Fármacos diuréticos y antidiuréticos

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CATEDRA DE FISIOLOGÍA

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¿La sobrecarga hidriga, la natremia, la presión arteria, la Kalemia , la función renal de nuestros pacientes es siempre la misma ?

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¿El efecto del mismo diurético en el mismo paciente es siempre el mismo o se limita en el tiempo?

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PARA PODER ELEGIR EL DIURETICO ADECUEDO DEBEMOS SABER QUE MECANISMO INTERFERIR

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¿QUE DIURETICO ELEGIR SEGÚN CADA CASO?

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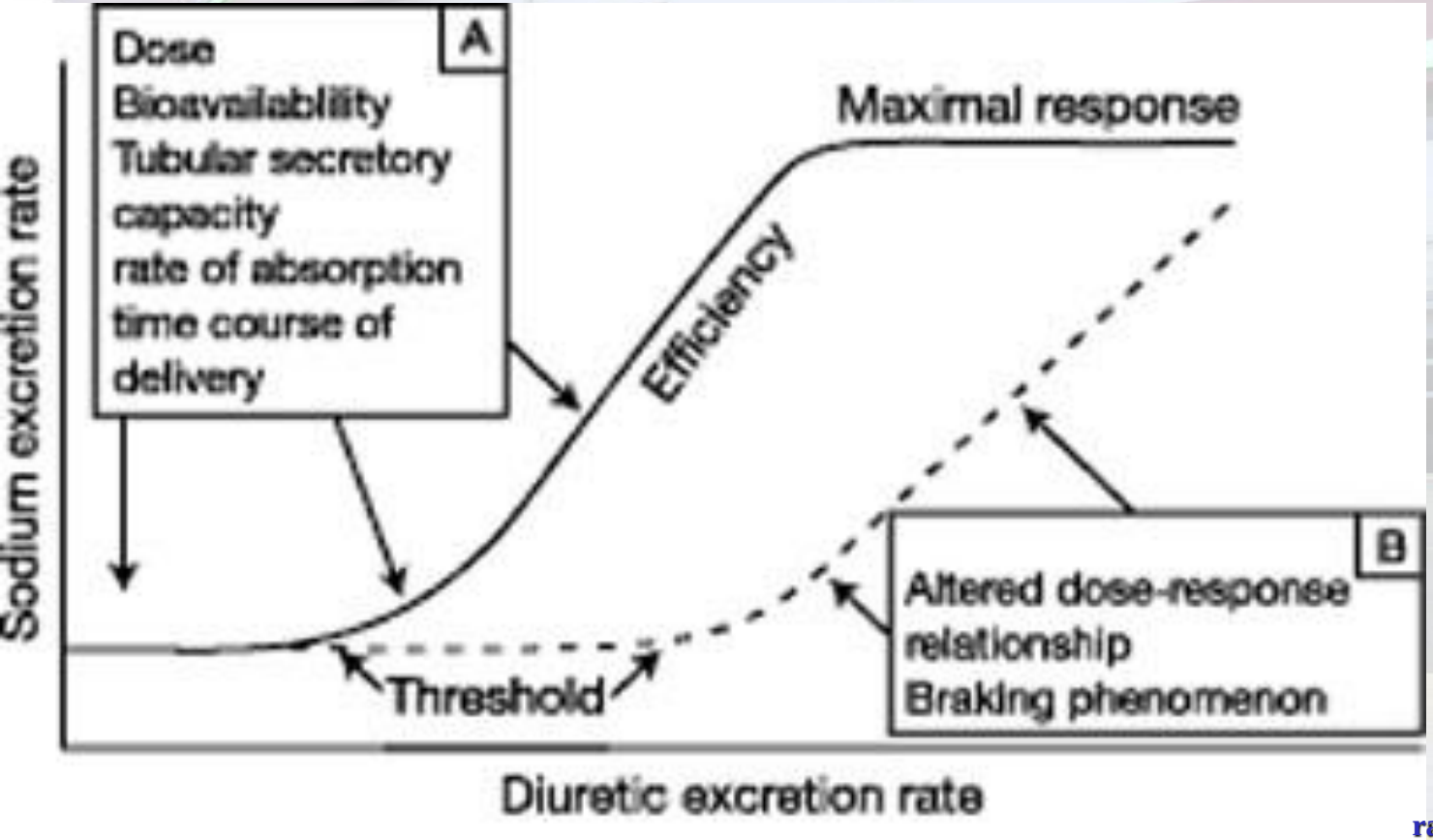
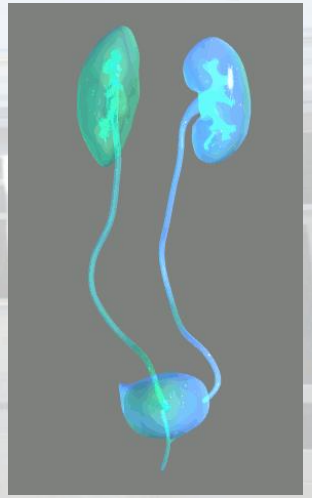
A mayor eficiencia mayor impacto sobre sodio y potasio el efecto primera dosis se pierde progresivamente





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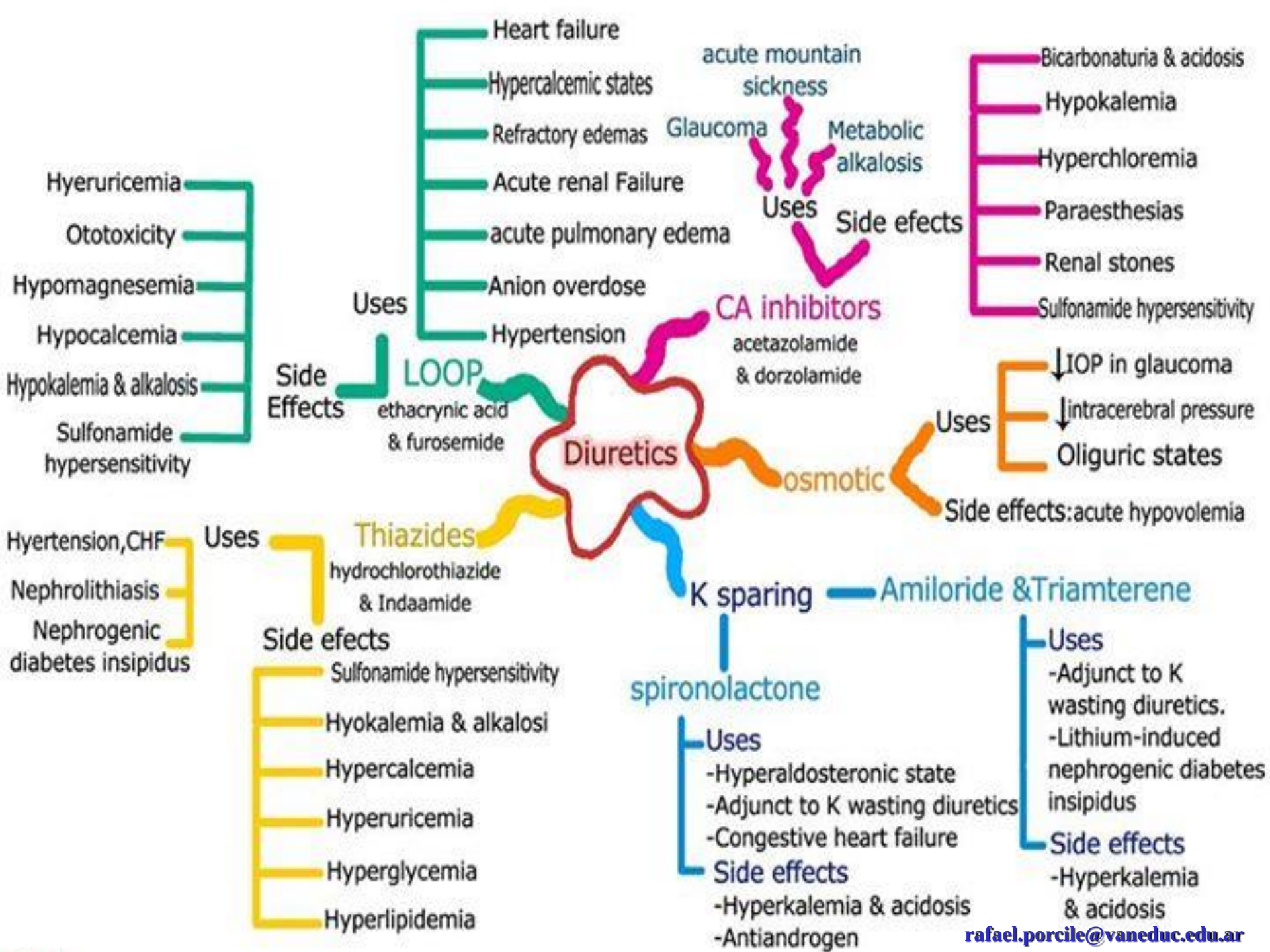

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Diurético de máxima eficaca

MAXIMA EFICACIA = DIFICIL MANEJO

- ***Diuréticos de máxima eficacia.*** Actúan en los segmentosdiluyentes; la fracción de eliminación de Na+ essuperior al 15 %.

- Los más importantes son los sulfamoilbenzoatos **furosemida, bumetanida** y **piretanida,**
- Derivadode la sulfonilurea **torasemida** (torsemida),
- Derivado del ácido fenoxiacético **ácido etacrínico** y la tiazolidona**etozolina**

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¿Diuréticos de media eficacia?

¿discriminar bien cual es el problema que predomina en el paciente?

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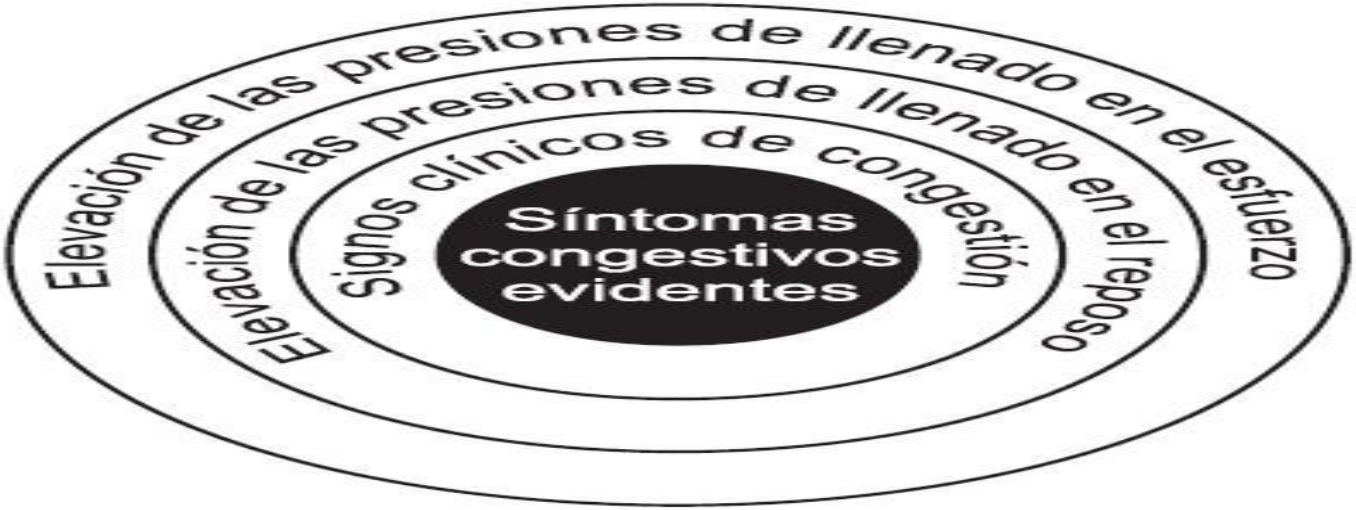

Potenciales objetivos terapéuticos relacionados con la elevación de las presiones de llenado ventricular en pacientes con insuficienc
on el permiso de Wolters Kluwer Health.

¿Diuréticos de media eficacia?

¿discriminar bien cual es el problema que predomina en el paciente?

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Diuréticos de eficacia mediana.

Actúan en la porción final del segmento diluyente cortical y en el primer segmento del túbulo distal;

la fracción de eliminación deNa+ es del 5-10 %. Pertenecen a este grupo

Las benzotiadiazinas(tiazidas e hidrotiazidas):
hidroclorotiazida,
Clortalidona
indapamida

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¿Diuréticos de baja eficacia?

¿el paciente necesita un "poquito" de diurético?

¿Cual es el tamaño del problema?

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Diuréticos de eficacia ligera.

La fracción de eliminaciónde Na_+ es inferior al 5 %.
Su sitio de acción es variable:

α) Ahorradores de K_+: actúan en el último segmentodel túbulo distal por inhibición de la aldosterona: **espironolactona** y **canrenoato de potasio,**

o con independencia de la aldosterona: **amilorida**

β) Inhibidores de la anhidrasa carbónica:
acetazolamida diclorfenamida

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¿Son inocuos?

Table 148. Adverse Effects of Diuretics

Adverse reaction	Comments
Hypotension	Most common after initiation of therapy or increase in dose
Decreased GFR	Highest risk in patients with concurrent ACE inhibitor or ARB therapy or in those with renal artery disease
Electrolyte abnormalities	
Hypokalemia	Occurs with thiazide and loop diuretics Dose and sodium intake-dependent
Hyperkalemia	Occurs with potassium-sparing diuretics and can be prolonged
Metabolic alkalosis	Occurs with thiazide and loop diuretics Dose and sodium intake-dependent and can be refractory to treatment in the presence of hypomagnesemia
Hyponatremia	Occurs with thiazide and loop diuretics.
Hypomagnesemia	Occurs with thiazide and loop diuretics Dose and sodium intake-dependent
Hypercalciuria	Occurs with loop diuretics
Hypocalciuria	Occurs with thiazide-type diuretics
Allergic reactions	No significant cross-reaction with sulfonamide antibiotics, but hypersensitivity to a sulfonamide antibiotic is associated with an increased risk for subsequent allergic reactions for many drugs
Effects on the fetus	Avoid use of spironolactone, other compounds should be used cautiously with electrolyte disturbances to be avoided, a number of diuretics traverse the placenta

Potential Complications of Diuretics and Their Associated Mechanisms.

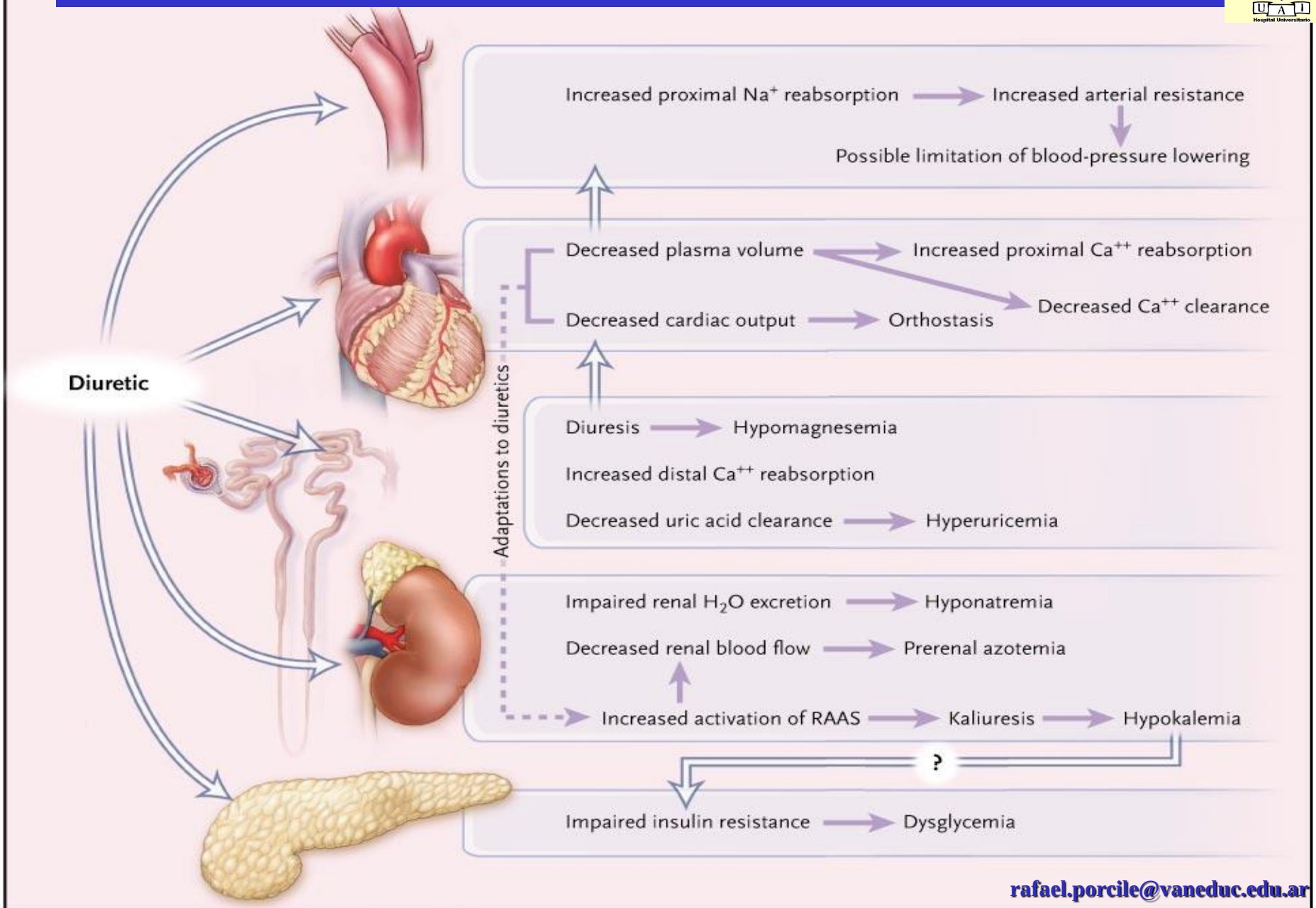

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Table 3. Common Clinical Problems Encountered with Thiazides, and Possible Solutions.*

Clinical Problem	Possible Solution
Attack of acute gouty arthritis	Obtain uric acid level, and discontinue thiazide if level is elevated. Recheck level after resolution of the attack, and assess the need for prophylaxis. Use another antihypertensive agent if uricosuric prophylaxis is not tolerated or indicated.
Hypokalemia (serum potassium ≤3.5 mmol/liter)	Correct hypomagnesemia if present. Add potassium-sparing agent or supplemental potassium chloride. Advise salt restriction. If blood pressure is not controlled, consider adding a RAAS inhibitor.†
Increase in serum creatinine from baseline level	Assess hydration status and discontinue any concurrent and unnecessary nephrotoxic drugs (e.g., NSAIDs). Recognize that a slight elevation in creatinine may be the result of improved blood-pressure control in patients with microvascular disease, in whom renal function is dependent on blood pressure for adequate perfusion.
No apparent response to hydrochlorothiazide at a dose of 25 mg/day	Assess lifestyle and advise salt restriction if needed. Consider increase in diuretic dose, switch to longer-acting thiazide such as chlorthalidone, or addition of RAAS inhibitor.†
Report of dizziness on standing	Check for orthostasis. Reduce diuretic dose if necessary. Assess hydration status, and insure diuretic is administered in the morning. Instruct the patient to stand up slowly.
Discovery of asymptomatic hyponatremia	Assess concurrent medications (e.g., SSRIs) and determine risks and benefits of continuing thiazide. Evaluate patient for excessive water intake.
Thiazide therapy recommended for patient with documented history of allergy to a sulfa antibiotic	Sulfa antibiotic allergy is not a contraindication to receiving a thiazide. The risk for cross-sensitivity appears to be more dependent on an underlying propensity for atopy than on any specific cross-reactivity among the classes. If true allergy to thiazide is documented, ethacrynic acid (a non–sulfa-containing loop diuretic) can be used.
Report of muscle cramps	Check serum potassium level and normalize if low. Consider another diuretic if electrolyte levels are normal.
Impaired fasting glucose level or diabetes at baseline	Institute appropriate management of cardiovascular risk factors. Thiazide use is not precluded.
Development of diabetes during thiazide therapy	Institute appropriate management of diabetes and related cardiovascular risk factors. The average excess increase in glucose attributed to thiazide use is approximately 3–5 mg/dl (0.2–0.3 mmol/liter). Thiazides will probably be necessary for achieving blood-pressure targets. The addition of a RAAS inhibitor† should be considered, especially if blood pressure is not controlled.
Nocturia or incontinence	Avoid thiazide dosing in the afternoon or evening. Limit evening fluid intake. Consider discontinuing thiazide if symptoms are intolerable.
Baseline GFR <30–40 ml/min/1.73 m^2 of body-surface area	Substitute furosemide or torsemide. A practical formula for determining the dose of furosemide, in milligrams to be given twice daily, is as follows: (patient age + blood urea nitrogen level) ÷ 2. Torsemide can be given once daily.
Development of sun sensitivity	Encourage sunscreen use.

* GFR denotes glomerular filtration rate, NSAID nonsteroidal antiinflammatory drug, and SSRI selective serotonin-reuptake inhibitor.
† Examples of renin–angiotensin–aldosterone system (RAAS) inhibitors are angiotensin-converting–enzyme inhibitors and angiotensin II–receptor blockers.

¿Como modificar mediante la terapéutica el volumen extravascular y extravascular de nuestros pacientes

SIN HACERLES DAÑO?

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CONDICIONEMIENTO DEL FILTRADO GLOMERULAR COMO HERRAMIETA TERAPEUTICA

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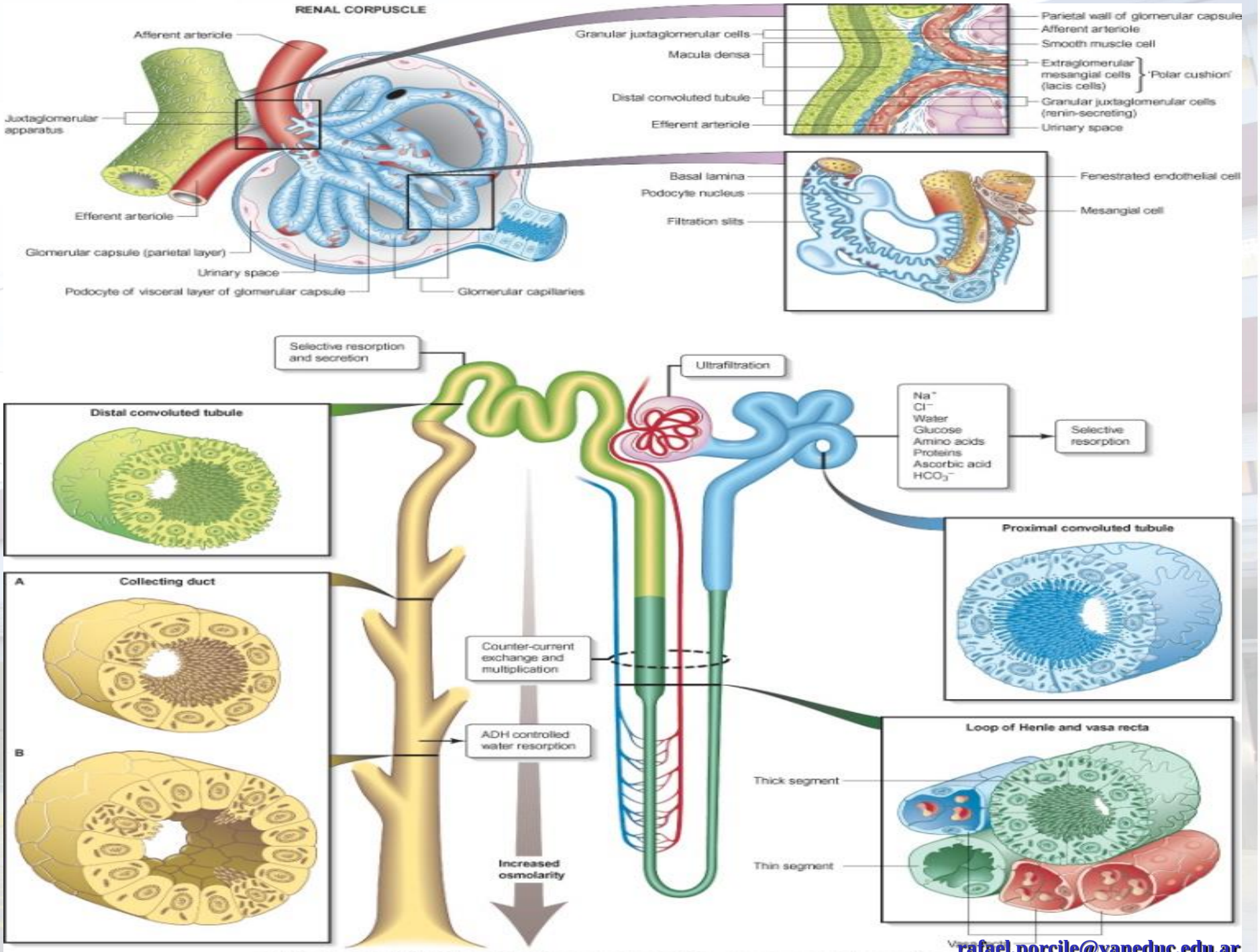
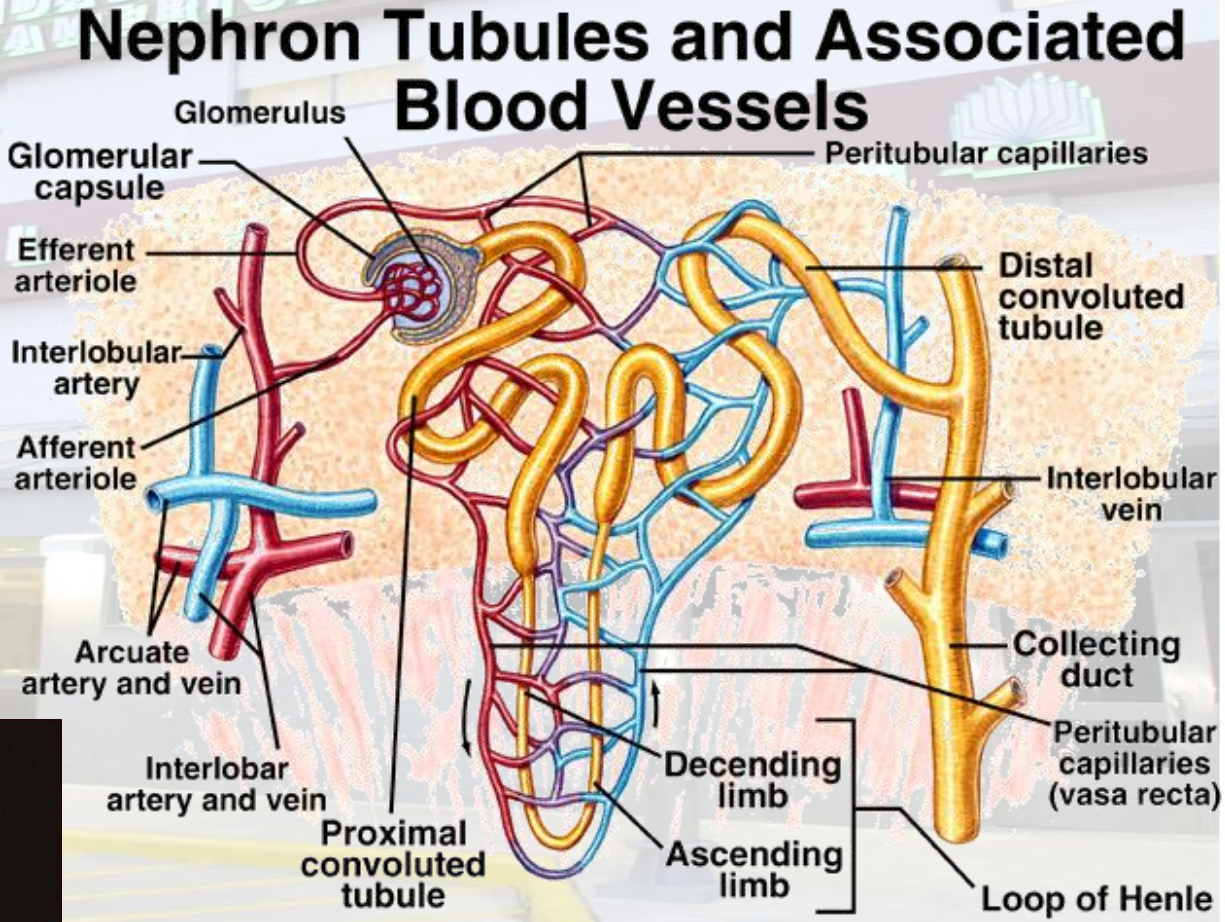
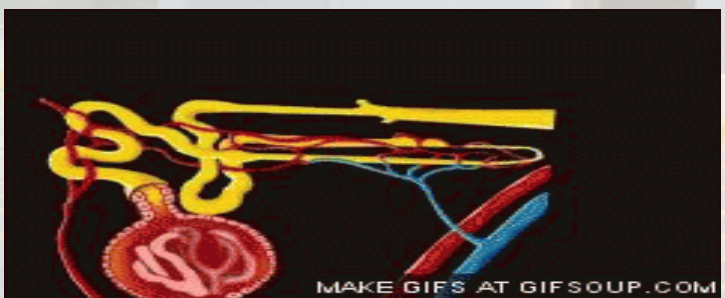


Vasos sanguíneos renales

- Capilares peritubulares:
- Llevan sangre a los vasos rectos.
  - Nefronas yuxtamedulares.
- Llevan sangre a las venas .
  - Nefronas corticales.





