Welcome to

ERKNet/ERA Educational Webinars on
Pediatric Nephrology & Rare Kidney Diseases

WEBINAR

28/06/22

Tom.Nijenhuis@Radboudumc.nl

Gitelman syndrome
Adult view

Speaker: Tom Nijenhuis (Nijmegen, Netherlands)

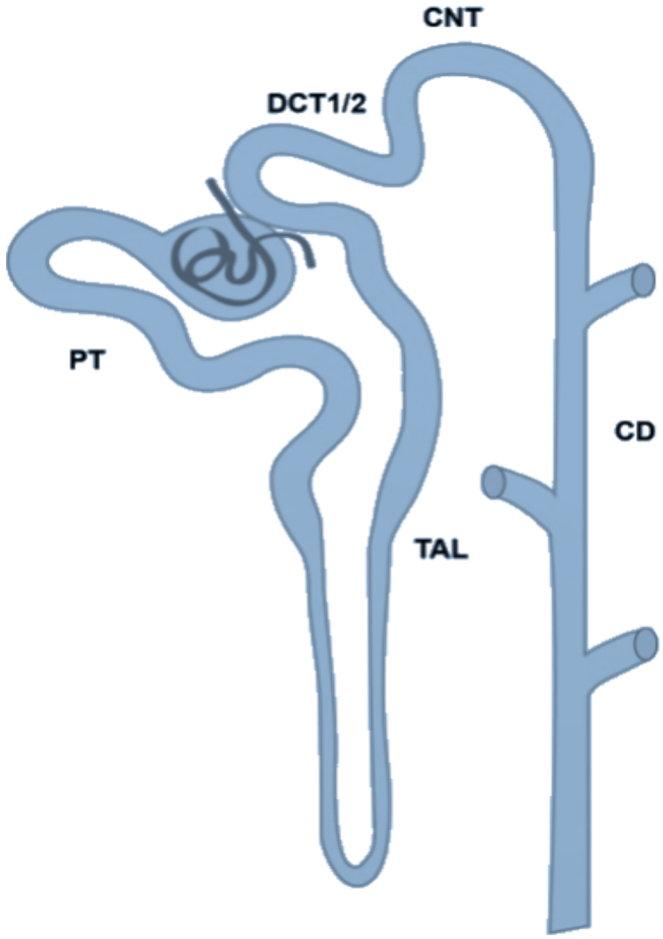
Patient: Voice: Gitelman patient

Moderator: Elena Levtchenko (Leuven, Belgium)

ERKNet
The European
Rare Kidney Disease
Reference Network

ERA
LEADING EUROPEAN NEPHROLOGY

Without renal tubules, we would lose…



UF ~ 180 liter water per day

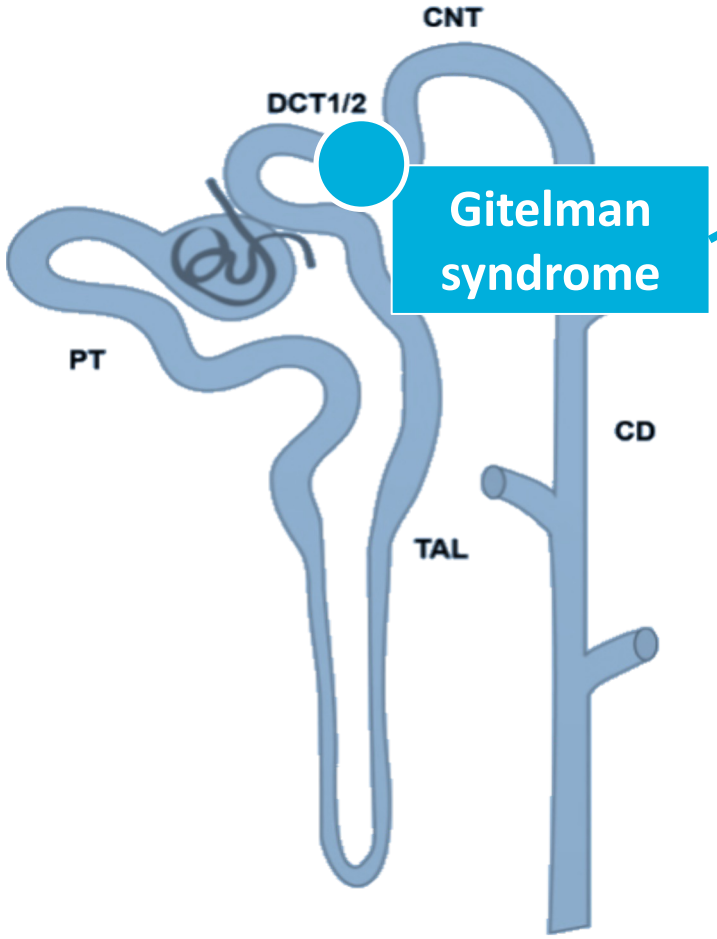
Na ~ 1.5 kg salt per day

K ~ 48 bananas per day

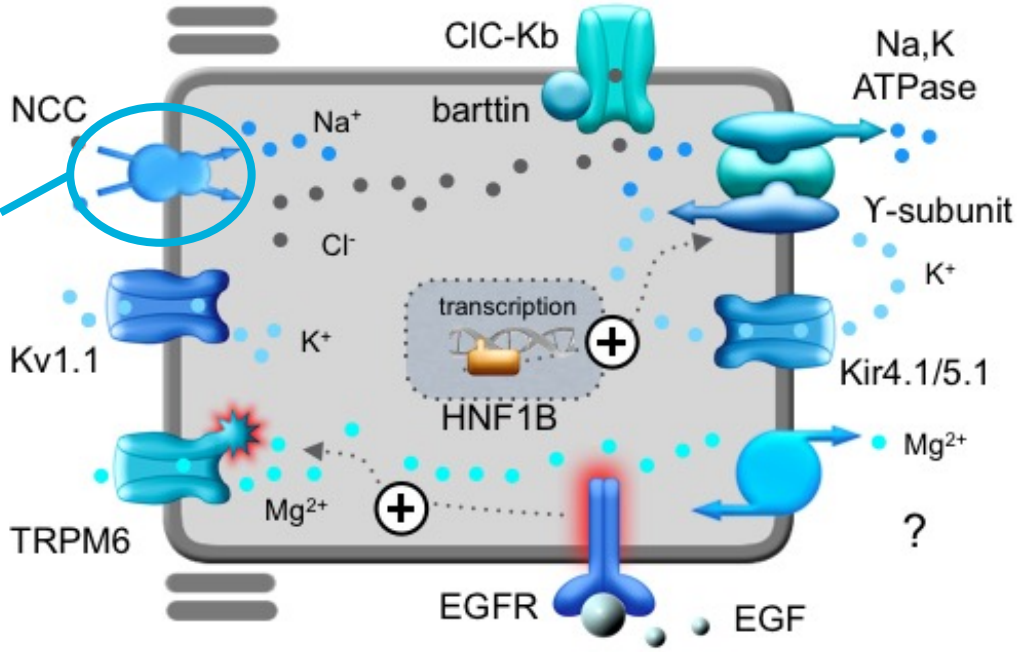
Ca ~ 7 liters milk per day

Mg ~ 2 kg almonds per day

Gitelman syndrome: salt-losing tubulopathy



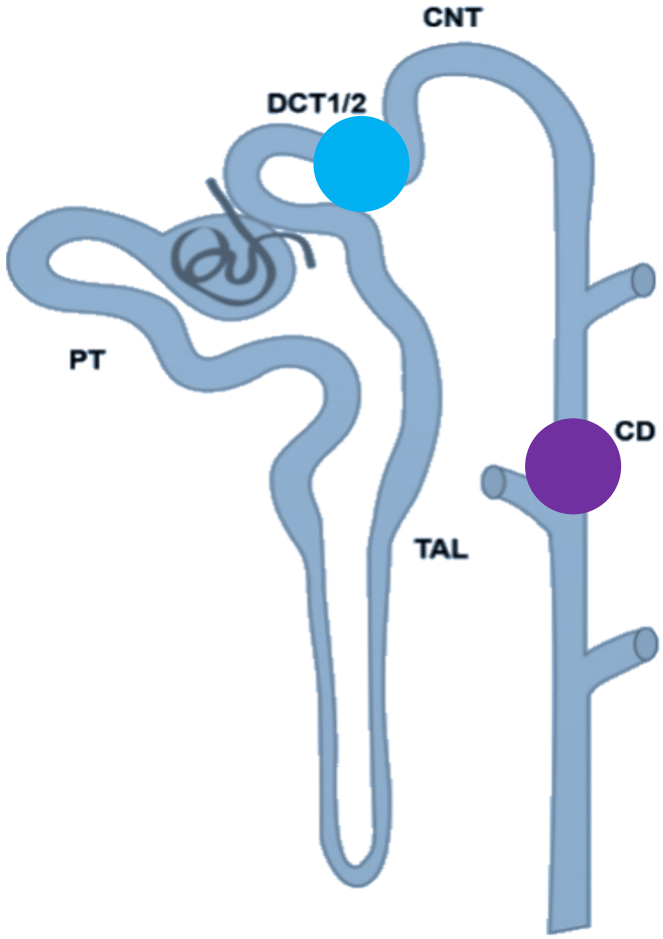
Distal convoluted tubule (DCT)



