

La gestione della febbre...

...nel bambino disidratato e nel bambino pre-termine



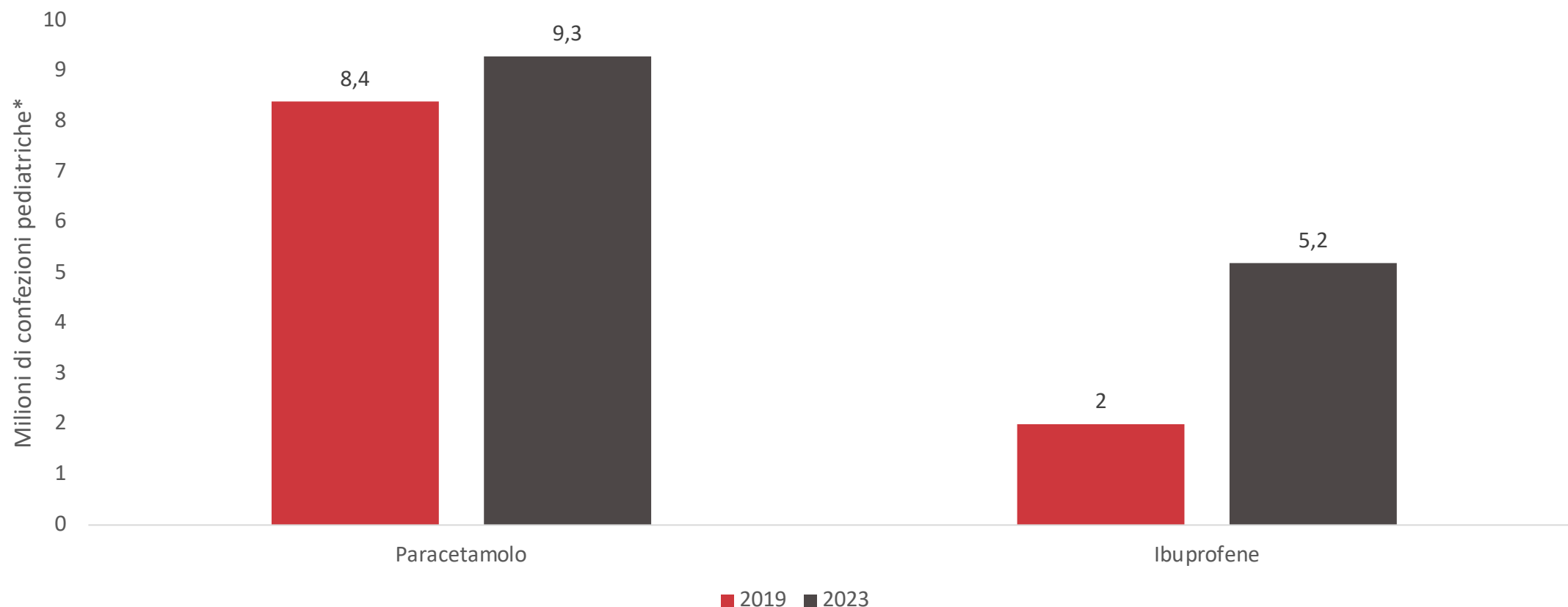
Enrico Vidal

UOC Nefrologia Pediatrica

Azienda Ospedale Università Padova

enrico.vidal@aopd.veneto.it

Richiesta di FANS e paracetamolo

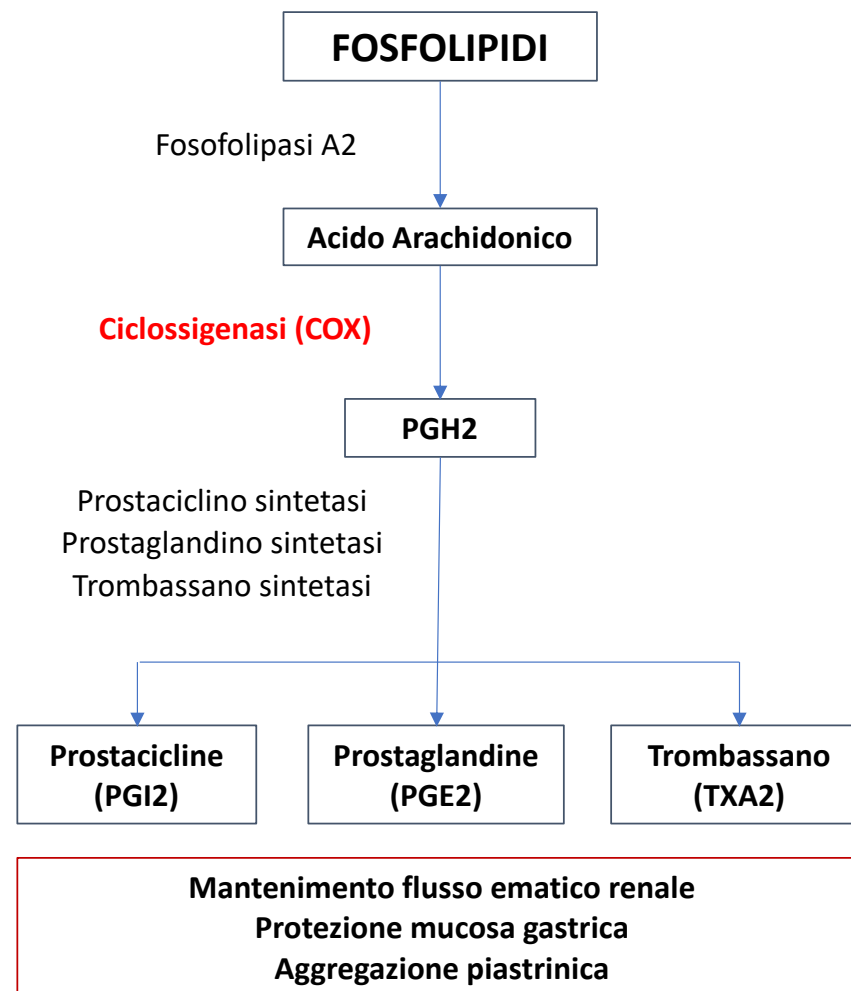


***Ibuprofene:** sciroppo

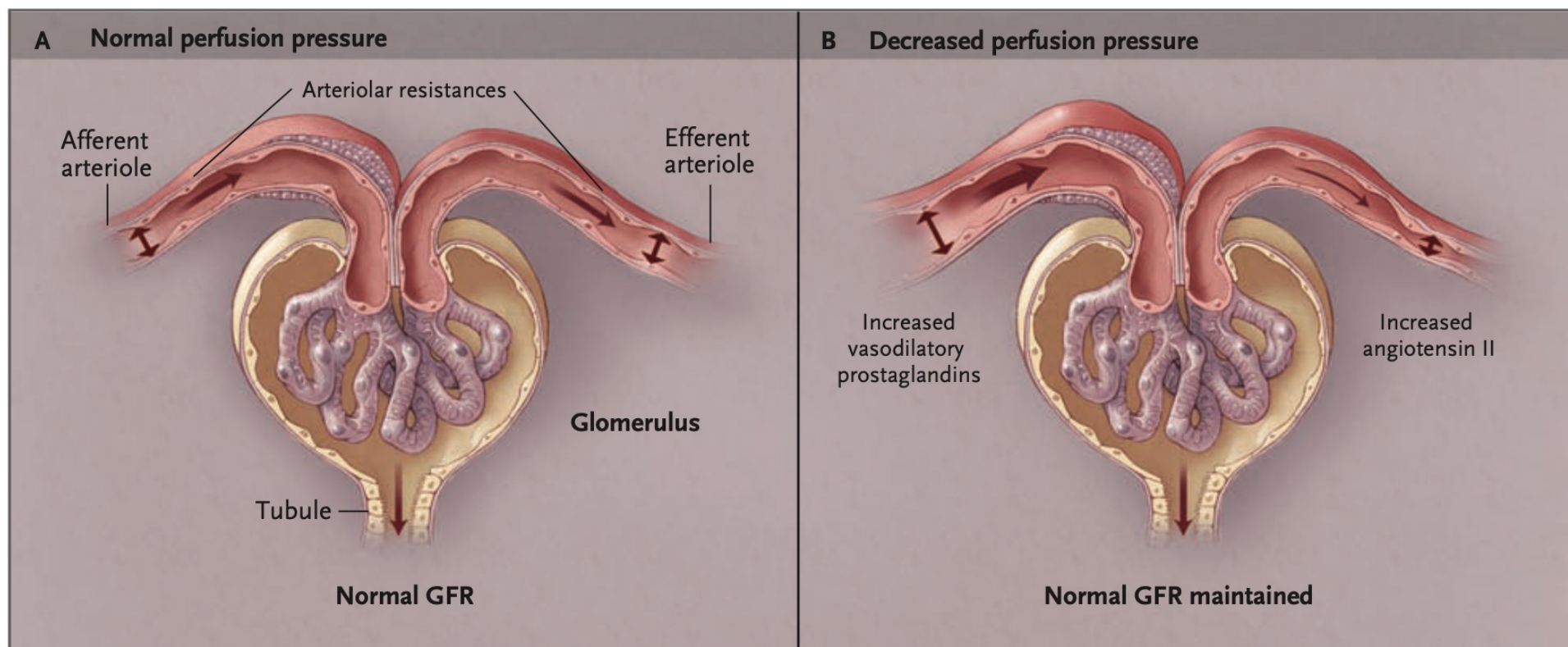
Paracetamolo: sciroppo, gocce, orosolubile/dispersibile, supposte



Cascata dell'acido arachidonico e biosintesi degli eicosanoidi



Mantenimento flusso ematico renale



Ciclossigenasi

Ciclossigenasi
COX1 (cr. 9)
COX2 (cr. 1)
COX3 (cr. 9)

Ciclossigenasi

Ciclossigenasi	Sede
COX1 (cr. 9)	Periferica
COX2 (cr. 1)	Periferica
COX3 (cr. 9)	Centrale

Ciclossigenasi

Ciclossigenasi	Sede	Attività	Azione
COX1 (cr. 9)	Periferica	Costitutiva	Citoprotezione (stomaco) Aggregazione piastrinica Protezione perfusione renale
COX2 (cr. 1)	Periferica	Costitutiva Inducibile*	Infiammazione Dolore Febbre Protezione perfusione renale
COX3 (cr. 9)	Centrale	Costitutiva	Dolore Febbre