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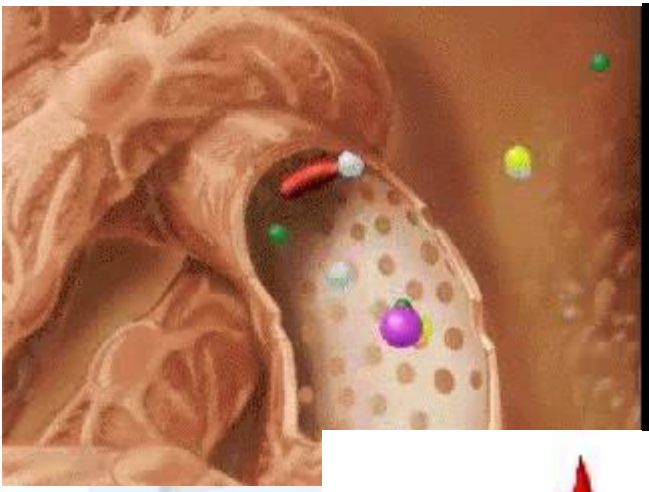

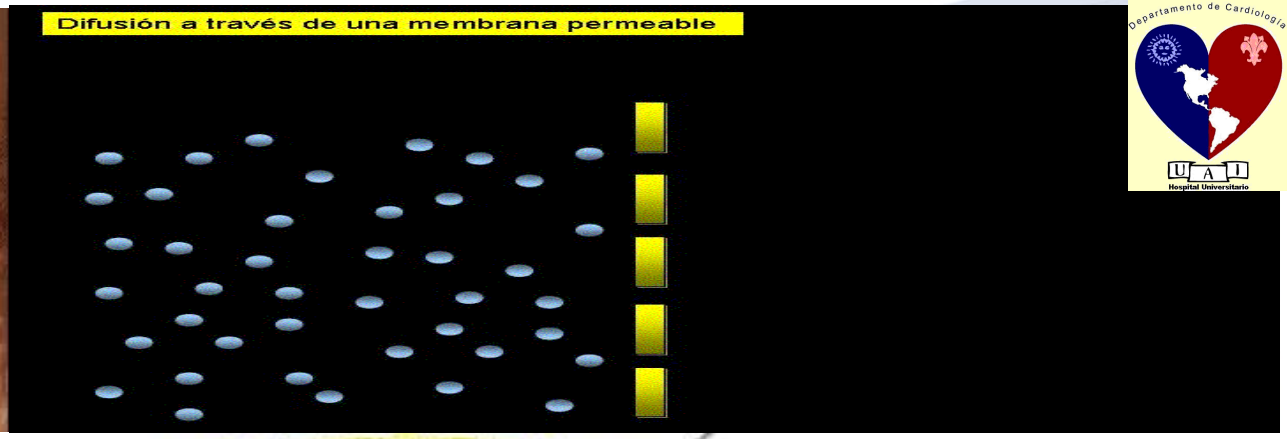

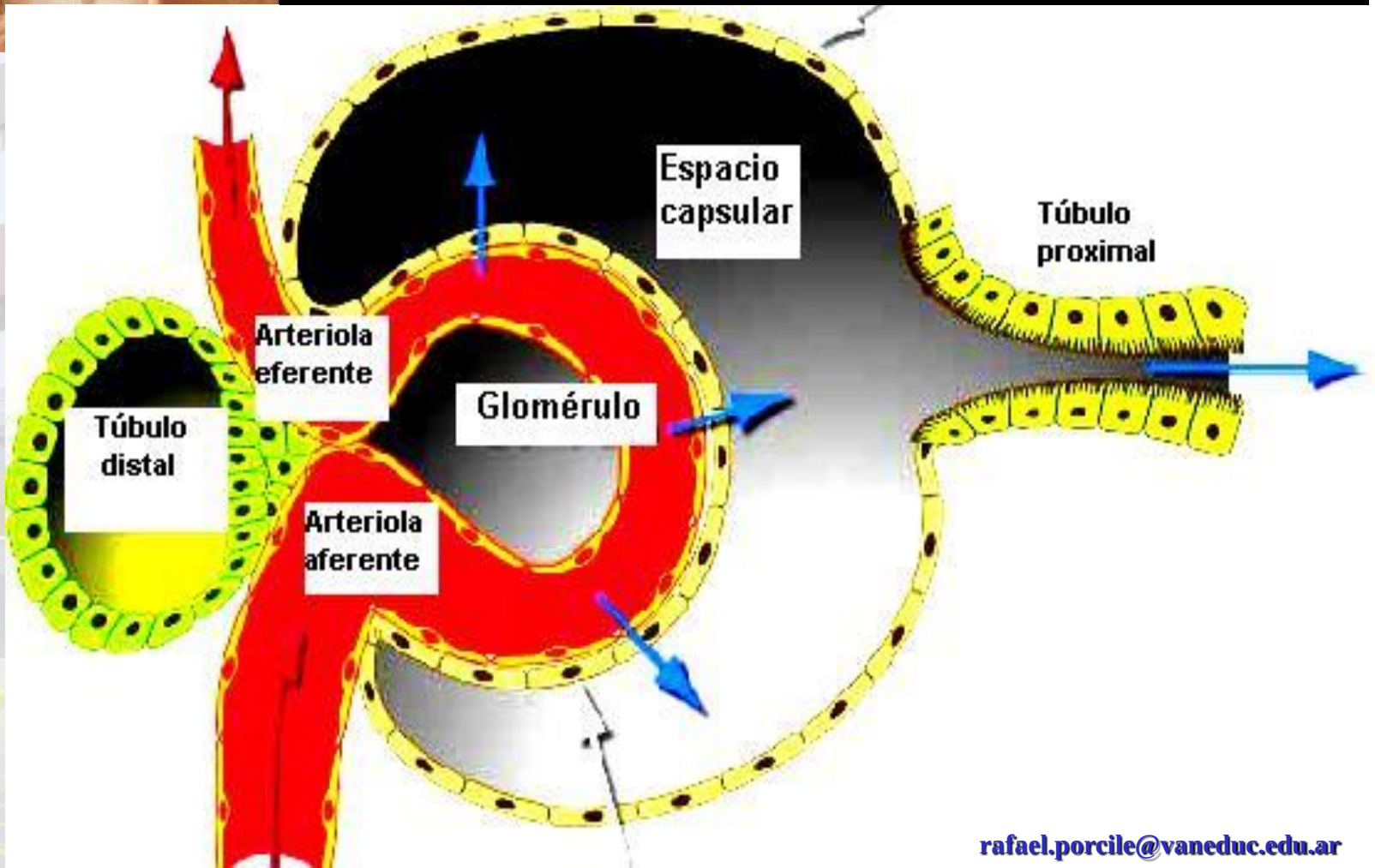

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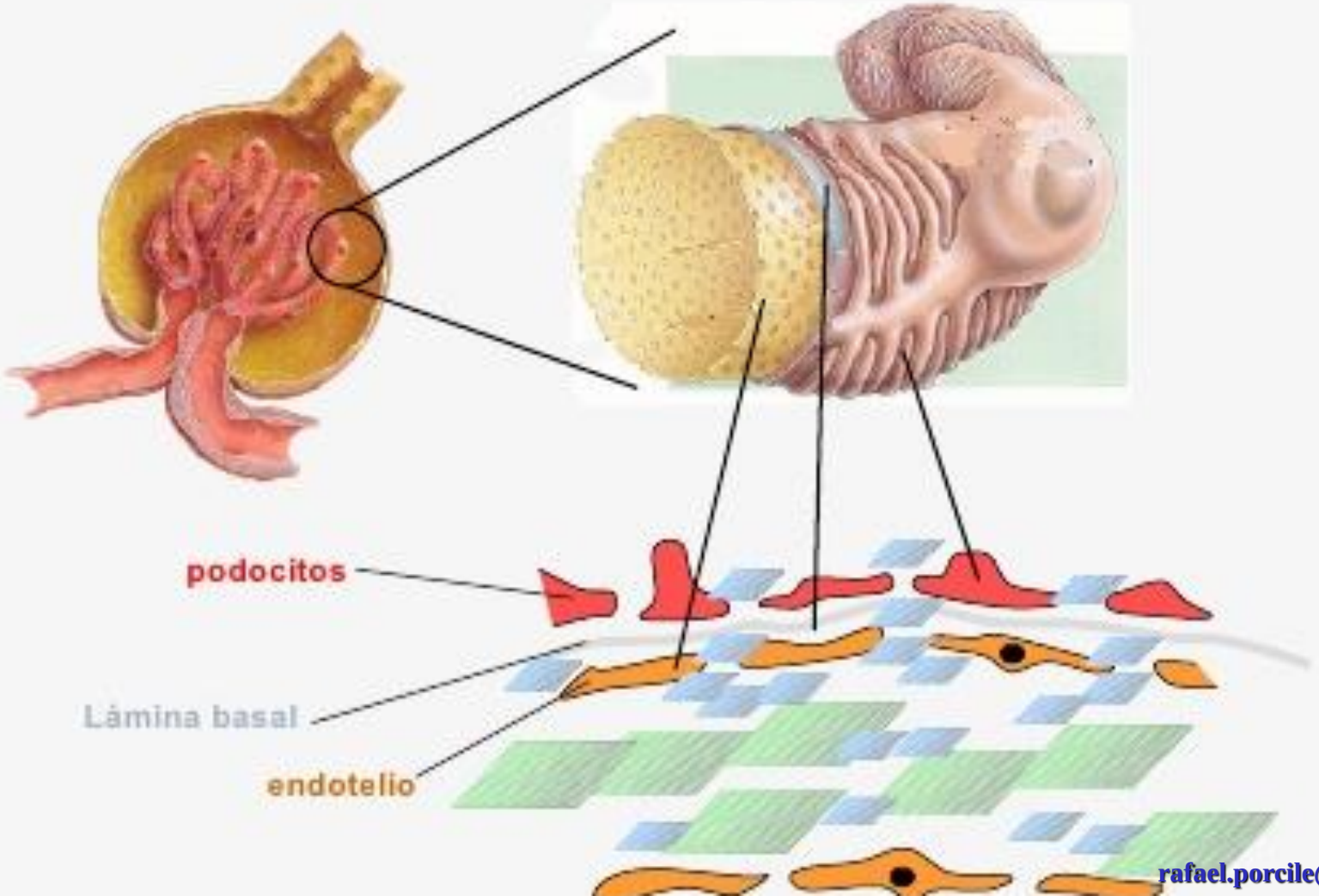
La pared de los capilares glomerulares es muy permeable



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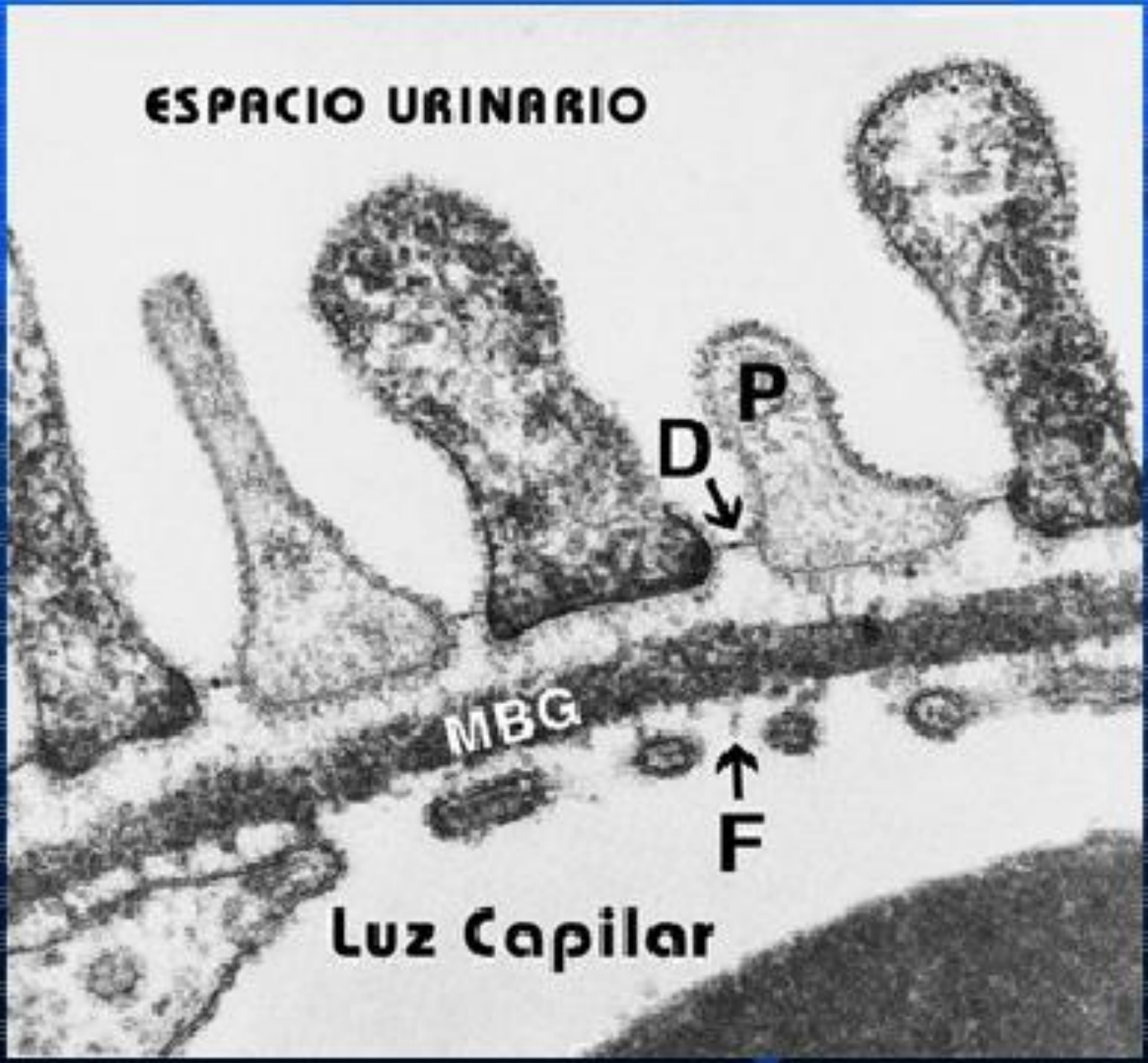

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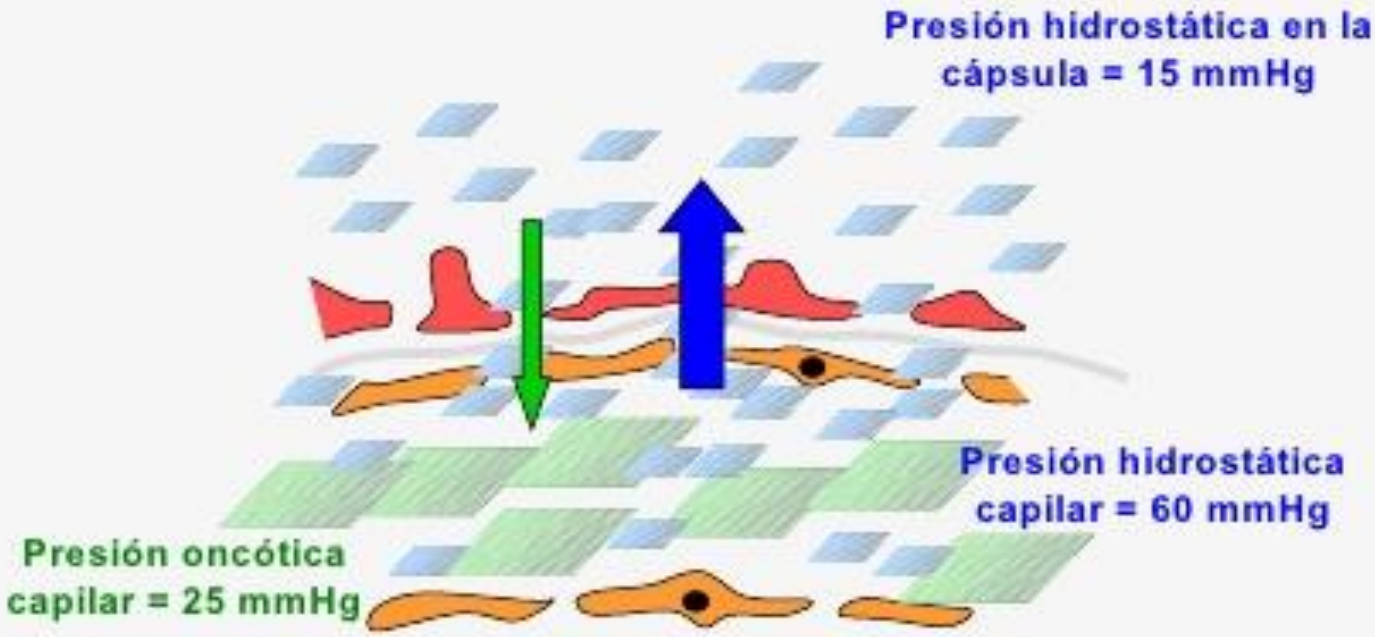
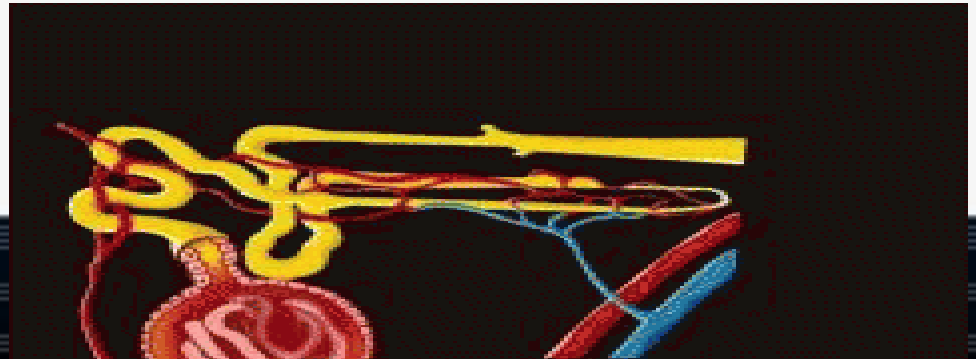
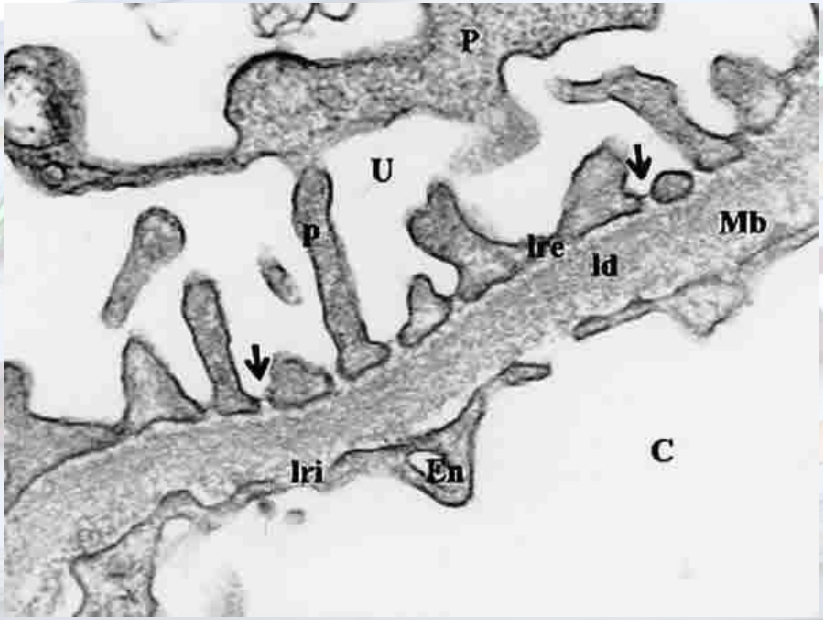
La presión hidrostática capilar favorece la filtración, y la presión oncótica capilar la dificulta.





Barrera Hemato-Urinaria



Capilar glomerular

En endotelio, Mb membrana basa (Id lámina densa, Ire lámina rara externa, Iri lámina rara interna) P Podocito, p pedicelos, flechas diafragmas de las hendiduras de filtración, U espacio urinario.

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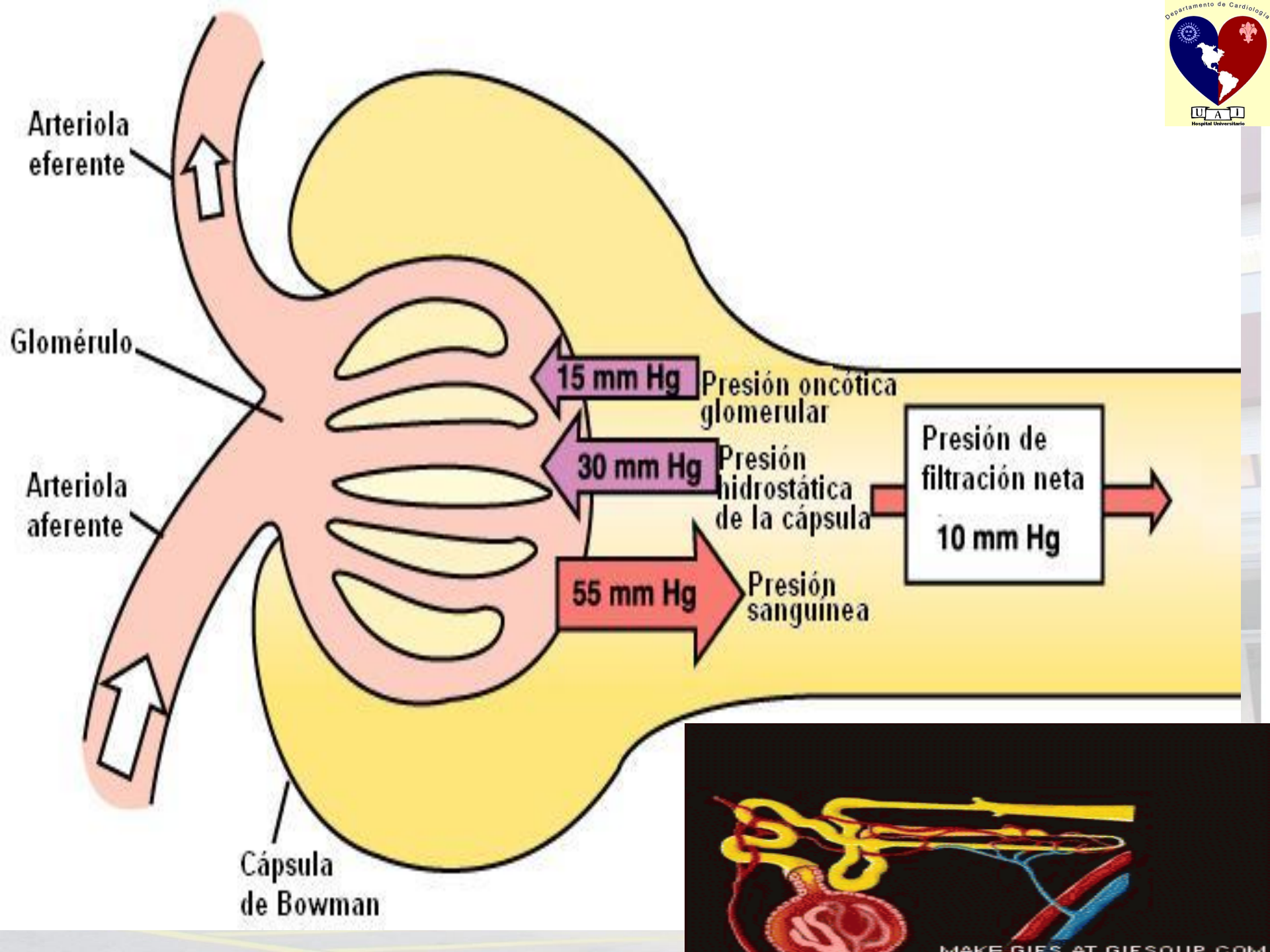

Arteriola eferente
Glomérulo
Arteriola aferente
Cápsula de Bowman
15 mm Hg
Presión oncótica glomerular
30 mm Hg
Presión hidrostática de la cápsula
55 mm Hg
Presión sanguinea
Presión de filtración neta
10 mm Hg

PROXIMAL CONVOLUTED TUBULE

Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium-potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
Glucose	100% (symporters and facilitated diffusion)
Amino acids	100% (symporters and facilitated diffusion)
Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
Urea	50% (diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
Creatinine	small amount

At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).

LOOP OF HENLE

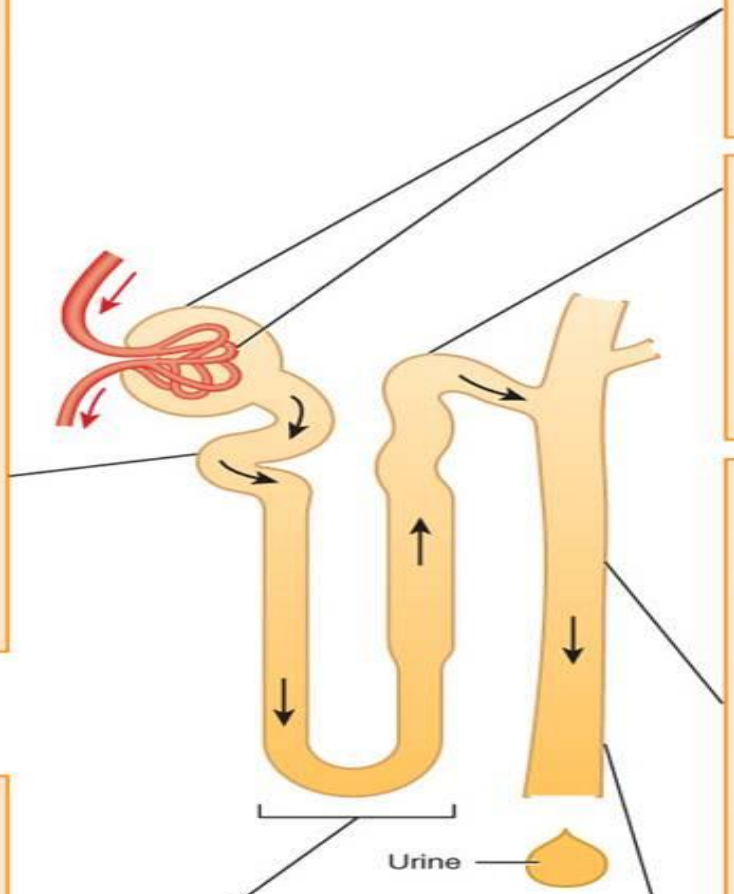
Reabsorption (into blood) of:

Water	15% (osmosis in descending limb)
Na^+	20–30% (symporters in ascending limb)
K^+	20–30% (symporters in ascending limb)
Cl^-	35% (symporters in ascending limb)
HCO_3^-	10–20% (facilitated diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

Urea	variable (recycling from collecting duct)

At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).



RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid

DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

PRINCIPAL CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

Water	5–9% (insertion of water channels stimulated by ADH)
Na^+	1–4% (sodium-potassium pumps)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

K^+	variable amount to adjust for dietary intake (leakage channels)

Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.

INTERCALATED CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

HCO_3^- (new)	varible amount, depends on H^+ secretion (antiporters)
Urea	variable (recycling to loop of Henle)

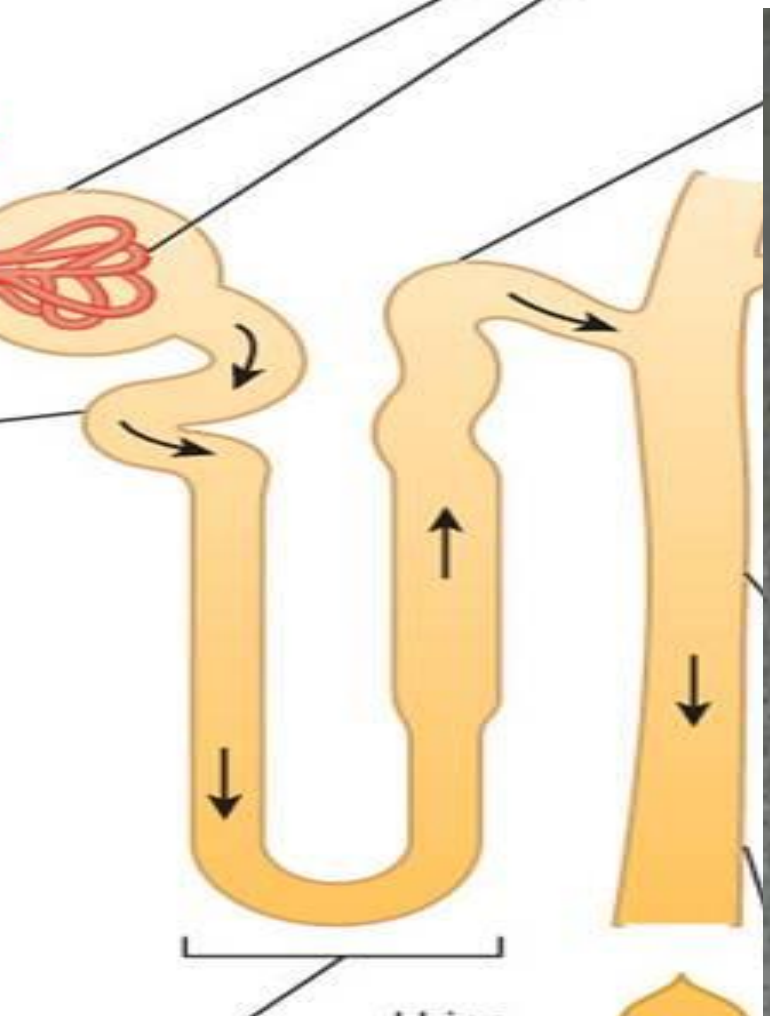
Secretion (into urine) of:

H^+	variable amounts to maintain acid-base homeostasis (H^+ pumps)

RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid



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REGULACÍON DE FLUJO PLASMATICO RENAL

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Mecanismo locales :regulación intrínseca

Factores metabólicos:

feedback túbulo-glomerular

El aumento de la concentración de Cloruro (posiblemente también de sodio) en el túbulo distal genera una señal que produce vasoconstricción arteriolar aferente. La reducción de la concentración de cloruro genera una señal en sentido opuesto.

Endotelio óxido nítrico y endotelina

Autorregulación (respuesta miógena) una vasodilatación arteriola aferente frente a la reducción de la presión y una vasoconstricción frente al aumento de la presión de perfusion.

Mecanismos sistémicos:regulación extrínseca

Nerviosos El tono basal simpático es mínimo, por lo que dichos vasos se encuentran dilatados en reposo.
El incremento de la actividad simpática supone incremento del tono y disminución del FPR

HumoralesVasoconstricción renal:, AII ADH , Adr, NAdr, TxA2. Adenosina

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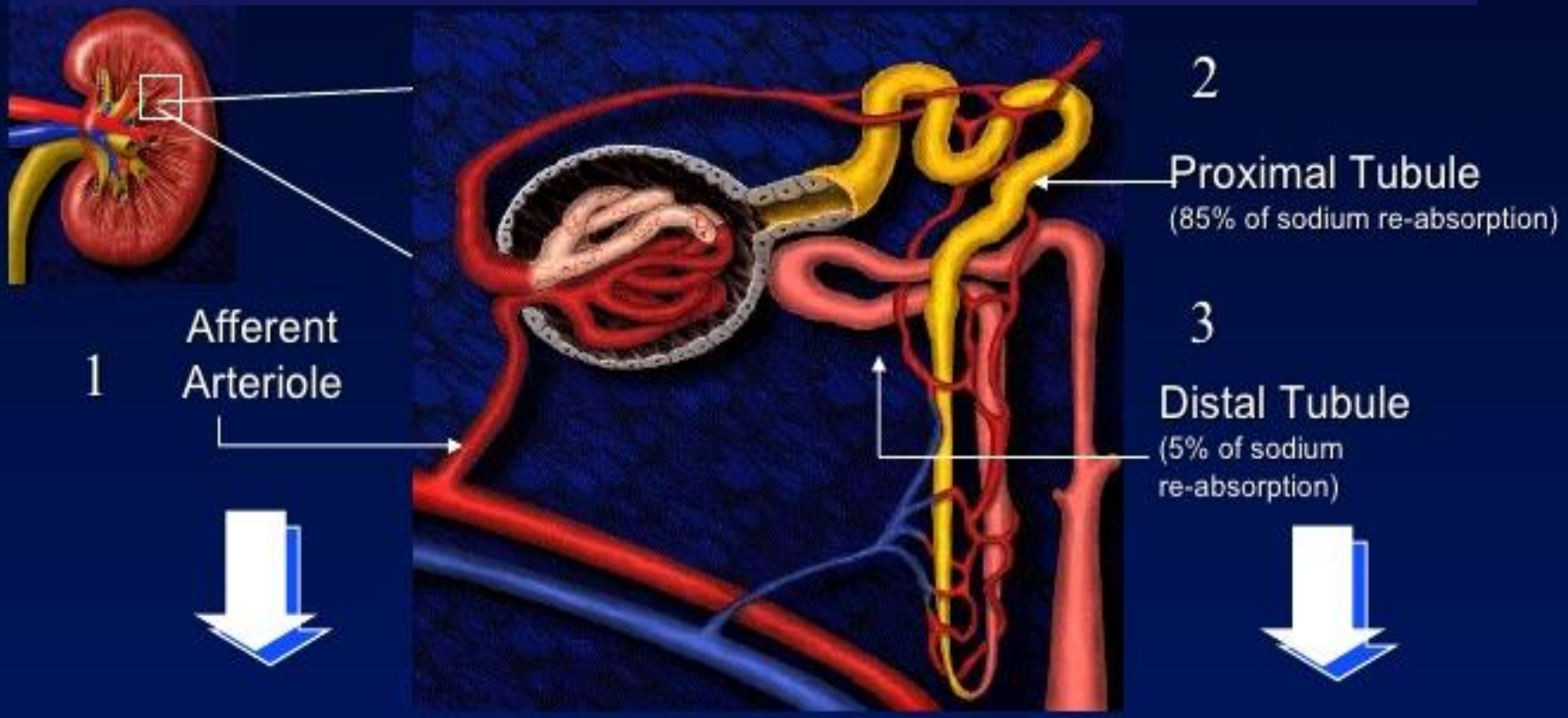
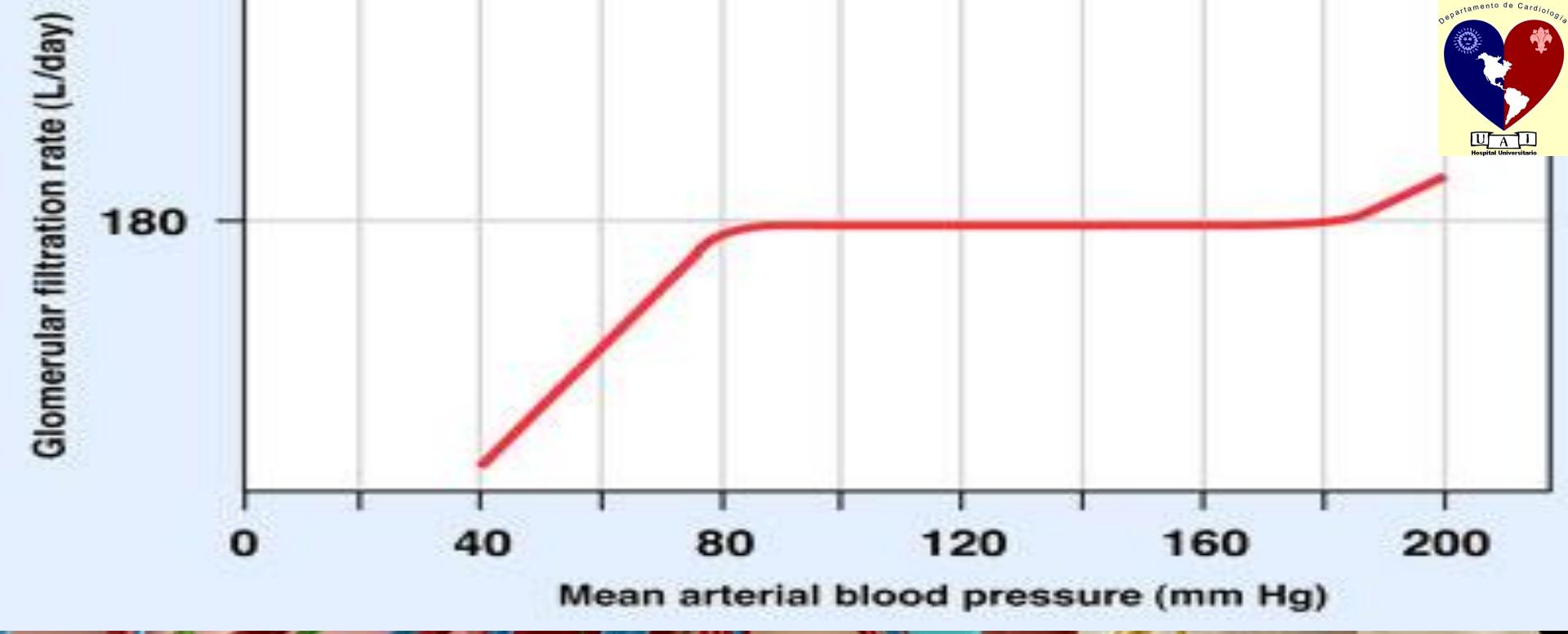
Mechanism of Action: Adenosine A_1 Receptor Blocker

La adenosina condiciona la vasodilatacíon de la arteriola aferente modificando el flujo plasmático renal





CUALQUIER INTERVENCIÓN TERAPEURICA QUE LLEVE LA TAM POR DEBAJO DE 80 O POR ENCIMA DE 180 CONDICIONA EL FILTRADO GLOMERULAR . TAM INFERIOR A 50 INTERRUMPE EL FILTRADO GLOMERULAR

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COMO CONDICIONAR TERAPEUTICAMNTE EL FILTRADO GLOMERULAR

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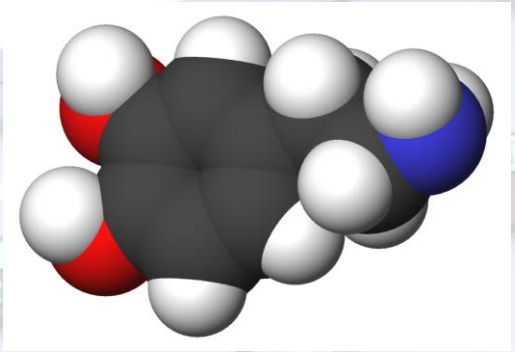
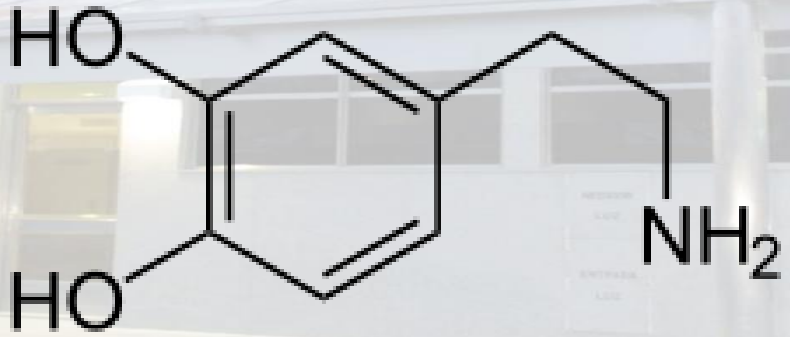


Dopamina



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¿Alguien sabe si la dopamina realmente modifica el filtrado glomerular?