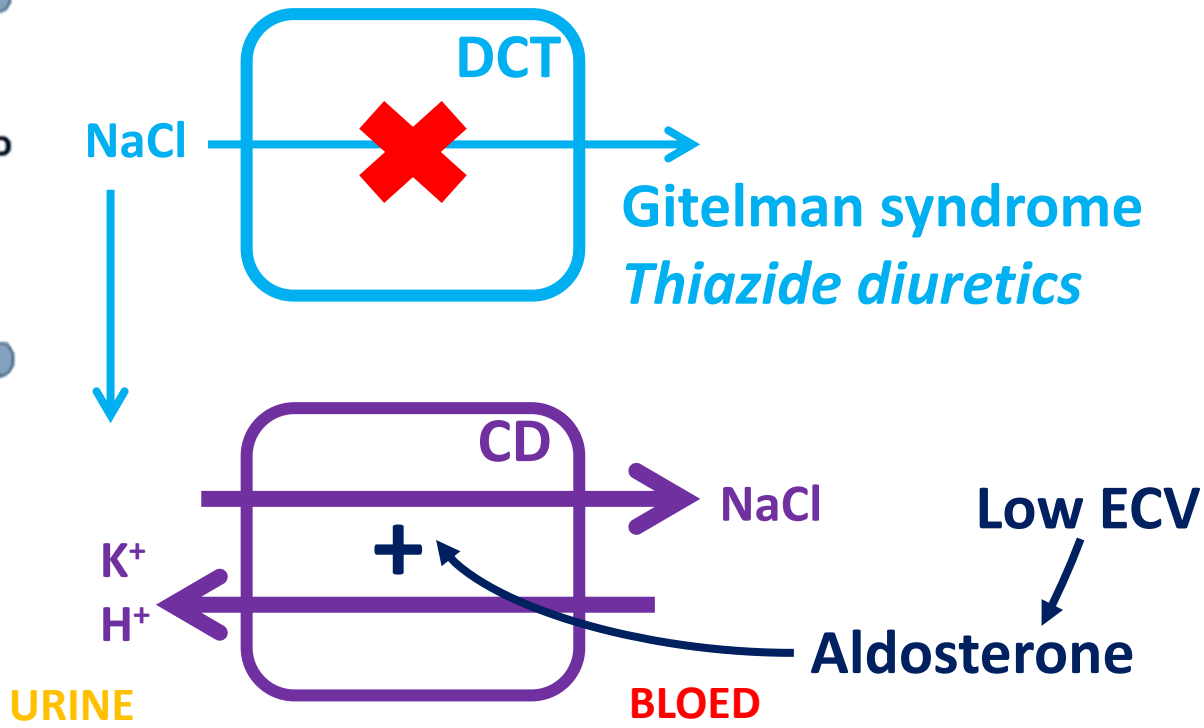
Autosomal recessive disorder

Mutations in *SLC12A3*, encoding the Na,Cl-cotransporter (NCC)

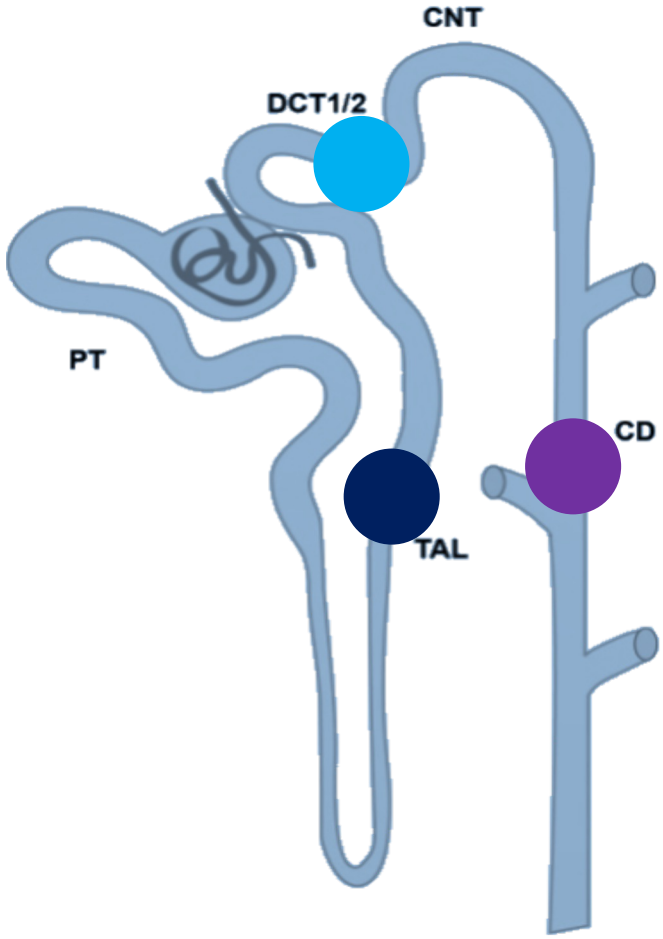
Hypokalemic alkalotic salt-losing nephropathy

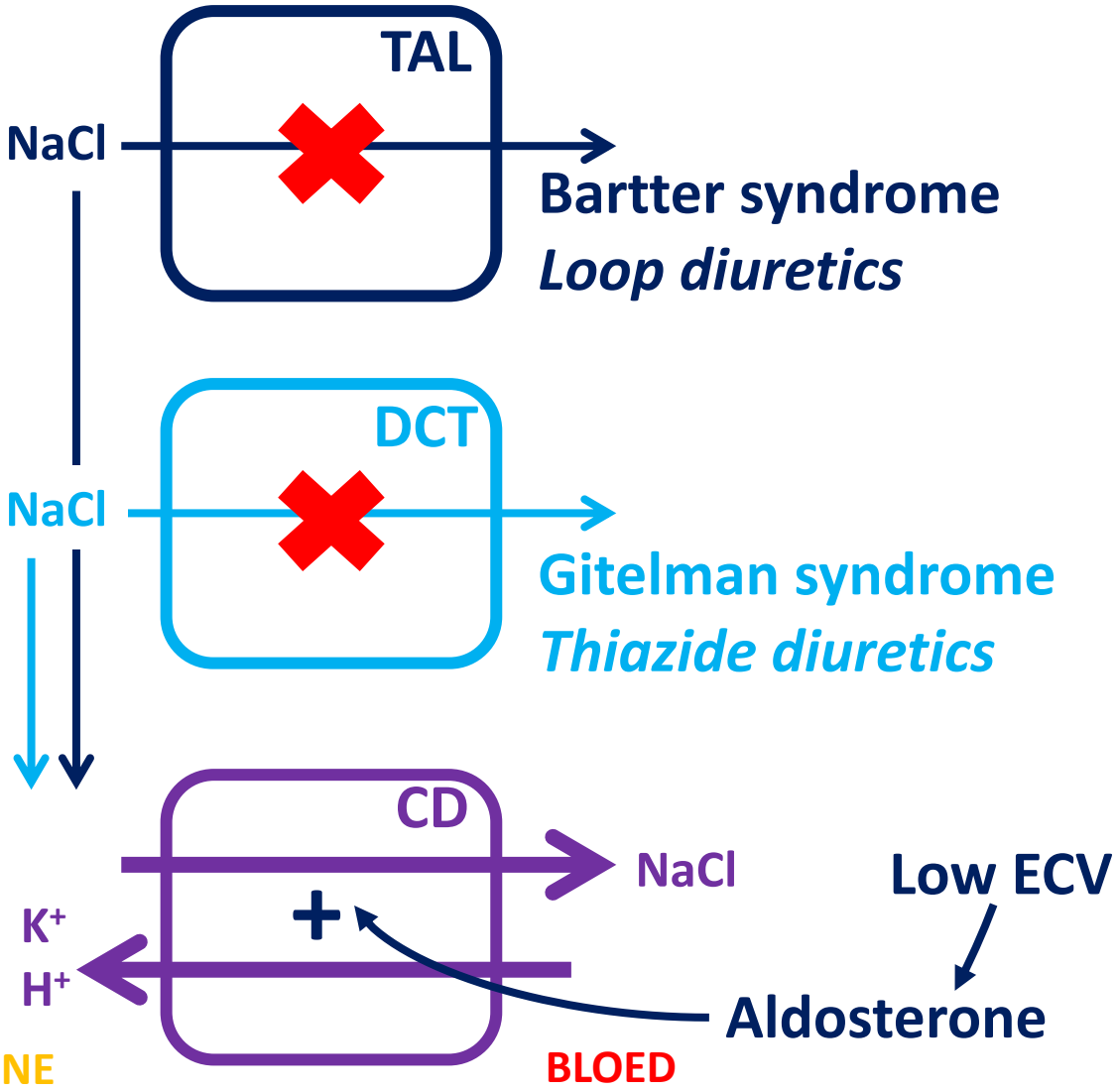


Salt-losing tubulopathies induce hypokalemic alkalosis by increasing distal tubular flow and sodium delivery to ENaC