*↑ espressione da 10 a 18 volte

Paracetamolo

Paracetamolo
in dosi terapeutiche



SNC

COX-3

Paracetamolo
in dosi terapeutiche



**Nei tessuti
periferici**

COX-1

COX-2

Paracetamolo

Paracetamolo
in dosi terapeutiche



SNC

~~COX-3~~

Paracetamolo
in dosi terapeutiche

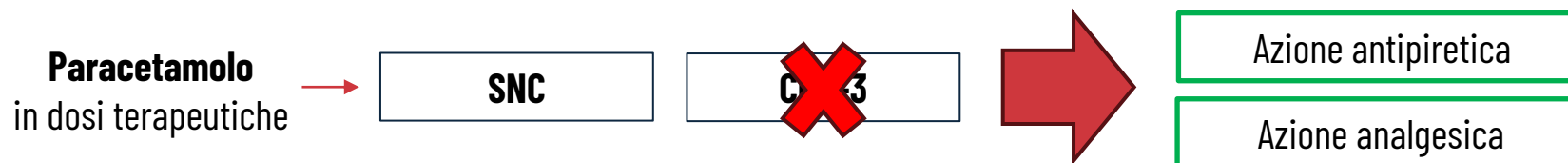


**Nei tessuti
periferici**

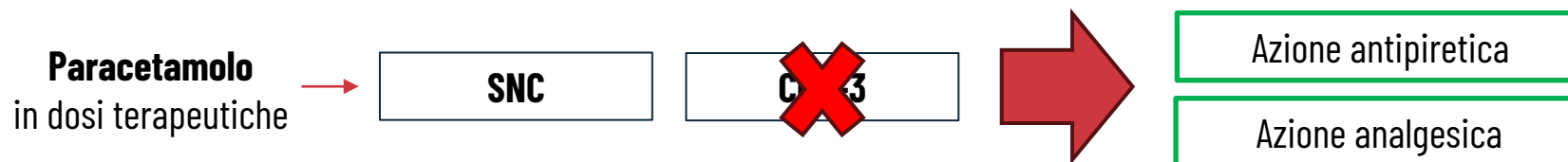
COX-1

COX-2

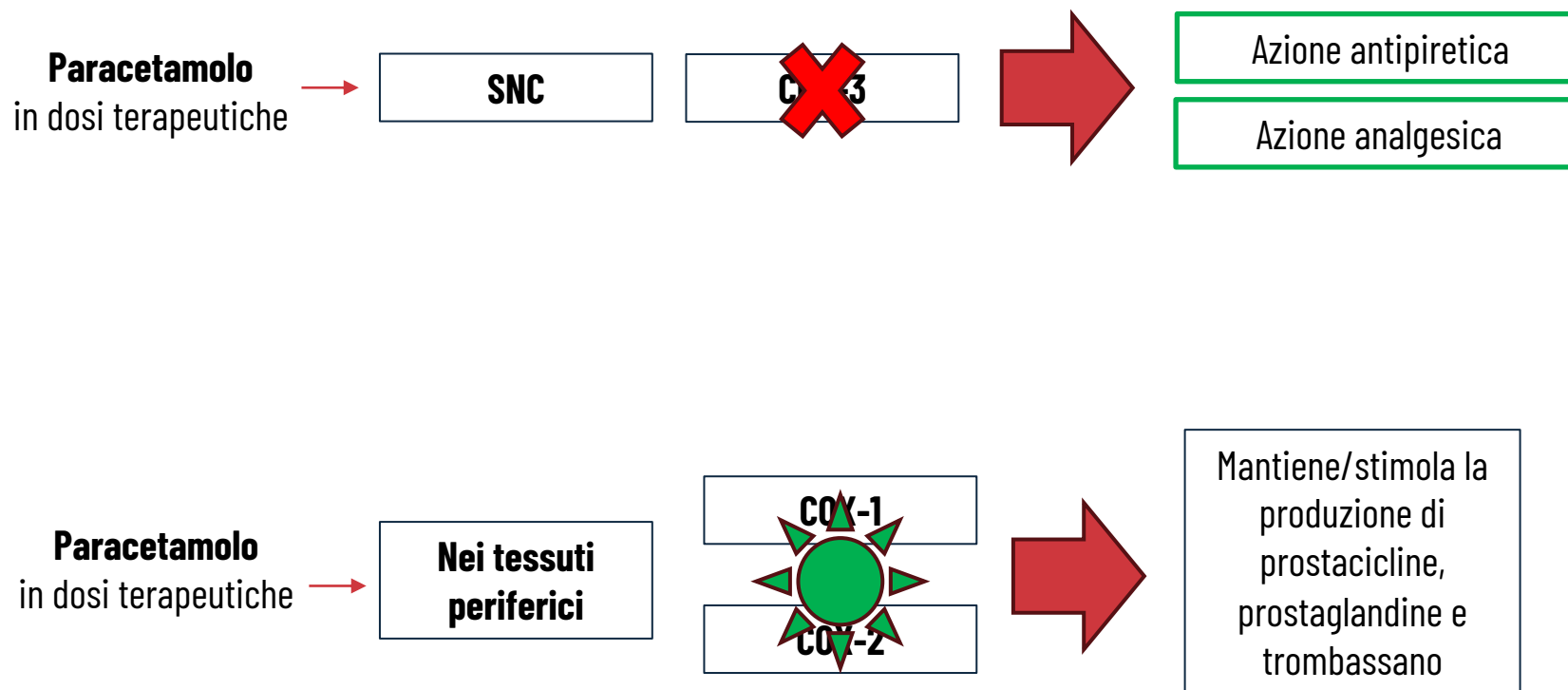
Paracetamolo



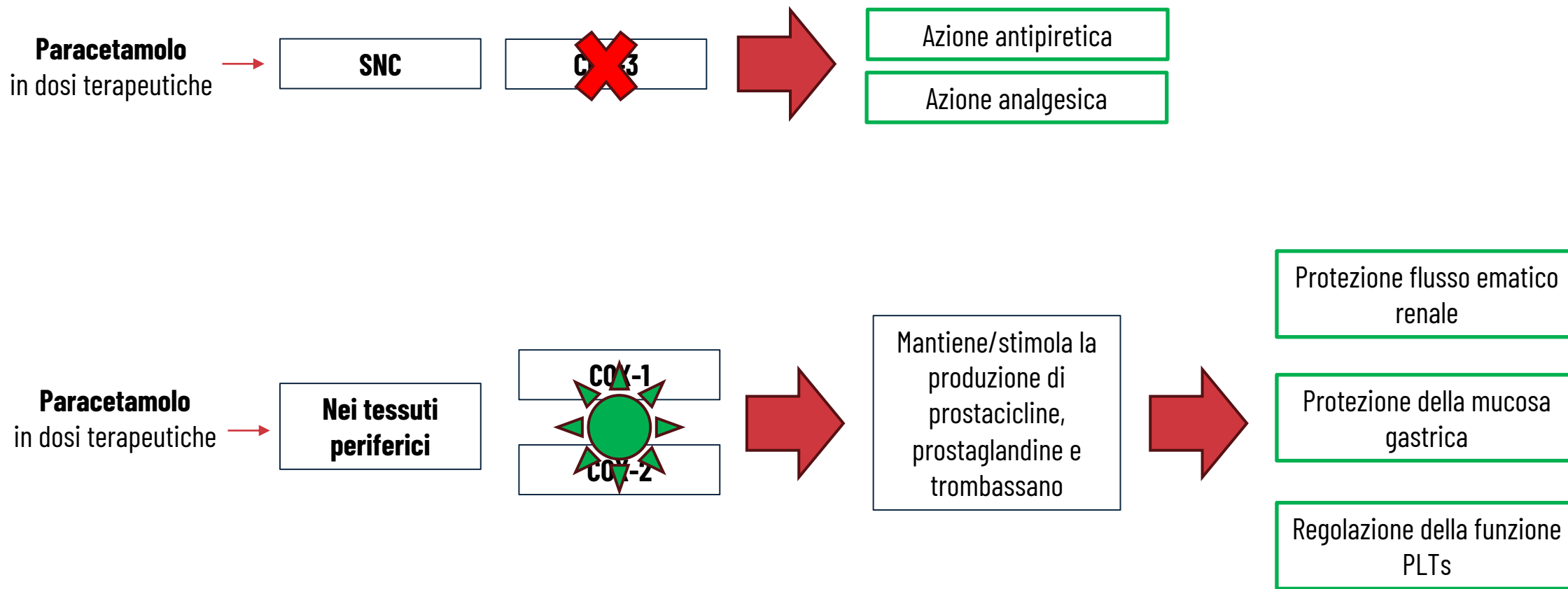
Paracetamolo



Paracetamolo



Paracetamolo



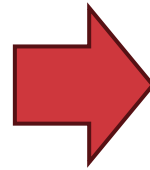
FANS

FANS
in dosi
terapeutiche



SNC

COX-3



Nessun effetto sulle
COX a livello centrale

FANS
in dosi
terapeutiche

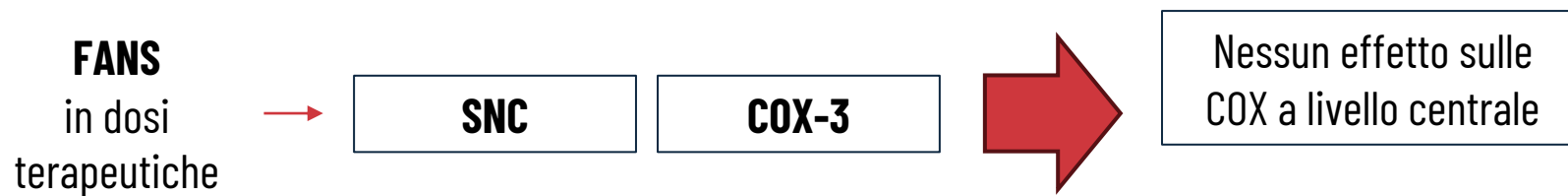


**Nei tessuti
periferici**

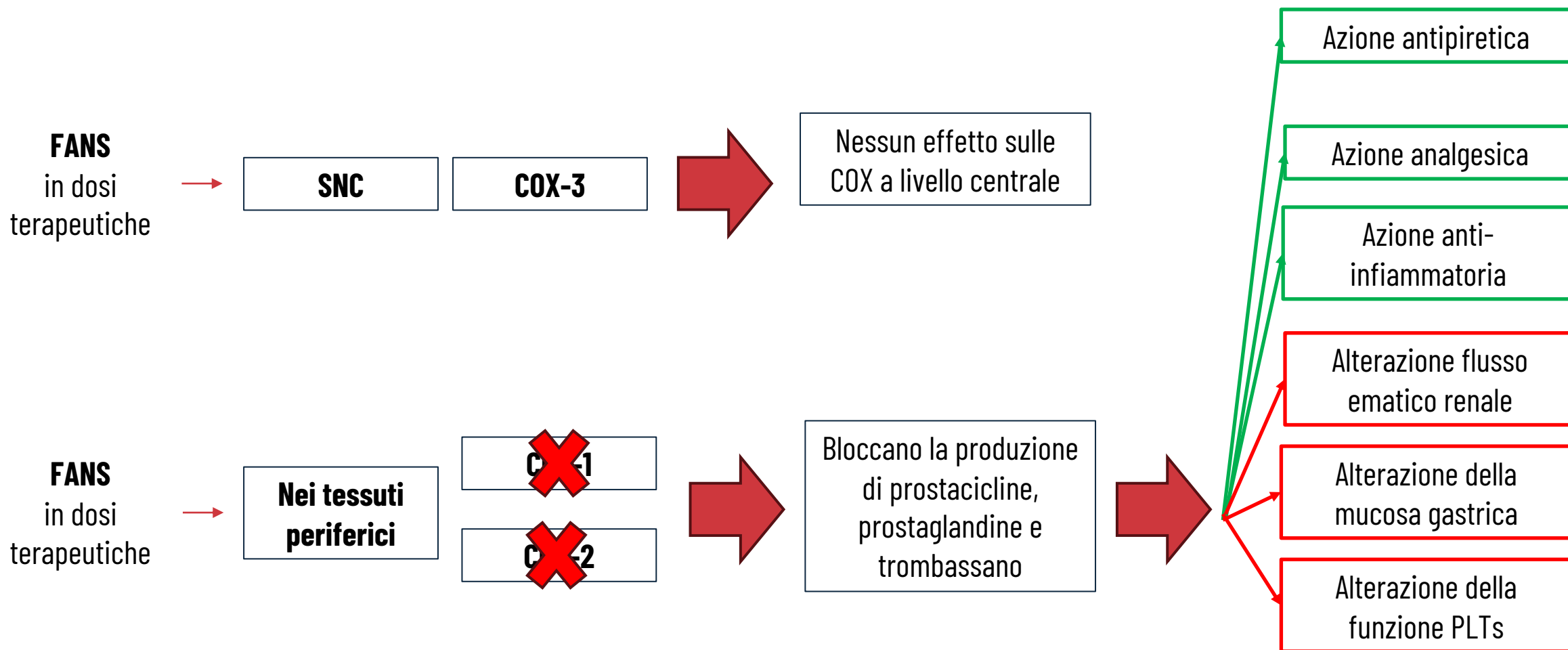
COX-1

COX-2

FANS



FANS



Parametri di farmacocinetica di alcuni FANS

Chemical Class	Prototype	Time to Peak (hours)	Half-life (hours)	Protein Binding (%)
Salicylates	Aspirin	0.5-1.0	0.25	80-90
Para-aminophenols	Paracetamol	0.5-1.0	2.0	10
Indoles	Indomethacin	1.0-2.0	12-15	92-99
Pyrro-lacetic Acids	Tolmetin	0.4-1.0	5.0	99
Propionic Acids	Ibuprofen	0.5-1.5	2.0-2.5	99
	Naproxen	1.0-2.0	12-15	99
	Ketoprofen	1.5-2.0	1.5	94
Enolic Acids	Piroxicam	2.0-4.0	36-45	99
Alkanones	Nabumetone	6.0	24	99

McCormack & Power. *Acute Pain Management*. (Sinatra et al. Eds.) CUP 2009.

Parametri di farmacocinetica di alcuni FANS



La maggior parte dei FANS hanno in genere una
percentuale di legame alle proteine plasmatiche molto alta



In caso di **ipoalbuminemia**, la quota di farmaco libera aumenta
e questo può determinare **effetti avversi**

Prescribing patterns, indications and adverse events of ibuprofen in children: results from a national survey among Italian pediatricians

Abstract

Background: Despite ibuprofen widely recognized safety profile, an increase of suspected adverse events has been reported in the last decade in parallel with its growing over-the-counter use. The aims of this study were to assess the therapeutic approach to the feverish child and to evaluate the main indications and the most frequent adverse events related to ibuprofen administration in children.

Methods: A specific questionnaire-form regarding the management of ibuprofen therapy in children was distributed among a sample of pediatricians all over the Italian territory between September and October 2020. An electronic data collection through a specifically designed web-based platform was performed among the participating pediatricians.

Results: One-hundred-eighty-one pediatricians completed the survey. In case of fever, 177 (98%) participants prescribe paracetamol, while only 4 (2%) preferred ibuprofen as first choice. One-hundred-twenty-eight pediatricians (71%) administer paracetamol alone, while 53 (29.2%) use the combined/alternating treatment with ibuprofen. Ibuprofen is mostly administered for musculoskeletal pain (30%), upper respiratory tract infection (20%), headache (15%) and post-surgical pain (9%). Sixty-three (35%) out of 181 participating pediatricians reported 191 adverse events during ibuprofen administration. The most common were gastrointestinal (GI), with