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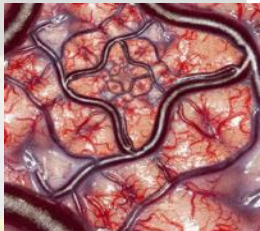
La Biblioteca Cochrane

Barrington K, Brion LP Dopamina versus ningún tratamiento para prevenir la disfunción renal en recién nacidos prematuros tratados con indometacina *La Biblioteca Cochrane Plus*, 2008 Número 4. Oxford

La dopamina **mejoró la diuresis**
[DMP: 0,68 ml/kg/hora
(IC del 95%: 0,22; 1,44)],
pero no hubo pruebas del efecto sobre la creatinina sérica



D1 agonistas
D2 antagonistas

	Receptores de grupo D1	Receptores del grupo D2
Radioligandos útiles para su estudio	Skf 38393 Dihidroxidina [^{3}H]SCH 23390 [^{125}I] SCH 23982	Quinpirole N-0437 [^{3}H] Nemonapride [^{3}H] Raclopride [^{3}H] Espiperone
Localización	Núcleo caudado, accumbens, putamen, corteza cerebral, tubérculo olfatorio, sistema cardiovascular.	Se encuentran en las mismas estructuras que los tipo D1, y en los lóbulos anterior y posterior de la pituitaria.
Características bioquímicas	Estimulan la adenilciclasa, aumentando los niveles intracelulares de AMP cíclico.	Disminuyen la actividad de la adenilciclasa
Características genéticas	Los genes que los codifican carecen de intrones	Los genes que los codifican tienen intrones.
Estructura	Cadena carboxi-terminal larga. Asa intracelular corta	Cadena carboxi-terminal corta. Asa intracelular larga

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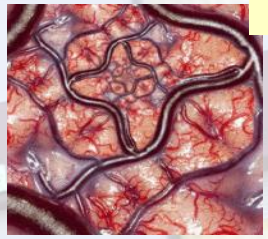
En Insuficiencia renal aguda



Incrementa el flujo plasmático renal
Filtración glomerular
Flujo urinario y promueve la natriuresis.

Entre 0,5 y 3,0 µg/Kg/min, se produce vasodilatación intrarrenal por activación de receptores específicos DA1

En dosis mayores a 3 ug/Kg/min y hasta 10 µg/Kg/min, dopamina se une a receptores alfa-adrenérgicos vasculares aumentando la frecuencia y el inotropismo cardíaco, elevando el débito cardíaco y secundariamente la perfusión renal.

Dosis superiores, con umbral de 5 y hasta 20 µg/Kg/min, hacen que los efectos beneficiosos tiendan a contrarrestarse por activación de receptores periféricos adrenérgicos alfa-1

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COMO MEDIR EL FILTRADO GLOMERULAR

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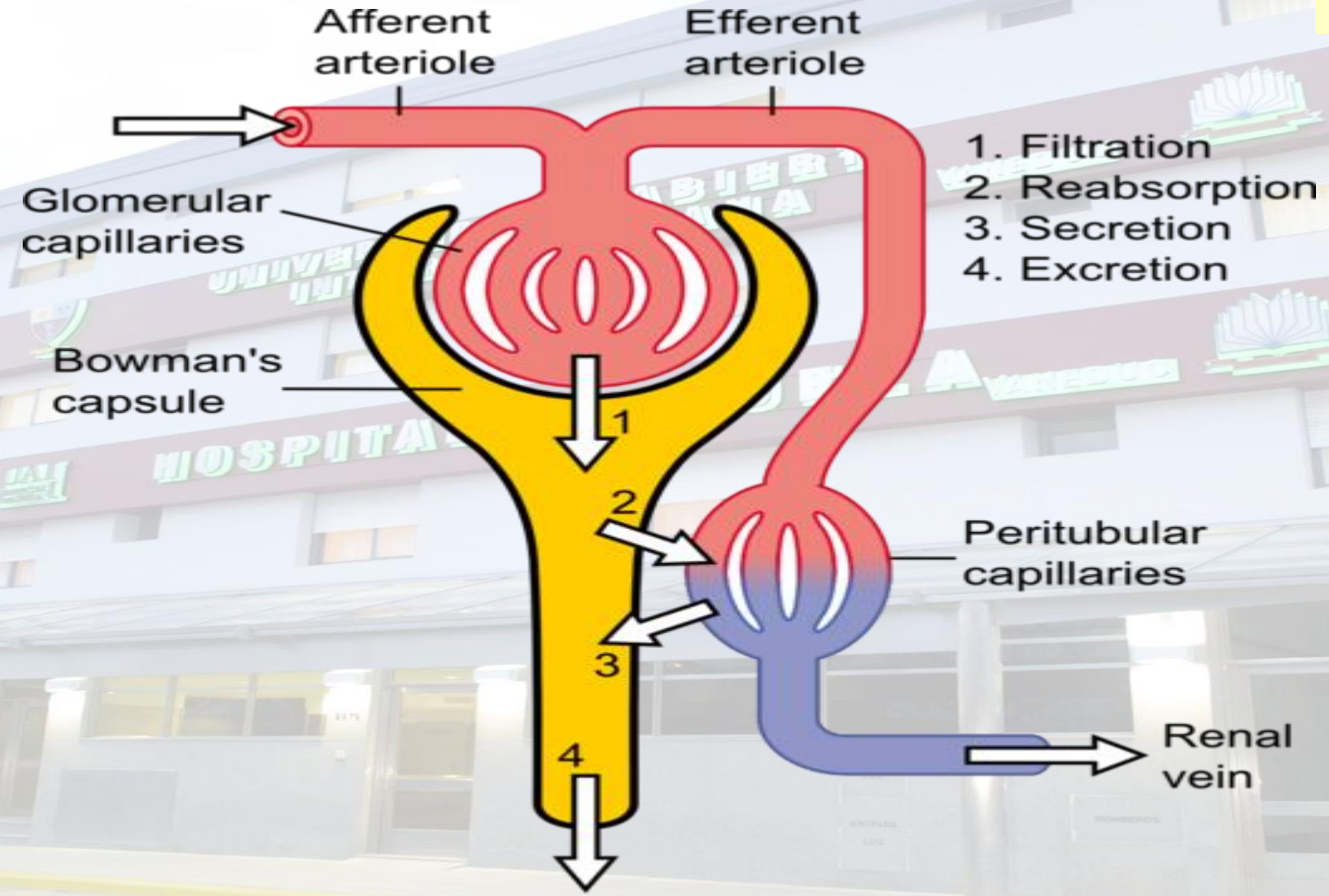

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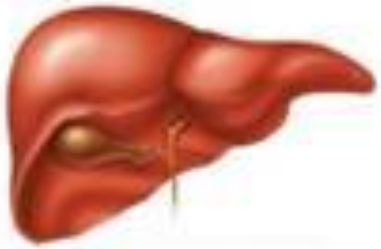
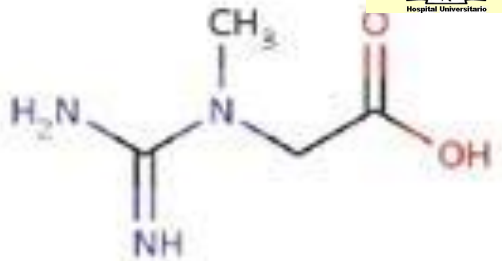
Síntesis de creatinina

Arginina +
Glicina

Metionina



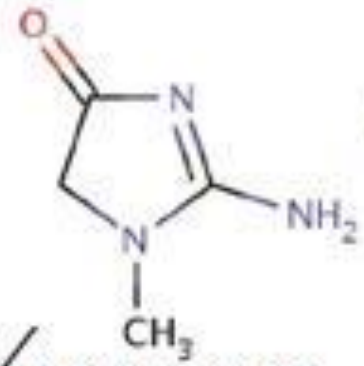
Creatina



+ ADP

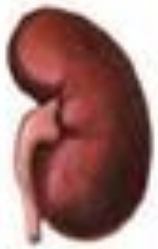
+ ATP

Creatinina
(en sangre)

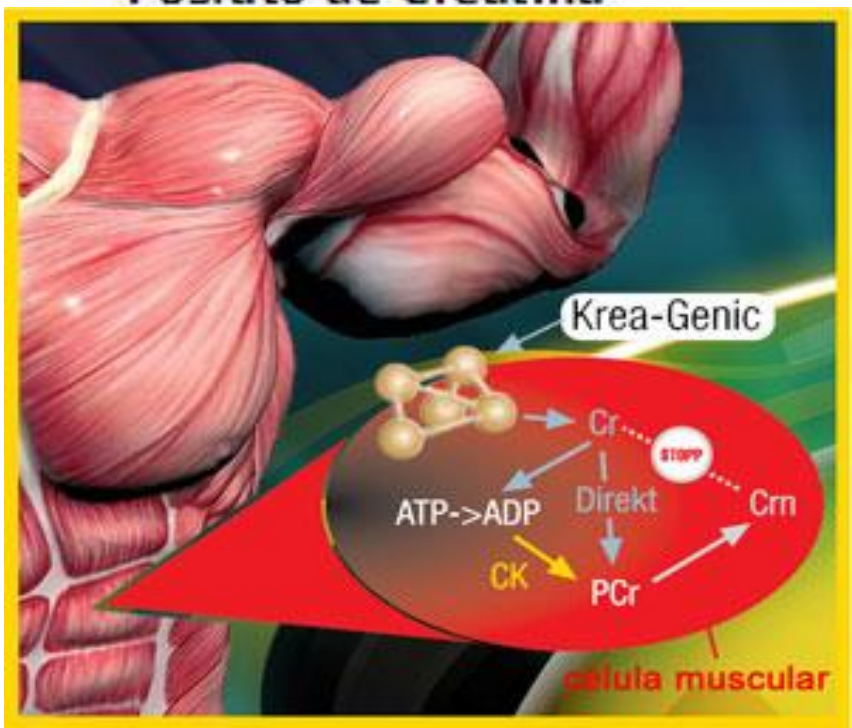


desfosforilación o
hidrólisis

filtración glomerular



Fosfato de Creatina



Ucr = Concentración urinaria de creatinina, mg/dl.
V = Volúmen del flujo urinario, ml/min.
Pcr = Concentración de creatinina en plasma, mg/dl.
ASC = Área de superficie corporal, m2.

$$Ccr = \frac{Ucr \times V}{Pcr} \times \frac{1{,}73}{ASC}$$

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[editar] Fórmula MDRD

$$\text{Aclaramiento creatinina} = \frac{(140 - \text{Edad}) \times \text{Peso (en kilogramos)}}{72 \times \text{Creatinina en plasma (en mg/dl)}} \times 0{,}85 \text{ si es mujer}$$

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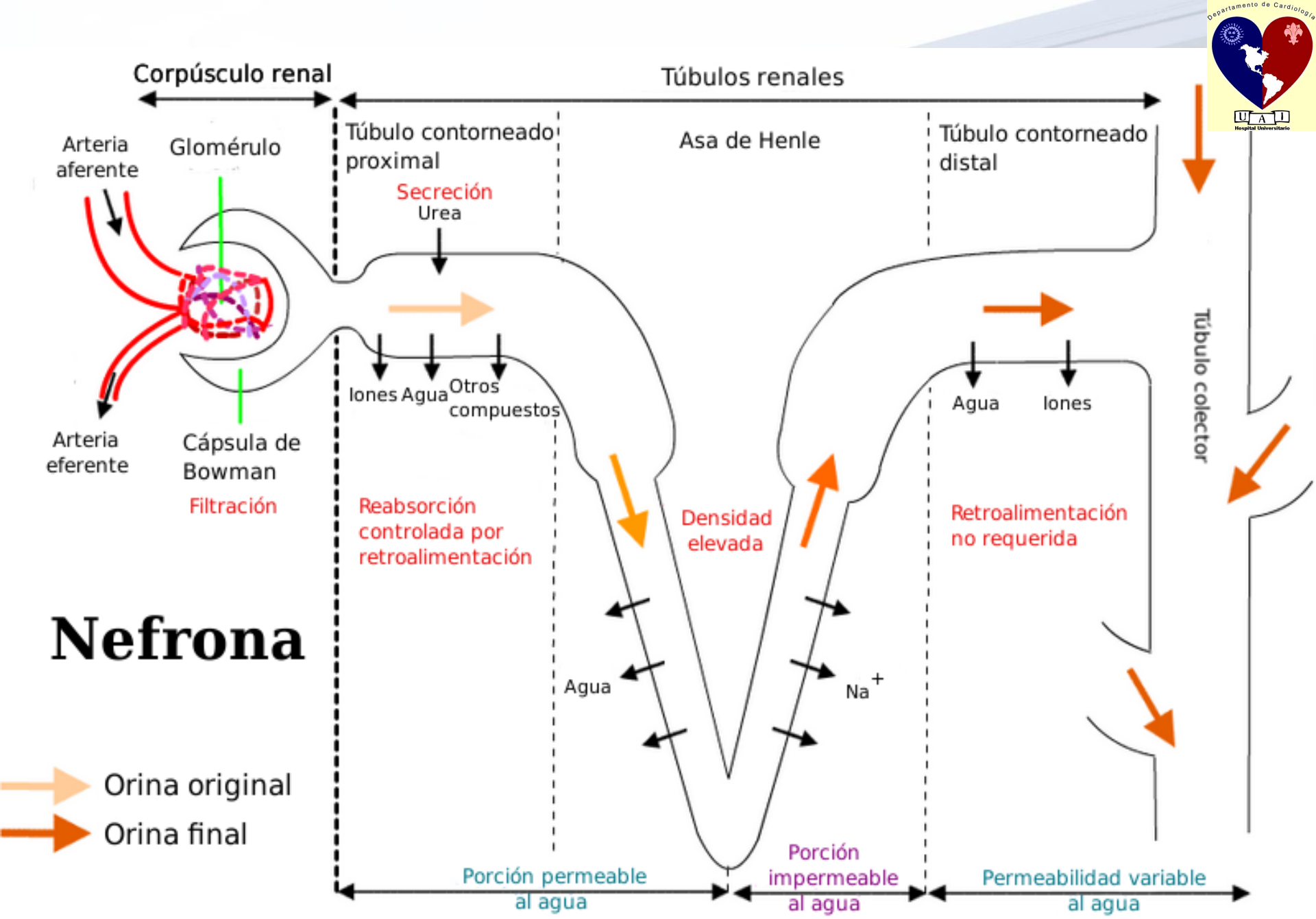

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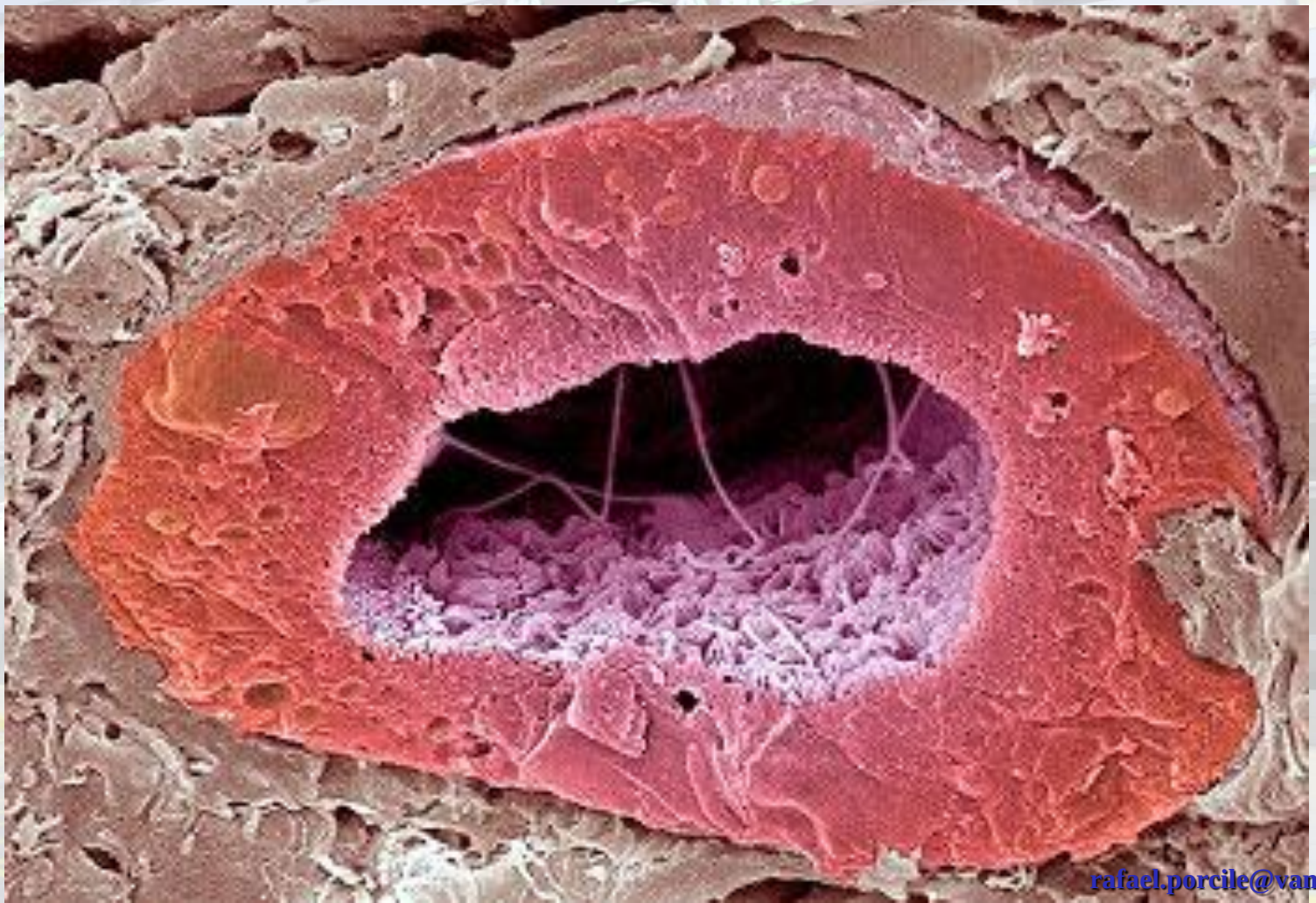
TUBULO CONTORNEADO PROXIMAL



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TUBO CONTORNEADO PROXIMAL

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INHIBIDORES DE LA REABSORCIÓN DE SODIO

DIURETICOS OSMOTICOS
- Manitol

DIURETISO INHIBIDORES DE LA ANIDRASA CARBONICA
-Acetazolamida

DIURÉTICOS DEL ASA
- Furosemida
-Bumetanida
-Torasemida

TIAZÍDICOS:
- Bendroflumetiacida
- Hidroclorotiazida
- Clortalidona
- Indapamida

AHORRADORES DE POTASIO
- Espironolactona
- Amilorida
- Triamtereno

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Túbulo contorneado proximal

- Diuréticos osmóticos
- Diuréticos bloqueantes de la anhidras carbónica

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PROXIMAL CONVOLUTED TUBULE

Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium-potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
Glucose	100% (symporters and facilitated diffusion)
Amino acids	100% (symporters and facilitated diffusion)
Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
Urea	50% (diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
Creatinine	small amount

At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).

LOOP OF HENLE

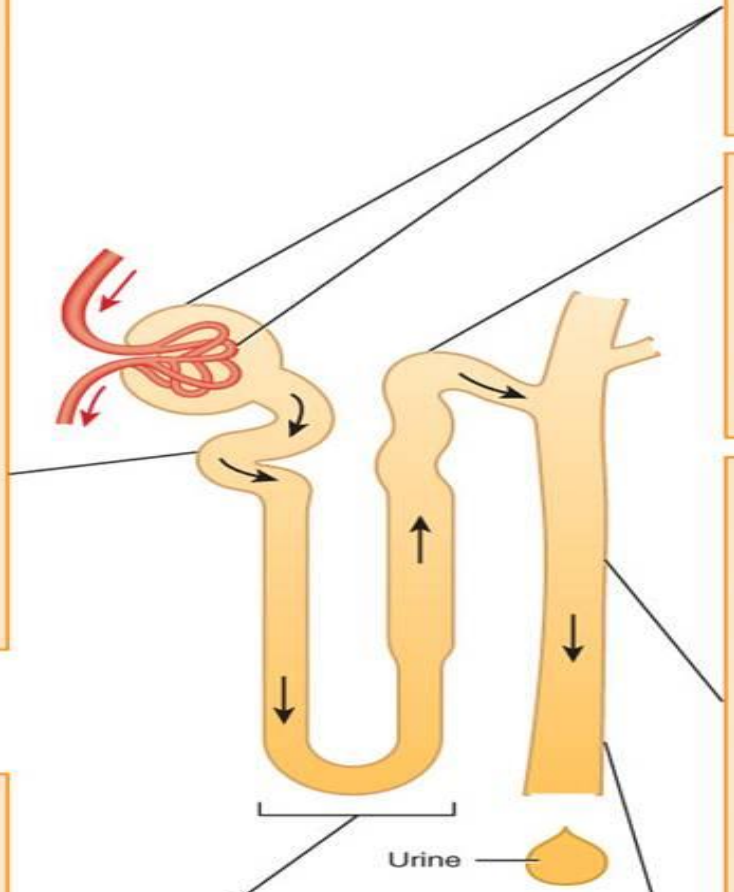
Reabsorption (into blood) of:

Water	15% (osmosis in descending limb)
Na^+	20–30% (symporters in ascending limb)
K^+	20–30% (symporters in ascending limb)
Cl^-	35% (symporters in ascending limb)
HCO_3^-	10–20% (facilitated diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

Urea	variable (recycling from collecting duct)

At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).



RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid

DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

PRINCIPAL CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

Water	5–9% (insertion of water channels stimulated by ADH)
Na^+	1–4% (sodium-potassium pumps)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

K^+	variable amount to adjust for dietary intake (leakage channels)

Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.

INTERCALATED CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

HCO_3^- (new)	varible amount, depends on H^+ secretion (antiporters)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

H^+	variable amounts to maintain acid-base homeostasis (H^+ pumps)

PROXIMAL CONVOLUTED TUBULE

Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium-potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
Glucose	100% (symporters and facilitated diffusion)
Amino acids	100% (symporters and facilitated diffusion)
Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
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Secretion (into urine) of:

H^+	variable (antiporters)
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Urea	variable (diffusion)
Creatinine	small amount

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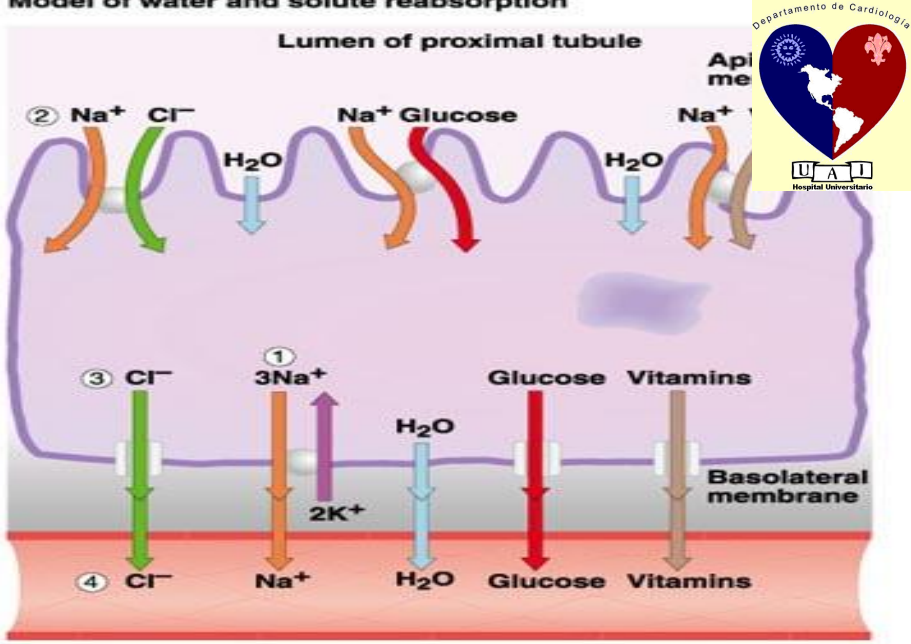

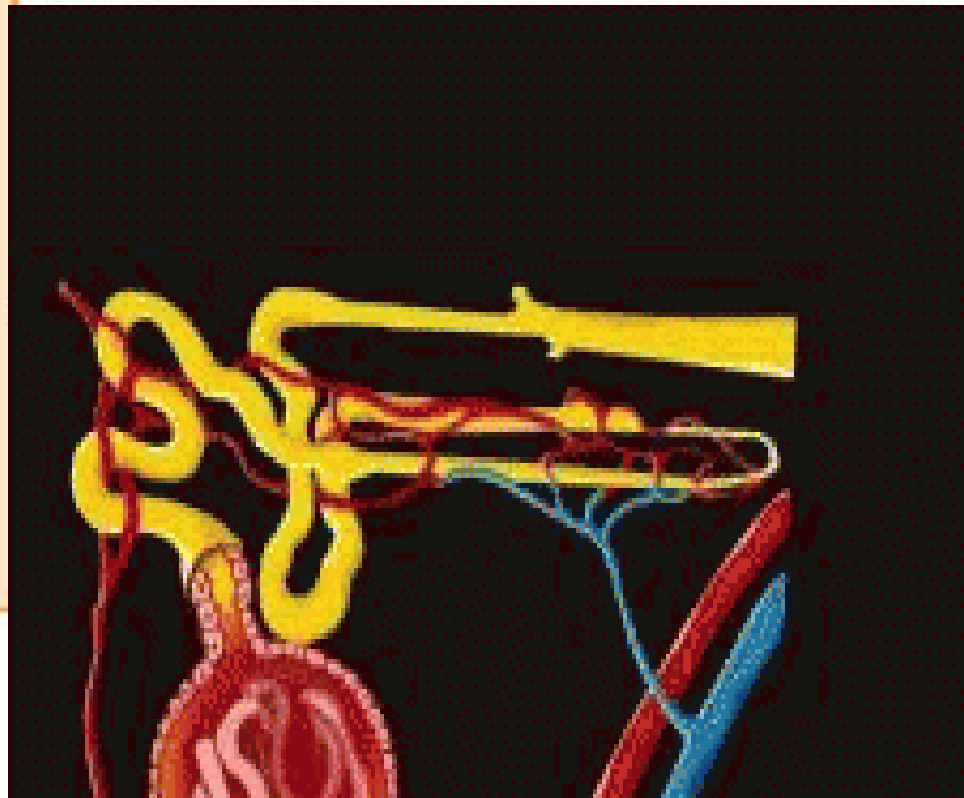

Unos 125 mL/min isotónica de 300 mOsm/Kg (280).
Al finalizar el trayecto tubular, la orina aportada por las nefronas corresponde a un flujo de 1 ml/min, cantidad que depende siempre de las necesidades hídricas del organismo, y llega a alcanzar una concentración muy diferente a la inicial (de 50 mOsm/kg hasta 1200 mOsm/kg).

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El organismo necesita eliminar diariamente 700 mOsm por día. La excreción de solutos requiere un volumen de agua tal que la concentración sea equivalente a la máxima que pueda lograrse en la médula renal.

Esa mínima cantidad de agua, que se había calculado en poco más de medio litro, constituye la diuresis diaria obligada.

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Los mecanismos de transporte que tienen lugar entre los túbulos de la nefrona y los capilares peritubulares son:

Reabsoción. Por la que el epitelio tubular recupera solutos y agua, incorporándolos al espacio intersticial, siendo finalmente absorbidos por los capilares peritubulares.

Secrección. Por la que las sustancias son aportadas desde el espacio intersticial a la luz del túbulo. La diferencia entre la cantidad reabsorbida y la secretada de una sustancia constituye la cantidad neta de dicha sustancia transferida por los túbulos

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CARGA TUBULAR

- Se denomina **carga tubular** de una sustancia a la cantidad de la misma que por unidad de tiempo pasa desde la sangre al túbulo de la nefrona; y su valor depende de la concentración plasmática de la sustancia y de la tasa de filtración glomerular

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Los productos reabsorbidos, como los que deban ser secretados, tienen dos caminos posibles:

La vía transcelular.

La vía paracelular

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Transporte máximo tubular

- Las sustancias con difusión facilitada y transporte activo, dependen de un mecanismo de naturaleza saturable y su velocidad máxima de reabsorción o secreción se denomina **transporte máximo** para esa sustancia.