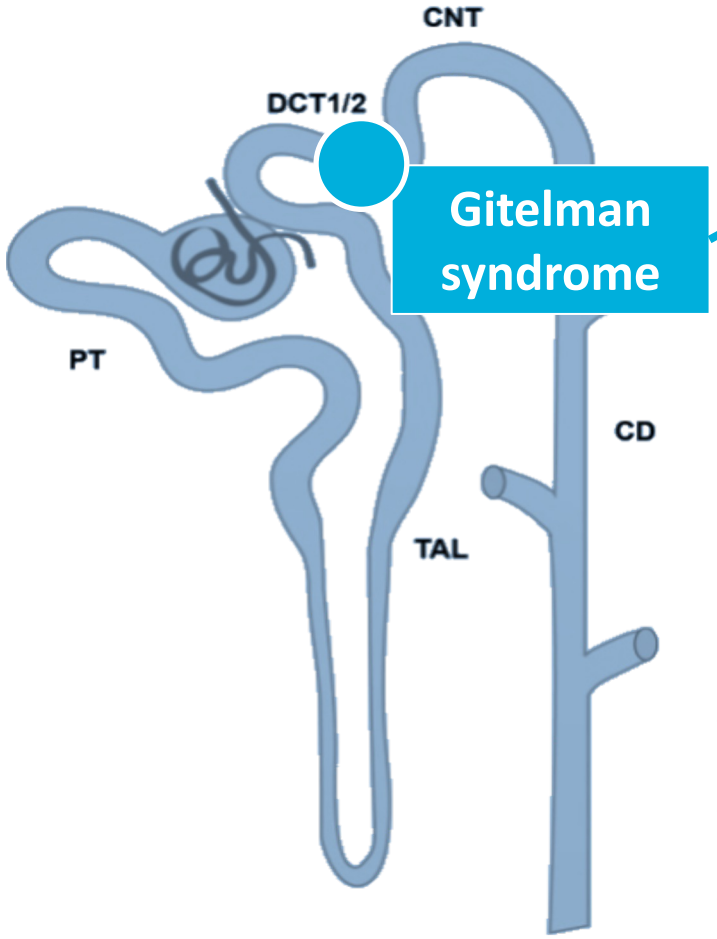


Hypokalemic alkalotic salt-losing nephropathy





Gitelman syndrome



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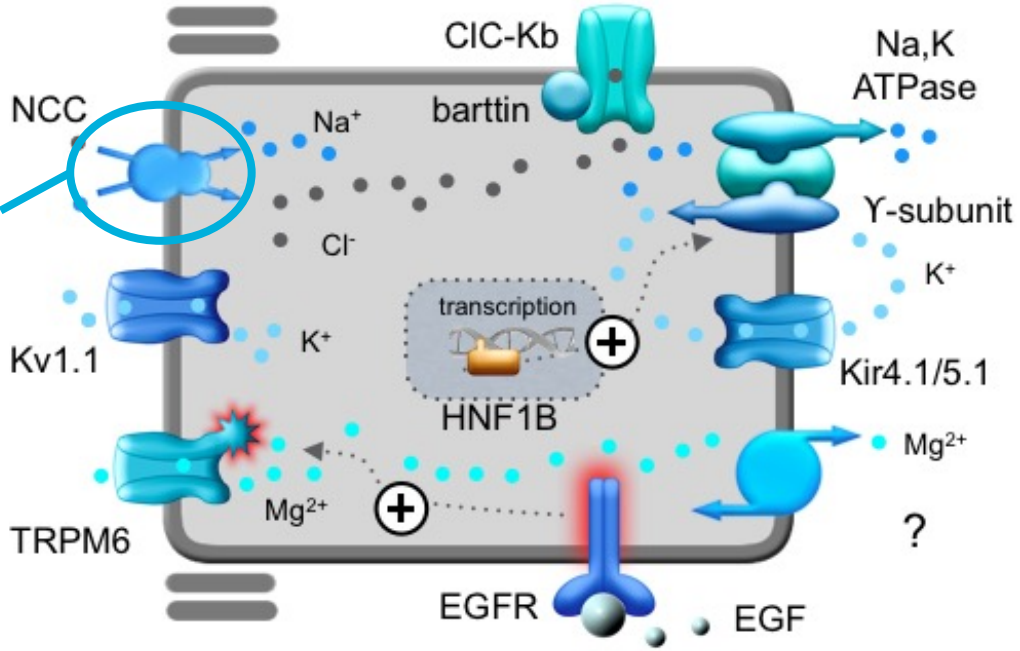

- Hypokalemic alkalosis
- Renal hypomagnesemia
- Hypocalciuria
- Normal to low blood pressure

Signs and symptoms in Gitelman syndrome

Table 1 | Clinical manifestations encountered in Gitelman syndrome patients

Most common (>50% of patients)	Prominent (20% to 50% of patients)	Occasional (<20%)	Rare (case reports)
Salt craving	Fainting	Early onset (before age 6)	Seizure
Cramps, muscle weakness	Polyuria	Failure to thrive	Ventricular tachycardia
Fatigue	Arthralgia	Growth retardation	Rhabdomyolysis
Dizziness	Chondrocalcinosis	Pubertal delay	Blurred vision
Nocturia	Prolonged QT interval	Vertigo, ataxia	Pseudotumor cerebri
Thirst, polydipsia	Febrile episodes	Carpopedal spasm, tetany	Sclerochoroidal ca
Paresthesia, numbness		Vomiting	
Palpitations		Constipation	
Low blood pressure		Enuresis	
		Paralysis	

Adapted, with permission, from Devuyst *et al.*[83]

Patient voice

Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference
Blanchard et al. *Kidney Int* 2017

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Patient's voice

Introduction

46 years old, diagnosed with Gitelman syndrome at 39

Childhood / Adolescence

Childhood

- Kindergarten: early symptoms linked to Gt
- Supplemented mineral(s)/regular blood check
- Elementary school: normal health, occasional light symptoms, no check-ups
- Did not use medication or supplements at that time

Adolescence

- Normal health, except for the occasional light symptoms, no check-ups
- Did not use medication or supplements at that time

Patient's voice

Adult age

- Early 30s, severe Gitelman Syndrome symptoms. Six months recuperation
- KCl and Mg supplementation
- Good health for 9 years. No major health symptoms related to Gt
  No regular check-ups
- 6,5 years ago: relapse. Diagnosis via DNA test/Dosage of KCl and Mg increased / Regular health check since then/Energy levels decreased/ Recuperation: 1 year

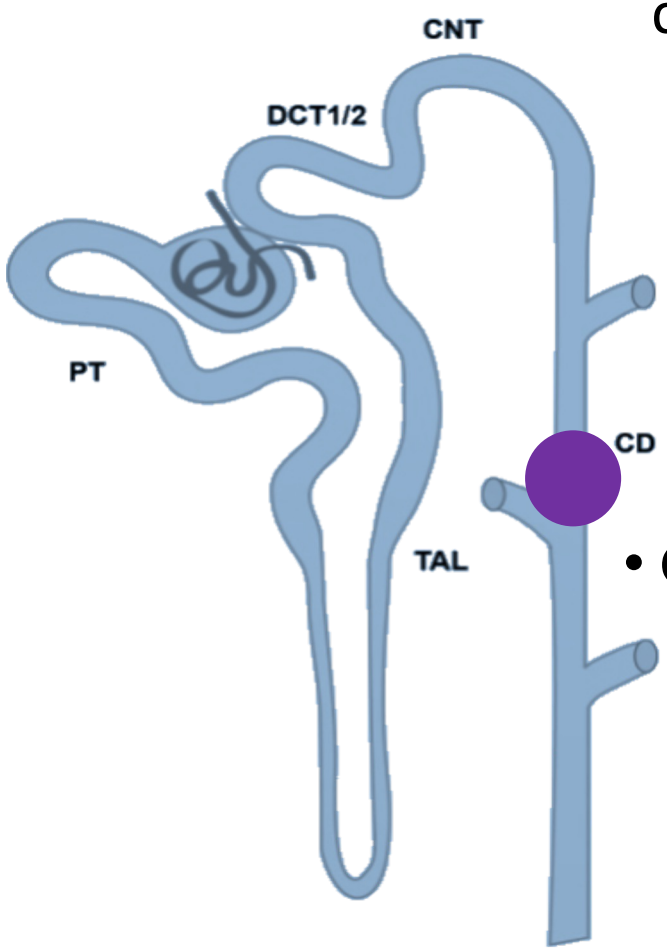
Challenges / Needs / Concerns

- Ups-and-downs in physical health
- Emotional health: uncertainty, frustrations and anxiety, not trusting the body, fear, over compensation (work)

Patient's voice

- Acceptance, adaptation ,quality of life, work-life balance, social life, dealing with misunderstandings
- Increase awareness about Gt among healthcare professionals
- Personalized treatment
- Finding the suitable supplement/dosage, side effects
- Coverage healthcare insurance
- Availability of medication: production stop/delays
- Testing on mineral levels: cell vs. serum (costs, availability, etc.) /self-tests
- Long term effects of prolonged lower mineral level(s)? Other ways of prevention next to trying to maintain acceptable mineral levels?