GI bleeding being reported in 30/191 cases (15.7%), epigastric pain in 29/191 (15.1%), non-specified abdominal pain in 22/191 (11.1%) and nausea/vomiting in 21/191 (11%). Severe adverse events including kidney damage (3.1%), complicated infections (0.5%), pneumonia associated empyema (0.5%), soft tissue infection (0.5%) and disseminated intravascular coagulation (0.5%) were also reported. The adverse events led to a hospitalization in 12% of children. In 53/191 cases (28%) the adverse events were related to a wrong dosage or prolonged therapy or errors in frequency of administration.

(Continued on next page)

Sono farmaci sicuri?

Table 1 Reported adverse events following ibuprofen administration

Adverse event	N (%) (Total Number = 191)
Skin rash	40 (21)
Gastrointestinal bleeding	30 (15.7)
Epigastric pain	29 (15.1)
Abdominal pain	22 (11.5)
Nausea/Vomiting	21 (11)
Hypersensitivity	13 (6.8)
Acute kidney injury	6 (3.1)
Irritability	6 (3.1)
Diarrhea	5 (2.6)
Angioedema	4 (2.1)
Anemia	2 (1)
Liver damage	2 (1)
Dizziness	1 (0.5)
Insomnia	1 (0.5)
Bronchospasm	1 (0.5)
Non specified complicated infection	1 (0.5)
Pneumonia-associated empyema	1 (0.5)
Soft tissue infection during chickenpox	1 (0.5)
Leukopenia	1 (0.5)
Thrombocytopenia	1 (0.5)
Headache	1 (0.5)
Nasal bleeding	1 (0.5)
Disseminated intravascular coagulation	1 (0.5)

Riportati da 63/181 partecipanti (35%)



Danno renale acuto (AKI) – Definizione

	SCr	Urine output
Stage 1	Increase 1.5-1.9 x baseline or increase $\geq 27 \mu\text{mol/L}$	$< 0.5 \text{ mL/kg/hour}$ for 6-12 hour
Stage 2	Increase 2-2.9 x baseline	$< 0.5 \text{ mL/kg/hour}$ for ≥ 12 hour
Stage 3	Increase > 3 x baseline OR SCr $\geq 354 \mu\text{mol/L}$ OR Initiation of RRT OR eGFR $< 35 \text{ mL/min/1.73m}^2$	$< 0.3 \text{ mL/kg/hour}$ for ≥ 24 hour OR anuric for ≥ 12 hour

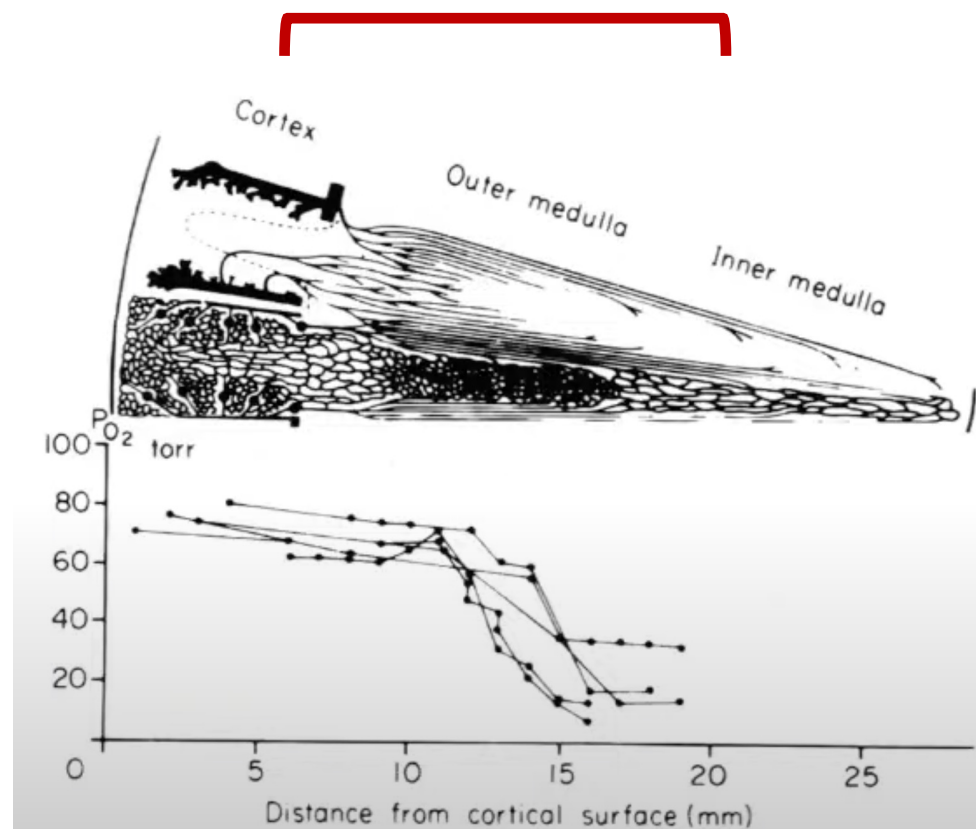
Drug-induced AKI in children

Ci sono due meccanismi

1. Emodinamico (78%) legato all'inibizione della sintesi delle PG ad azione vasodilatante
2. Nefrite tubulo-interstiziale acuta (22%), attraverso un meccanismo idiosincrasico immuno-mediato.

Drug-induced AKI in children

Elevato flusso ematico e consumo
di O₂



Drug-induced AKI in children

Ci sono due meccanismi

1. Emodinamico (78%) legato all'inibizione della sintesi delle PG ad azione vasodilatante
2. Nefrite tubulo-interstiziale acuta (22%), attraverso un meccanismo idiosincrasico immuno-mediato.

BMJ Open Aetiology, course and treatment of acute tubulointerstitial nephritis in paediatric patients: a cross-sectional web-based survey

Sarah Wente-Schulz, Marina Aksenova,[?] Atif Awan,[?] Cahyani Gita Ambarsari, * Francesca Becherucci,⁵ Francesco Emma,[°] Marc Fila [©]

Telma Francisco,[°]

Ibrahim Gokce," Bora Gülhan,"[°] Matthias Hansen,"* Timo Jahnukainen, 12

Mahmoud Kallash,¹³ Konstantinos Kamperis,

14 Sherene Mason,¹⁵

Antonio Mastrangelo, 16 Francesca Mencarelli," Bogna Niwinska-Faryna,*[°]

Michael Riordan, Rina R Rus, 1[°] Seha Saygili,^{2°} Erkin Serdaroglu,¹¹ Sevgin Taner,²²

Rezan Topaloglu, 1[°] Enrico Vidal,²³ Robert Woroniecki,²⁴ Sibel Yel,²⁵ Jakub Zieg,²⁶

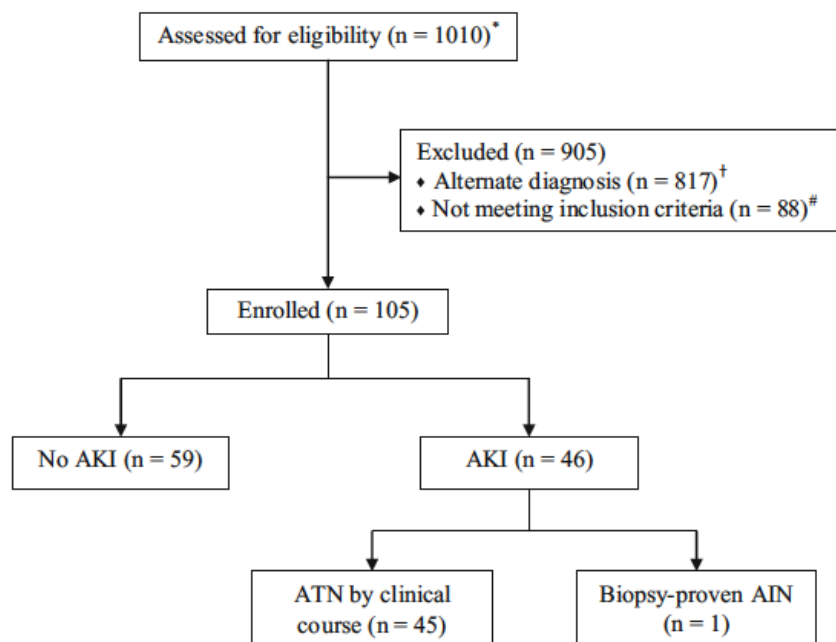
Lars Pape [©].²⁷ The international TIN study group

