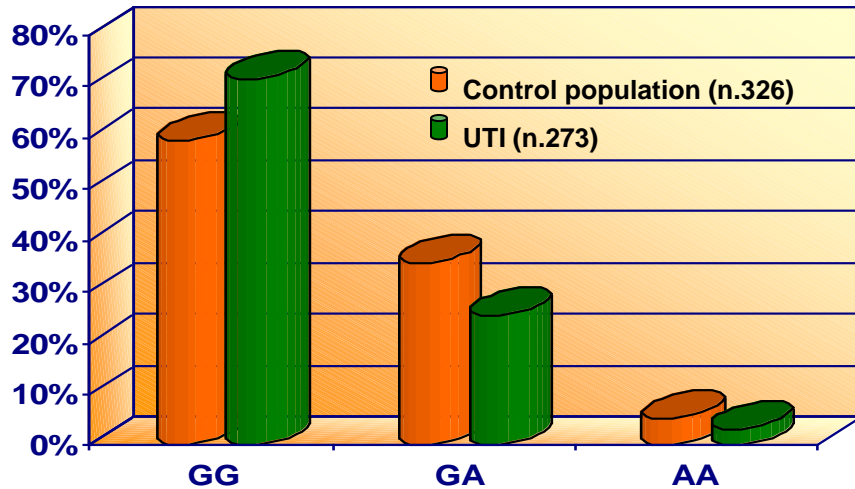


Renal damage vs Bladder function

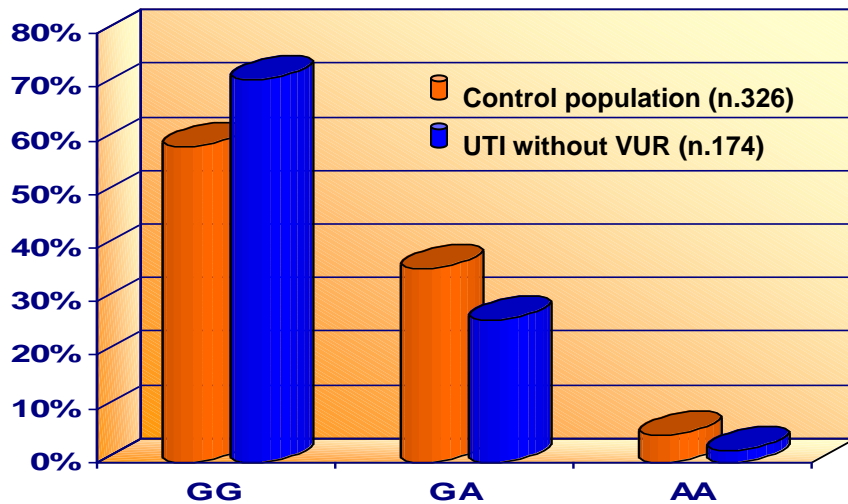




RESULTS



Statistical analysis (Fisher's test) of RANTES-403G>A genotype frequencies showed a significant difference between UTI group and control population ($p=0.007$)



Statistical analysis (Fisher's test) of **RANTES-403G>A genotype frequencies** showed a significant difference between **UTI group without VUR** (documented by voiding cystography) and control population ($p=0.020$)

The frequency of polymorphism $\Delta 32$ of CCR5 receptor in children with UTI does not differ from that of the control population.



Genomwide **linkage analysis** in UPJO spontaneously affected mouse strains

- Locus cromosoma 6 (gene *Id2*) ($Z = 4.4$)
- Locus cromosoma 2 (gene *Agtr1b*) ($Z = 3.9$)
- Locus cromosoma 15 (gene *Aqp2*)



<i>Id2</i> ^{-/-} e +/-	→	UPJO
<i>Agtr1</i> ^{-/-}	→	UPJO
S256L <i>Aqp2</i>	→	UPJO

Id2: fattore di trascrizione che promuove la crescita e inibisce la differenziazione.

Agtr1: induzione di cellule muscolari lisce del tessuto ureterale e della pelvi.