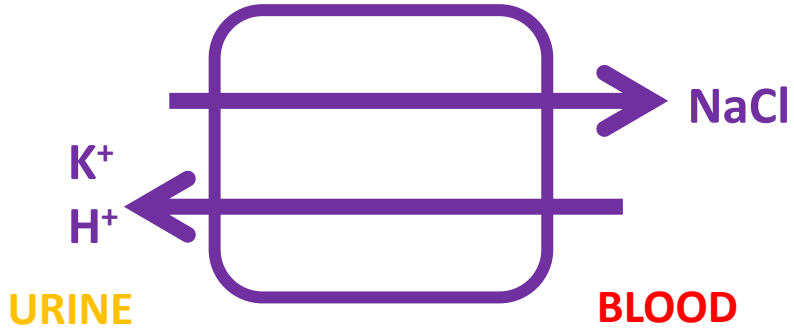
Differential diagnosis of hypokalemic alkalosis



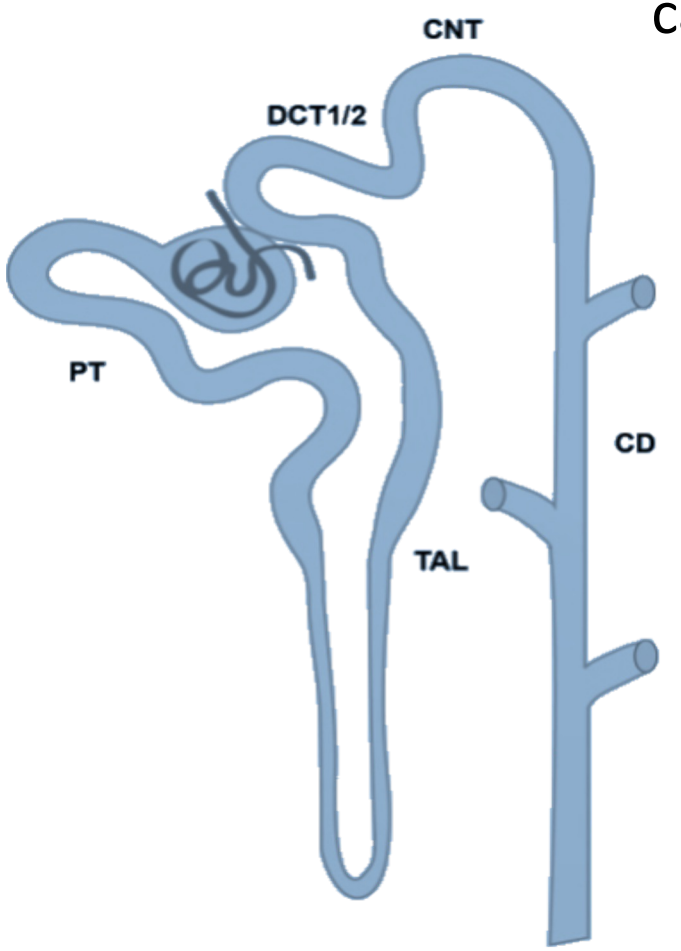
- **Hypokalemic alkalosis** results from acquired causes or rare (genetic) tubular disorders

acquired	genetic
loop diuretics	Bartter syndrome
thiazide diuretics	Gitelman syndrome
anorexia/bulimia laxative	
liquorice	Liddle's syndrome
hyperaldo	11-betaHSD mutations (AME)

- Gain-of-function mutations in the epithelial sodium channel ENaC cause **Liddle's syndrome**



Differential diagnosis of hypokalemic alkalosis



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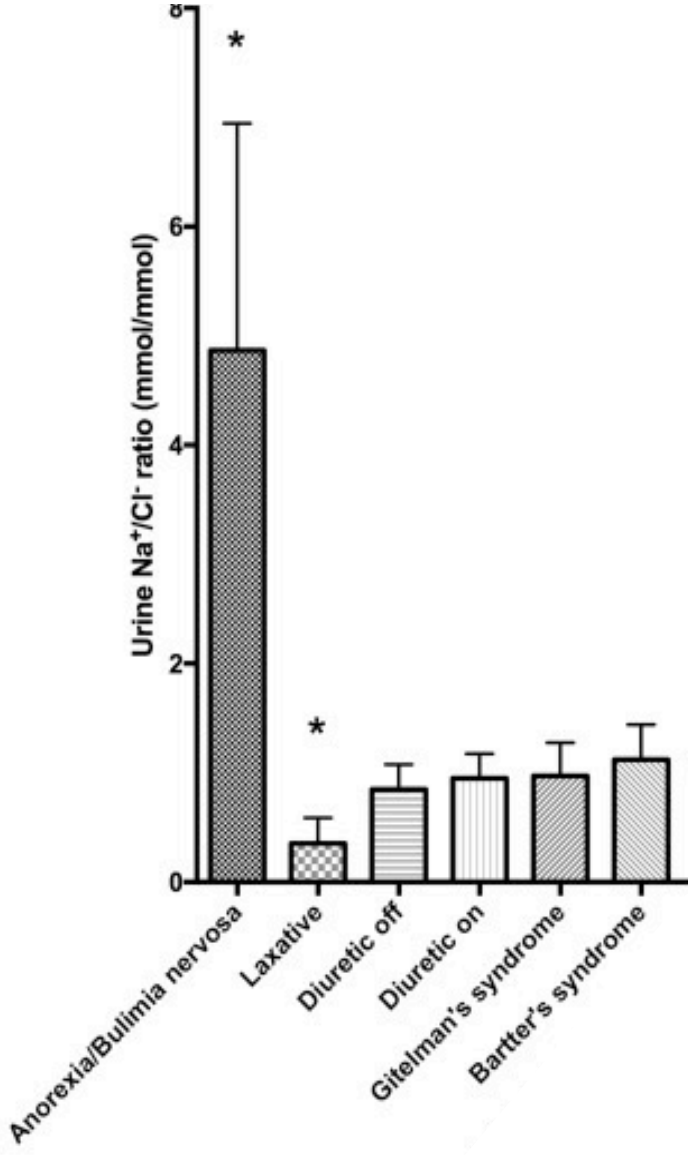
thiazide diuretics	Gitelman syndrome
anorexia/bulimia	
laxative	
liquorice	~~Liddle's syndrome~~
~~hyperaldo~~	~~11-betaHSD mutations (AME)~~

Na and Cl excretion in hypokalemic alkalosis



- **GI loss** -> low urine Na and Cl
- **Renal loss** -> high urine Na and Cl

- **Anorexia/Bulimia:** gastric juice contains more Cl than Na -> less Cl than Na in urine
- **Laxatives:** stool contains more K and Na than Cl -> less Na than Cl in urine

- **Diuretics/salt-losing nephropathies:** urine Na and Cl high and coupled (ratio~1)
- **Diuretics:** variably high and low urinary Na and Cl

Identification of the Causes for Chronic Hypokalemia: Importance of Urinary Sodium and Chloride Excretion. Wu et al. *Am J Med* 2017

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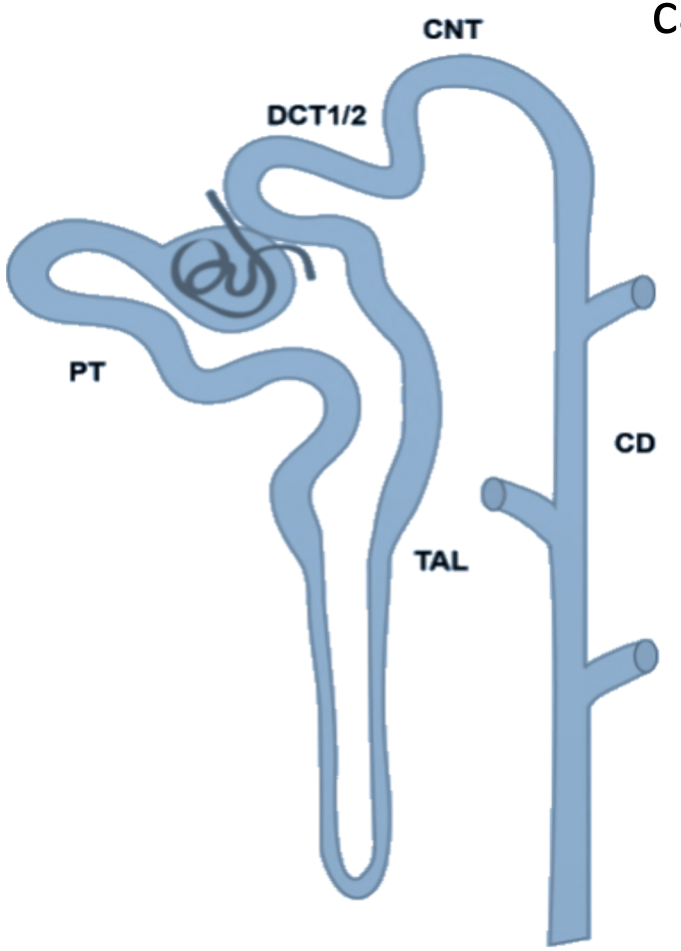
Differential diagnosis of hypokalemic alkalosis



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acquired	genetic
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~~thiazide diuretics~~	Gitelman syndrome
~~anorexia/bulimia~~	
~~laxative~~	
~~liquorice~~	~~Liddle's syndrome~~
~~hyperaldo~~	~~11-betaHSD mutations (AME)~~

Diagnosing Gitelman syndrome

Table 2 | Diagnostic criteria for Gitelman syndrome

Criteria for suspecting a diagnosis of GS

- Chronic hypokalemia (<3.5 mmol/l) with inappropriate renal potassium wasting (spot potassium-creatinine ratio >2.0 mmol/mmol [>18 mmol/g])
- Metabolic alkalosis
- Hypomagnesemia (<0.7 mmol/l [<1.70 mg/dl]) with inappropriate renal magnesium wasting (fractional excretion of magnesium >4%)
- Hypocalciuria (spot calcium-creatinine ratio <0.2 mmol/mmol [<0.07 mg/mg]) in adults.[a]
- High plasma renin activity or levels
- Fractional excretion of chloride > 0.5%[b]
- Low or normal-low blood pressure
- Normal renal ultrasound

Criteria for establishing a diagnosis of GS

- Identification of biallelic inactivating mutations in *SLC12A3*

Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference
Blanchard et al. *Kidney Int* 2017

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Diagnosing Gitelman syndrome