Table 1 Drugs and toxic agents as causes of tubulointerstitial nephritis (TIN) in 52 patients with acute TIN

NSAIDs (without comedication)	25	48%
Ibuprofen	6	
Flurbiprofen	3	
Morniflumate	3	
Ketoprofen	1	
Unspecified	12	
Antimicrobials	11	21%
Acyclovir	1	
Amoxicillin±clavulanic acid	3	
Trimethoprim/sulfamethoxazole	1	
Midecamycin	1	
Penicillin	2	
Unspecified	1	
Combination of antibiotics	2	
NSAIDs+antimicrobials	5	10%
Others	11	21%
Bee venom	2	
Herbal medicines	3	
Mesalazine	2	
Levetiracetam+oxcarbazepine	1	
Paracetamol+chlorphenamine maleate	1	
Hydrochlorothiazide	1	
Smoking	1	

NSAIDs, non-steroidal anti-inflammatory drugs.

Ibuprofen-associated acute kidney injury in dehydrated children with acute gastroenteritis



Characteristic	No acute kidney injury (n=59)	Acute kidney injury (n=46)	p value
Gender (female/male)	28/31	27/19	0.25
Age (years)	1.74 (0.16–14)	0.66 (0.16–15.75)	<0.001
Weight (kg)	10.8 (3.5–37)	7.72 (3.15–56.7)	<0.001
Age- and sex-specific body mass index percentile ^a	46 (3–99)	37 (3–99)	0.36
Percentage of dehydration	7 (3–10)	7 (3.5–10)	0.08
Vomiting	10 (17 %)	12 (26 %)	0.25
Fever	24 (41 %)	14 (31 %)	0.27
Ibuprofen exposure	29 (49 %)	34 (74 %)	0.01

Ibuprofen-associated acute kidney injury in dehydrated children with acute gastroenteritis

Table 2 Risk factors for acute kidney injury in 105 dehydrated children with acute gastroenteritis^a

Characteristic	<i>p</i> value	Odds ratio	95 % Confidence interval
Age (years)	0.64	0.95	0.79–1.16
Weight (kg)	0.29	0.96	0.89–1.04
Ibuprofen exposure	<0.001	2.47	1.78–3.42

^a Multivariate analysis adjusted for percentage of dehydration

NSAID-associated acute kidney injury in hospitalized children- a prospective Pediatric Nephrology Research Consortium study

25 patients with NSAID-associated AKI

Median age: 15.5 years

2/25 (8%) <5 years of age

20/25 (80%) had volume depletion (emesis, diarrhea, and/or poor fluid intake)

Median hospital length of stay: 4 days (IQR 2-6)

NSAID use: 2 days (IQR 1-5)

Took normal dose: 15/24 (62%)

Cause of AKI	Center 1	Center 2	Center 3	Center 4	Totals
NSAID-Associated AKI	11	4	8	2 ^a	23 (3.1%)
Unexplained AKI	3	0	2	0	5 (0.7%)
Multifactorial	56	22	131	–	209 (28%)
Other Nephrotoxin Exposure	83	6	10	–	99 (13%)
Heart Disease	61	11	20	–	92 (12%)
Isolated Ischemic Insult	54	16	10	–	80 (11%)
Kidney Transplant	34	5	13	–	52 (7%)
Glomerulonephritis	10	8	26	–	44 (6%)
Hemolytic uremic syndrome (HUS)	11	2	31	–	44 (6%)
Shock (cardiogenic or septic)	15	15	8	–	38 (5%)
Pyelonephritis	8	3	6	–	17 (2%)
Other	11	15	11	–	37 (5%)
Totals	357	107	276	–	740

^a Center 4 did not submit AKI screening logs, so these 2 cases of NSAID-associated AKI are not included in the calculation

Uso ragionato di paracetamolo ed ibuprofene in età pediatrica

Raccomandazione 25

Occorre considerare possibili fattori concomitanti in grado di incrementare il rischio di tossicità da farmaci antipiretici (Livello della Prova V; Forza della Raccomandazione A)

Per il paracetamolo:

- contemporaneo trattamento con: carbamazepina, isoniazide, fenobarbitale, primidone, rifampicina.

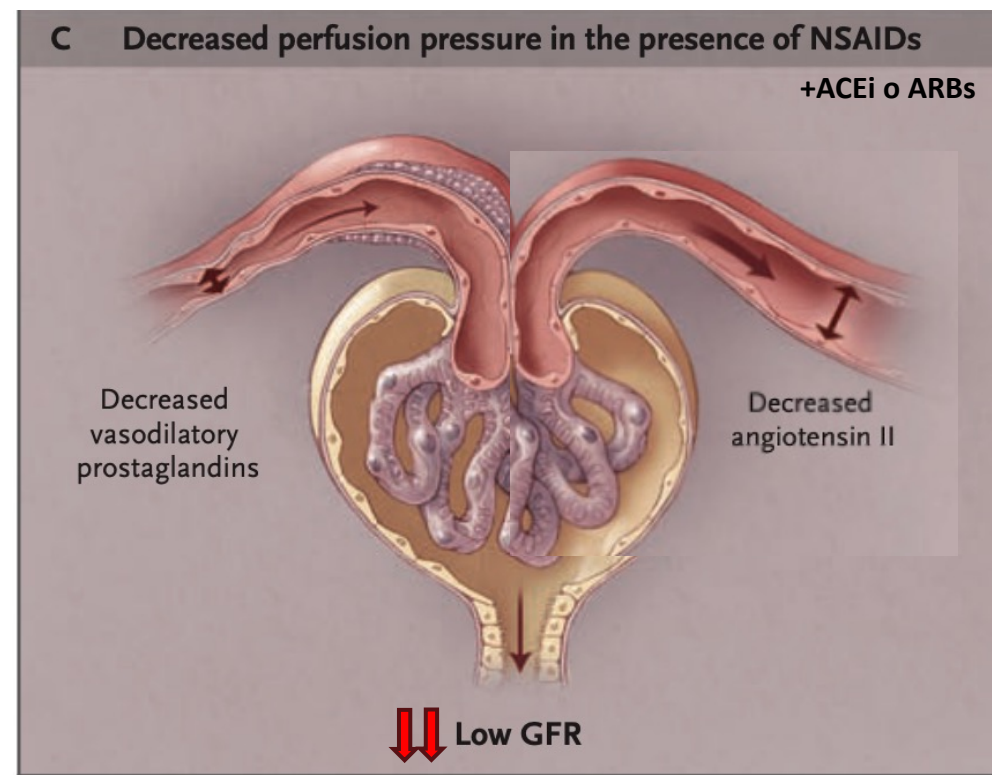
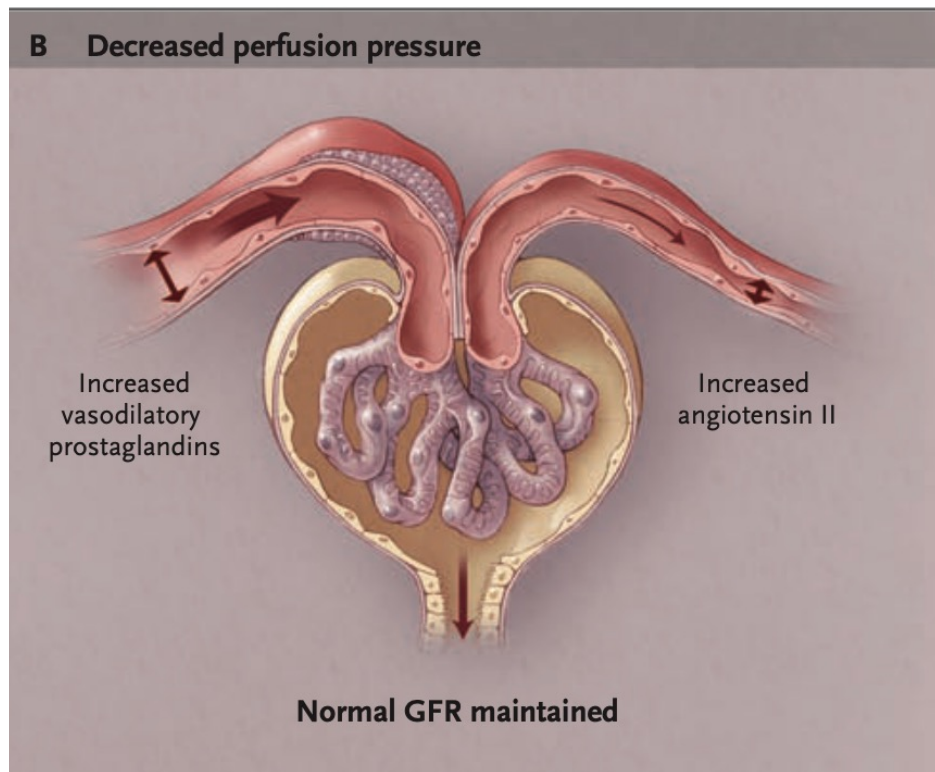
Per l'ibuprofene:

- contemporaneo trattamento con: ACE inibitori, ciclosporina, metotrexate, litio, baclofene, diuretici, chinolonici,
- dicumarolici;disidratazione;
- varicella.

Linee Guida della Società Italiana di Pediatria (2012-2016)

***Gestione del Segno/Sintomo
Febbre in Pediatria***

Uso ragionato di paracetamolo ed ibuprofene in età pediatrica



Il caso di Matteo

- Bambino di 3 anni.
- Condotta dal pediatra curante per febbricola, contrazione della diuresi e «malessere generale».
- Circa 10 giorni prima, il bambino aveva già presentato febbre per 3 giorni ed un episodio di vomito. Iniziata terapia con ibuprofene (5 ml x 3/die) che ha proseguito per 5 giorni.
- Terzogenito, nato a 36 SG, AGA.
- Anamnesi patologica remota negativa.
- Eseguito esame delle urine in Ambulatorio con riscontro di PS 1025, pH 6, Hb ++, proteinuria +++.
- Prescritti esami di laboratorio.