Aqp2: acquaporina regolatrice della permeabilità all'acqua dei dotti collettori

Basi molecolari Nefrourogenesi e CAKUT





STUDI DI KNOCK-OUT GENICO NEL TOPO

Chen F *Pediatr Nephrol* 2009
Cain JE *Pediatric Res* 2010
Murawsky I *J Pediatr Nephrol* 2011

Table 1 | Transgenic mouse models of obstructive ureter malformation

Gene	Expression	Nature of protein	Genetic constitution	Type of ureter malformation	Ref.
<i>Involved in specifying the budding site</i>					
<i>Agtr2</i>	um	Angiotensin II receptor	<i>Agtr2</i> ^{-/-}	Ectopic UB, duplex ureter, hydroureter	4
<i>Bmp4</i>	um	Secreted bone morphogenetic protein	<i>Bmp4</i> ^{-/-}	Ectopic UB, duplex ureter, ectopic UVJ, hydroureter	5,6
<i>Foxc1(Mf1)</i>	um	Forkhead transcription factor	<i>Foxc1</i> ^{-/-}	Ectopic UB, duplex ureter, hydroureter	7
<i>Foxc2 (Mfh1)</i>	um	Forkhead transcription factor	<i>Foxc1</i> ^{+/-} <i>Foxc2</i> ^{+/-}	Ectopic UB, duplex ureter, hydroureter, ureter agenesis	7
<i>L1cam</i>	ue	Adhesion molecule	<i>L1</i> ^{-/-} and <i>L1</i> ^{+/-}	Ectopic UB, duplex ureter, megaureter, hydronephrosis	8
<i>Nfia</i>	ue, um	Nuclear factor I transcription factor	<i>Nfia</i> ^{+/-} and <i>Nfia</i> ^{-/-}	Duplex ureter, VUR, UPJ defects, hydro-ureter, hydronephrosis	9
<i>Robo2</i>	mm	SH2 receptor	<i>Robo2</i> ^{-/-}	hydronephrosis, megaureter	10
<i>Slt2</i>	ue	Robo2 ligand	<i>Slt2</i> ^{-/-}	Ectopic UB, multiple ureters, hydroureter	10
<i>Spry1</i>	Wd, mm	RTK/ERK antagonist	<i>Spry1</i> ^{-/-}	Ectopic UB, multiple ureters, hydronephrosis	11
<i>Spry2</i>	Wd, mm	RTK/ERK antagonist	<i>Pax2(4.0)::hSpry2</i> , Wd, ue overexpression	Ectopic UB, double ureter, hydroureter	12
<i>Involved in ureter differentiation</i>					
<i>Adams1</i>	um	Secreted protease	<i>Adams1</i> ^{-/-}	Defective peristalsis, hydronephrosis	13
<i>Bmp5</i>	um	Secreted bone morphogenetic protein	<i>short ear</i> ^{-/-}	Hydroureter, hydronephrosis	14,15
<i>Dlgh1</i>	ue, um	MAGUK scaffolding protein	<i>Dlgh1</i> ^{-/-}	SM and stromal defects, short hydroureter, hydronephrosis, ectopia of distal ureter ends	16,17
<i>Foxd1 (BF2)</i>	um	Forkhead transcription factor	<i>Foxd1</i> ^{-/-}	Short ureter	18
<i>Gata2</i>	ue, um	Zn-finger transcription factor	<i>Gata2</i> ^{-/-} , YAC rescue	Megaureter, hydroureter, hydronephrosis	19
<i>Id2</i>	ue, um	bHLH DNA binding inhibitor	<i>Id2</i> ^{-/-} and <i>Id2</i> ^{+/-}	UPJ defect, hydronephrosis	20
<i>Shh</i>	ue	Secreted Sonic hedgehog	<i>Hoxb7^{Cre/+}, Shh^{floxex2/floxex2}</i>	SM defects, short hydroureter, hydronephrosis	21
<i>Smad4</i>	ue, um	TGFβ-signaling effector	<i>Bmp7^{Cre/+}, Smad4^{floxex2/floxex2}</i>	Hydroureter, hydronephrosis	22
<i>Tbx18</i>	um	T-box transcription factor	<i>Tbx18</i> ^{-/-}	Lack of SM, short hydroureter, hydronephrosis	23
<i>Upk3a</i>	uro	Transmembrane glycoprotein component	<i>Upk3a</i> ^{-/-}	VUR, hydroureter, hydronephrosis	24
<i>Upk2</i>	uro	Transmembrane glycoprotein component	<i>Upk2</i> ^{-/-}	VUR, hydroureter, hydronephrosis	25
<i>Involved in formation of junctional complexes</i>					
<i>Ace</i>	Kidney	Angiotensin I converting enzyme	<i>Ace</i> ^{-/-}	Defective pyeloureteral peristalsis, hydronephrosis	26
<i>Agt</i>	Kidney	Secreted angiotensinogen	<i>Agt</i> ^{-/-}	Defective pyeloureteral peristalsis, hydronephrosis	27,28
<i>Agtr1a/1b</i>	um	Angiotensin II receptor	<i>Agtr1a</i> ^{-/-} , <i>Agtr1b</i> ^{-/-}	Hydroureter, pyeloureteral peristalsis, pelvis agenesis	29
<i>Calcineurin b</i>	um	Protein phosphatase	<i>Calcineurin beta</i> ^{-/-}	Defective pyeloureteral peristalsis, hydronephrosis	30
<i>Nfia</i>	ue, um	Nuclear factor I transcription factor	<i>Nfia</i> ^{+/-} and <i>Nfia</i> ^{-/-}	Duplex ureter, VUR, UPJ defects, hydroureter, hydronephrosis, megaureter	9
<i>Rara/Rarb2</i>	ue (cnd)	RA receptor/transcription factor	<i>Rara</i> ^{-/-} , <i>Rarb2</i> ^{-/-}	Ectopia of distal ureter ends, hydroureter, megaureter	31,32
<i>Renin</i>	Kidney	Enzyme, which generates AngI from Agt	<i>Renin</i> ^{-/-}	Defective pyeloureteral peristalsis, hydronephrosis	33
<i>Ret</i>	Wd, ue	Gdnf receptor	<i>Ret</i> ^{-/-}	Ectopia of distal ureter ends	34