Table 2 | Diagnostic criteria for Gitelman syndrome

Features against a diagnosis of GS

- Use of thiazide diuretics or laxatives
- Family history of kidney disease transmitted in an autosomal dominant mode
- Absence of hypokalemia (unless renal failure); inconsistent hypokalemia in absence of substitutive therapy
- Absence of metabolic alkalosis (unless coexisting bicarbonate loss or acid gain)
- Low renin values
- Urine: low urinary potassium excretion (spot potassium-creatinine ratio <2.0 mmol/mmol [<18 mmol/g]); hypercalciuria
- Hypertension,[c] manifestations of increased extracellular fluid volume
- Renal ultrasound: nephrocalcinosis, nephrolithiasis, unilateral kidneys, cystic kidneys
- Prenatal history of polyhydramnios, hyperechogenic kidneys
- Presentation before age 3 years[c]

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Blanchard et al. *Kidney Int* 2017

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“Gitelman-like” tubulopathies

	Gitelman syndrome
Gene	*SLC12A3*
Inheritance	AR
Salt-losing	+
Alkalosis	+
Serum K	↓
Serum Mg	↓
Serum Ca	=/↑
Urine Ca	↓
RAAS	↑
Blood pressure	=/↓
eGFR	=
(Extra)renal signs and symptoms	-

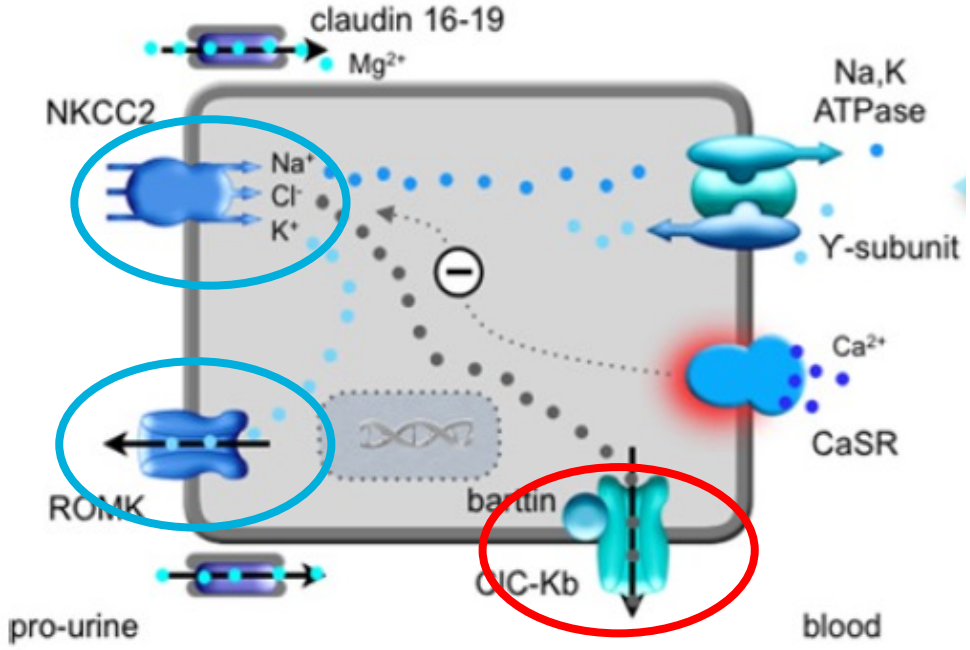
“Gitelman-like” tubulopathies

	Gitelman syndrome	Bartter sy type III
Gene	*SLC12A3*	*CLCNKB*
Inheritance	AR	AR
Salt-losing	+	+
Alkalosis	+	+
Serum K	↓	↓
Serum Mg	↓	=/↓
Serum Ca	=/↑	=
Urine Ca	↓	↑/=/↓
RAAS	↑	↑
Blood pressure	=/↓	=/↓
eGFR	=	=/↓
(Extra)renal signs and symptoms	-	Nephrolithiasis Nephro-calcinosis

„Bartter-like syndromes“

Set of inherited tubular disorders with hypokalemic metabolic alkalosis

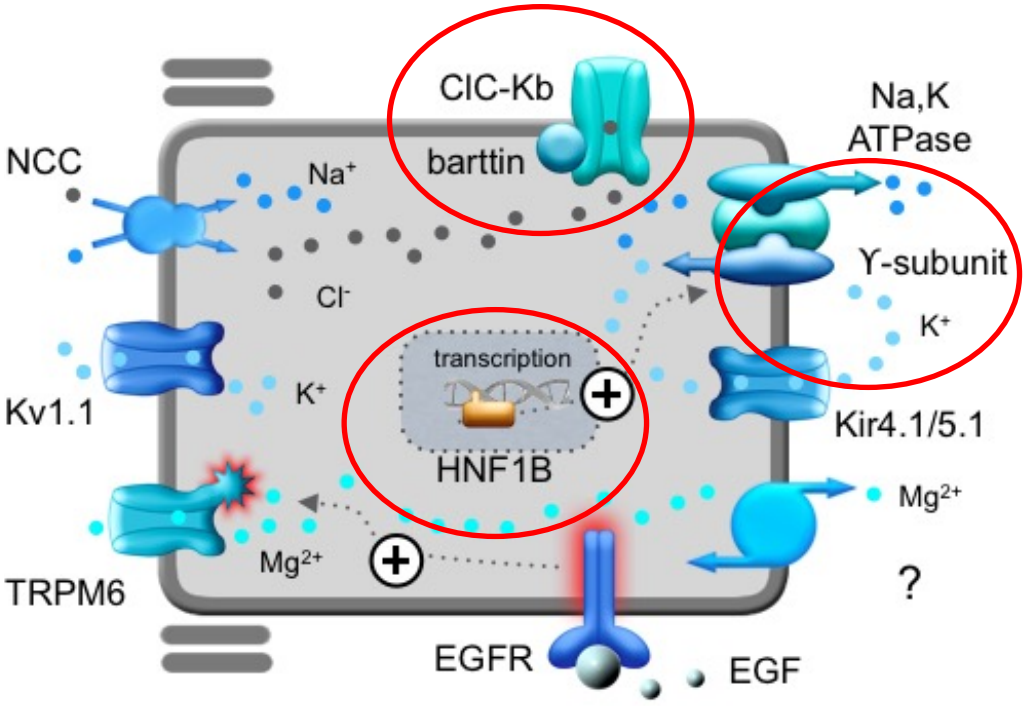
- antenatal Bartter syndrome — NKCC2, KCNJ1
- classic Bartter syndrome — ClC-Kb
- Gitelman syndrome — NCC



“Gitelman-like” tubulopathies

	Gitelman syndrome	Bartter sy type III
Gene	*SLC12A3*	*CLCNKB*
Inheritance	AR	AR
Salt-losing	+	+
Alkalosis	+	+
Serum K	↓	↓
Serum Mg	↓	=/↓
Serum Ca	=/↑	=
Urine Ca	↓	↑/=/↓
RAAS	↑	↑
Blood pressure	=/↓	=/↓
eGFR	=	=/↓
(Extra)renal signs and symptoms	-	Nephrolithiasis Nephro-calcinosis

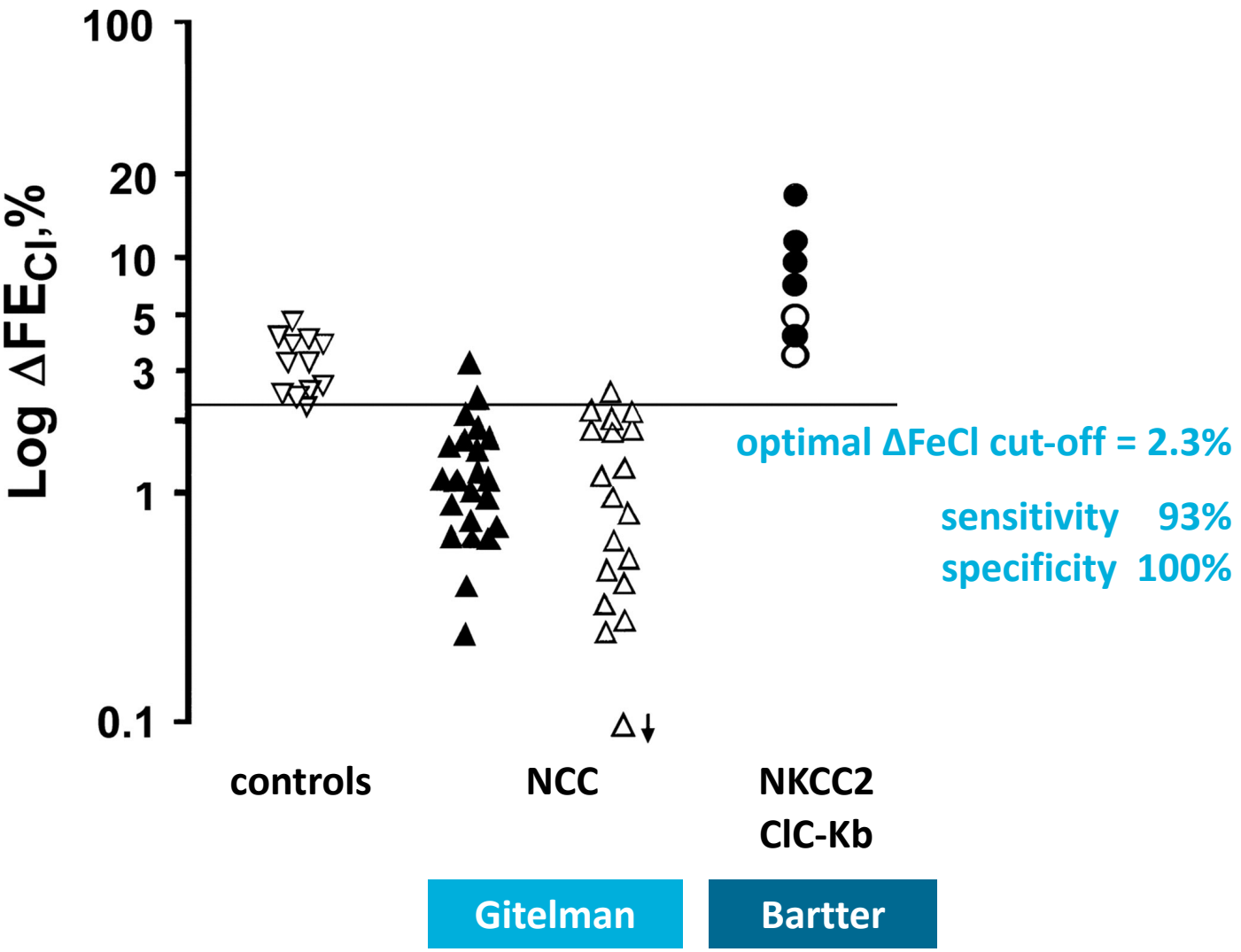
Distal convoluted tubule (DCT)