Il caso di Matteo

BUN 100 mg/dL
(36 mmol/L)

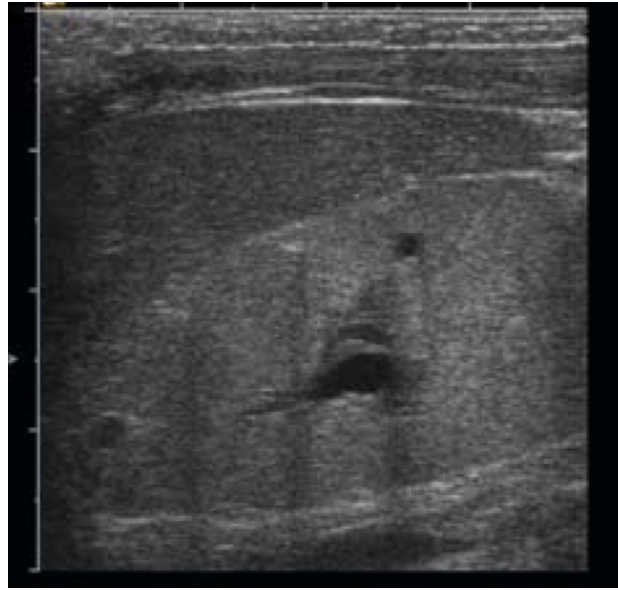
Creatinina 7.3 mg/dL
(646 umol/L)

Proteidemia 6.1 g/dL

ESAME URINE
Proteinuria, emoglobinuria,
U-Pr/U-Cr >500 mg/g

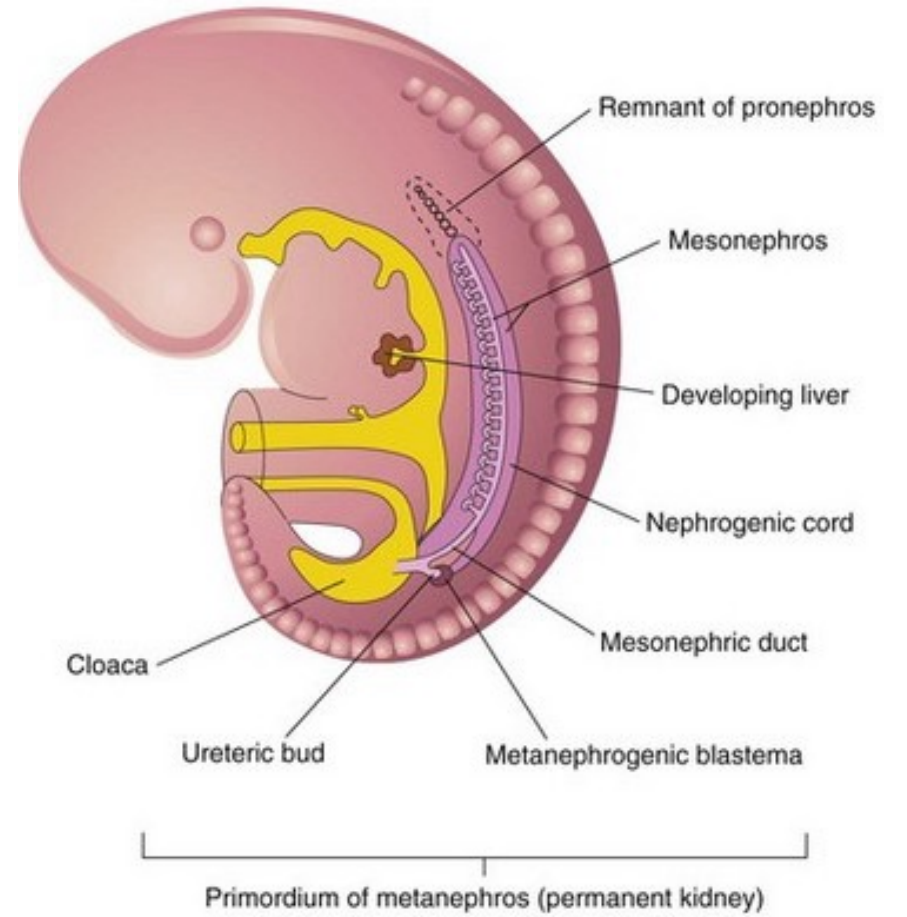
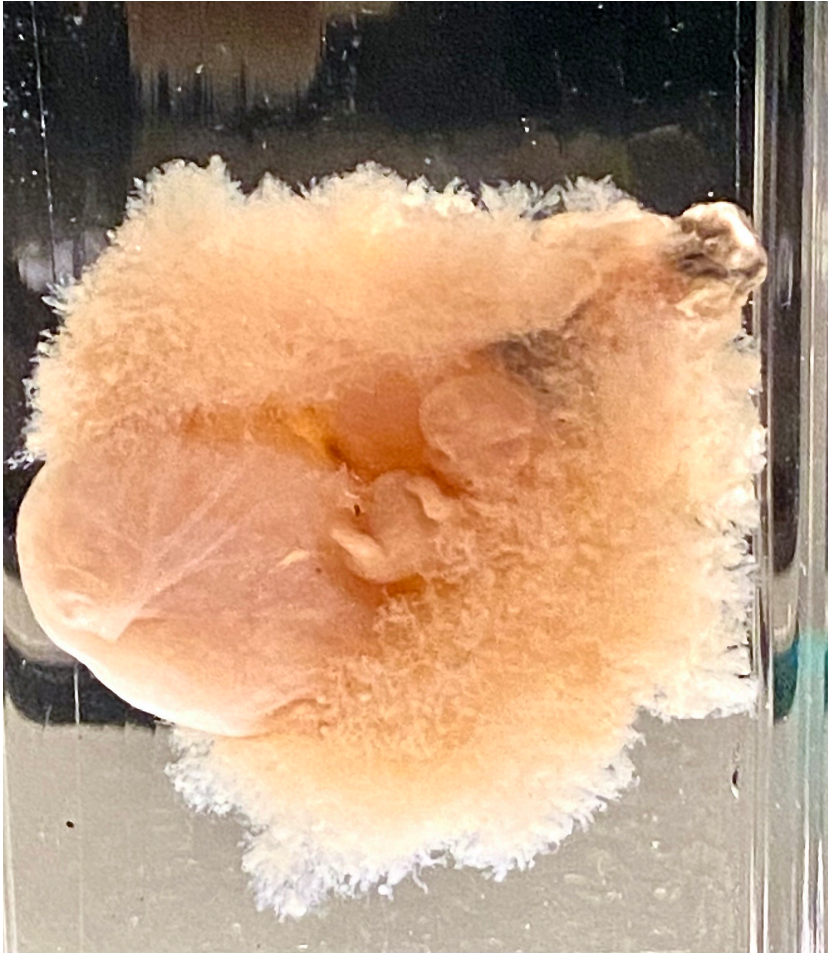
Il caso di Matteo

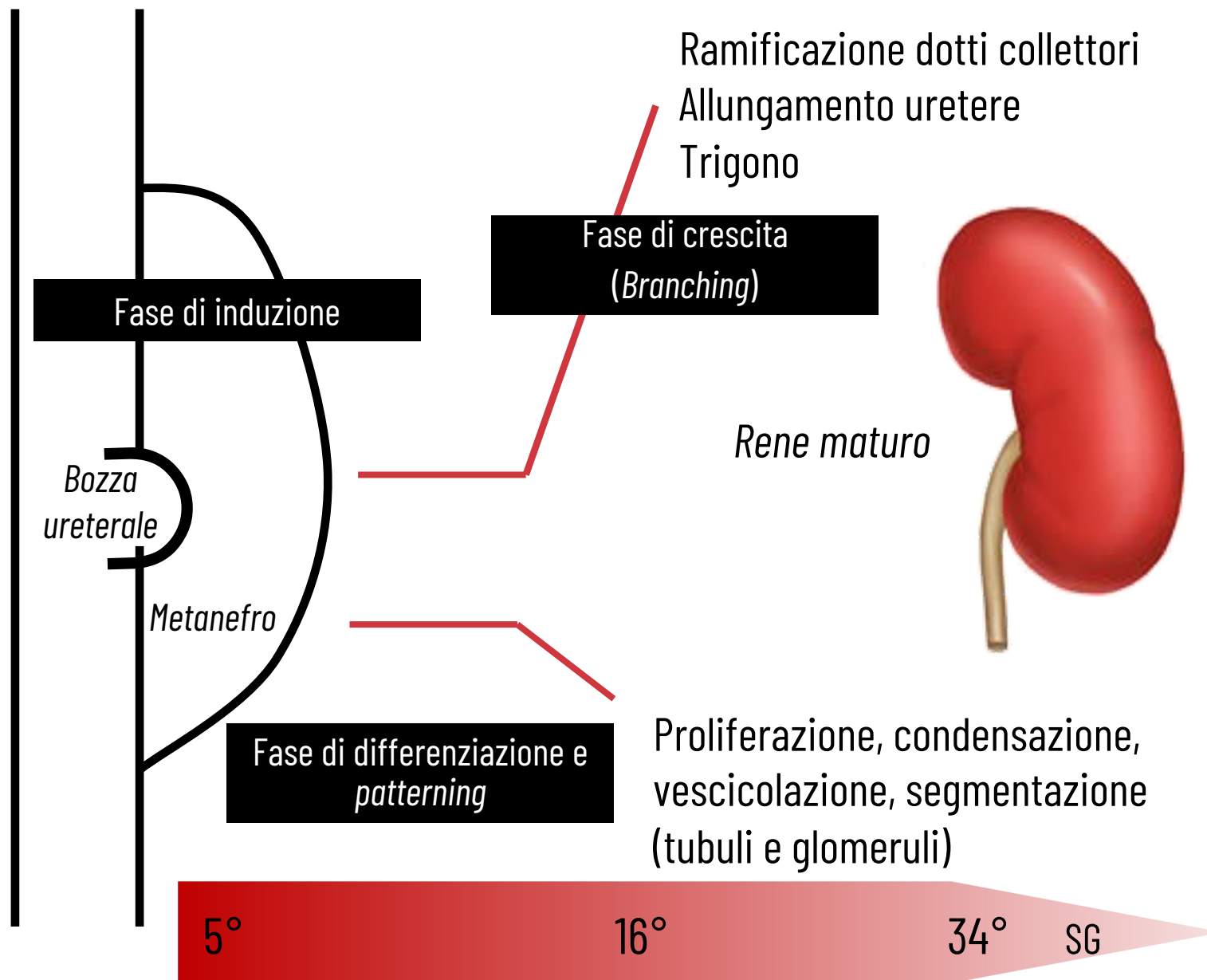
- Condotto in PS, l'esame obiettivo risulta nella norma. Non segni di disidratazione, non fluid overload.
- Emocromo: GB 14000/mmc, Hb 10.2 g/dL, PLTs 324000/mmc.
- Costituenti biochimici: creatinina 7.9 mg/dL, BUN 120 mg/dL, Na 133 mmol/L, K 6.1 mmol/L.
- PCR 1.84 mg/dL.
- Indici di emolisi -.
- EGA venoso: pH 7.29, HCO₃⁻ 12 mmol/L, BE -17 mmol/L.