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El valor de Tmg es de 320 mg/min e indica el máximo de glucosa que puede transportar el sistema. Sin embargo, debido a que unas nefronas difieren de otras en su capacidad de saturación, el umbral de glucosa se sitúa en un carga tubular de 220 mg/min, **equivalente a una concentración plasmática de 180 mg/dL, (Umbral renal) a partir de la cual comienzan a aparecer cantidades significativas de glucosa en orina.**

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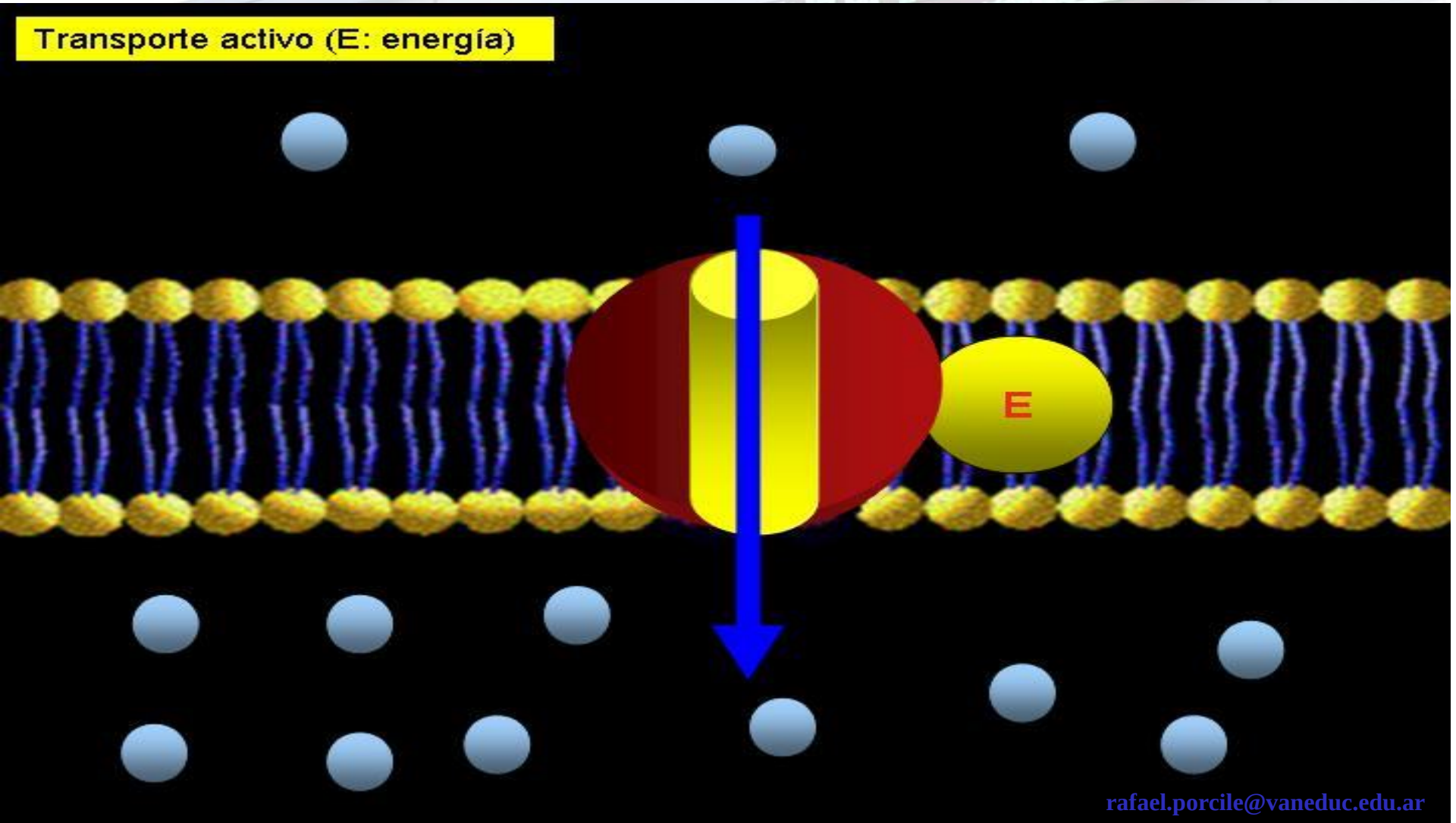
REABSOCION DE GLUCOSA



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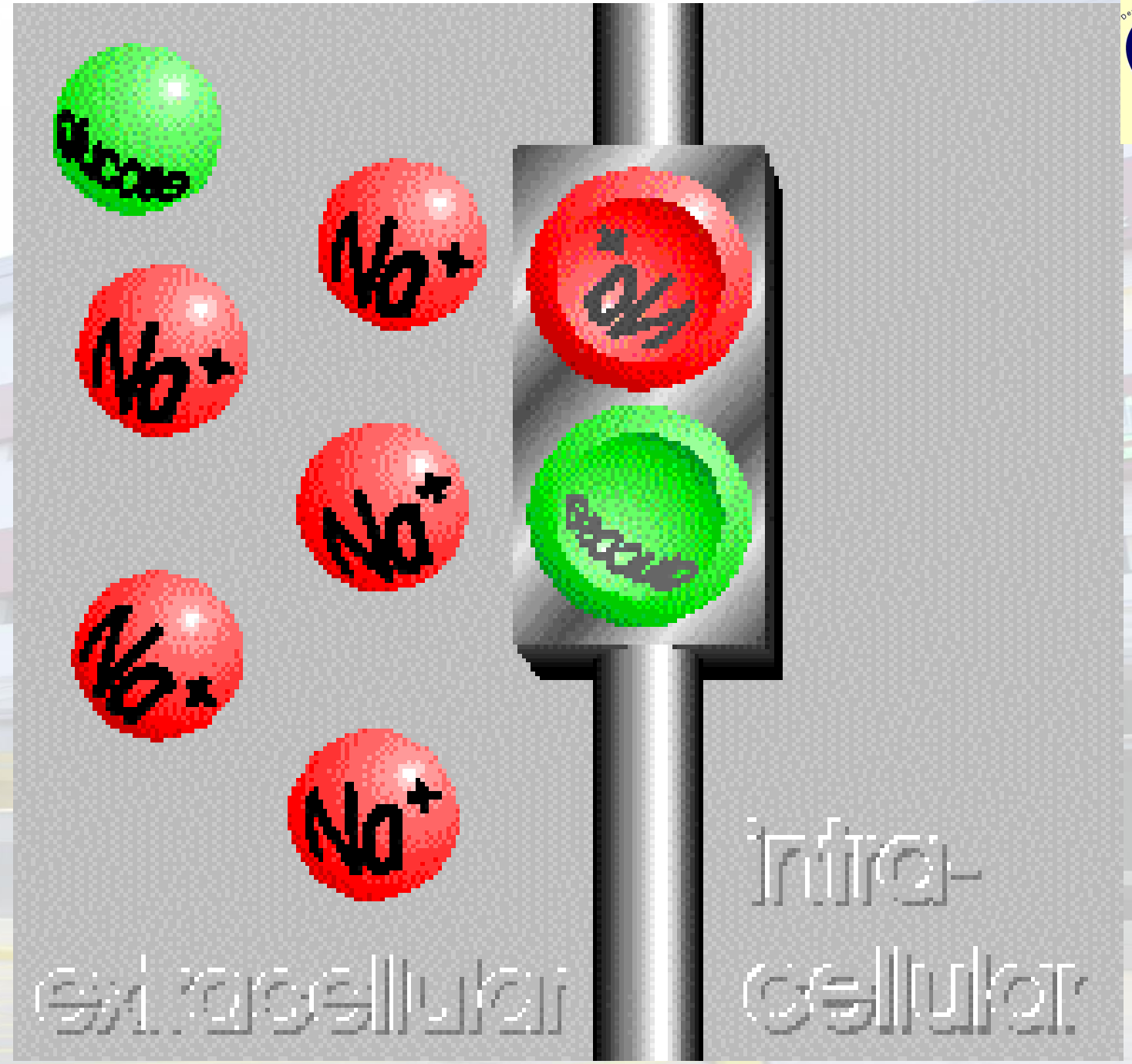

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La carga tubular condición diuresis osmótica

διαβήτης

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διαβήτης

Diabeteses que significa correr a través.

Compuesto de

δια (dia-): a traves; y

βήτης (bÃtes): correr; derivado de

διαβαίνειν (diabaÃnein): atravesar.

Hace referencia al paso rápido del agua, debido a la sed y orina frecuentes

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COMO CONDICIONAR TERAPEUTICAMNTE EL TUBULO CONTORNEADO PROXIMAL

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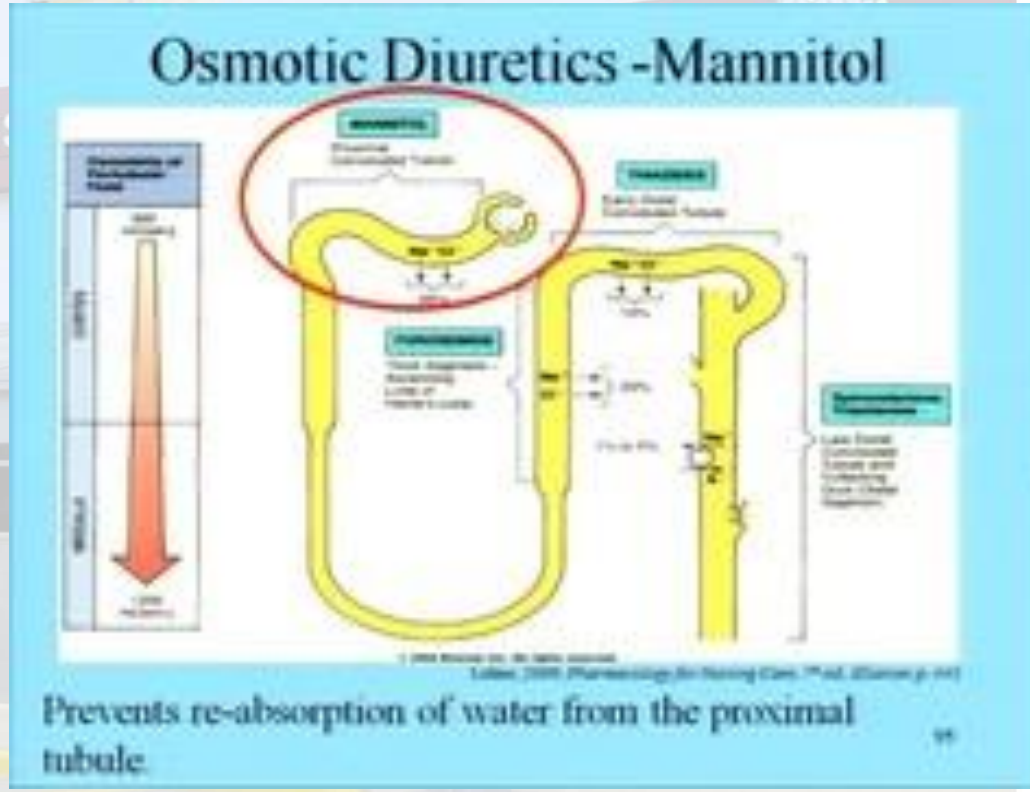
Diuréticos osmóticos



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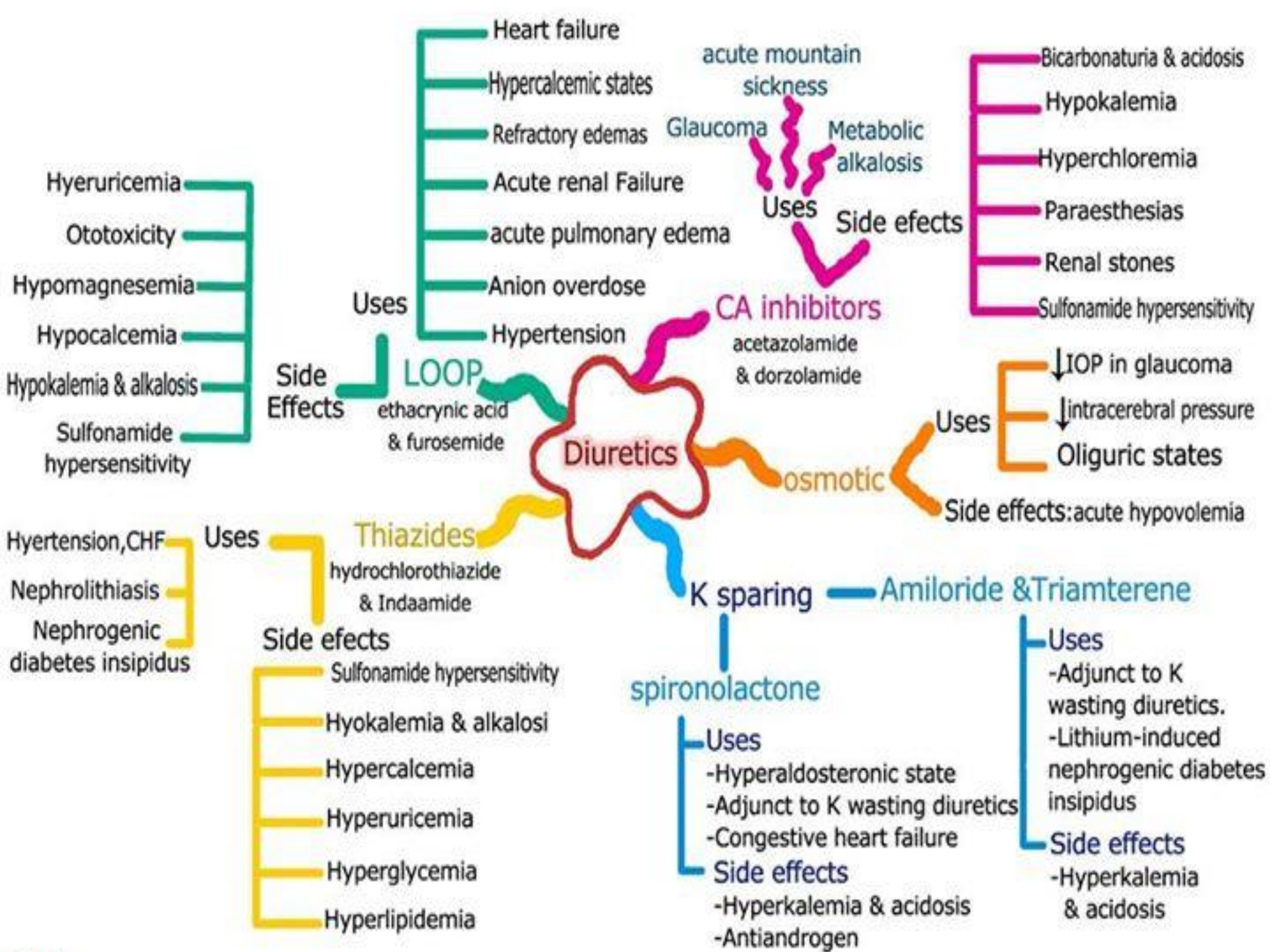
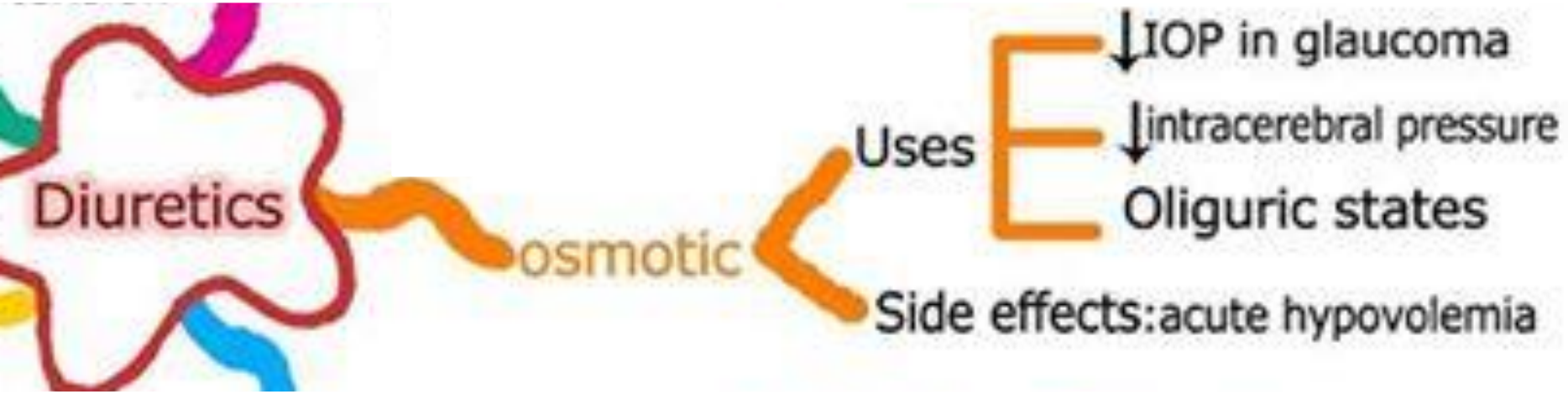

Diuretics
CA inhibitors
acetazolamide & dorzolamide
acute mountain sickness
Glaucoma
Metabolic alkalosis
Uses
Side efects
Bicarbonaturia & acidosis
Hypokalemia
Hyperchloremia
Paraesthesias
Renal stones
Sulfonamide hypersensitivity
LOOP
ethacrynic acid & furosemide
Uses
Heart failure
Hypercalcemic states
Refractory edemas
Acute renal Failure
acute pulmonary edema
Anion overdose
Hypertension
Side Effects
Hyeruricemia
Ototoxicity
Hypomagnesemia
Hypocalcemia
Hypokalemia & alkalosis
Sulfonamide hypersensitivity
osmotic
Uses
↓IOP in glaucoma
↓intracerebral pressure
Oliguric states
Side effects:acute hypovolemia
Thiazides
hydrochlorothiazide & Indaamide
Uses
Hyertension,CHF
Nephrolithiasis
Nephrogenic diabetes insipidus
Side efects
Sulfonamide hypersensitivity
Hyokalemia & alkalosi
Hypercalcemia
Hyperuricemia
Hyperglycemia
Hyperlipidemia
K sparing
Amiloride &Triamterene
Uses
-Adjunct to K wasting diuretics.
-Lithium-induced nephrogenic diabetes insipidus
Side effects
-Hyperkalemia & acidosis
spironolactone
Uses
-Hyperaldosteronic state
-Adjunct to K wasting diuretics
-Congestive heart failure
Side effects
-Hyperkalemia & acidosis
-Antiandrogen



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Diuréticos Osmóticos: M*anitol*

- Sustancia farmacológicamente inerte, sin embargo es una partícula no electrolítica osmóticamente activa, efecto que aumenta el volumen vascular transitoriamente y estimula la diuresis

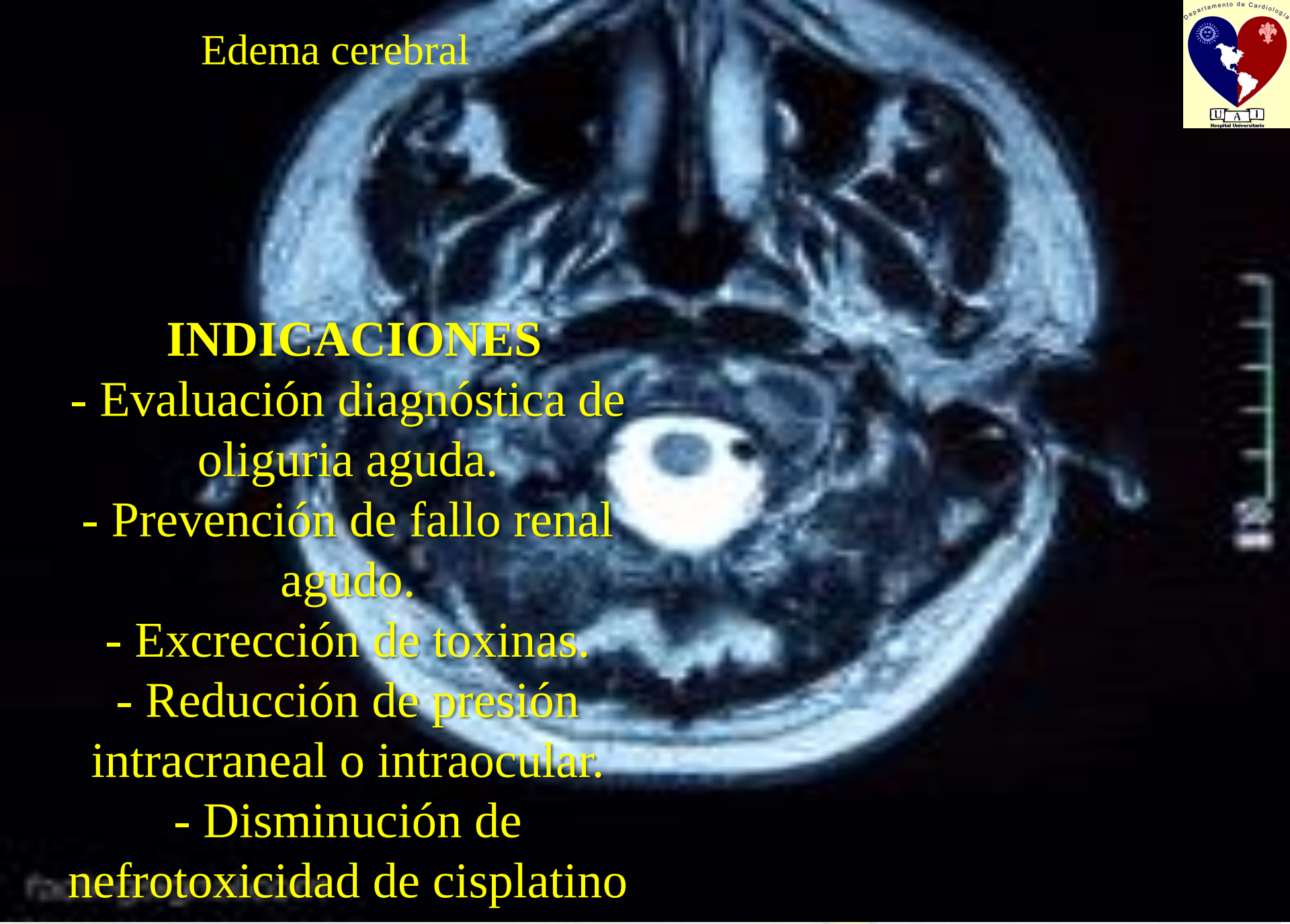
∀ ⇒ diuresis al filtrarse a través del glomérulo

- ↓ reabsorción pasiva de agua
- ↓ reabsorción de Na^+
- Administración intravenosa

Usos:

- Edema cerebral
- Hipertensión intracraneana (HIC)
- Tx hipertensión intraocular
- RAF: Expansión transitoria del volumen extracelular, hiponatremia, cefalea, náusea, vómito

Edema cerebral



INDICACIONES

- Evaluación diagnóstica de oliguria aguda.
- Prevención de fallo renal agudo.
- Excrección de toxinas.
- Reducción de presión intracraneal o intraocular.
- Disminución de nefrotoxicidad de cisplatino

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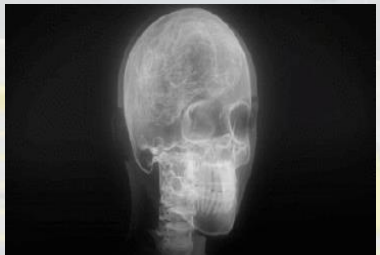
CONTRAINDICACIONES Y PRECAUCIONES

Manitol está contraindicado en los siguientes casos:

- Pacientes con anuria bien establecida debida a enfermedad renal
- Congestión pulmonar severa, franco edema pulmonar o insuficiencia cardíaca congestiva severa.
- Deshidratación grave.
- Edema no debido a enfermedad renal, cardíaca o hepática que esté asociado con fragilidad capilar anormal o permeabilidad de membrana.
- Hemorragia intracraneal activa, excepto durante craniotomía.



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HCO_3^-	80–90% (facilitated diffusion)
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Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
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At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).

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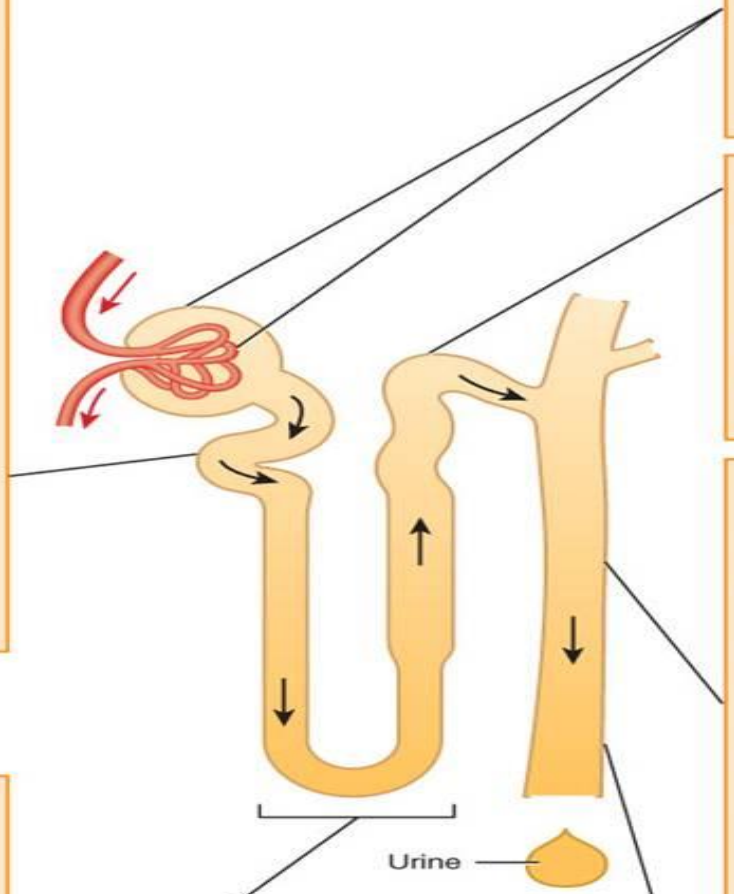
HCO_3^-	10–20% (facilitated diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

Urea	variable (recycling from collecting duct)

At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).



RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid

DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

PRINCIPAL CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

Water	5–9% (insertion of water channels stimulated by ADH)
Na^+	1–4% (sodium-potassium pumps)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

K^+	variable amount to adjust for dietary intake (leakage channels)

Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.

INTERCALATED CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

HCO_3^- (new)	varible amount, depends on H^+ secretion (antiporters)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

H^+	variable amounts to maintain acid-base homeostasis (H^+ pumps)

PROXIMAL CONVOLUTED TUBULE

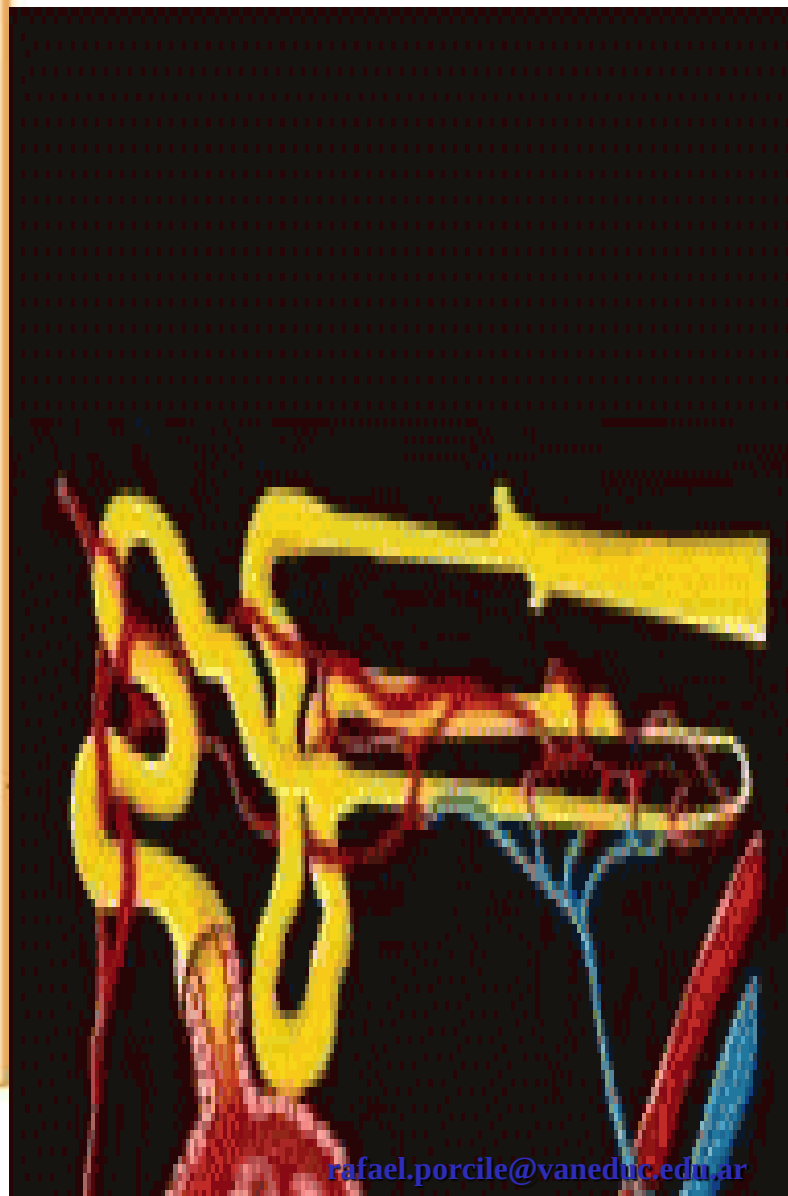
Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium-potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
Glucose	100% (symporters and facilitated diffusion)
Amino acids	100% (symporters and facilitated diffusion)
Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
Urea	50% (diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
Creatinine	small amount

At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).