“Gitelman-like” tubulopathies

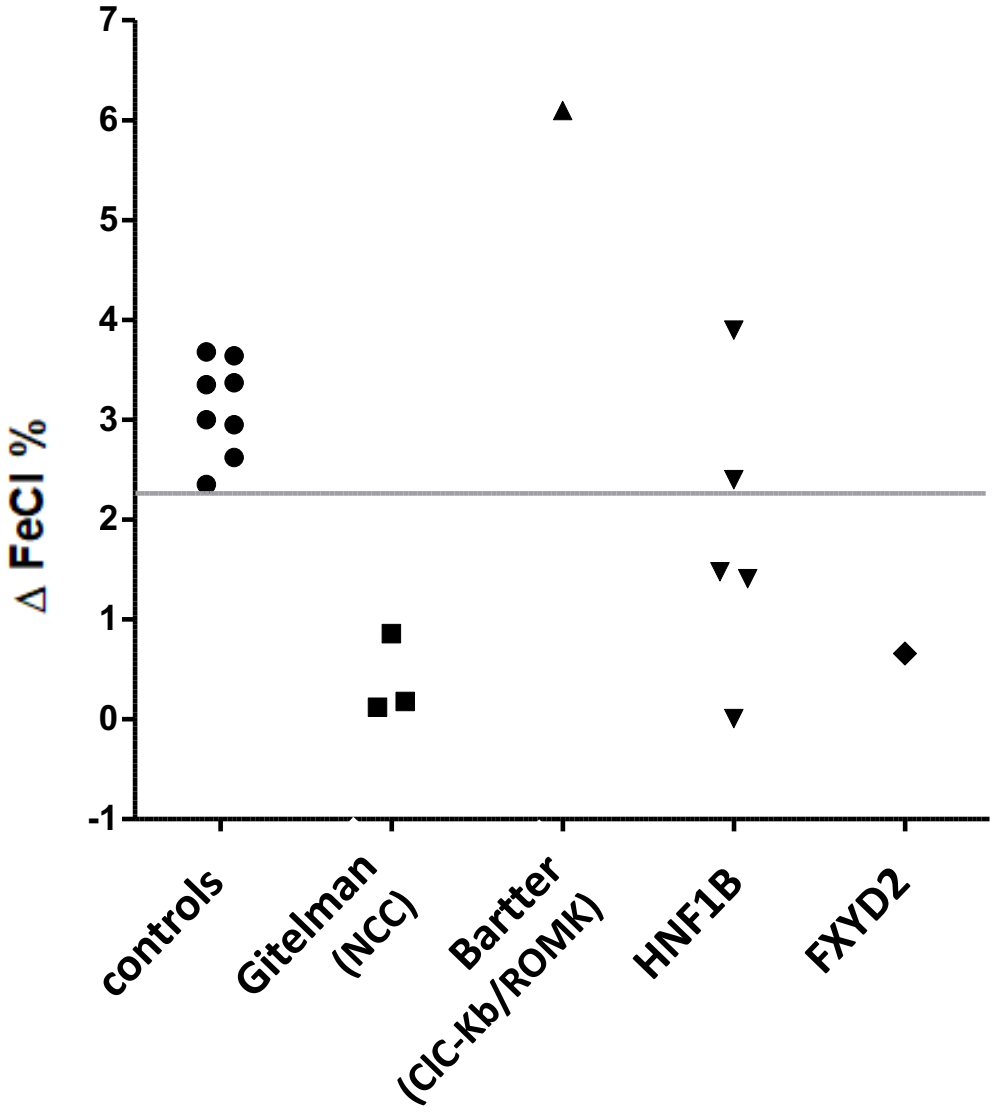
	Gitelman syndrome	Bartter sy type III	(ADTKD-) HNF1B	Isolated dominant hypoMg	Mito-chondrial tubulopathy
Gene	*SLC12A3*	*CLCNKB*	*HNF1B*	*FXYD2*	*MT-TI, MT-TF*
Inheritance	AR	AR	AD	AD	maternal
Salt-losing	+	+	?	?	?
Alkalosis	+	+	+/-	+/-	+/-
Serum K	↓	↓	=/↓	=/↓	=/↓
Serum Mg	**↓**	**=/↓**	**↓**	**↓**	**↓**
Serum Ca	=/↑	=	=	=	=
Urine Ca	↓	↑/=/↓	=/↓	=/↓	=/↓
RAAS	↑	↑	=	=	?
Blood pressure	=/↓	=/↓	=	?	?
eGFR	=	=/↓	=/↓	=	=/↓
(Extra)renal signs and symptoms	-	Nephrolithiasis Nephro-calcinosis	MODY5, gout, renal cysts, urogenital, liver tests	-	?

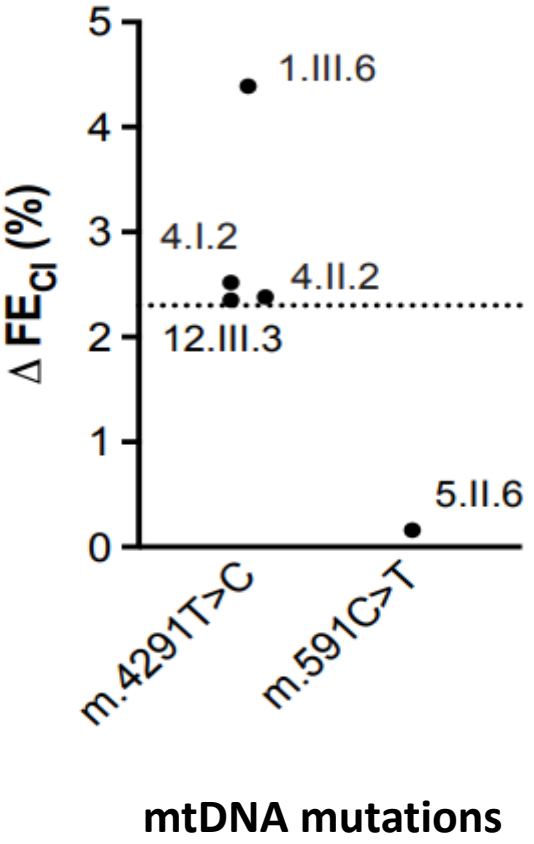
“Gitelman-like” tubulopathies - thiazide test?



Colussi et al. Clin J Am Soc Nephrol 2007

“Gitelman-like” tubulopathies - thiazide test?





Thiazide Responsiveness Testing in Patients With Renal Magnesium Wasting and Correlation With Genetic Analysis: A Diagnostic Test Study.
Bech et al, *Am J Kidney Dis.* 2016

Gitelman-Like Syndrome Caused by Pathogenic Variants in mtDNA.
Viering et al, *J Am Soc Nephrol.* 2022

Acquired “Gitelman-like” tubulopathy

BMC Nephrology

BioMed Central

Case report

Open Access

Gitelman-like syndrome after cisplatin therapy: a case report and literature review

Kessarin Panichpisal, Freddy Angulo-Pernett, Sharmila Selhi and Kenneth M Nugent*

Case presentation: A 42- year-old woman presented with a 20 year-history of hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria after cisplatin-based chemotherapy for ovarian cancer. This patient has had chronic muscle aches and fatigue and has had episodic seizure-like activity and periodic paralysis. Only thirteen other patients with similar electrolyte abnormalities have been described in the literature. This case has the longest follow-up.