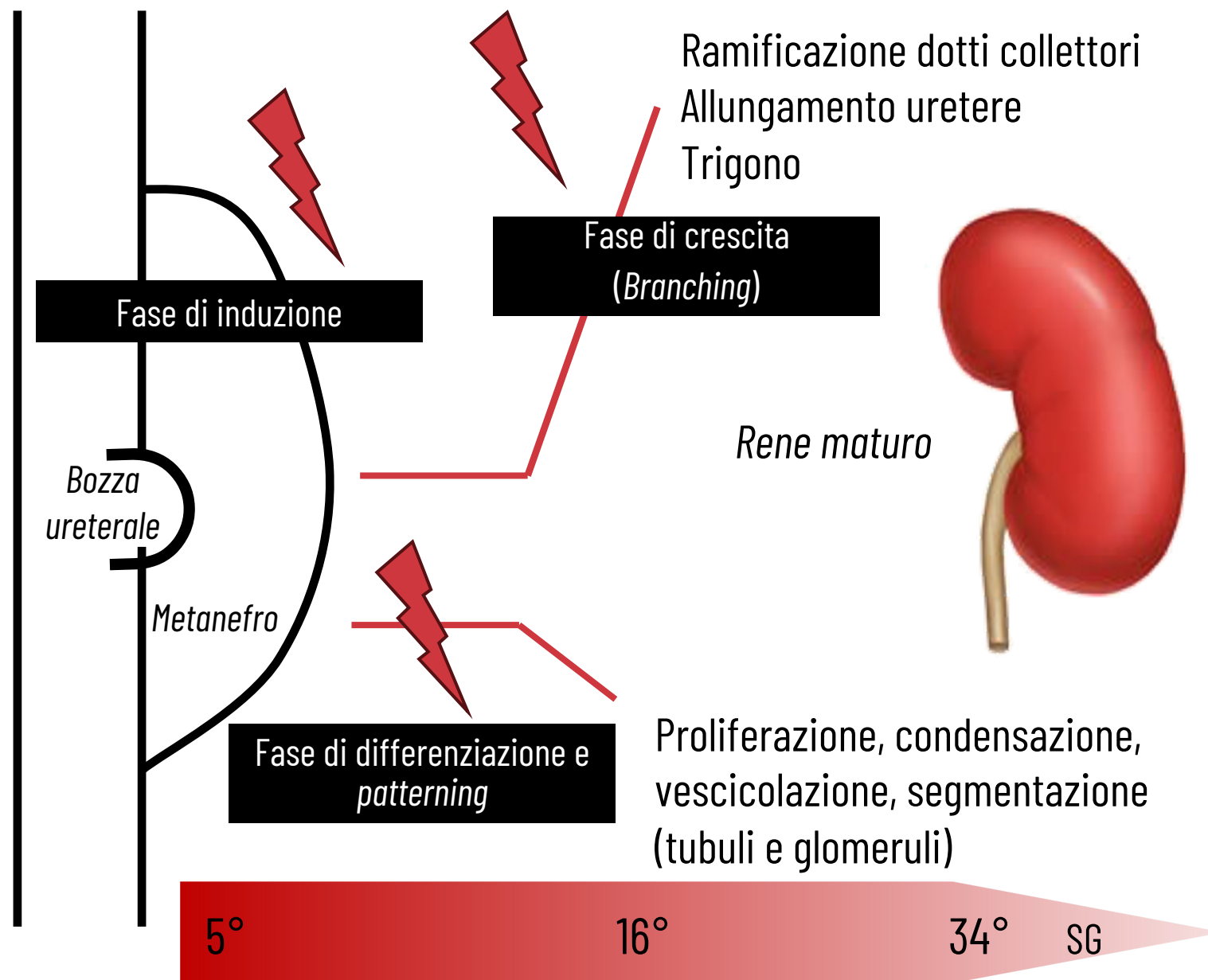
Il caso di Matteo

- Trasferito in Nefrologia pediatrica
- Per stato di anuria, visti anche i dismetabolismi, posizionato CVC per emodialisi ed eseguite 6 sedute dialitiche in 2 settimane.
- STOP dialisi per progressivo aumento della diuresi e miglioramento della funzionalità renale.
- Dimesso in terapia con prednisone, omeprazolo, colecalciferolo, ferro, sodio bicarbonato, amlodipina, EPO.
- Ad 1 mese dalla dimissione, S-creatinina 1.6 mg/dL (eGFR 28 ml/min/1.73 mq).



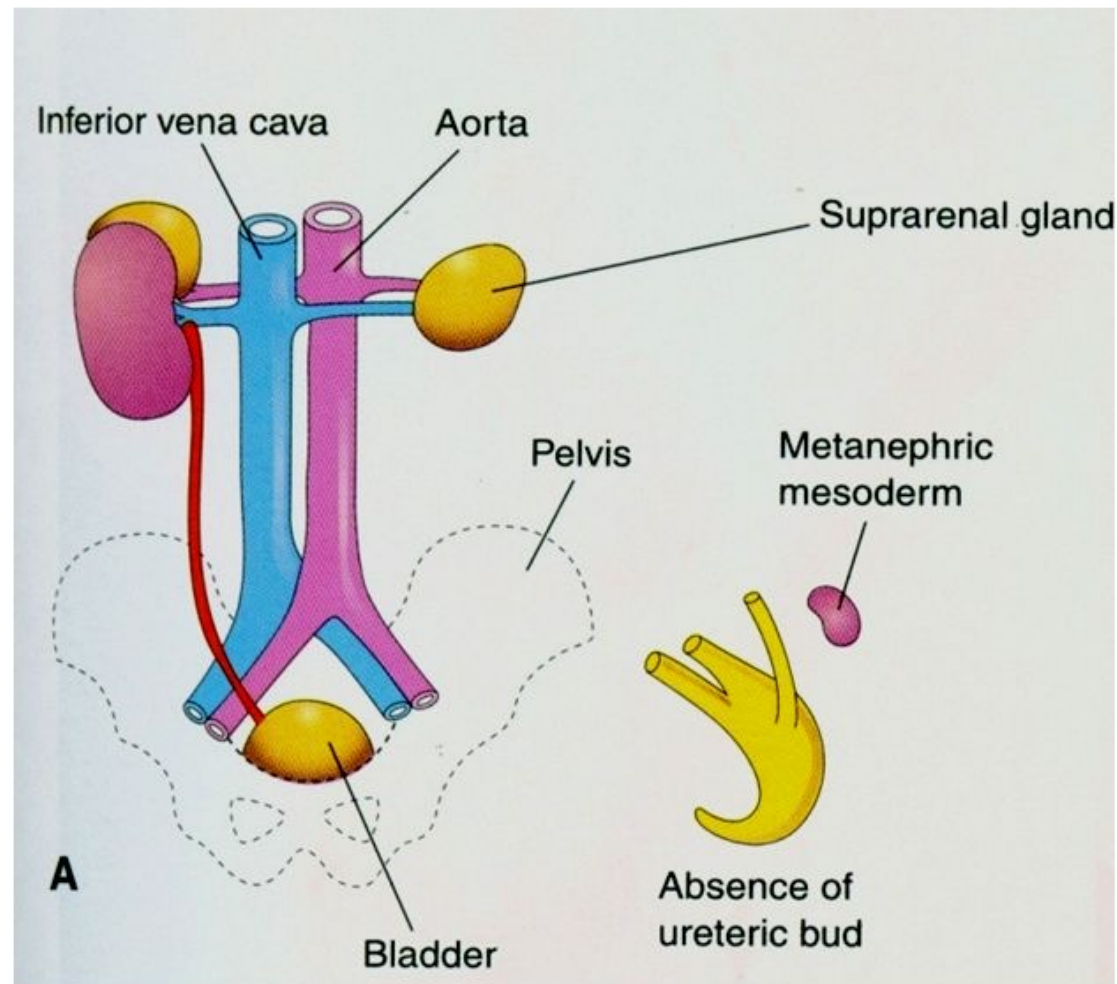






Errori fase di induzione

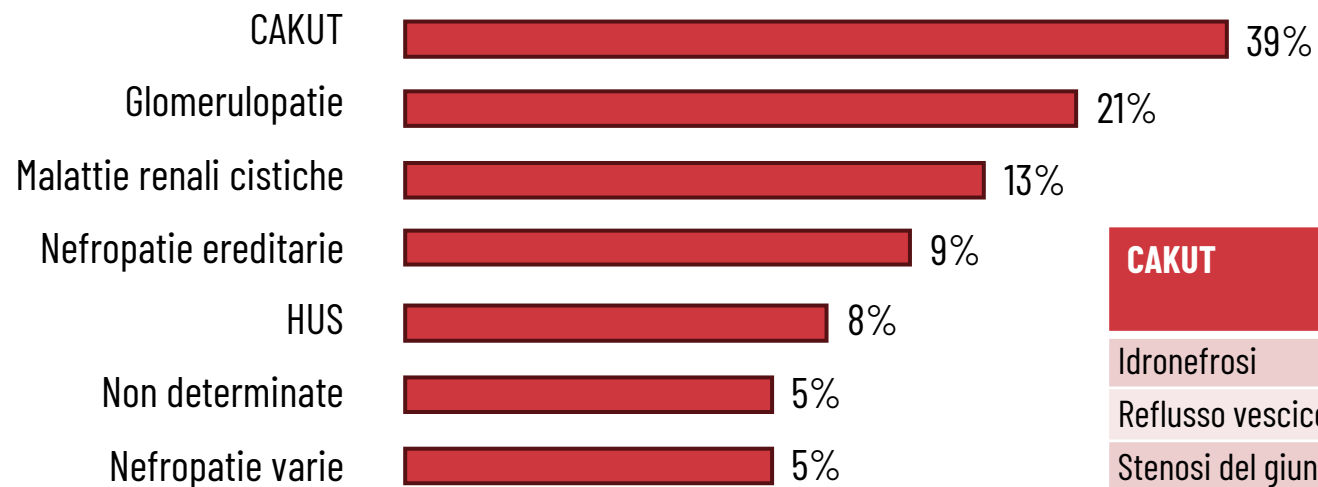
Agenesia renale



♂, 3 anni, agenesia renale destra



Cause di ESRD nei pazienti incidenti in dialisi cronica n=335 (anni 2008-2016)



CAKUT	Incidenza (nati)
Idronefrosi	1:100
Reflusso vescico-ureterale	1:100 (?)
Stenosi del giunto pielo-ureterale	1:500
Agenesia unilaterale	1:1000
Ipoplasia unilaterale	1:1000
Displasia unilaterale	1:1000
Megauretere ostruttivo	1:1000
Rene a ferro di cavallo	1:1000
Ectopia crociata con fusione	1:2000
ipoplasia bilaterale	1:4000
Valvole dell'uretra posteriore	1:5000
Displasia bilaterale	1:7500
Agenesia bilaterale	1:10000

Possibile ridotto patrimonio nefronico, ma realizzabile ipertrofia compensatoria del rene Controlaterale

Ridotto patrimonio nefronico

GUIDELINES



Management of the congenital solitary kidney: consensus recommendations of the Italian Society of Pediatric Nephrology

Claudio La Scola¹ · Anita Ammenti² · Cristina Bertulli¹ · Monica Bodria³ · Milena Brugnara⁴ · Roberta Camilla⁵ · Valentina Capone⁶ · Luca Casadio⁷ · Roberto Chimenz⁸ · Maria L. Conte⁹ · Ester Conversano¹⁰ · Ciro Corrado¹¹ · Stefano Guarino¹² · Ilaria Luongo¹³ · Martino Marsciani¹⁴ · Pierluigi Marzuillo¹² · Davide Meneghesso¹⁵ · Marco Pennesi¹⁰ · Fabrizio Pugliese¹⁶ · Sara Pusceddu¹⁷ · Elisa Ravaoli⁹ · Francesca Taroni⁶ · Gianluca Vergine⁹ · Licia Peruzzi⁵ · Giovanni Montini^{6,18}