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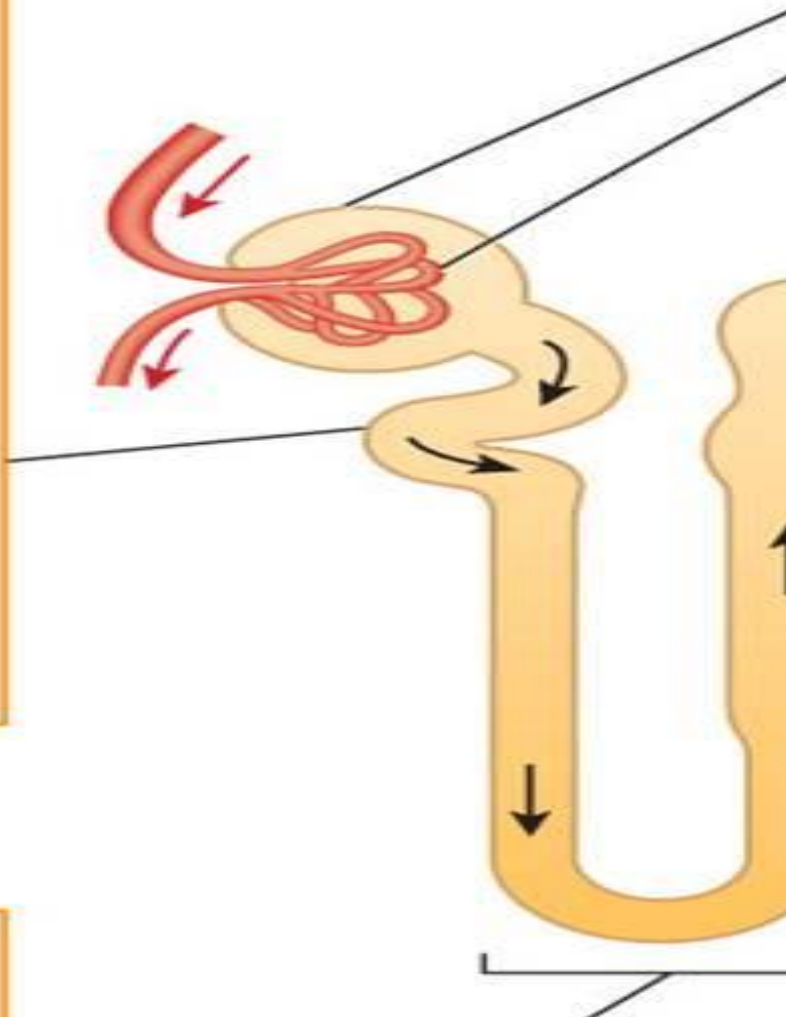

LOOP OF HENLE

Reabsorption (into blood) of:

COMO CONDICIONAR TERAPEUTICAMNTE EL TUBULO CONTORNEADO PROXIMAL

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INHIBIDORES DE LA REABSORCIÓN DE SODIO

DIURETICOS OSMOTICOS

- Manitol

DIURETISO INHIBIDORES DE LA ANIDRASA CARBONICA

-Acetazolamida

DIURÉTICOS DEL ASA

- Furosemida
-Bumetanida
-Torasemida

TIAZÍDICOS:

- Bendroflumetiacida
- Hidroclorotiazida
- Clortalidona
- Indapamida

AHORRADORES DE POTASIO

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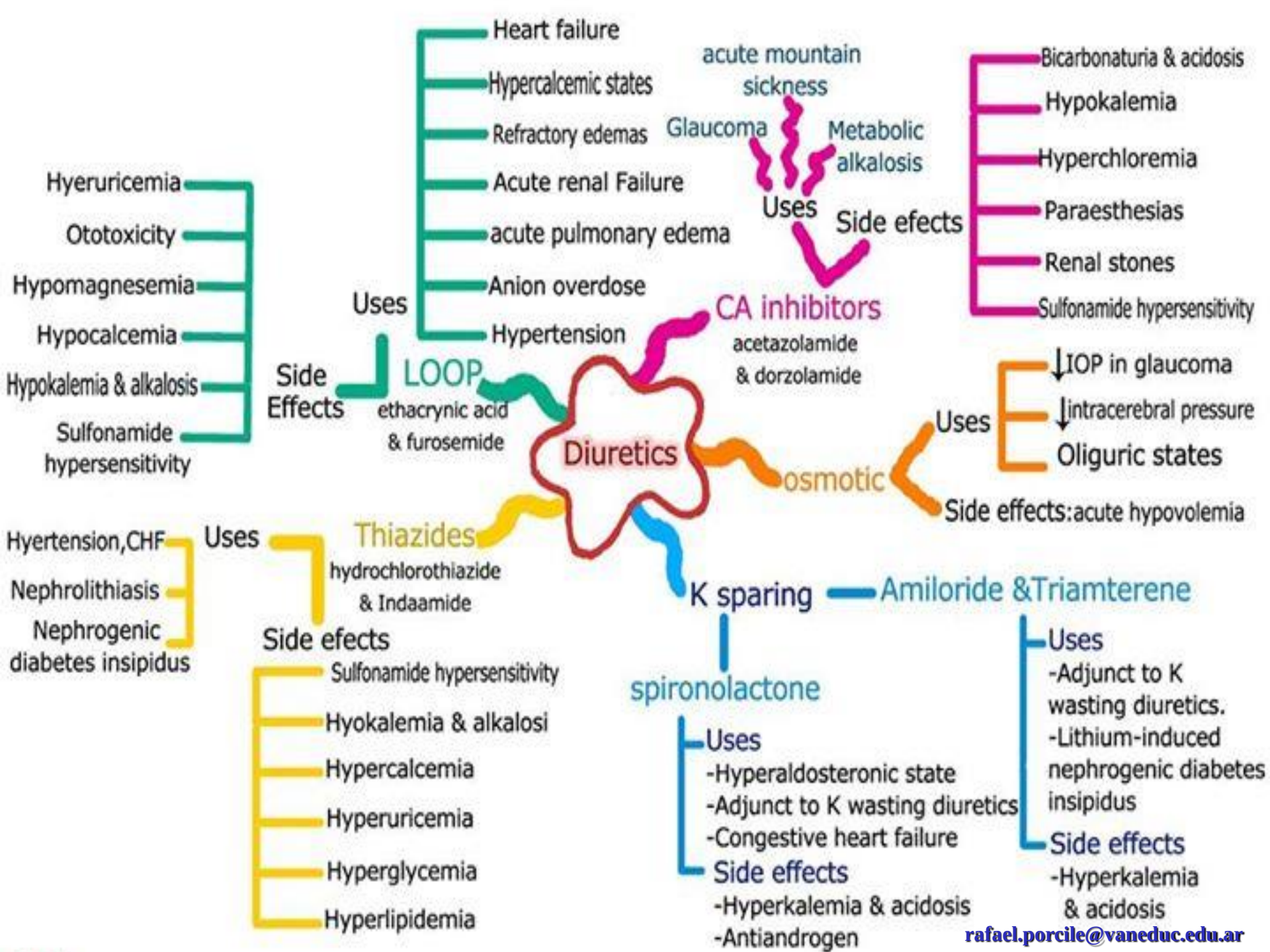

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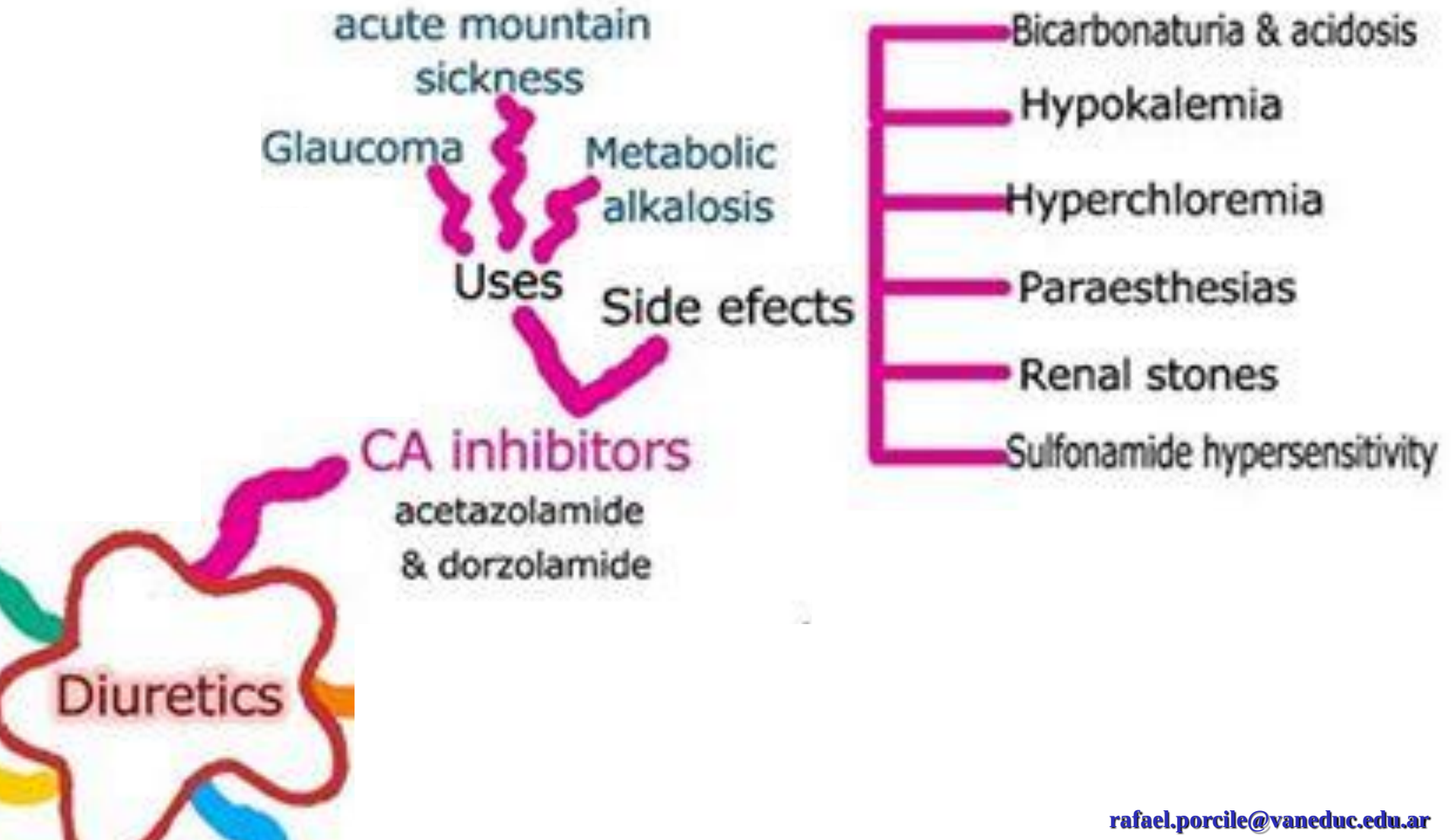

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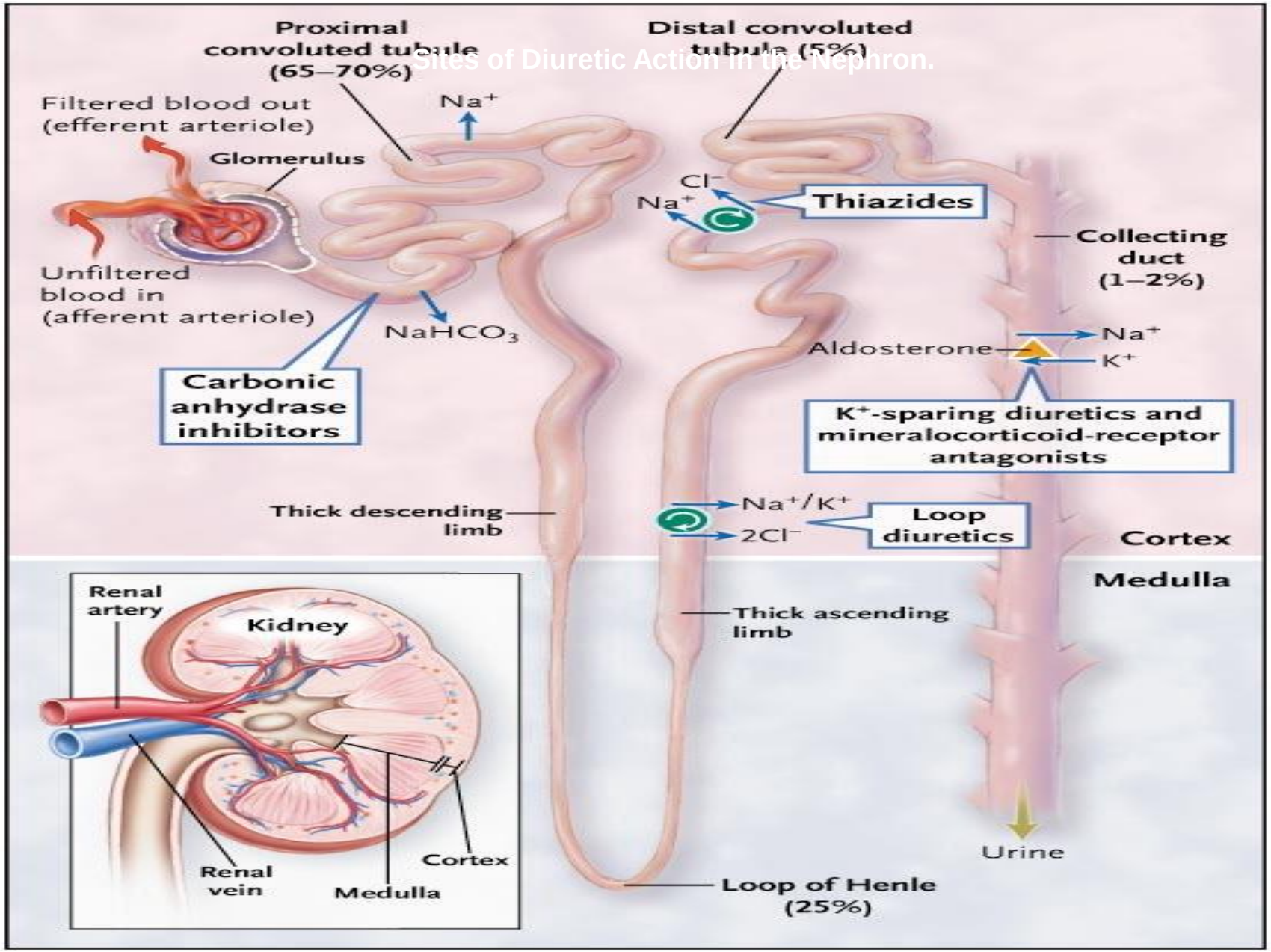

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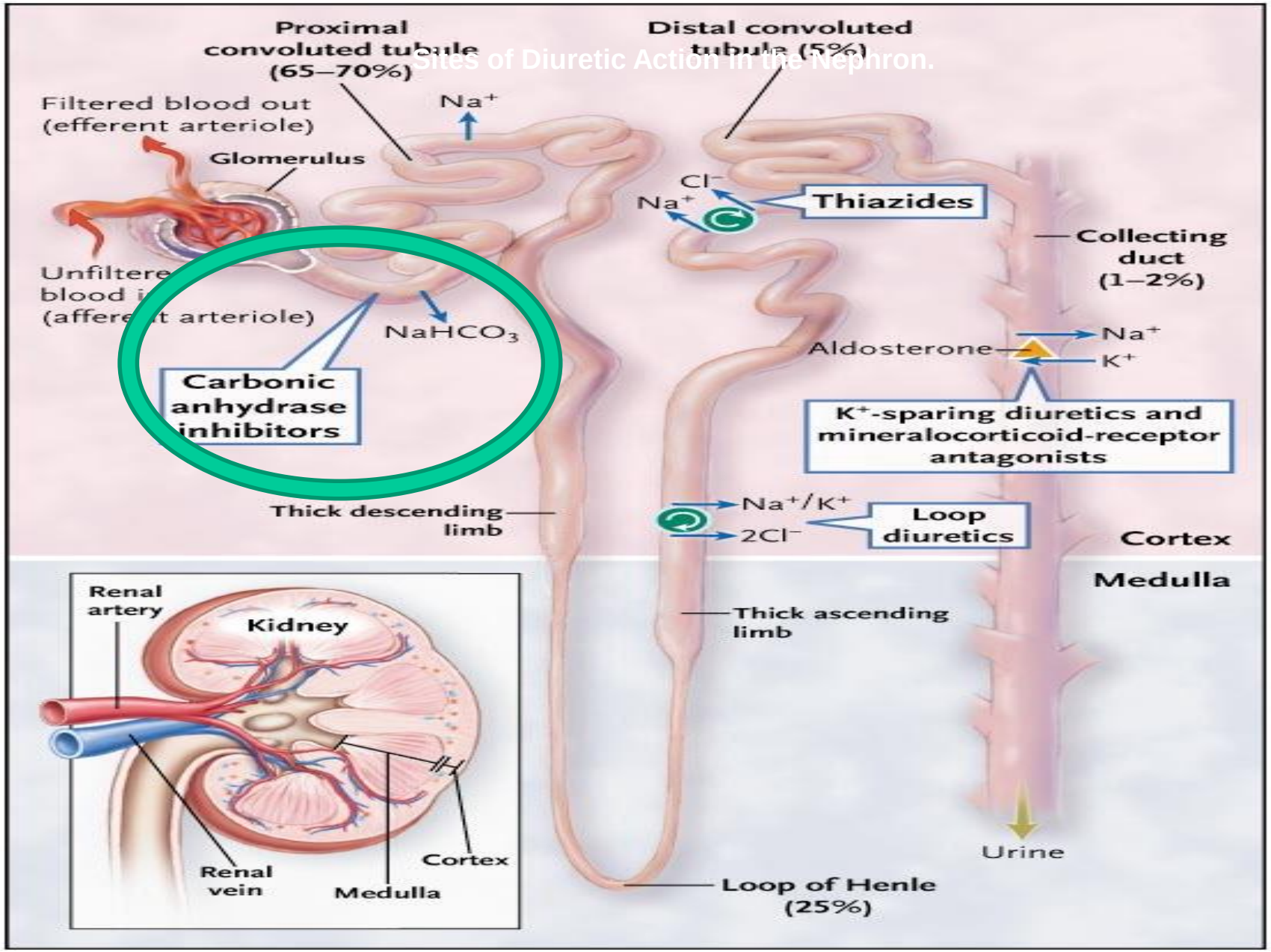

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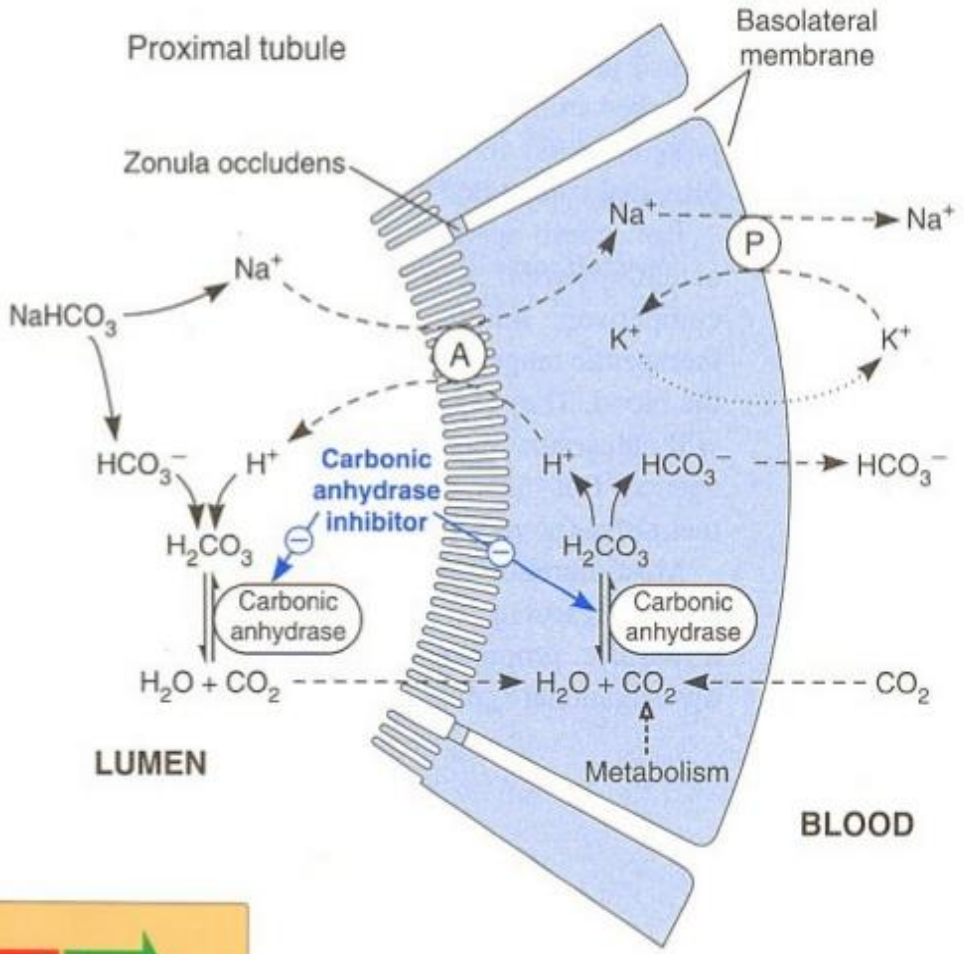
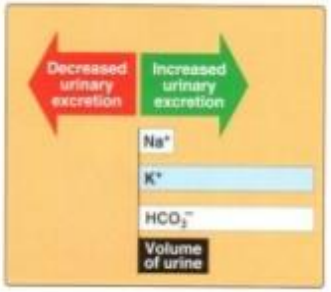
Anhidrasa Carbónica:

- Anhidrasa carbónica: cataliza la reacción:
- CO_2 y $H_2O \rightarrow$ H+ y HCO_3^-
- deshidratar al H_2CO_3
- Reabsorción de HCO_3^- (bicarbonato)





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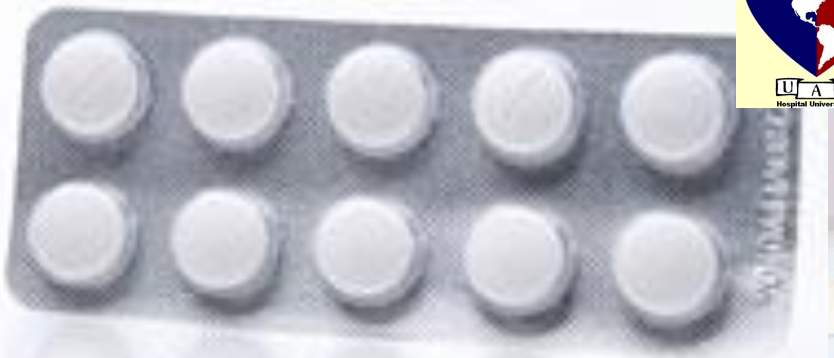

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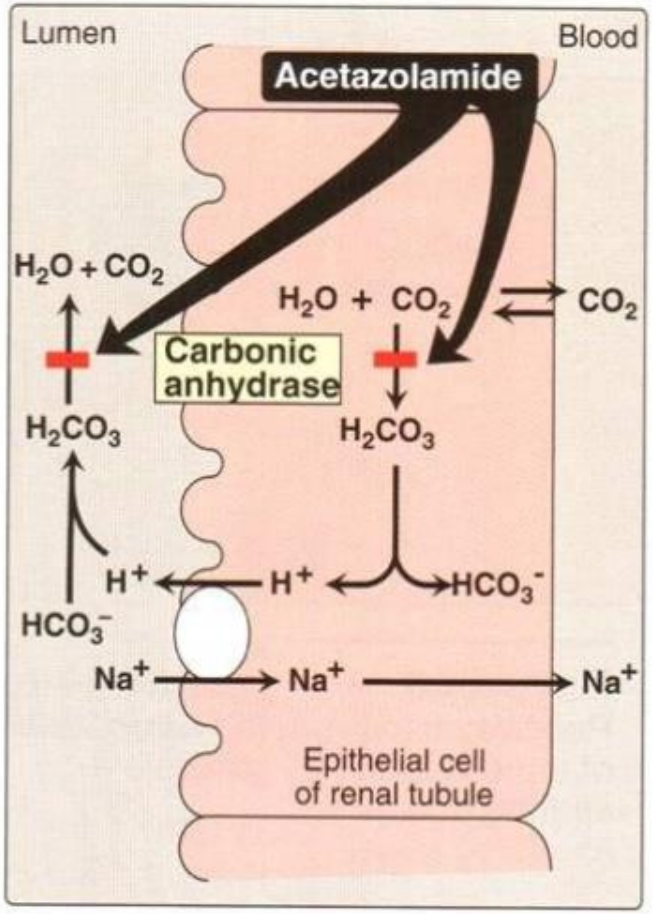
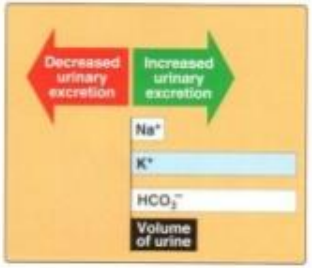
Inhibidores de Anhidrasa Carbónica: Acetazolamida.

- Disminuyen la habilidad de intercambiar Na^+ por $H^+ \rightarrow$ diuresis leve.
- Impide la reabsorción de bicarbonato (HCO_3^-)
- Retención de bicarbonato en el lumen: ↑ pH urinario

- La pérdida de bicarbonato induce acidosis metabólica
- Efecto diurético muy limitado





- Edema por insuficiencia cardiaca congestiva
- Edema de origen medicamentoso
- Cuadros de retención hidrosalina
- Glaucoma de ángulo abierto
- Glaucoma cónico simple
- Glaucoma secundario

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CARTA AL DIRECTOR

Acetazolamida en los viajes en altitud

Acetazolamide in high altitude trips

Sr. Director:

En los últimos años presenciamos el aumento del llamado «turismo de aventura», lo que nos afecta, puesto que muchas veces acuden pacientes a la consulta y solicitan información sobre los posibles riesgos para el viaje, la preparación del botiquín, etc.

En los viajes a regiones del planeta por encima de los 3.000 m, sobre todo para realizar senderismo o alpinismo, casi todo el mundo experimenta algún síntoma del síndrome del mal agudo de montaña (MAM) con una gran variabilidad interindividual, con más síntomas y más intensos conforme más alto o más rápido subamos. Se ha documentado que la incidencia del MAM es mayor del 43% por encima de los 4.300 m y del 34% por encima de los 3.650 m[1].

Para prevenir el MAM se ha generalizado el uso de acetazolamida[2,3], con numerosos estudios pero con limitaciones metodológicas dadas las dificultades para ello. Este tratamiento (que con esta indicación no está aprobado en España) se recomienda por parte de las agencias organizadoras, los guías locales y los servicios públicos de sanidad exterior. También los viajeros llegan a conocer de este por la información que circula de boca en boca y sobre todo a través de Internet. Aunque precisa receta médica en nuestro país, es posible conseguirlo sin prescripción médica en lugares donde la cobertura sanitaria es casi inexistente.

La acetazolamida es un diurético inhibidor de la anhidrasa carbónica y su mecanismo de actuación no es del todo conocido. Parece dificultar el transporte del dióxido de carbono de la célula al interior del alvéolo; la acidosis tisular resultante probablemente es la causante de la estimulación de los quimiorreceptores y del aumento de la frecuencia respiratoria, y previene, a su vez, la respiración de Cheyne-Stockes que se da durante el sueño y la menor hipoxemia secundaria (fenómeno frecuente en el proceso de aclimatación). Este estímulo respiratorio es aumentado por parte de una mayor excreción renal de bicarbonato, que aumenta la acidosis metabólica. Estos procesos son parte de la aclimatación normal del organismo, pero la acetazolamida los acelera.

Sin embargo, hay que tener en cuenta las limitaciones de los estudios que han llevado a esta recomendación. Estos se han realizado en alturas no mayores de 4.900 m[4], alguno en alturas mayores pero con una muestra pequeña[5]. Otro de los más importantes tomó como muestra a porteadores nepalíes[6]. Hay que tener en cuenta que estos muchas veces viven a alturas superiores a los 3.000 m y tienen una mejor «adaptabilidad» genéticamente determinada.

Según mi experiencia sobre el terreno, es un medicamento efectivo y seguro usado en casos seleccionados, con frecuentes pero bien tolerados y transitorios efectos secundarios, y que ha evitado, en alguna ocasión, que la vida del paciente corriera peligro ante la dificultad para descender o la imposibilidad de un rápido rescate. Sin embargo, también he comprobado cómo se abusa de este por el intenso deseo de subir, pero también por la falta de información, ya que la mejoría de los síntomas provoca que los montañeros puedan pensar en seguir ascendiendo, lo que aumenta el riesgo de complicaciones del MAM (edema pulmonar y edema cerebral de altitud), con riesgo vital, por tanto, en un medio aislado, salvaje y hostil, muchas veces sin posibilidad de atención sanitaria ni de rescate.

Considero entonces, que es un fármaco que valorar para este tipo de viajes. Se debe informar siempre sobre sus limitaciones, según los estudios realizados, y por supuesto sobre sus contraindicaciones y sus riesgos; insistir en que la forma más segura de aclimatar es una ascensión progresiva y cuidadosa, con una correcta hidratación, e informar, además, sobre los síntomas y los signos del MAM, cómo valorar su gravedad, sus posibles complicaciones y la actuación ante estos.

Bibliografía

1. Schoene RB. Illnesses at high altitude. Chest. 2008;134:402–16.
2. Dumont L, Mardirosoff C, Tramèr MR. Efficacy and harm of pharmacological prevention of acute mountain sickness: Quantitative systematic review. BMJ. 2000;321:267–72.
3. Van Patot MC, Leadbetter III G, Keyes LE, Maakestad KM, Olson S, Hackett PH. Prophylactic low-dose acetazolamide reduces the incidence and severity of acute mountain sickness. High Alt Med Biol. 2008;9:289–93.

0212-6567/$ - see front matter
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5 minutos …

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Fármacos diuréticos y antidiuréticos

Segunda parte

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DEPARTAMENTO DE CARDIOLOGIA

CATEDRA DE FISIOLOGÍA

Universidad Abierta Interamericana

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ASA DE HENLE

DIURETICOS DE ASA

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ASA DE HENLE

MECANISMO DE CONTRA CORRIENTE

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Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium-potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
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Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
Urea	50% (diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
Creatinine	small amount

At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).

LOOP OF HENLE

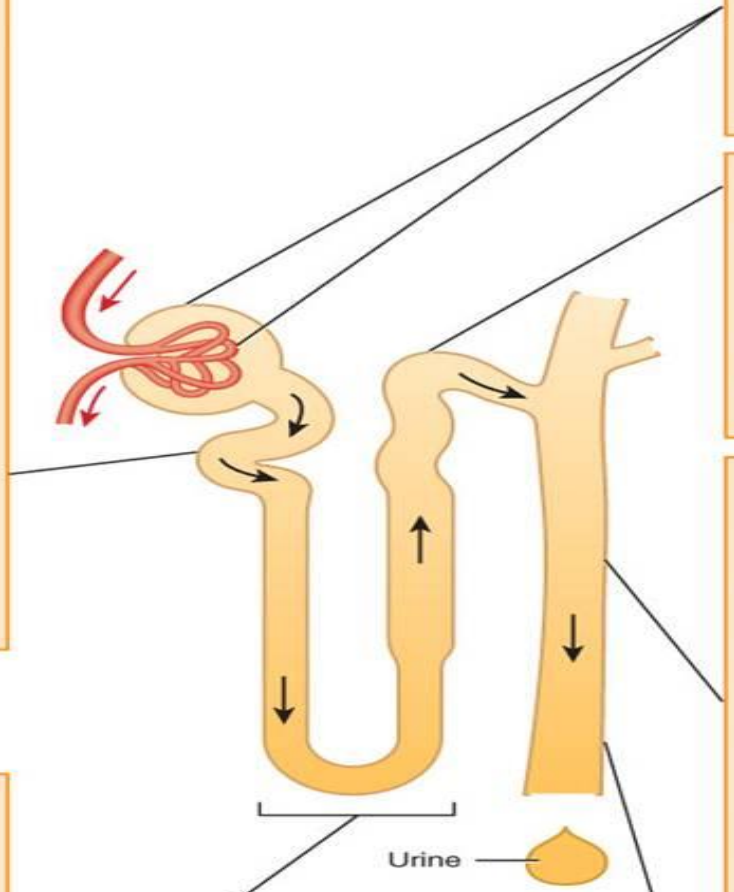
Reabsorption (into blood) of:

Water	15% (osmosis in descending limb)
Na^+	20–30% (symporters in ascending limb)
K^+	20–30% (symporters in ascending limb)
Cl^-	35% (symporters in ascending limb)
HCO_3^-	10–20% (facilitated diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

Urea	variable (recycling from collecting duct)

At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).



RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid

DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

PRINCIPAL CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

Water	5–9% (insertion of water channels stimulated by ADH)
Na^+	1–4% (sodium-potassium pumps)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

K^+	variable amount to adjust for dietary intake (leakage channels)

Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.

INTERCALATED CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

HCO_3^- (new)	varible amount, depends on H^+ secretion (antiporters)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

H^+	variable amounts to maintain acid-base homeostasis (H^+ pumps)

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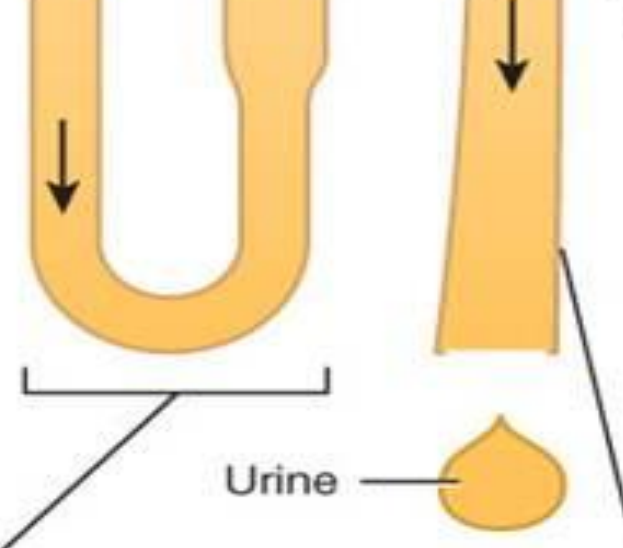
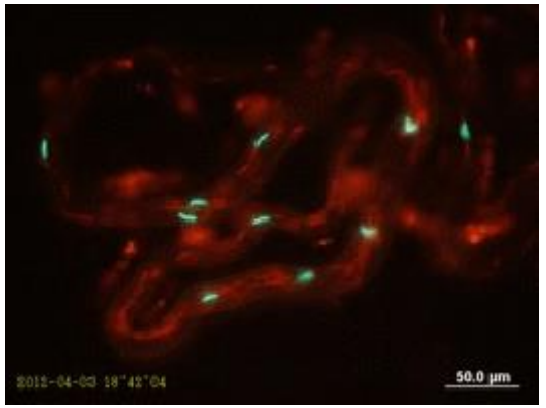
At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).