Diagnosing "Gitelman-like" syndromes

Table 2 | Diagnostic criteria for Gitelman syndrome

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Criteria for establishing a diagnosis of GS

- Identification of biallelic inactivating mutations in *SLC12A3*

Genetics establishes diagnosis and dictates nomenclature

Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference
Blanchard et al. *Kidney Int* 2017

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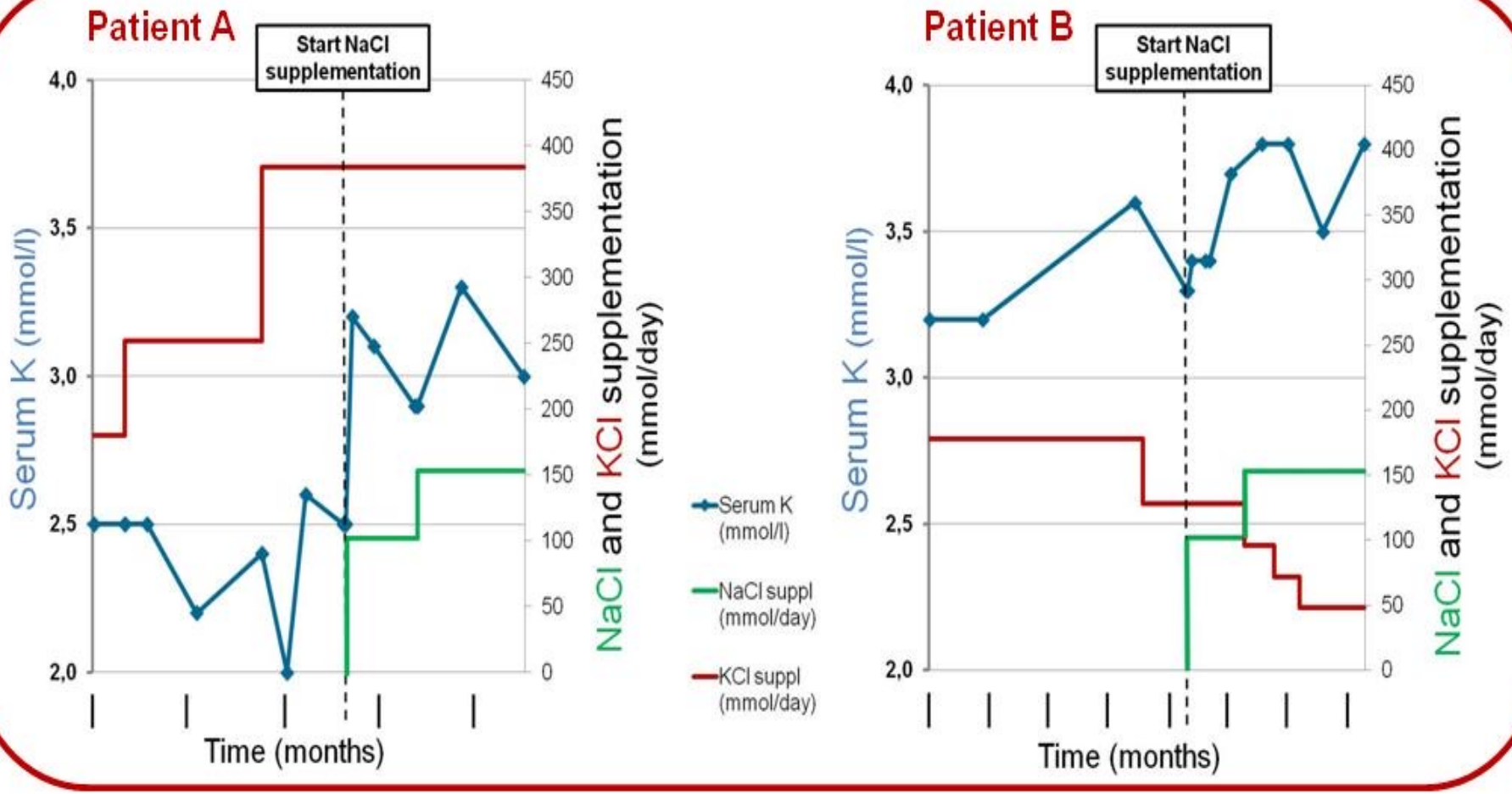
Gitelman syndrome - Treatment

- Ad libitum NaCl intake!
  - Pharmacological NaCl supplementation?



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Blanchard et al. *Kidney Int* 2017

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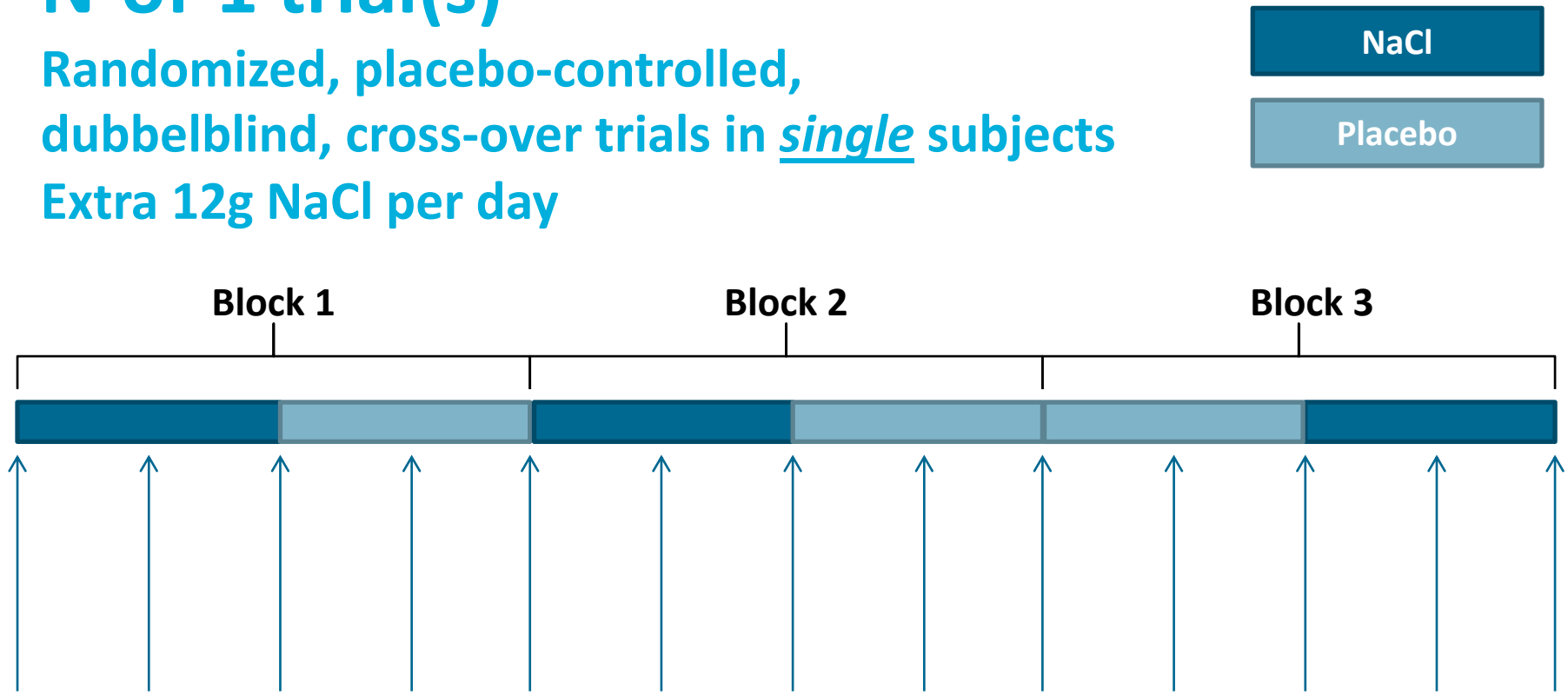
Supraphysiological salt supplementation

N-of-1 trial(s)

Randomized, placebo-controlled, dubbelblind, cross-over trials in *single* subjects

Extra 12g NaCl per day



- **Serum Potassium**
- **PROMS: Personalized symptom and generic QoL (Gitelman symptom score and SF36) questionnaires**

time

Renal hypokalemia - Treatment

- Ad libitum NaCl intake!
  - Pharmacological NaCl supplementation?

- Potassium supplementation
  - Acute and severe symptoms: intravenous K correction
  - Chronic and/or milder symptoms: oral K supplementation
  - Preferably K-chloride, in slow-release form

- Other:
  - Potassium-sparing diuretics (but aggravate salt-wasting)
  - Indomethacin (NSAIDs)?
  - RAAS inhibition?
  - Correct the hypomagnesemia

- Goal: K > 3.0 mmol/l

Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference
Blanchard et al. *Kidney Int* 2017

Renal hypomagnesemia - Treatment

- Magnesium supplementation
  - Acute and severe symptoms: intravenous Mg correction
  - Chronic and/or milder symptoms: oral Mg supplementation

- Other:
  - Potassium-sparing diuretics?

- Goal: Mg ~0,60 mmol/l

~0.6 mmol/l ???

Doctors perspective

Patient perspective

Renal hypomagnesemia – Oral supplementation

Magnesium salts	Carbonate[46]	Chloride[38]*	Citrate[39,40]†	Fumarate[43]	Gluconate[38]‡	Glycinate[45]	L-lactate[48,49]	Oxide[37,40]	K Mg citrate[41]*	DL aspartate[47]	L aspartate[3]	Hydroxide[44]¶	Salicylate[36]‖	Sulfate[42]#	Aminoate[50]
Elemental Mg++/ dose, mg (mEq)	232 (19.0)	64 (5.26)	—(25)	530 (44.16)	27 (2.2, tablets) 54 (4.4, liquid)	100 (8.33)	84 (7)	241 (19–8)	—(24.5)	5	5	2 × 10.3 mmol	600	56.5 mmoles	500 (41.6)
Solubility in water	Nearly insoluble	High	Very good	Good	Moderate	Good	Excellent	Extremely low, 8.6 mg/l	High solubility	Good	Good	Practically insoluble	Freely soluble	Moderately soluble	
Bioavailability	Extremely low	Good	Good	Good	Good; similar to chloride	Good	Excellent	Extremely low	Good; similar to Mg citrate				86–100%		
Oral absorption, % (mEq)		19.68 (1.04)	29.64 (ionic)		19.25 (0.82–0.43)	23.5	42.3 (2.96)	22.8 (0.39) (2% ionic)		44.5	41.7			4 (oral dose), limited and variable extent	
Delivery system	Tablets	Enteric coated tablets	Liquid, tablets	Tablets	Tablets, liquid	Ingestion	Sustained-release caplets	Tablets, capsules	Tablet	Tablet	Tablet	Tablet (Maalox)	Tablet	IV solution	Tablet
Dosage	70 mg elemental Mg (each tablet)	640 mg/d, 1–2 tabs TID	25 mEq Mg, 2–5 tablets	1 Tablet	648 mg/d, 2–4 tablets TID	100 mg	1–2 caplets q 12 h	2–4 tabs TID	7 tablets, 3–5 mEq Mg ea	1 Tablet	1 Tablet	2 Tablets	600 mg, 1 tablet	Intravenous Mg 9.9–49.3 mg/ml	1 Tablet, 3 tablets (100 mg ea Mg)
Side effects	GI distress, diarrhea	GI distress, diarrhea	Laxative, evacuant		GI distress, diarrhea		Minor GI disturbances	Emesis, diarrhea	No GI side effects			Occasional regurgitation and mild diarrhea			
							Sustained	Virtually	Yielded						

However, ….