bHLH, basic helix-loop-helix; cnd, common nephric duct; Gdnf, glial cell derived neurotrophic factor; MAGUK, membrane-associated guanylate kinase; mm, metanephric mesenchyme; RA, retinoic acid; RTK/ERK, cell receptor tyrosine kinase/extracellular signal-regulated kinase; SM, smooth muscle; ue, ureteric epithelium; um, ureteric mesenchyme; UPJ, ureteropelvic junction; uro, urothelium; TGFβ, transforming growth factor-β; UVJ, ureterovesicular junction; VUR, vesicoureteric reflux; Wd, Wolffian duct.

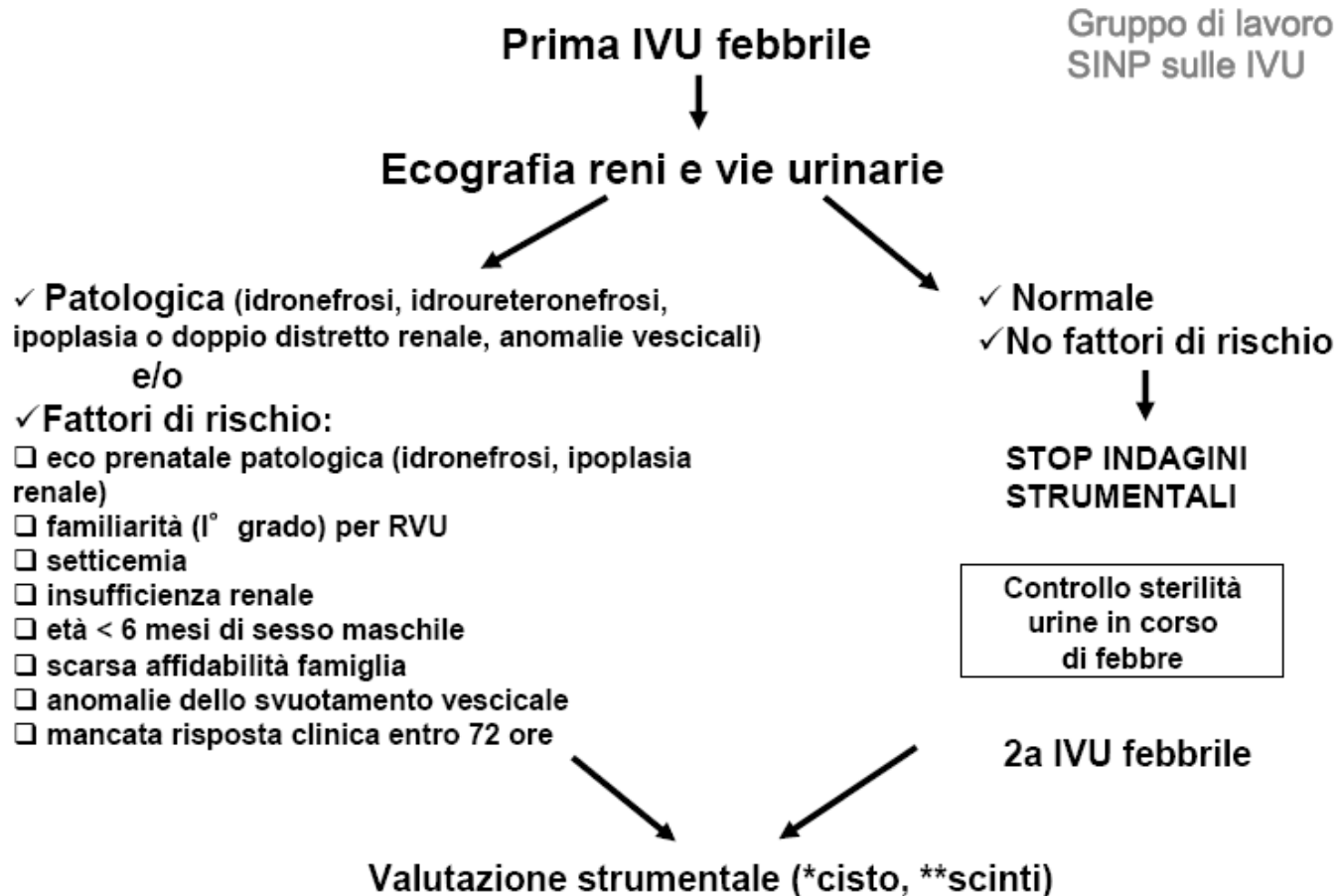
Mouse model	Mouse phenotype in addition to VUR
Abnormal kidney phenotype: dysplasia and hypoplasia	
<i>Agtr2</i> ^{-/-}	Renal hypoplasia, cystic kidneys, obstruction, duplex systems, hydroureter, cranial and duplicated ureteric buds
<i>Hoxb7/Ret</i> ^{+/-}	Renal dysplasia, decreased nephron number, decreased branching of ureteric buds, shorter intravesical ureters, caudal ureteric buds
<i>Pax2</i> ^{1Neu+/-}	Hypoplastic kidneys, decreased nephron number, decreased branching of ureteric buds, duplex systems, bifid ureters, delay in urinary tract development, shorter intravesical ureters, caudal ureteric buds
<i>Lim1</i> ^{lacZ} <i>Pax2Cre</i> <i>Fgfr2</i> ^{Mes+/-}	Renal hypoplasia, hydronephrosis, duplex systems, bifid ureters, hydroureters, smaller ureteric buds Renal hypo/dysplasia, duplex systems, obstruction, ectopic ureters with a more caudal uretero-vesical junction, cranial and duplicated ureteric buds
Normal kidney phenotype	
C3H/HeJ C3H/HeN	Normal kidneys, shorter intravesical ureters, caudal ureteric buds, delay in urinary tract development (HeJ)
DDD	Normal kidneys, hydronephrosis, gaping ureteric orifices
DBA/2J, AKR/J, CBA/J	Normal kidneys, only VUR reported
Abnormal bladder phenotype	
<i>Upk2</i> ^{-/-}	Hydronephrosis, obstruction, reduced renal function
<i>Upk3</i> ^{-/-}	Hydronephrosis, obstruction, reduced renal function, large ureteric orifices, leaky bladder