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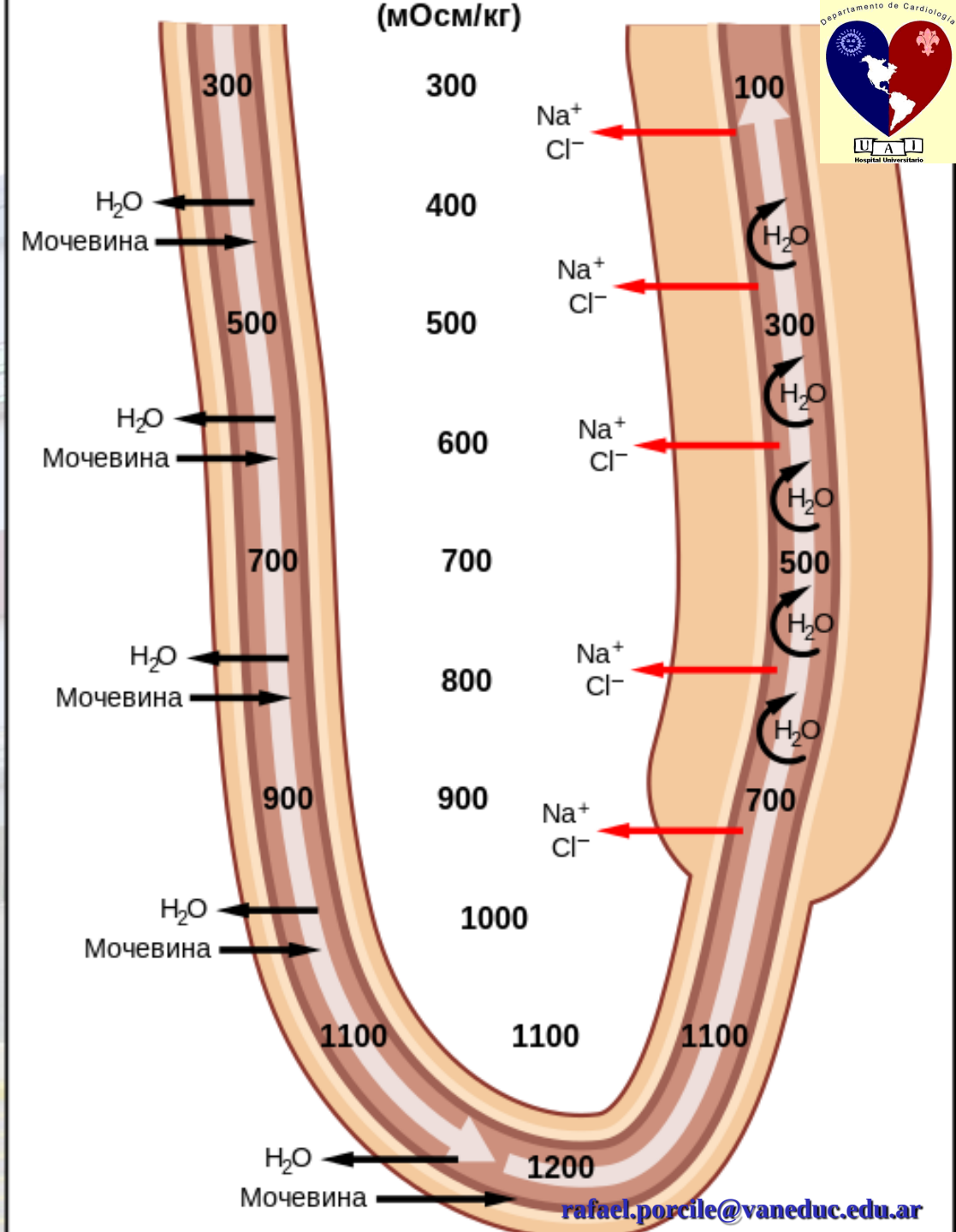

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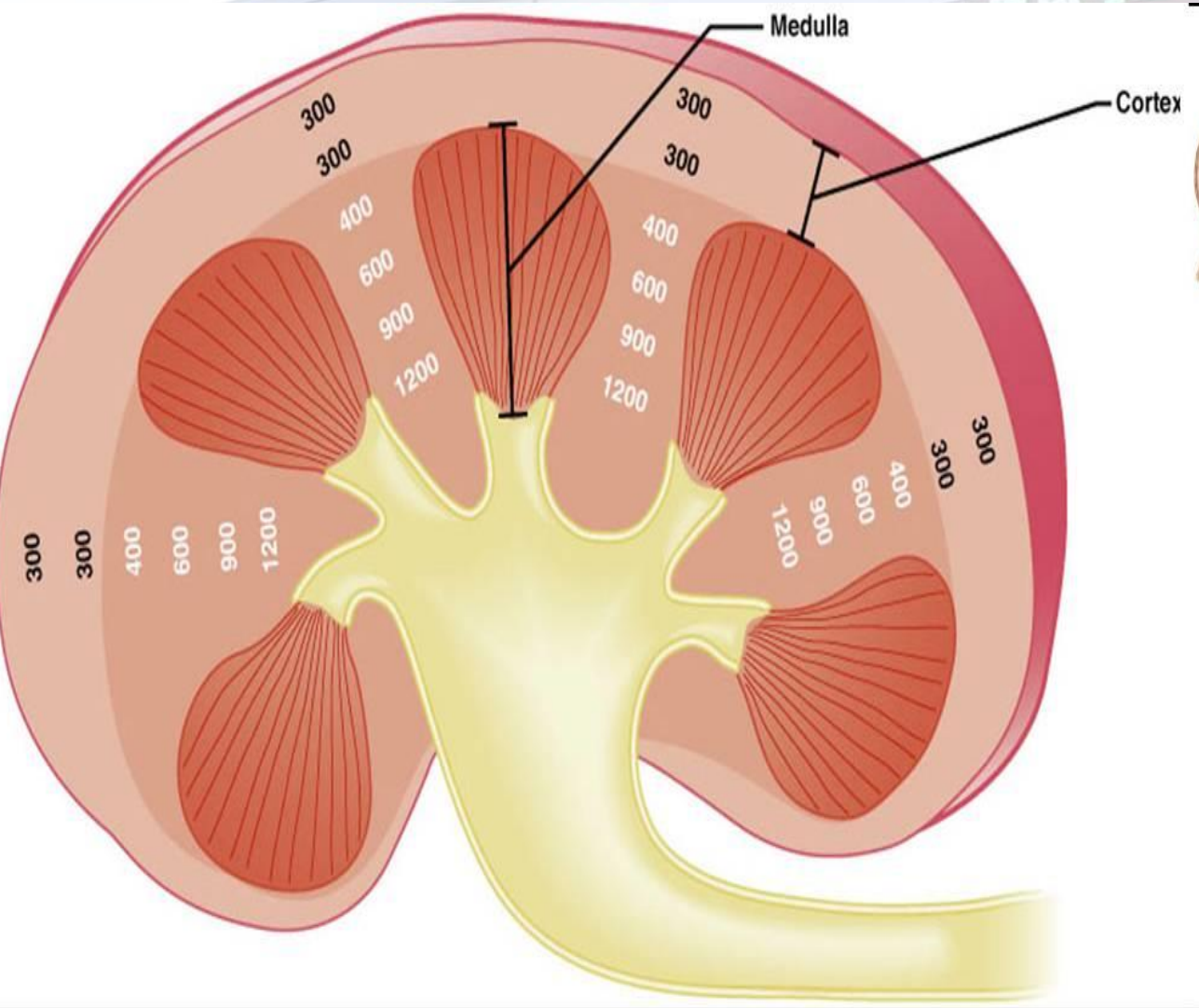
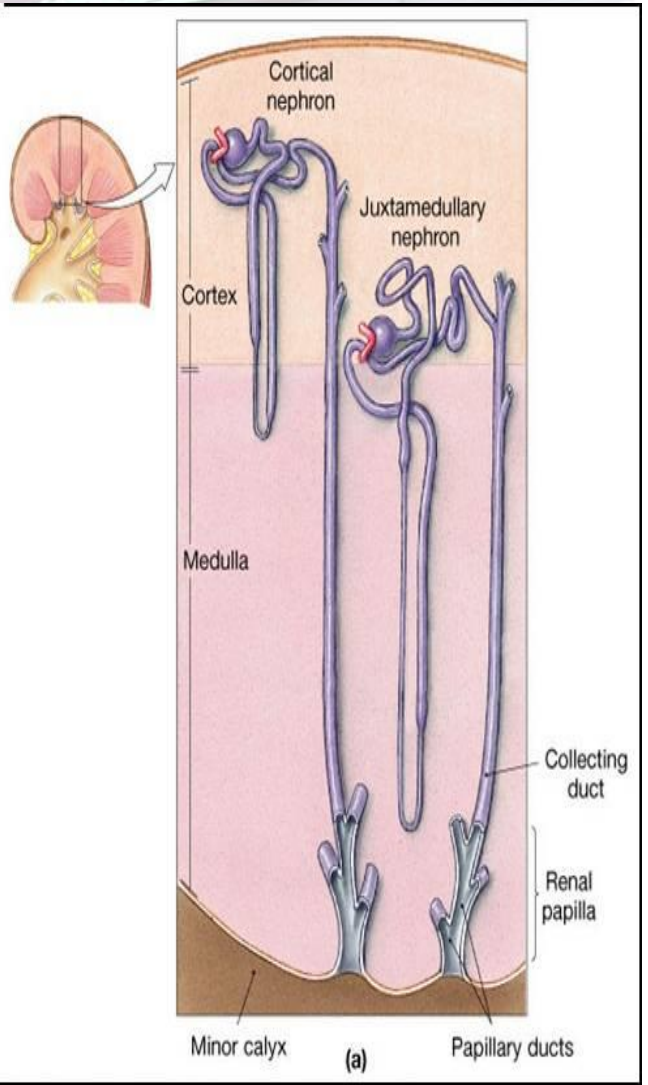
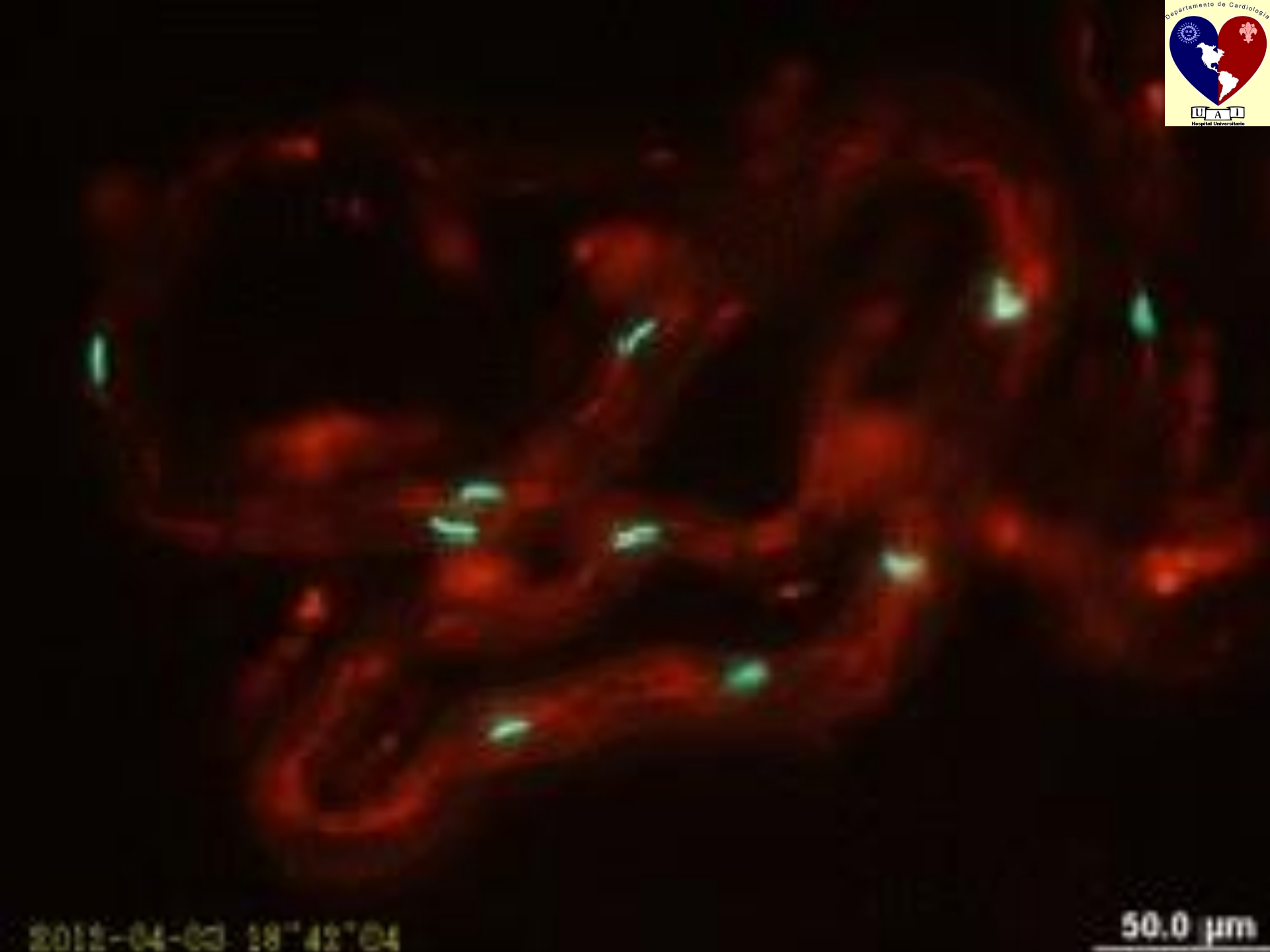
OSMOLARIDAD INTRA RENAL






Departamento de Cardiología
U A I
Hospital Universitario
2012-04-03 18"43"04
50.0 µm

El gradiente osmótico existente en la médula renal, se genera por efecto del flujo de filtración opuesta en las dos ramas del asa de Henle Complejas interacciones entre las ramas ascendentes y descendentes del asa, forman y mantienen un gradiente osmótico en el intersticio medular, esencial para generar una orina concentrada.

La rama ascendente transporta activamente cloruro de sodio hacia el intersticio, incrementando la concentración medular. El medio intersticial circundante al túbulo se torna más concentrado a medida que el fluido tubular se diluye. La máxima concentración del soluto se encuentra próxima al fondo del asa.

El intersticio medular muestra un gradiente de 300 a 1200 miliosmoles. El fluido que ingresa en la porción cortical del asa ha sido diluido en aproximadamente 100 miliosmoles. El fluido tubular es 200 miliosmoles menos concentrado que el fluido intersticial.

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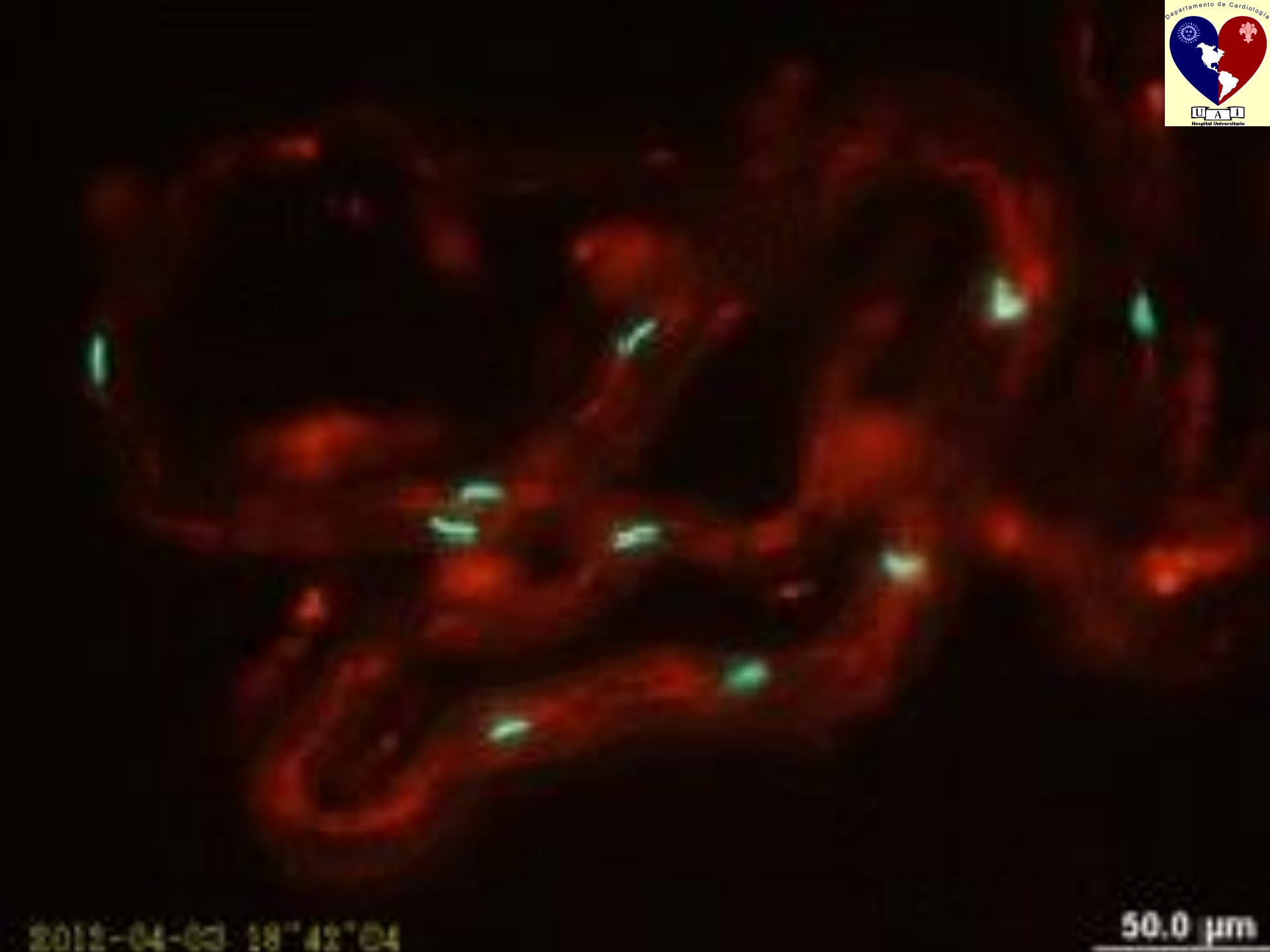
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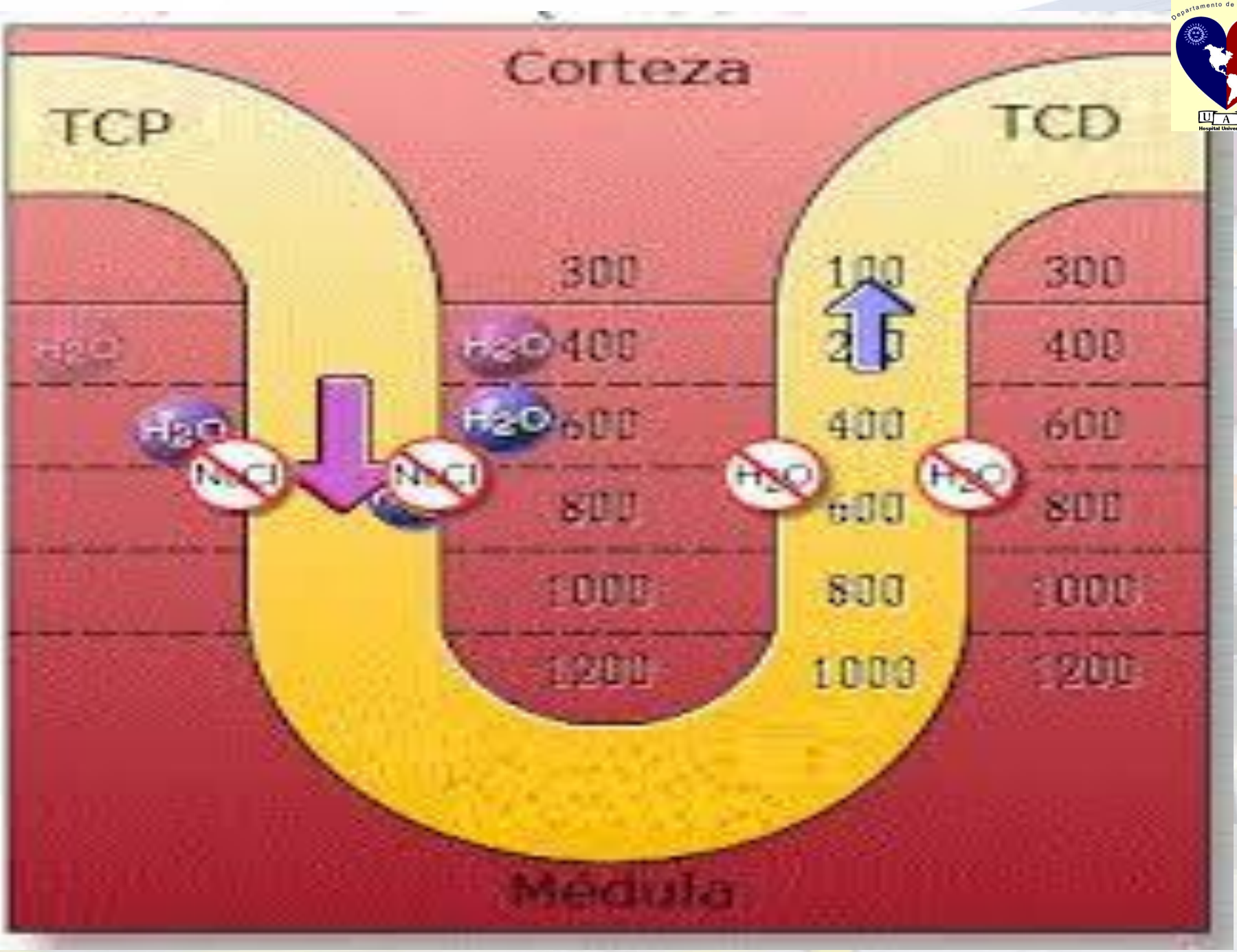

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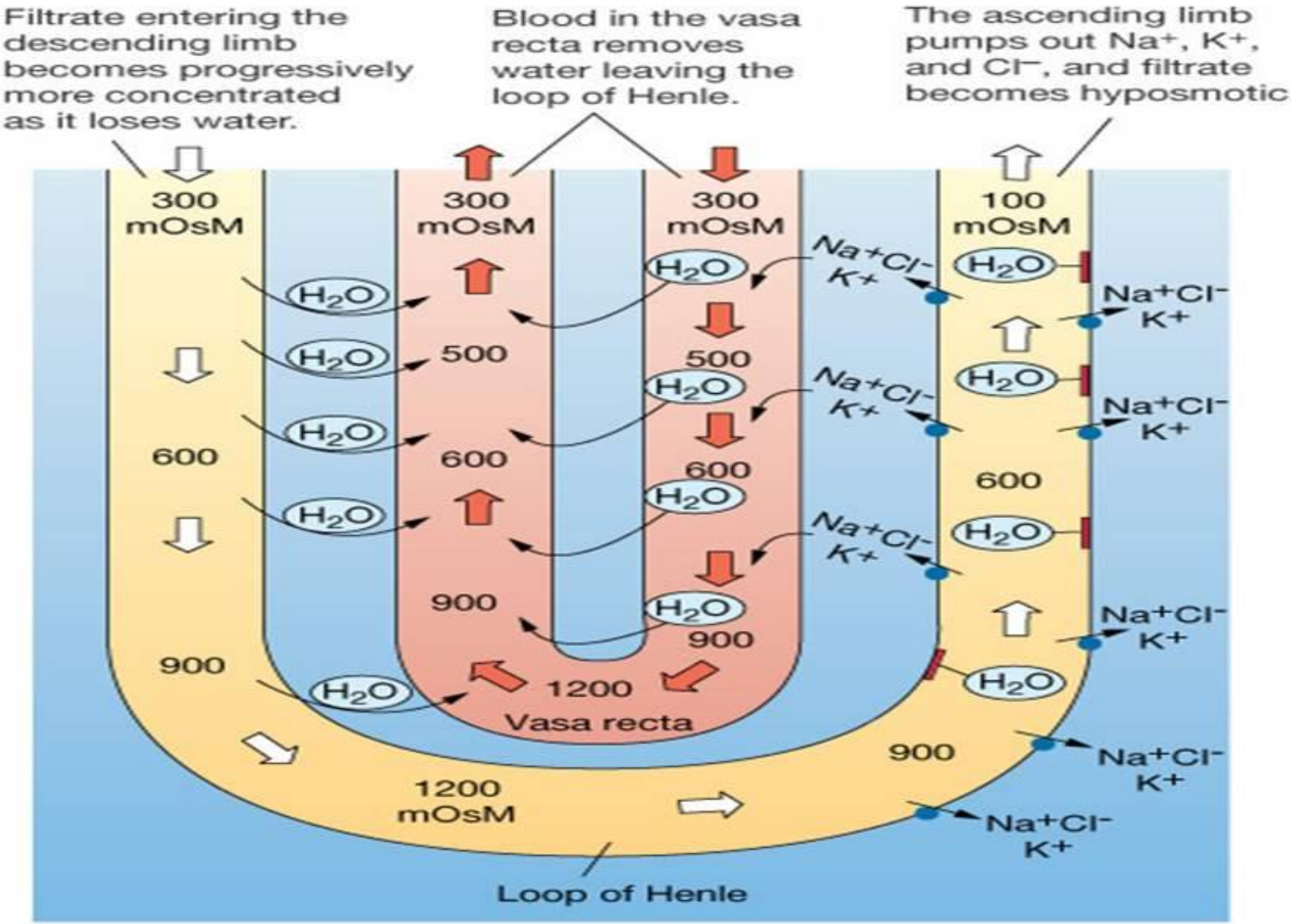
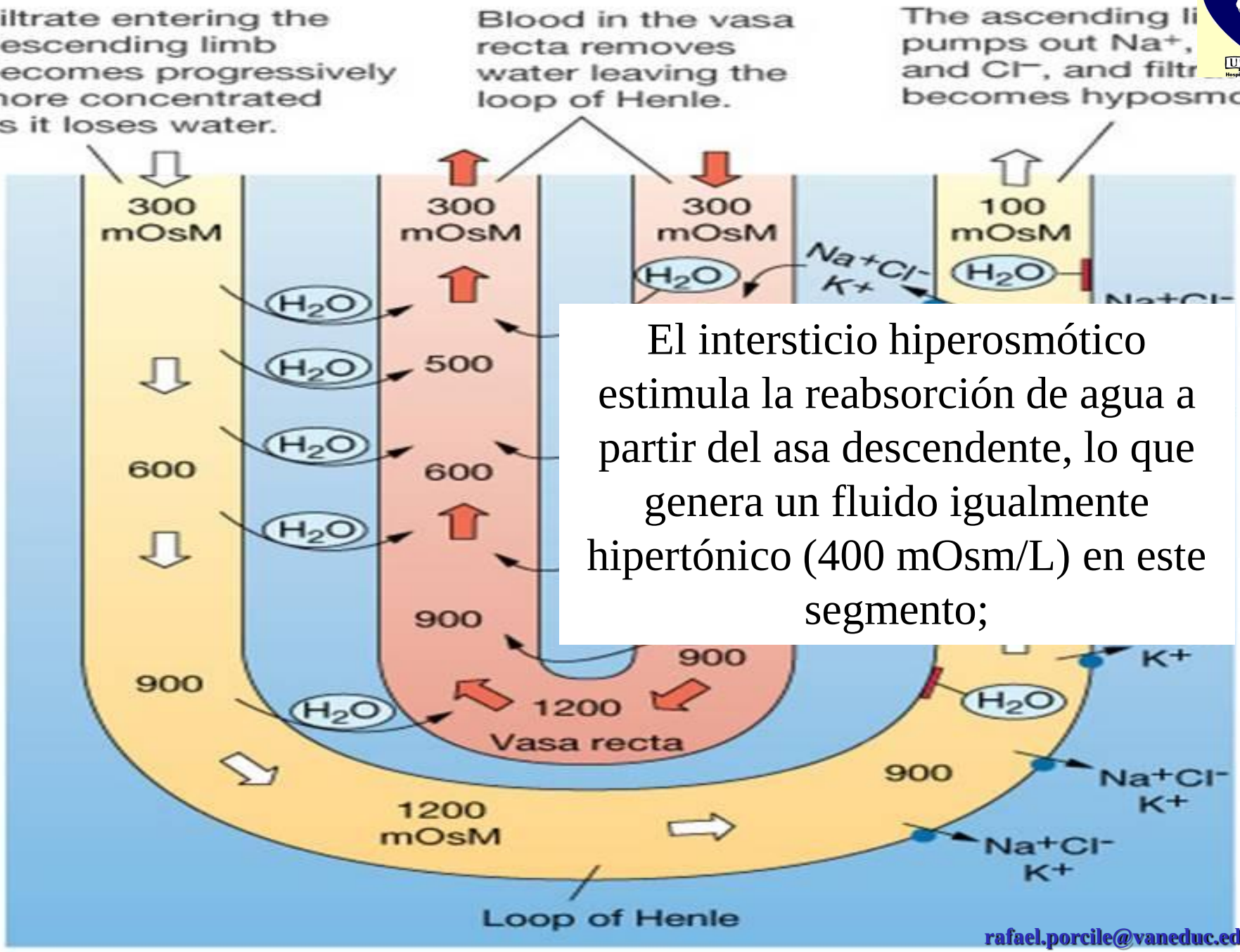

Filtrate entering the descending limb becomes progressively more concentrated as it loses water.
Blood in the vasa recta removes water leaving the loop of Henle.
The ascending limb pumps out Na+, K+, and Cl−, and filtrate becomes hyposmotic.
300 mOsM
300 mOsM
300 mOsM
100 mOsM
H2O
Na+Cl− K+
500
600
900
1200
Vasa recta
1200 mOsM
Loop of Henle



El intersticio hiperosmótico estimula la reabsorción de agua a partir del asa descendente, lo que genera un fluido igualmente hipertónico (400 mOsm/L) en este segmento;

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CORTEZA

MEDULA

ASA DE HENLE

TUBO COLECTOR

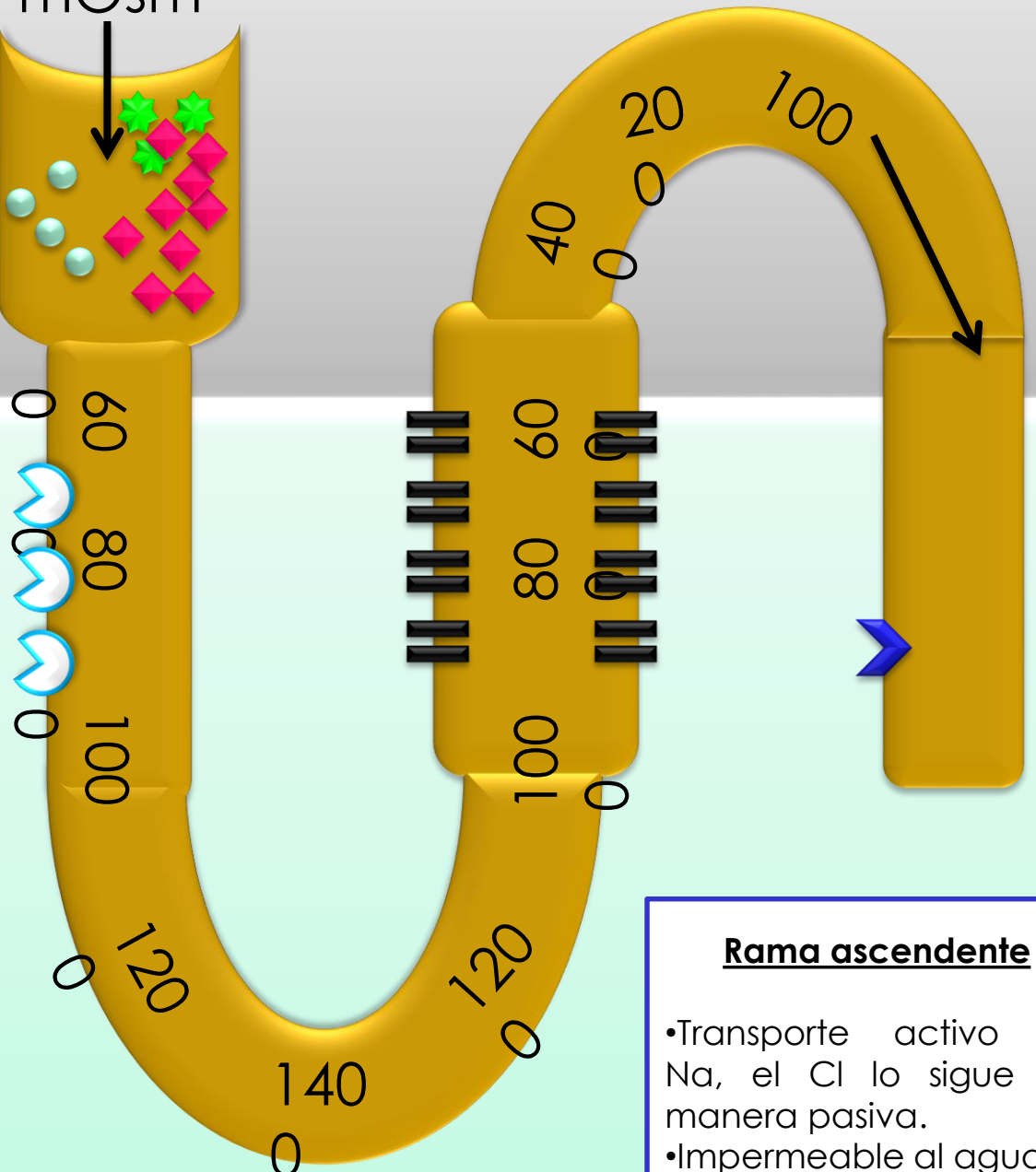
H2O

NaCl

Urea

300 mOsm

Capilar



Rama descendente

Pasivamente permeable al agua

Rama ascendente

- Transporte activo de Na, el Cl lo sigue de manera pasiva.
- Impermeable al agua.