- Almost all have GI side-effects, mostly diarrea
- Practical availability
- Theory vs practice: both (serum Mg) response and side-effects unpredictable

Bioavailability and Pharmacokinetics of Magnesium After Administration of Magnesium Salts to Humans
Ranade and Somberg. *Am J Therap* 2001

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Renal hypomagnesemia – Oral supplementation

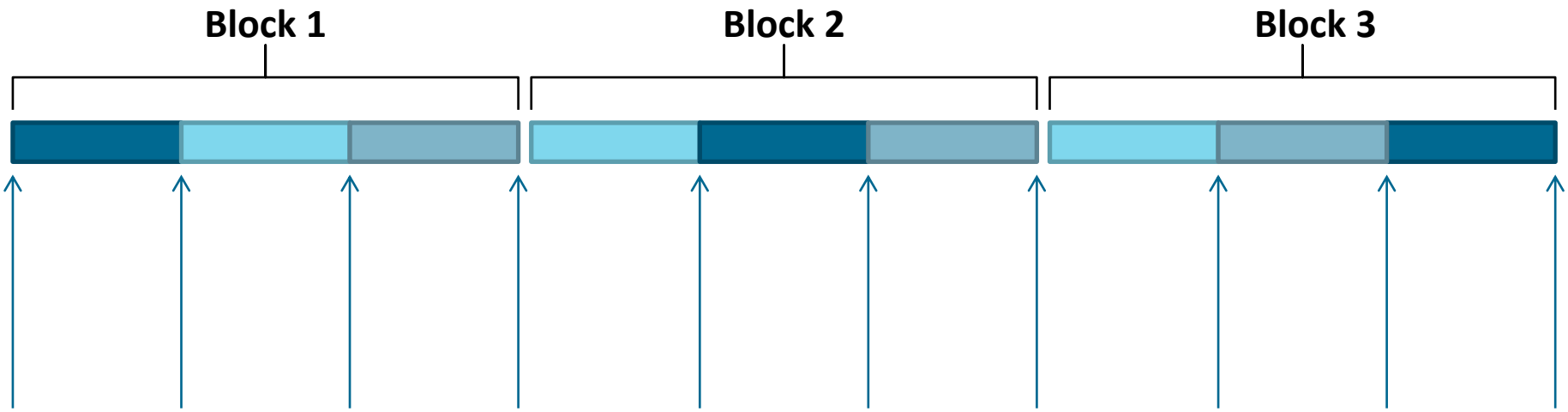
N-of-1 trials

Randomized, dubbelblind, crossover trial in *single* subjects

Mg gluconate

Mg aspartate

Mg lactate



- **PROMS: patient-specific outcome questionnaire and generic QoL (SF36) questionnaire**
- **Serum Mg**

time

The use of N-of-1 trials to individualize treatment in patients with renal magnesium wasting.
Bech, Wetzels, Groenewoud, Nijenhuis. *Am J Kidney Dis* 2019.

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Renal hypomagnesemia – Oral supplementation

N-of-1 trials

Patient A

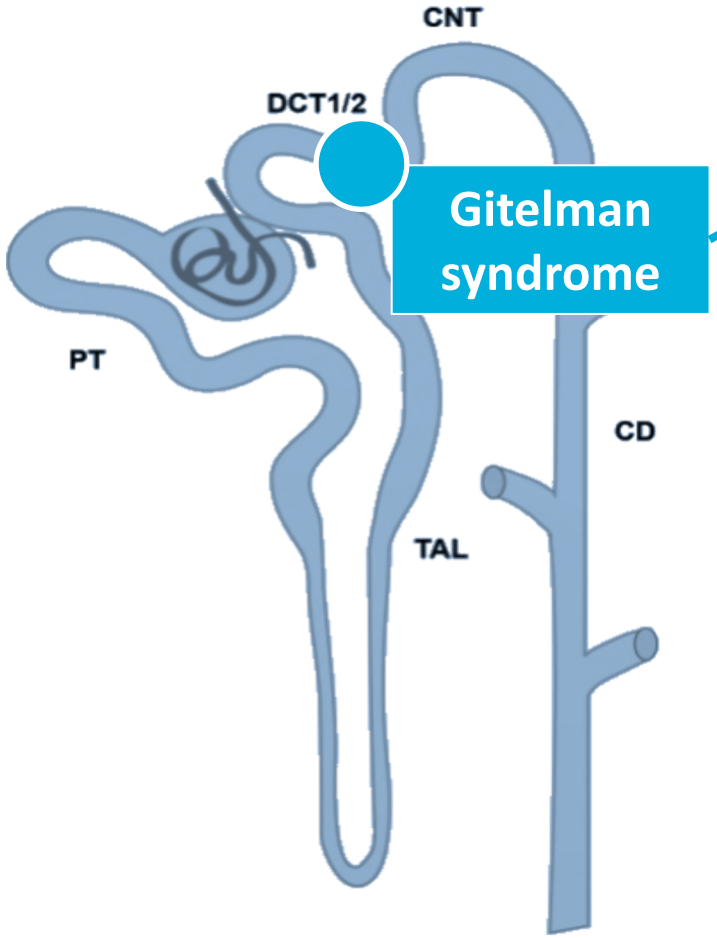
	Magnesium gluconate	Magnesium aspartate	Magnesium lactate
Personalized complaint score (0-10; 10=maximal complaints)			
Muscle aches	9	5	7
Fatigue	9	7	8
Gitelman symptoms	9	6	7
Side effects	8	5	7
SF36 QoL questionnaire (0-100%; 100=maximal QoL)			
Physical functioning	30	65	55
Social functioning	25	48	48
Pain	12	67	22
Serum Mg (0.70-1.10)	0.60	0.60	0.69

Conclusion: personalized/individualized treatment approach needed

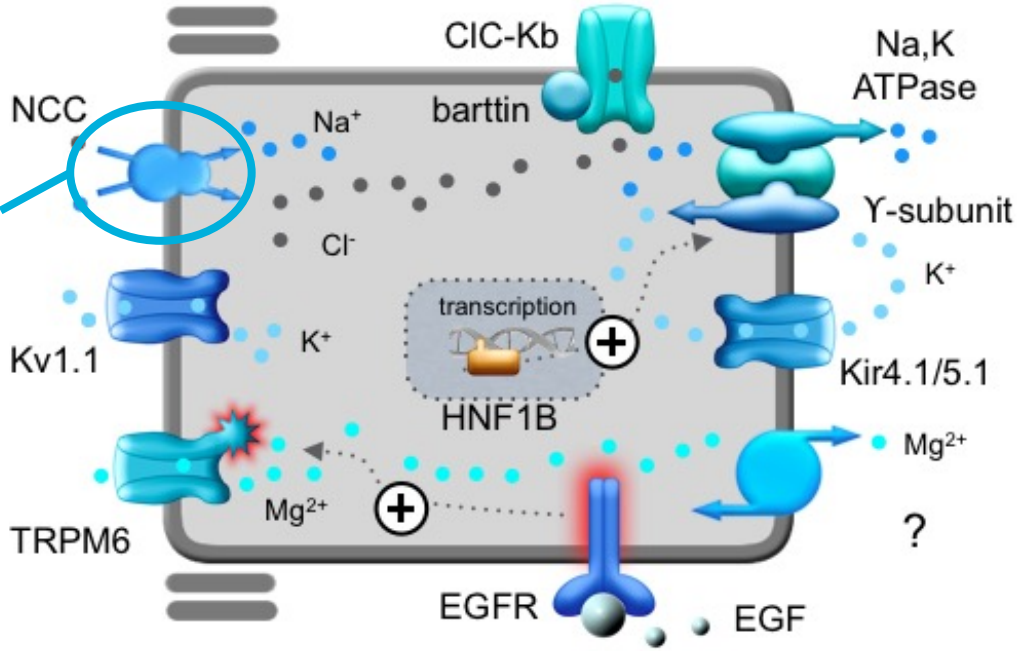
The use of N-of-1 trials to individualize treatment in patients with renal magnesium wasting.
Bech, Wetzels, Groenewoud, Nijenhuis. *Am J Kidney Dis* 2019.

Radboudumc

Gitelman syndrome



Distal convoluted tubule (DCT)



- Hypokalemic alkalosis
- Renal hypomagnesemia
- Hypocalciuria
- Normal to low blood pressure

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WEBINAR

28/06/22

Tom.Nijenhuis@Radboudumc.nl

Gitelman syndrome
Adult view

Speaker: Tom Nijenhuis (Nijmegen, Netherlands)

Patient: Voice: Gitelman patient

Moderator: Elena Levtchenko (Leuven, Belgium)

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