Table 8 Opinion-based recommendations for follow-up in children and adolescents with congenital solitary kidney

	Low risk*	Medium risk*		High risk*
		Without CAKUT	With ipsilateral CAKUT	
Setting	Primary pediatric care ¹	Pediatric nephrologist ¹ /pediatric nephrology unit		Pediatric nephrology unit
Ultrasound²	Yearly until 3 years of age, then every 5 years	Yearly until 3 years of age, then every 3 to 5 years	Further work-up depending on additional ipsilateral CAKUT findings	According to kidney function and clinical data
Proteinuria by urinalysis³	Yearly until 3 years of age, then every 5 years	Yearly		
Office Blood pressure	Yearly ≥ 3 years	Yearly		
Serum creatinine/eGFR	Not necessary	Yearly		
Abdominopelvic ultrasound in girls	Between thelarche and menarche	Between thelarche and menarche		Between thelarche and menarche

*Risk stratification:

- low risk: kidney length > 50th pct in the first 2 years of life and ≥ 95 th pct thereafter, and absence of ipsilateral CAKUT

- medium risk: CSK without compensatory enlargement, and/or with an ipsilateral CAKUT

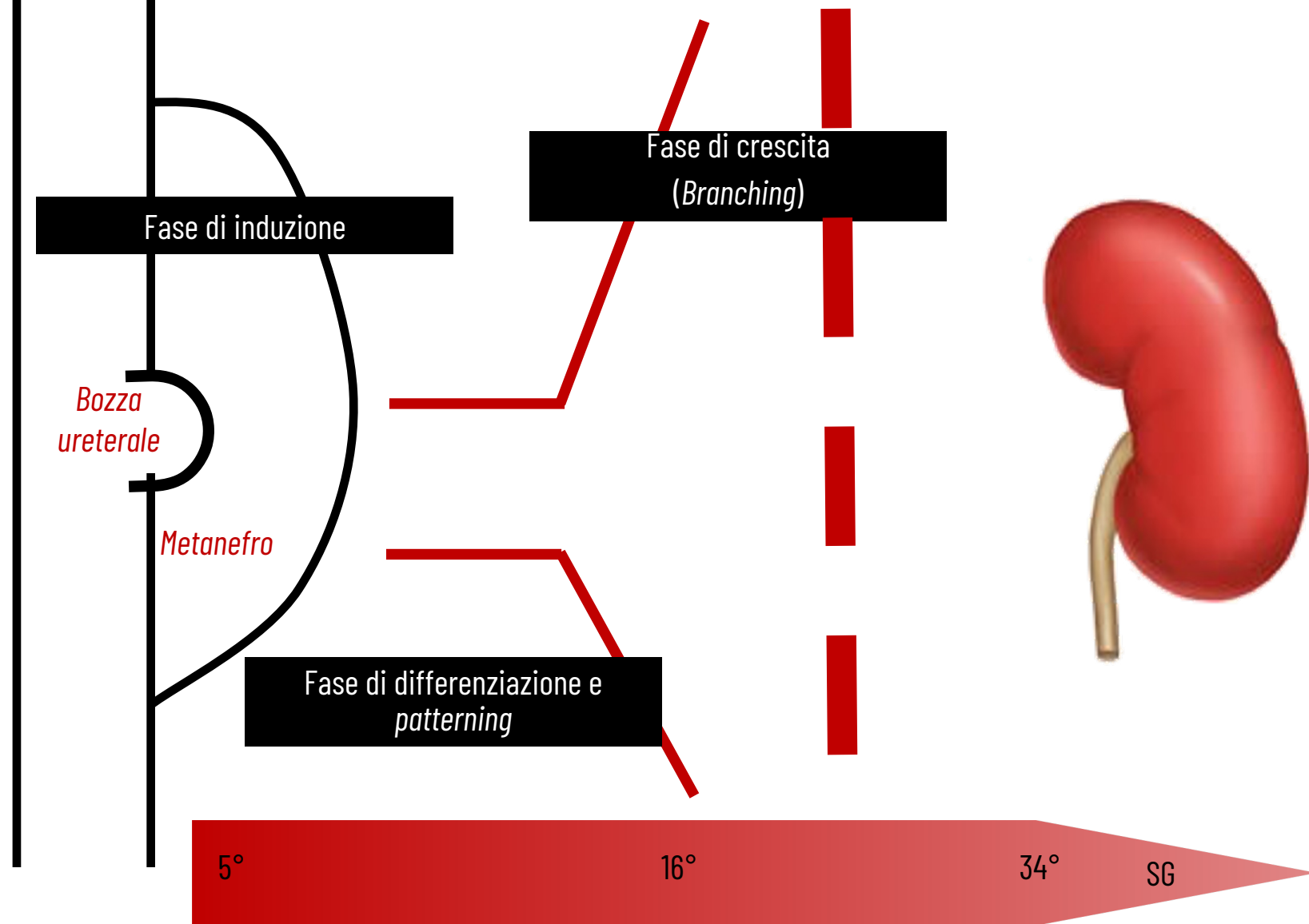
- high risk: decreased eGFR (i.e., mean eGFR for age -1 SD in children younger than 2 years, <90 ml/min per 1.73 m² in children older than 2 years) and/or proteinuria, and/or hypertension

1. As feasible according to the organization of the local health care system; 2. With measurement of kidney length/size; 3. If proteinuria is detected, quantification by urine protein/urine creatinine should be performed in the second morning urine sample, remembering that normal values are <0.5 mg/mg until two years of age and <0.2 thereafter

Legend: CAKUT congenital anomalies of kidney and urinary tract, eGFR estimated glomerular filtration rate

Which nutritional and lifestyle habits should be adopted for children with a CSK?

Additional risk factors for kidney damage, including nephrotoxic drugs, should be avoided or minimized [21, 92]. In this respect, we suggest that acetaminophen be used to reduce fever and to relieve pain, thus avoiding the use of non-steroidal anti-inflammatory drugs.



Prematurity Disrupts Nephrogenesis

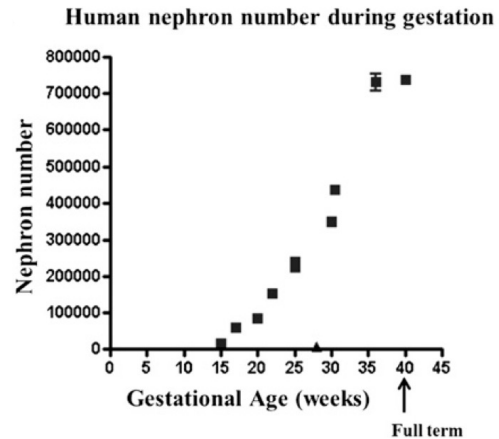
Conception

Week 5

Nephrogenesis commences

Week 9

Formation of nephrons begins



From ~ Week 20

Nephrogenesis rapidly ongoing

60% of nephrons during III trimester

Week 34-36

Nephrogenesis is complete in humans

No new nephrons formed after this time point

Black et al. Effects of Preterm Birth on the Kidney
In: Basic Nephrology and Acute Kidney Injury, 2012

Carmody and Charlton. Pediatrics 2013;131:1168-1179

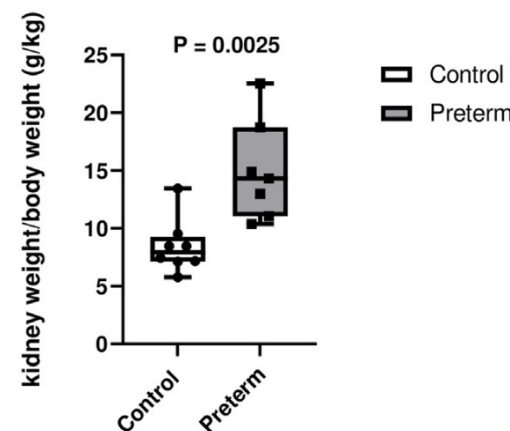
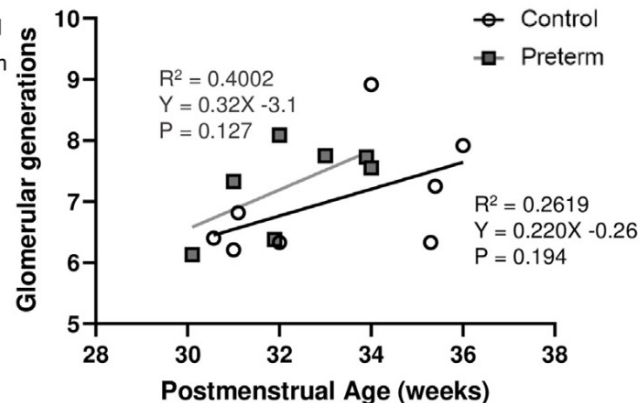
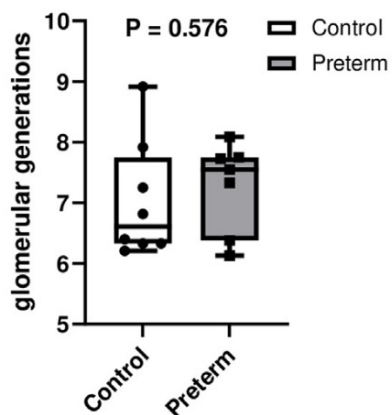
La gestione della febbre...nel bambino disidratato e nel bambino pre-termine