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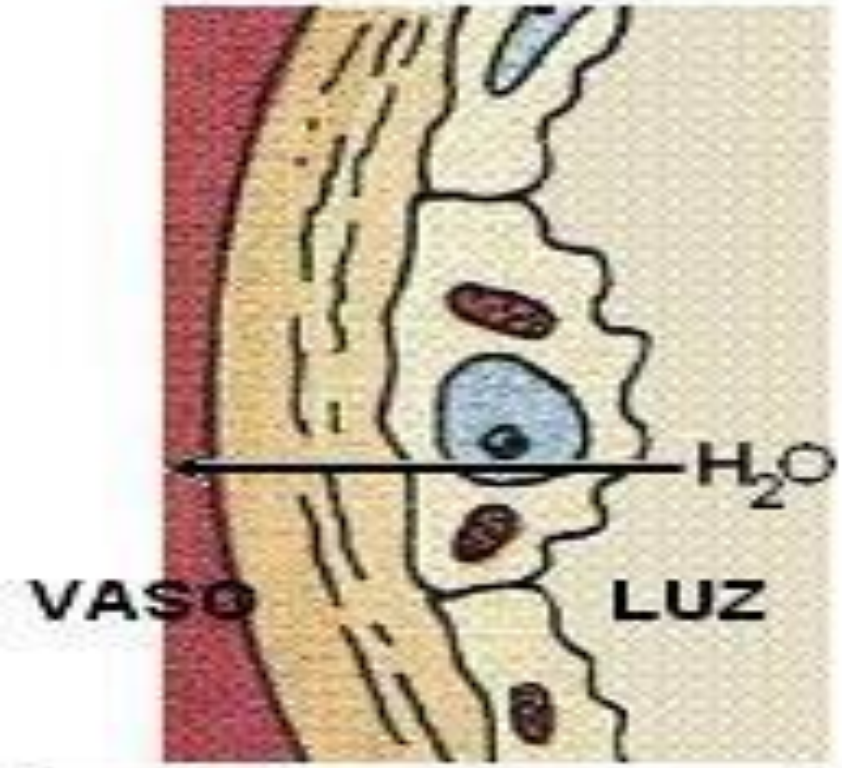
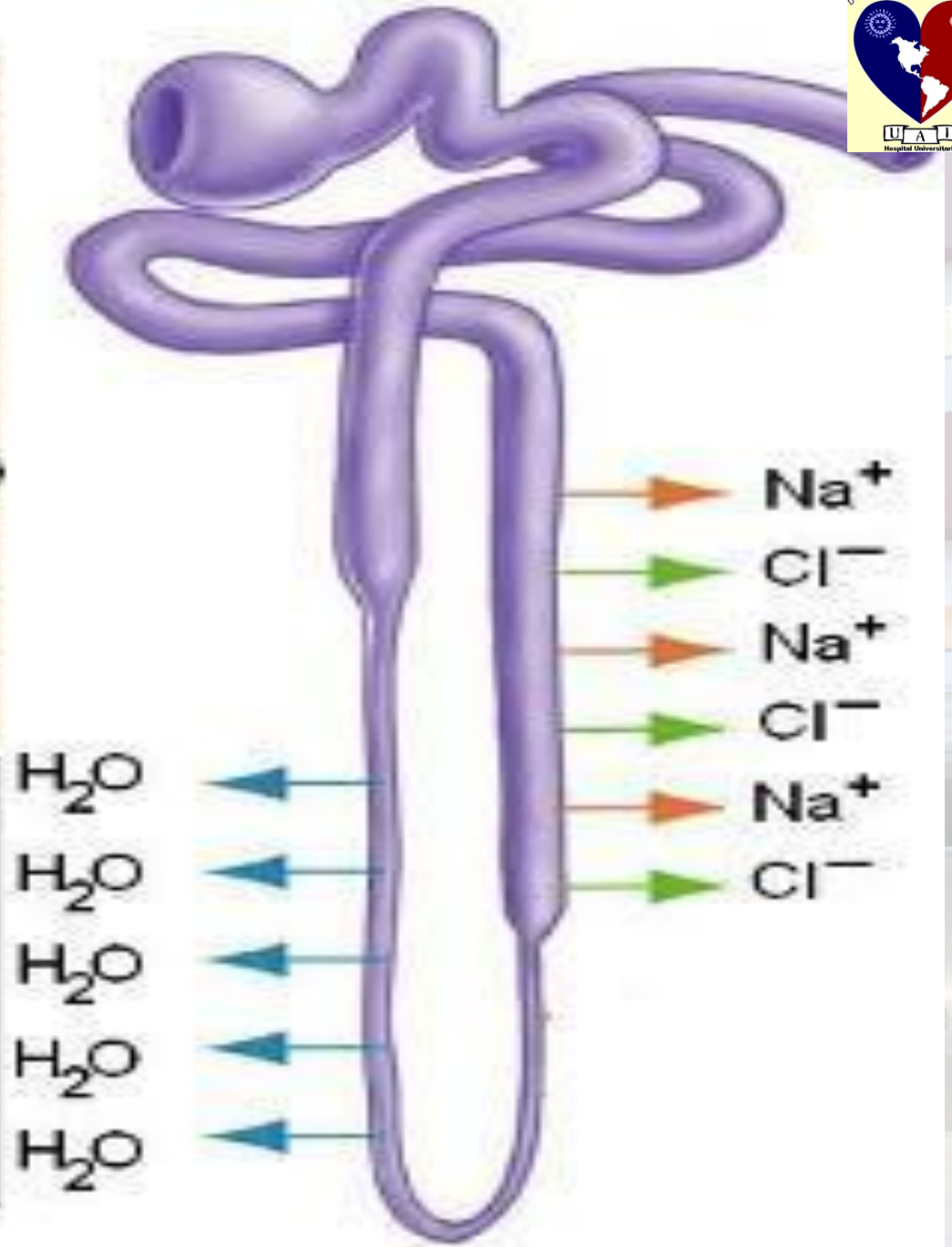


Rama descendente delgada del asa de Henle

- Reabsorción de agua
- Impermeable a solutos



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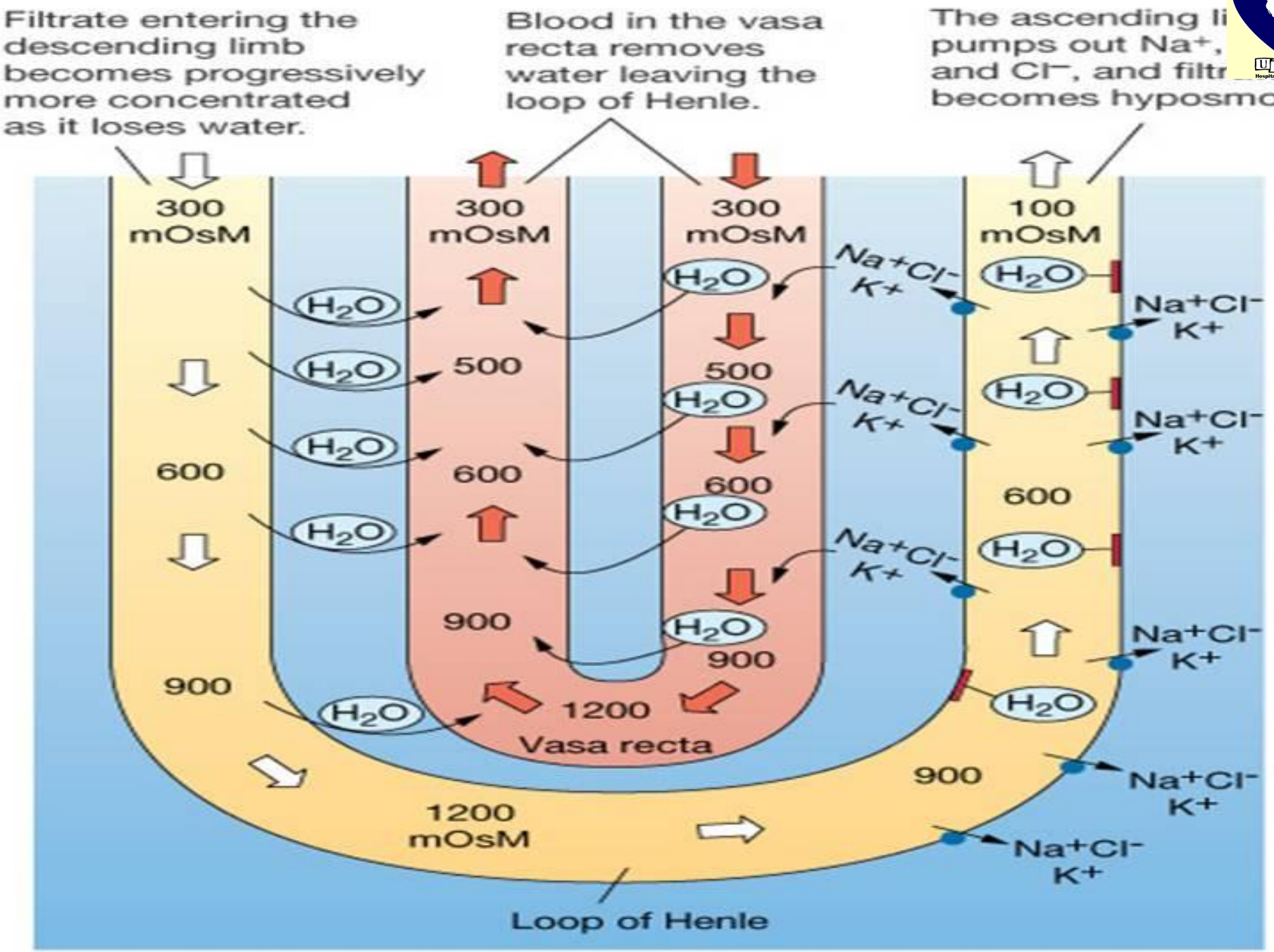
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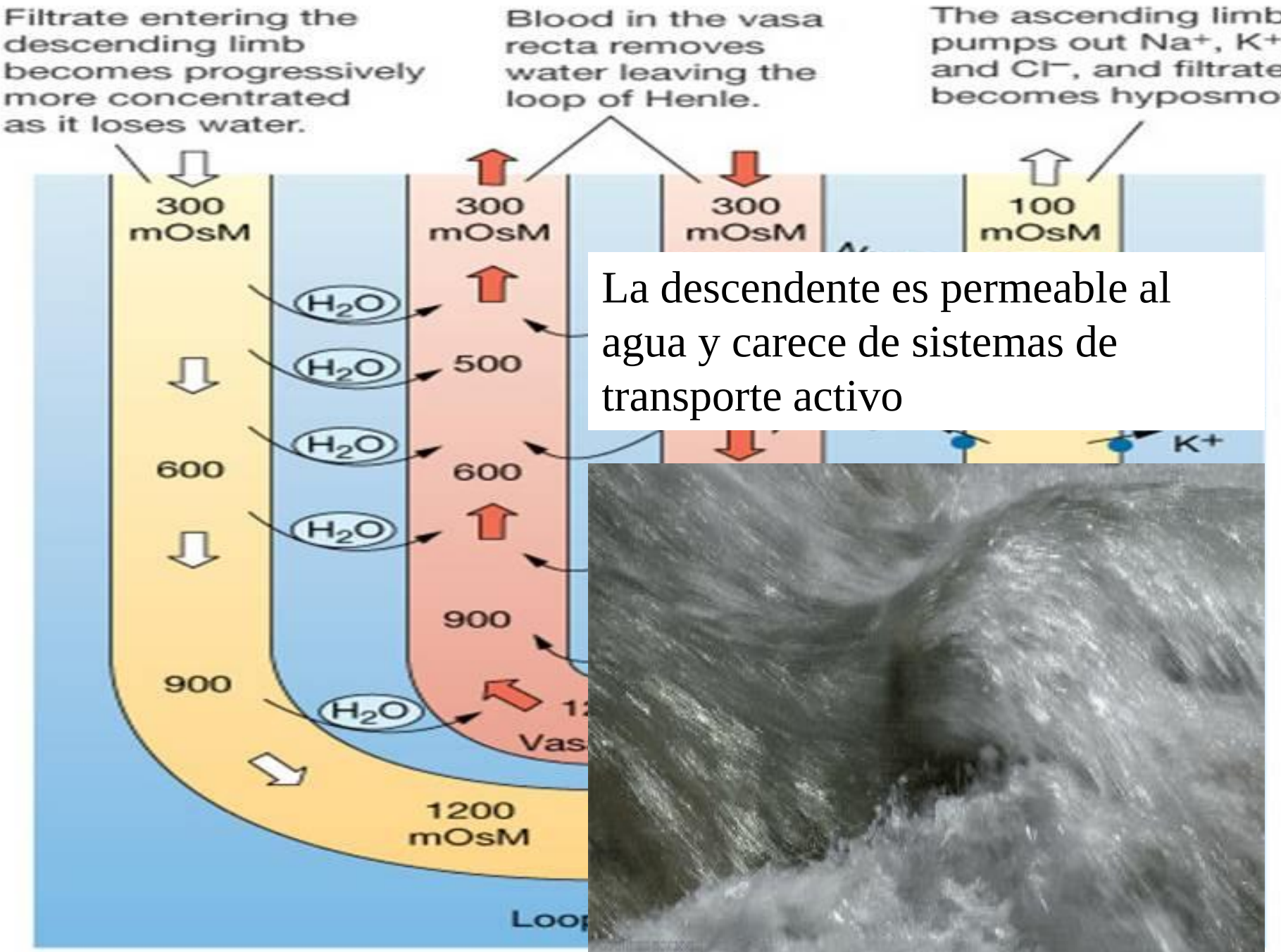
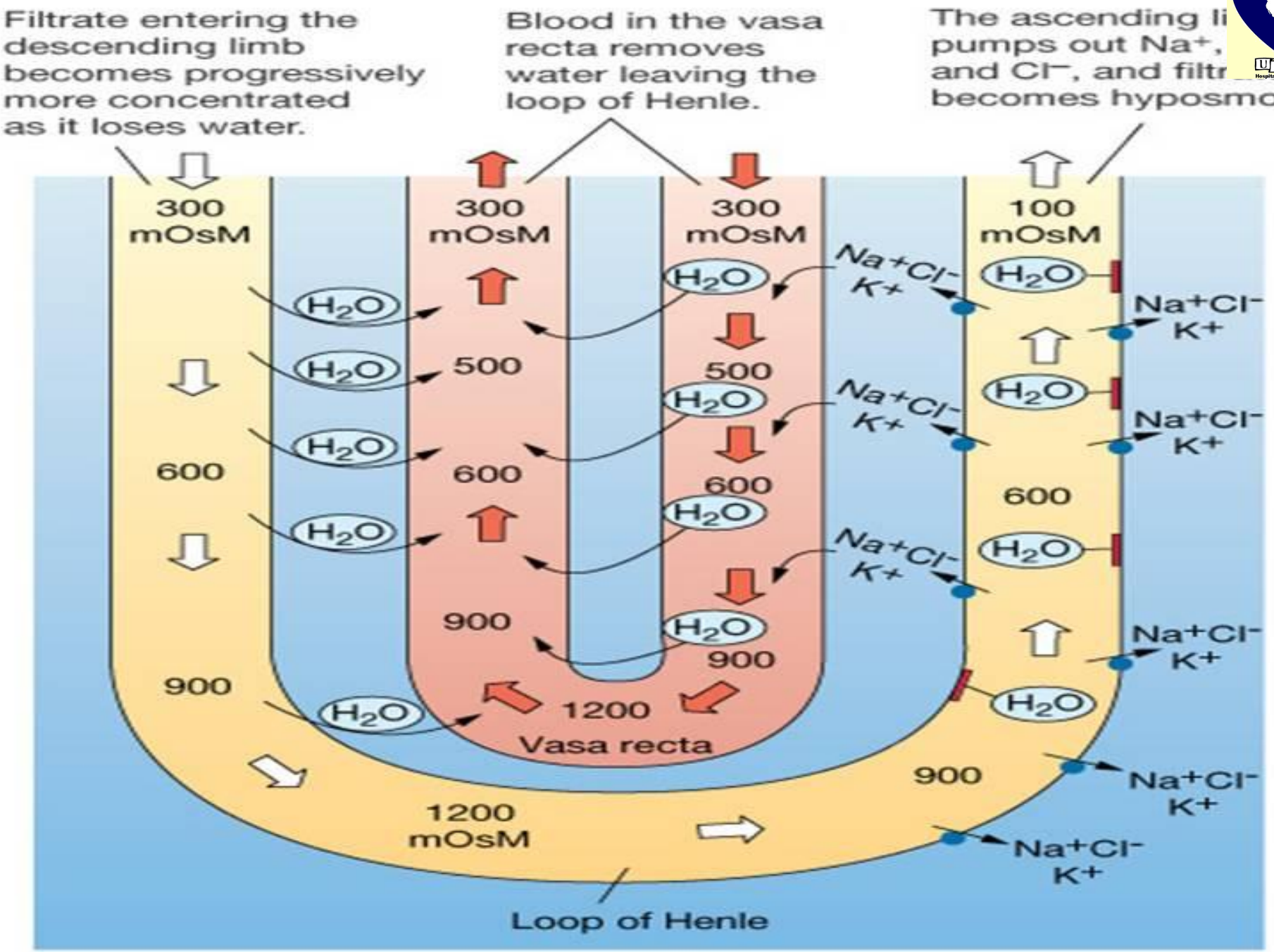
The ascending li
pumps out Na+,
and Cl−, and filtr
becomes hyposmotic.
300 mOsM
300 mOsM
300 mOsM
100 mOsM
H2O
Na+Cl−
K+
500
600
900
1200
Vasa recta
1200 mOsM
Loop of Henle



La descendente es permeable al agua y carece de sistemas de transporte activo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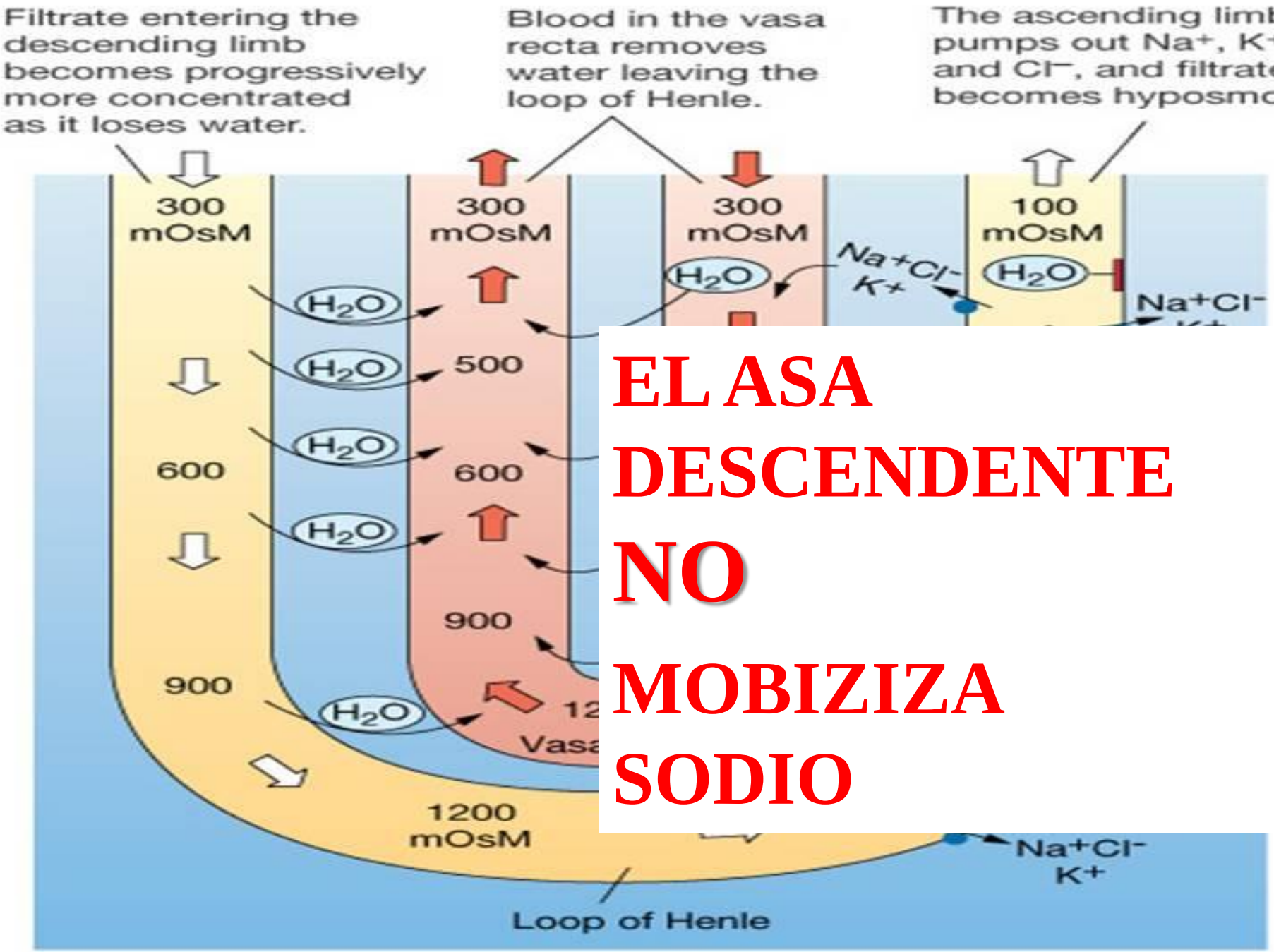
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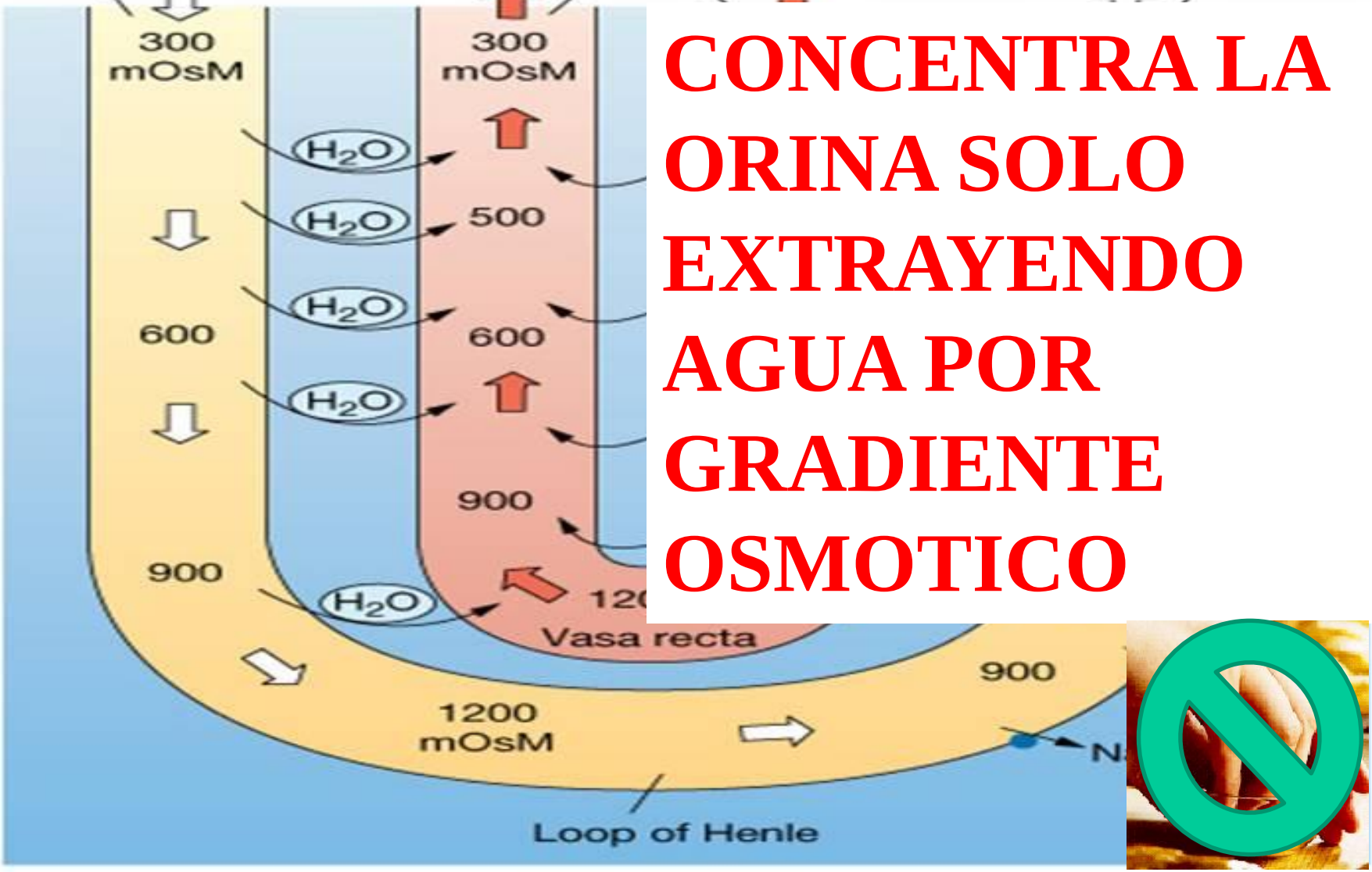
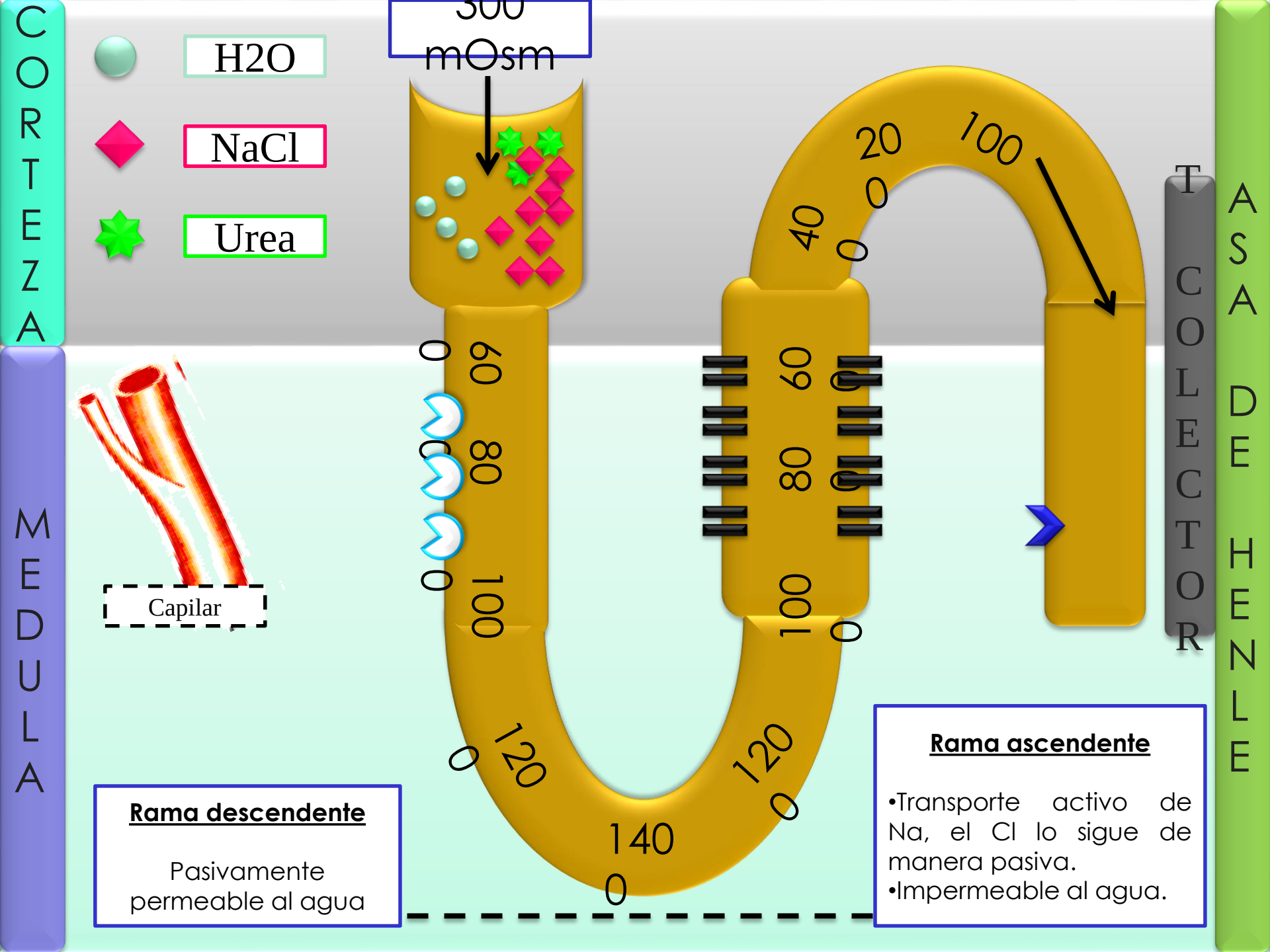
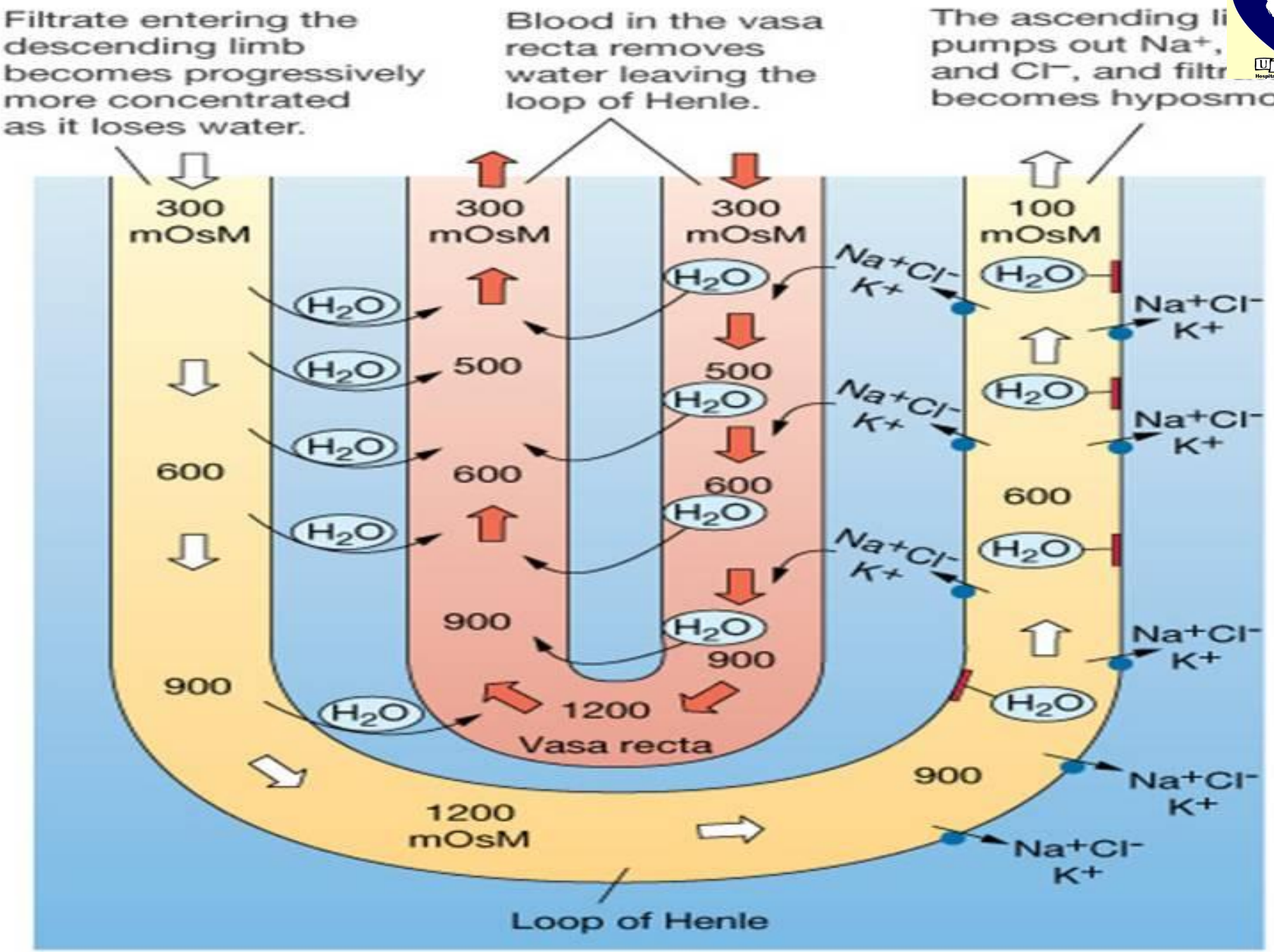
Na+Cl−
K+
500
600
600
900
900
1200 mOsM
Loop of Henle
EL ASA DESCENDENTE NO MOBIZIZA SODIO