LINEE GUIDA NICE:

Imaging strategies

	Simple UTI	Atypical UTI	Recurrent UTI
≤6 months			
US (acute)	NO	YES	YES
US (within 6 wks)	YES	NO	NO
DMSA (4-6 months)	NO	YES	YES
MCUG	NO	YES	YES
6 months – 3 years			
US (acute)	NO	YES	NO
US (within 6 wks)	NO	NO	YES
DMSA (4-6 months)	NO	YES	YES
MCUG	NO	NO	NO
≥3 years			
US (acute)	NO	YES	NO
US (within 6 wks)	NO	NO	YES
DMSA (4-6 months)	NO	NO	YES
MCUG	NO	NO	NO

LINEE GUIDA S.I.N.P.



PATIENTS

273 CHILDREN WITH UPPER URINARY TRACT INFECTION (♀ 66.3% ♂ 33.7% recruited in northeast Italy in a registered clinical trial)

- Ⓞ Age 2 months – 8 years
- Ⓞ Absence of complex urological malformations and/or severe renal damage (i.e. DMSA showing a split renal function <30%)
- Ⓞ UTI documented by:
 - pyuria: two concordant consecutive tests with white cell count $\geq 25/\mu\text{L}$
 - urine culture: two concordant consecutive tests with growth of a single microorganism ≥ 100.000 CFU/mL
 - fever $\geq 38^\circ\text{C}$
 - raised inflammatory indices in the first 48 hours (PCR ≥ 3 times upper limit of normal values, VES $\geq 30\text{mm}$)
- Ⓞ Renal dimercapto-succinic scan (DMSA) within 10 days from the beginning of the infection
- Ⓞ Informed consent from parents

CONTROL POPULATION: 326 CORD BLOOD SAMPLES (♀ 43.4% ♂ 56.6%, collected in the same geographic area)

GENOTYPING