Human Nephrogenesis can Persist Beyond 40 Postnatal Days in Preterm Infants

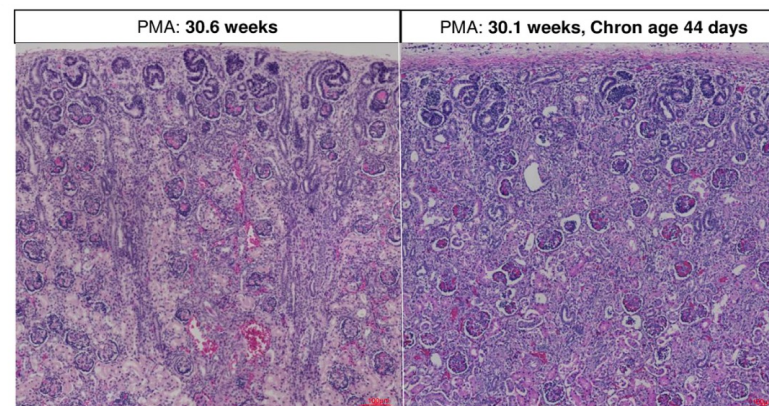
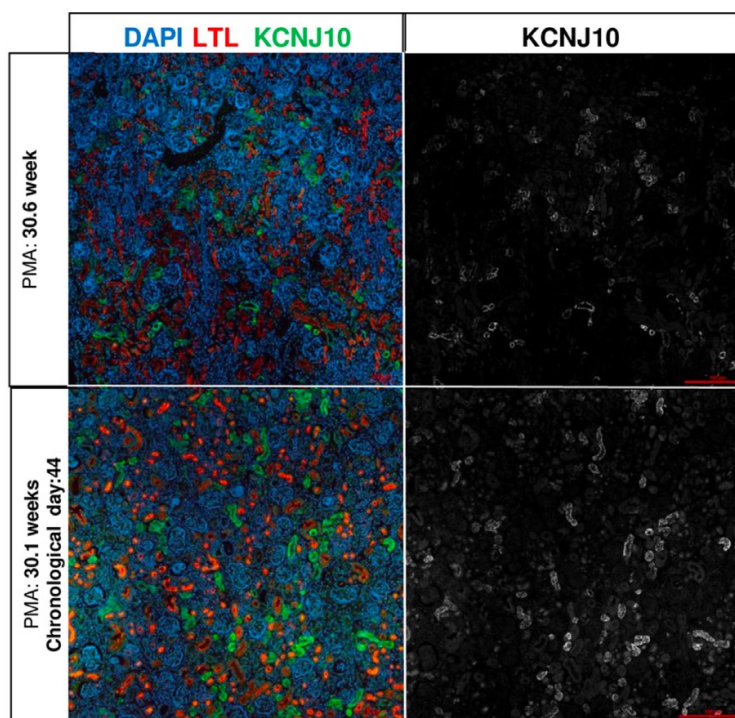
Characteristics	Control (n = 8)	Preterm (n = 7)
Gestational age (weeks)	33.01 ± 2.34 (30.00–36.00)	25.41 ± 1.51 ^a (23.90–28.00)
Postmenstrual age (weeks)	33.17 ± 2.25 (30.57–36.00)	32.27 ± 1.46 (30.1–34.00)
Chronological age (days)	1.00 ± 1.51 (0–4)	49.71 ± 8.24 ^a (41–62)
Male (%)	25	28.5
Postmortem interval (hours)	40.25 ± 29.63 (10–96)	32.29 ± 29.28 (14–96)
Birth weight (g)	1817.75 ± 420.61 (1022–2235)	760.80 ± 152.59 ^a (564–900)
Autopsy weight (g)	1809 ± 425.84 (1022–2235)	1489 ± 341.09 (910–1845)
Kidney weight (g)	15.83 ± 7.07 (5.90–28.90)	21.29 ± 3.47 (16.10–25.70)
Crown-heel length (cm)	39.22 ± 8.49 ^b (24.70–45.40)	39.33 ± 3.41 (34.40–44.40)
Crown-rump length (cm)	29.11 ± 4.66 ^b (21.50–33.00)	29.44 ± 1.40 (27.00–31.20)

^aP < 0.05 compared with control

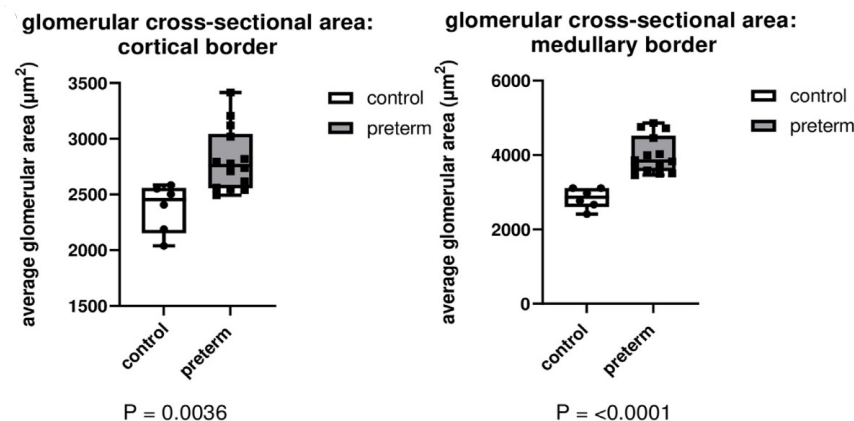
^bn = 5 for control group.



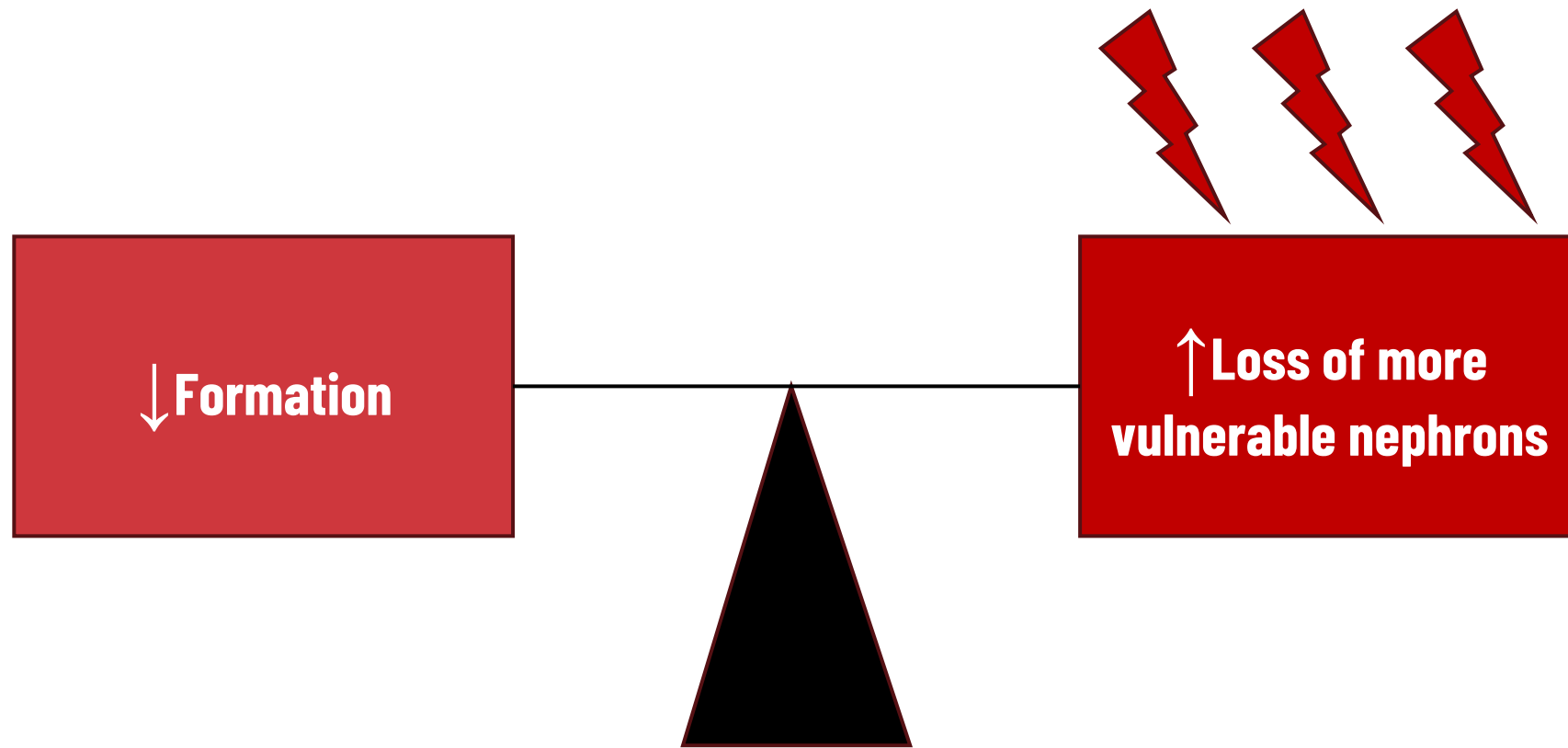
Human Nephrogenesis can Persist Beyond 40 Postnatal Days in Preterm Infants



Early nephron stress



EFFECTIVE NEPHRON ENDOWMENT

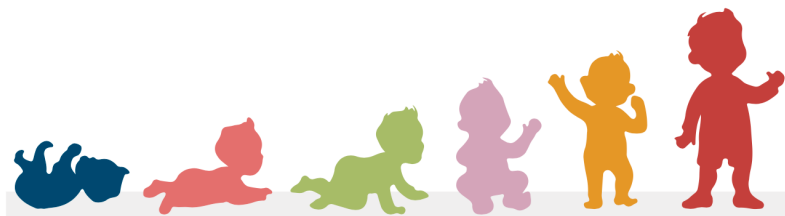


EFFECTIVE NEPHRON ENDOWMENT

Task force sul Follow-up del neonato pretermine



Il Follow-up del neonato PRETERMINE I primi sei anni di vita



A developmental approach to the prevention of hypertension and kidney disease: a report from the Low Birth Weight and Nephron Number Working Group

Valerie A Luyckx*, Norberto Perico*, Marco Somaschini, Dario Manfellotto, Herbert Valensise, Irene Cetin, Umberto Simeoni, Karel Allegaert, Bjorn Egil Vikse, Eric A Steegers, Dwomoa Adu, Giovanni Montini, Giuseppe Remuzzi, Barry M Brenner, for the writing group of the Low Birth

Weight and Nephron Number Working Group†

Lancet 2017; 390: 424-28

Proposed schedule for regular monitoring of preterm and LBW individuals throughout life

Monitoring of IUGR, preterm, LBW infants, and of those exposed to preeclampsia

- Age ≥ 3 to 5 years:
 - Annual BP measurements and urinalysis
- Age >5 to 19 years:
 - Screening (BP and urinalysis) should be done at well-child checks, medical visits or at 2-year intervals
- Age >19 to 40 years:
 - BP, urinalysis and BMI should be monitored every 2 years
- Age >40 years:
 - BP, urinalysis and BMI should be monitored annually

*When possible, a baseline renal ultrasound should be done to detect small kidneys, asymmetry, or structural abnormalities

**In very preterm newborns (GA <32 weeks) or in case of neonatal AKI, screening should be initiated before age 1 year

***If risk factors are detected (high BP, proteinuria, previous AKI, renal anomalies, cardiovascular disease, obesity or diabetes), renal function evaluation should be undertaken at least every 2 years

Proposed schedule for regular monitoring of preterm and LBW individuals throughout life

Monitoring of IUGR, preterm, LBW infants, and of those exposed to preeclampsia - «other»

- Fasting blood sugar should be monitored in individuals with elevated BMI after 30 years of age
- Any preterm or LBW women becoming pregnant should be monitored closely for gestational weight gain, fetal growth and pre-eclampsia
- **Education about lifestyle and avoidance of nephrotoxins is important for families of preterm or LBW children**
- Rapid catch-up growth should be avoided to prevent obesity-associated exacerbation of renal risk
- From childhood onwards, a prudent dietary pattern (reduced sodium, carbohydrates, and saturated fat) should be combined with enhanced physical activity and avoidance of smoking

Corretto utilizzo degli antipiretici nella gestione della febbre: il punto di vista del nefrologo pediatrico

Evitare l'uso di **FANS** nei pazienti con:

- Disidratazione
- Trattamento con ACE inibitori o diuretici
- Affetti da sindrome nefrosica (specie in fasi di recidiva)
- Affetti da CAKUT

Cautela nell'uso di FANS anche nei pazienti con **potenziale ridotto patrimonio nefronico** (neonati prematuri o di basso peso alla nascita).

Grazie per l' attenzione