CONCENTRA LA ORINA SOLO EXTRAYENDO AGUA POR GRADIENTE OSMOTICO


CORTEZA
MEDULA
ASA DE HENLE
TUBO COLECTOR
H2O
NaCl
Urea
300 mOsm
Capilar
0
60
80
100
120
140
20
40
Rama descendente
Pasivamente permeable al agua
Rama ascendente
•Transporte activo de Na, el Cl lo sigue de manera pasiva.
•Impermeable al agua.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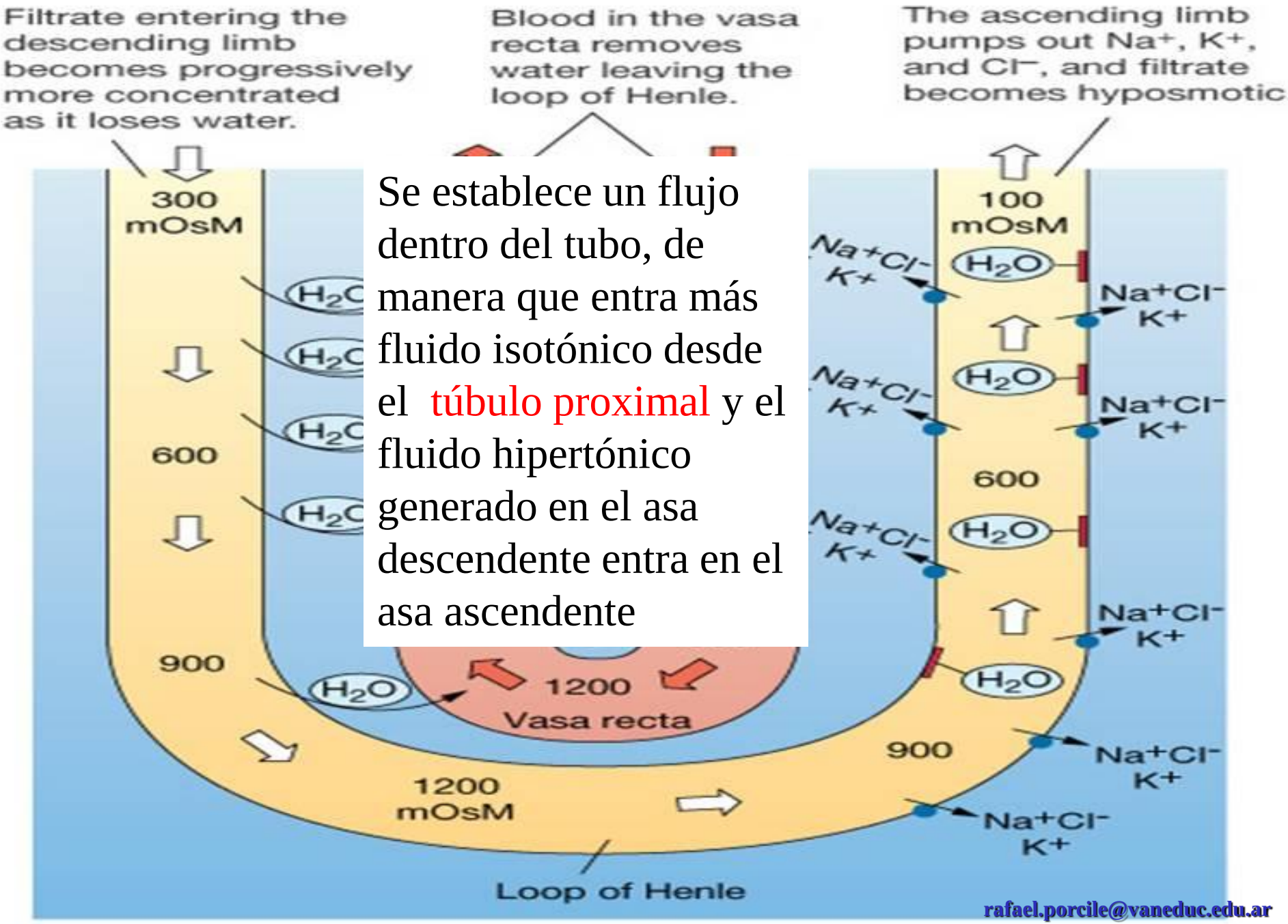
300 mOsM
300 mOsM
300 mOsM
100 mOsM
H2O
Na+Cl−
K+
500
600
900
1200
Vasa recta
1200 mOsM
Loop of Henle



Se establece un flujo dentro del tubo, de manera que entra más fluido isotónico desde el túbulo proximal y el fluido hipertónico generado en el asa descendente entra en el asa ascendente

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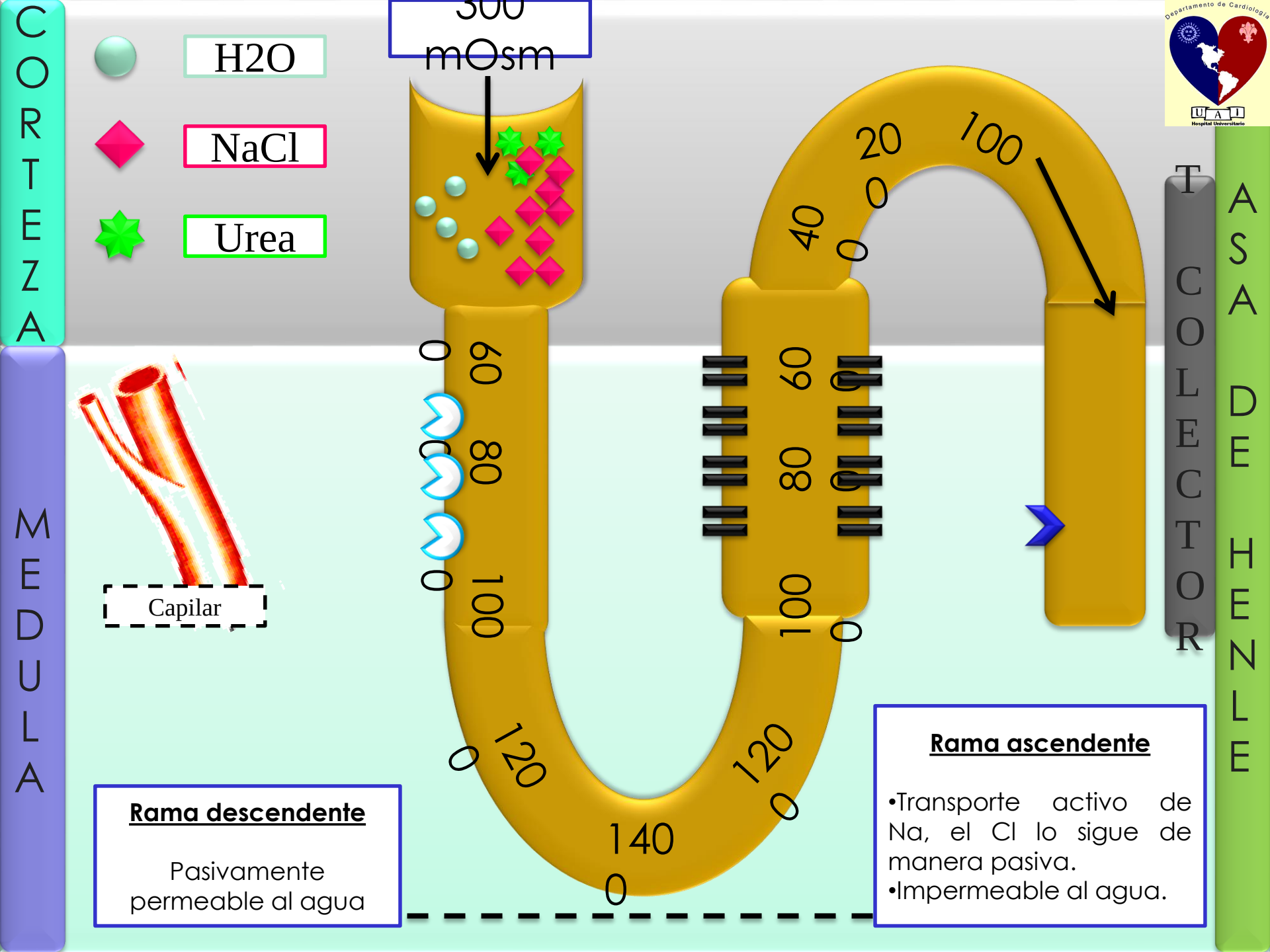
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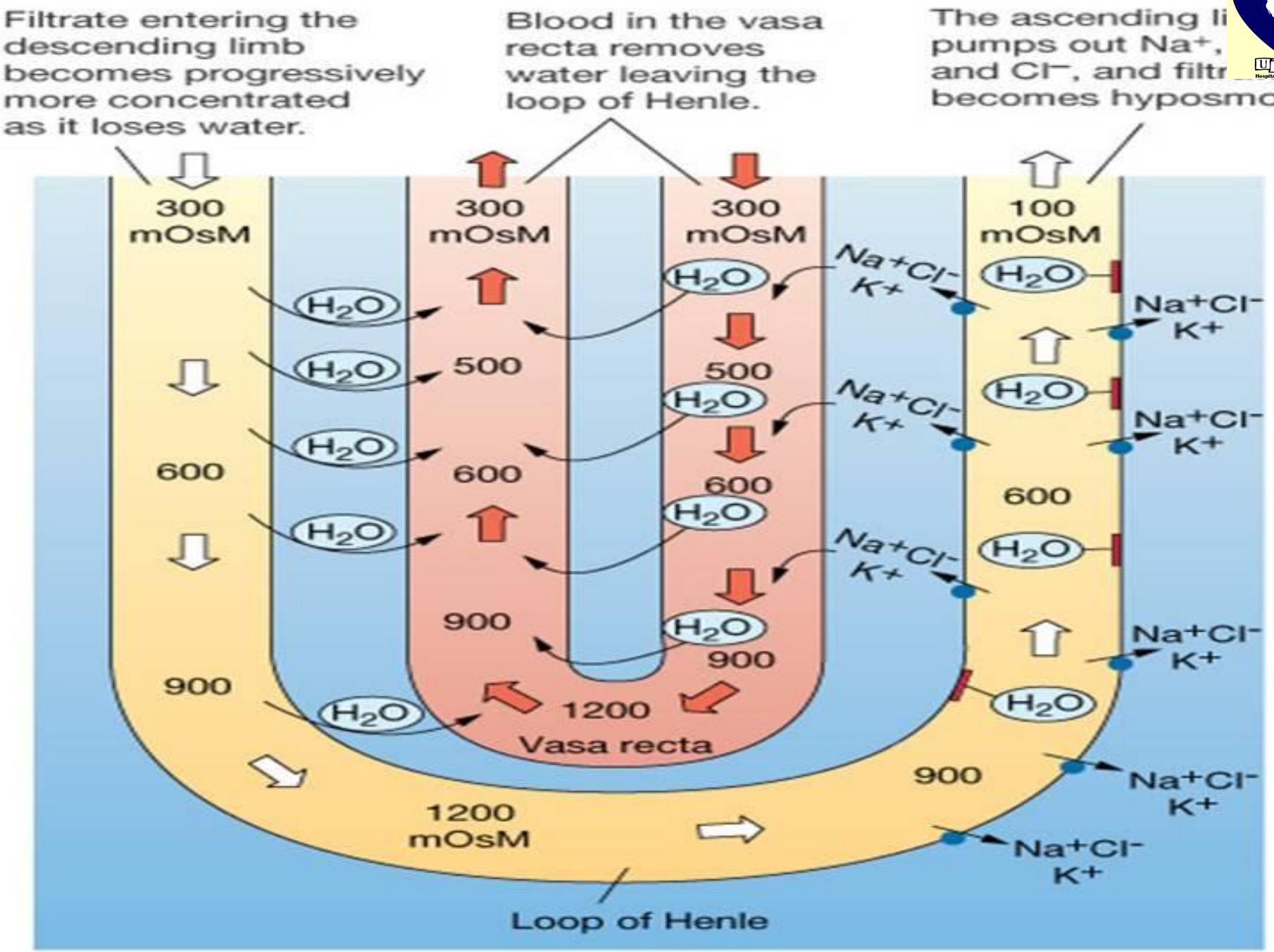
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300 mOsM
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H2O
Na+Cl−
K+
500
600
900
1200
Vasa recta
1200 mOsM
Loop of Henle

¿Como arreglamos esto?

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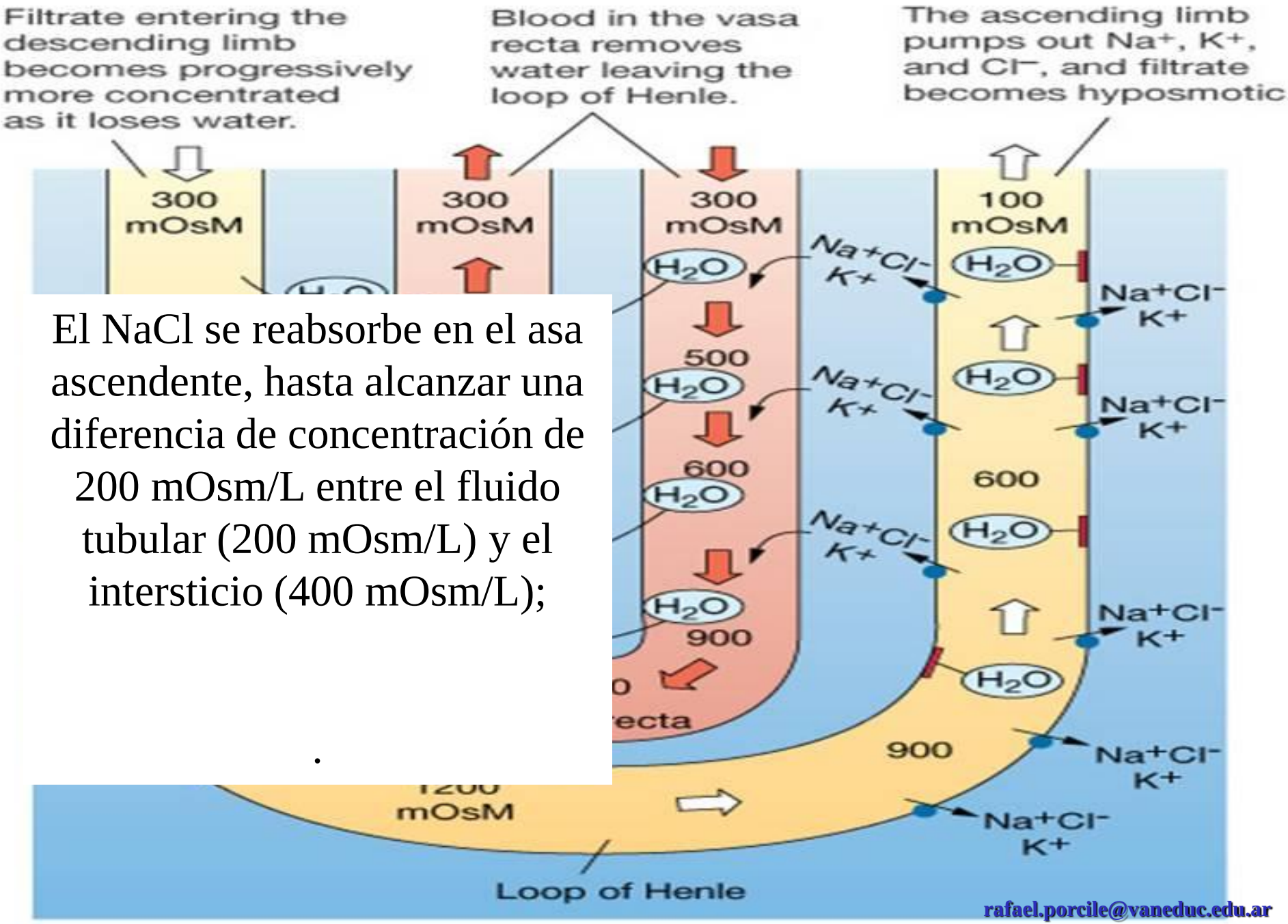

El NaCl se reabsorbe en el asa ascendente, hasta alcanzar una diferencia de concentración de 200 mOsm/L entre el fluido tubular (200 mOsm/L) y el intersticio (400 mOsm/L);

.

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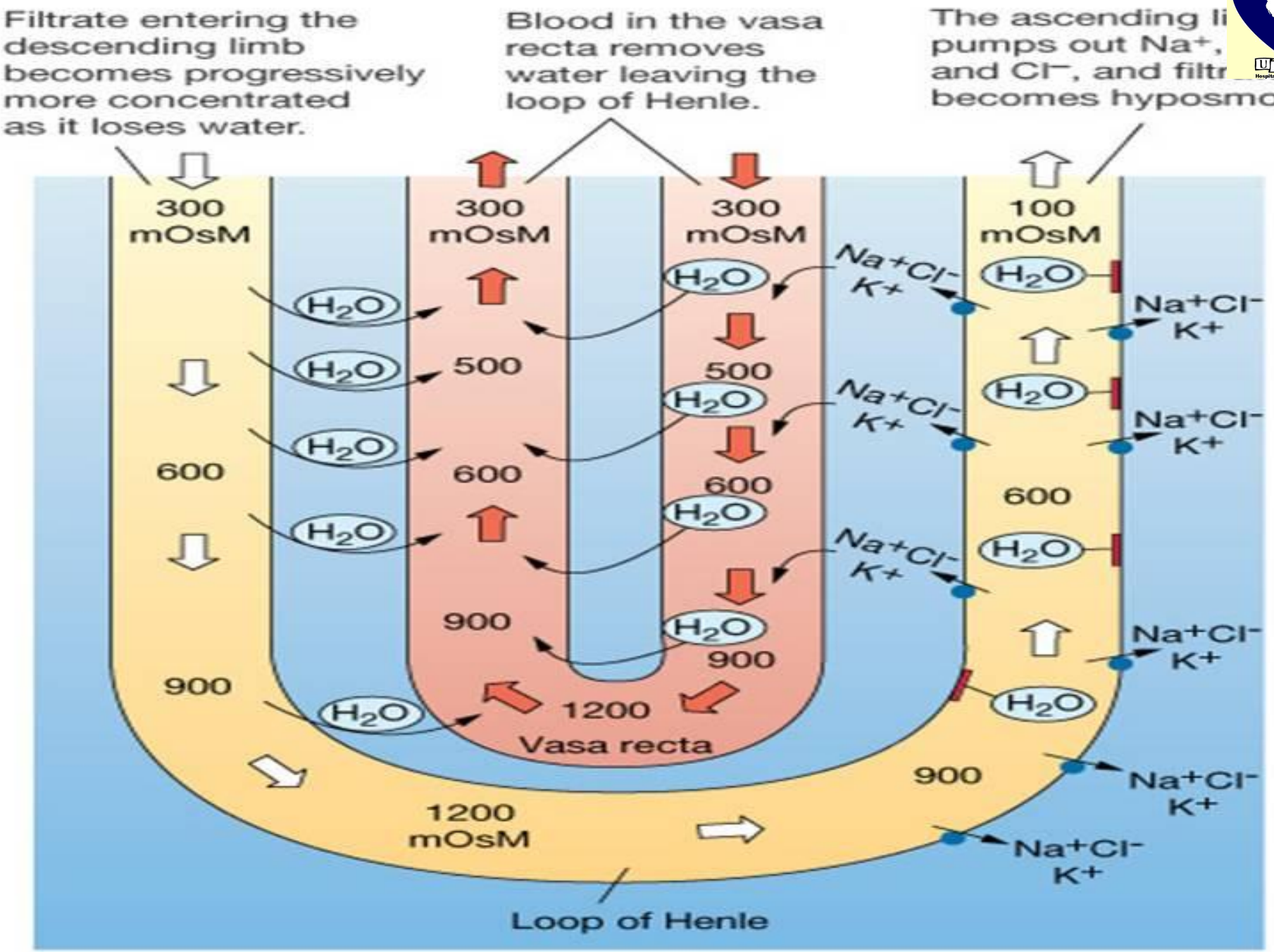
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900
1200
Vasa recta
1200 mOsM
Loop of Henle

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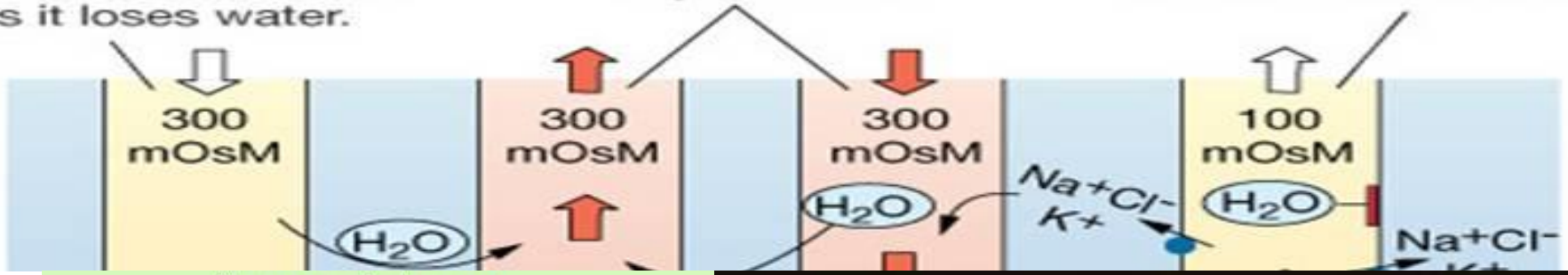
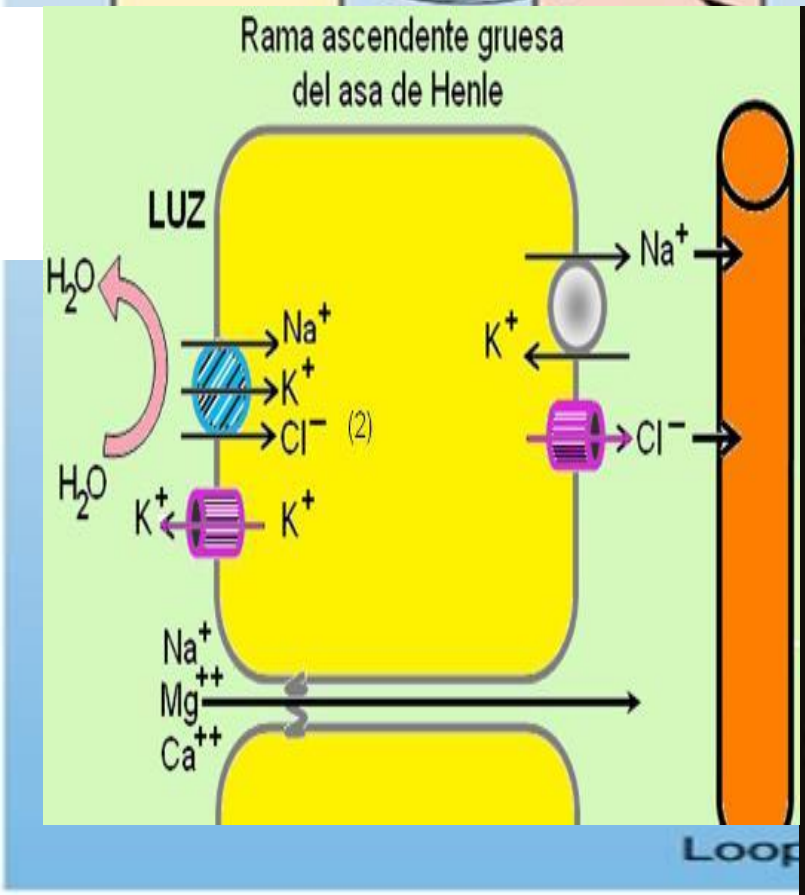
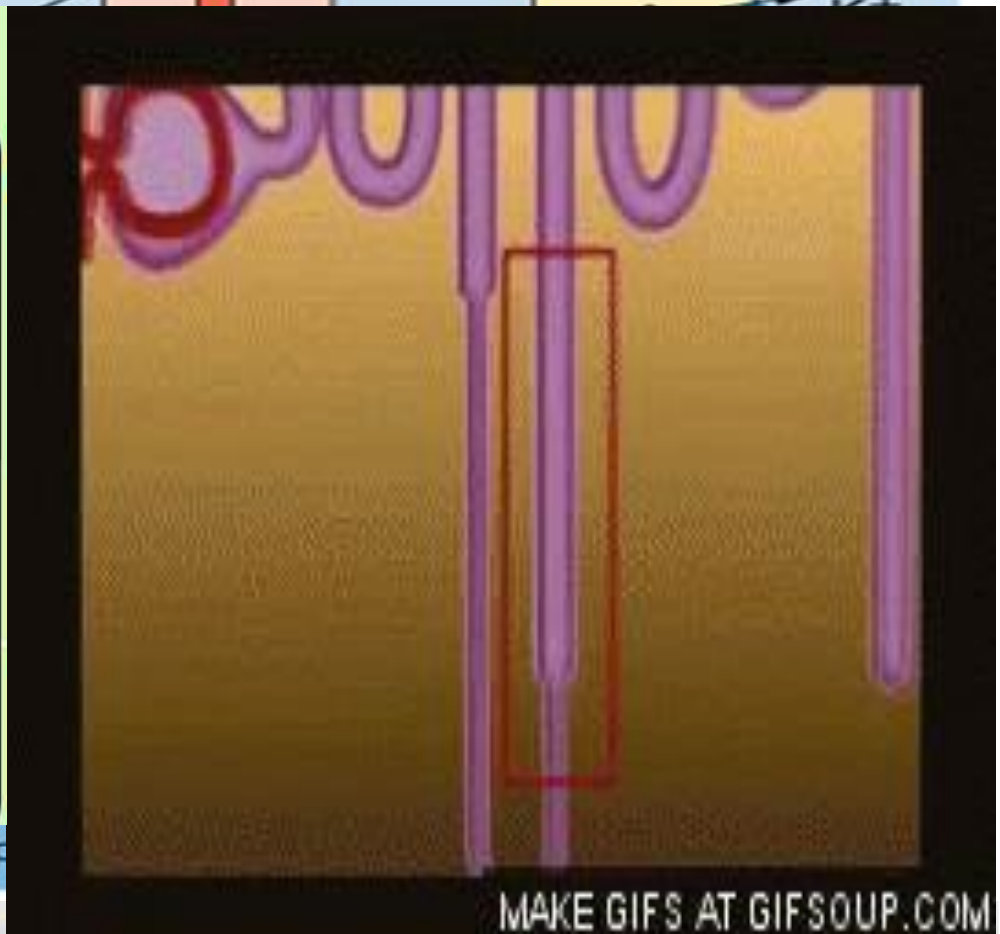
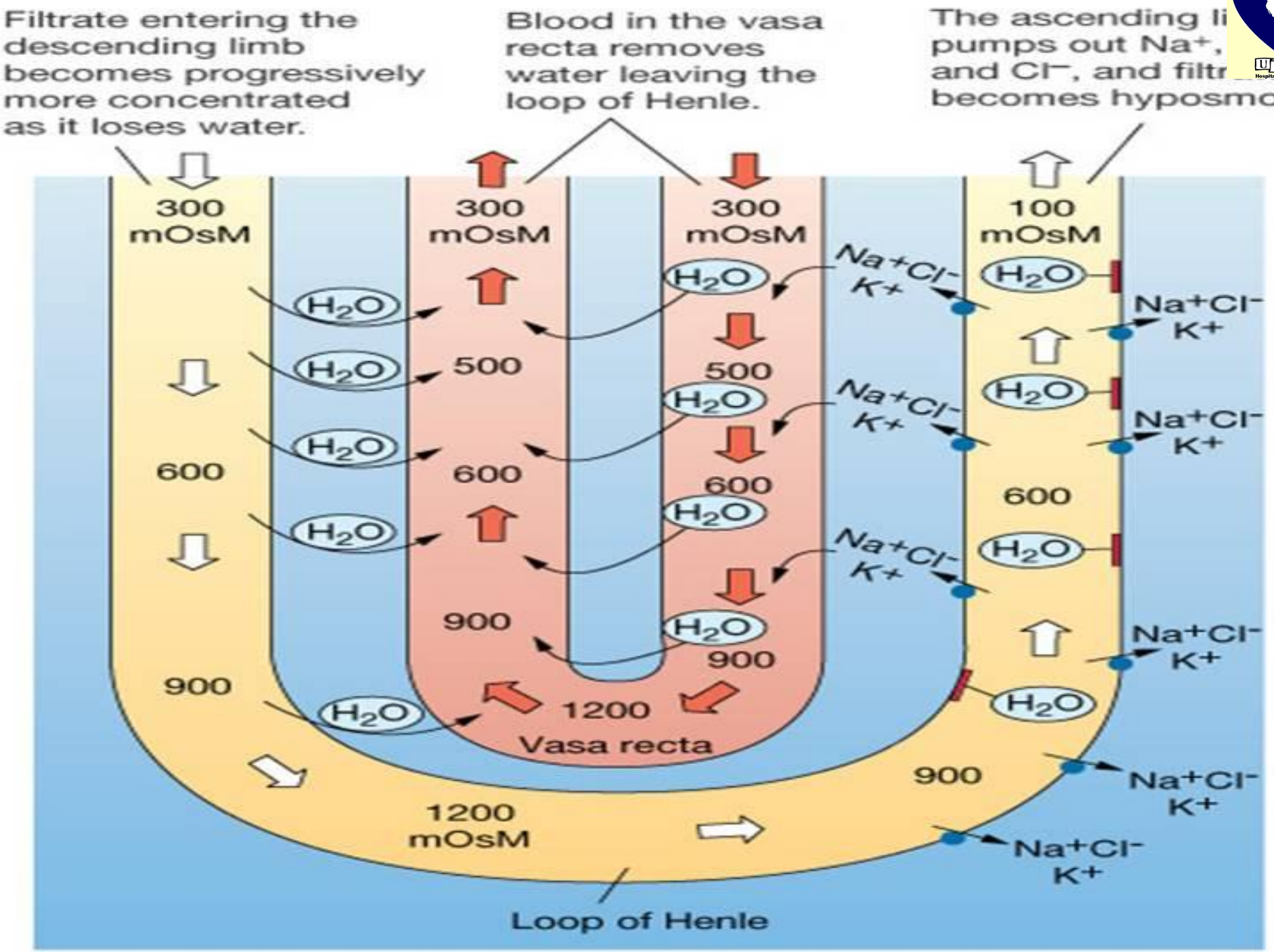
The ascending pumps out Na and Cl^-, and fi becomes hypo





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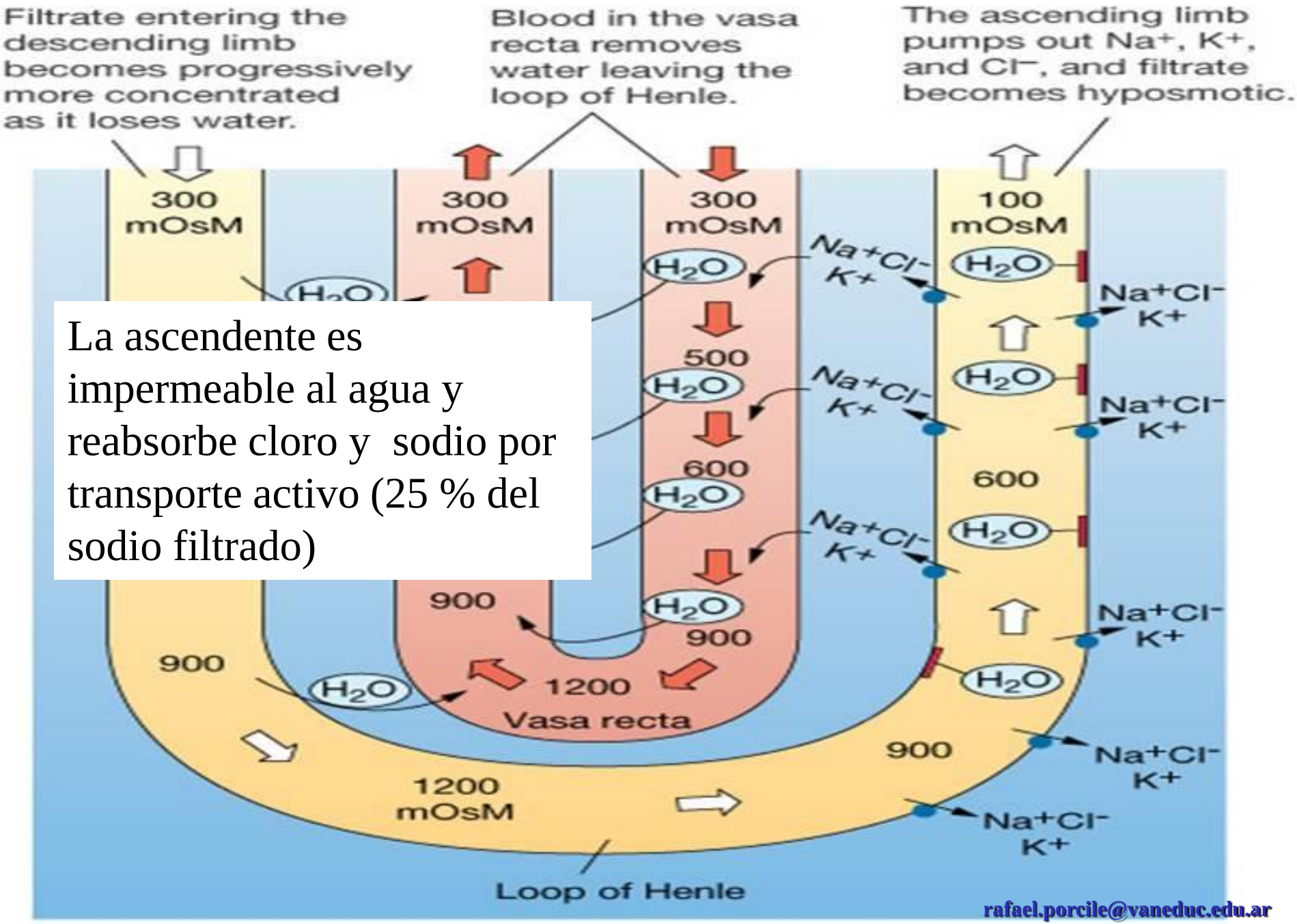
Loop of Henle



La ascendente es impermeable al agua y reabsorbe cloro y sodio por transporte activo (25 % del sodio filtrado)

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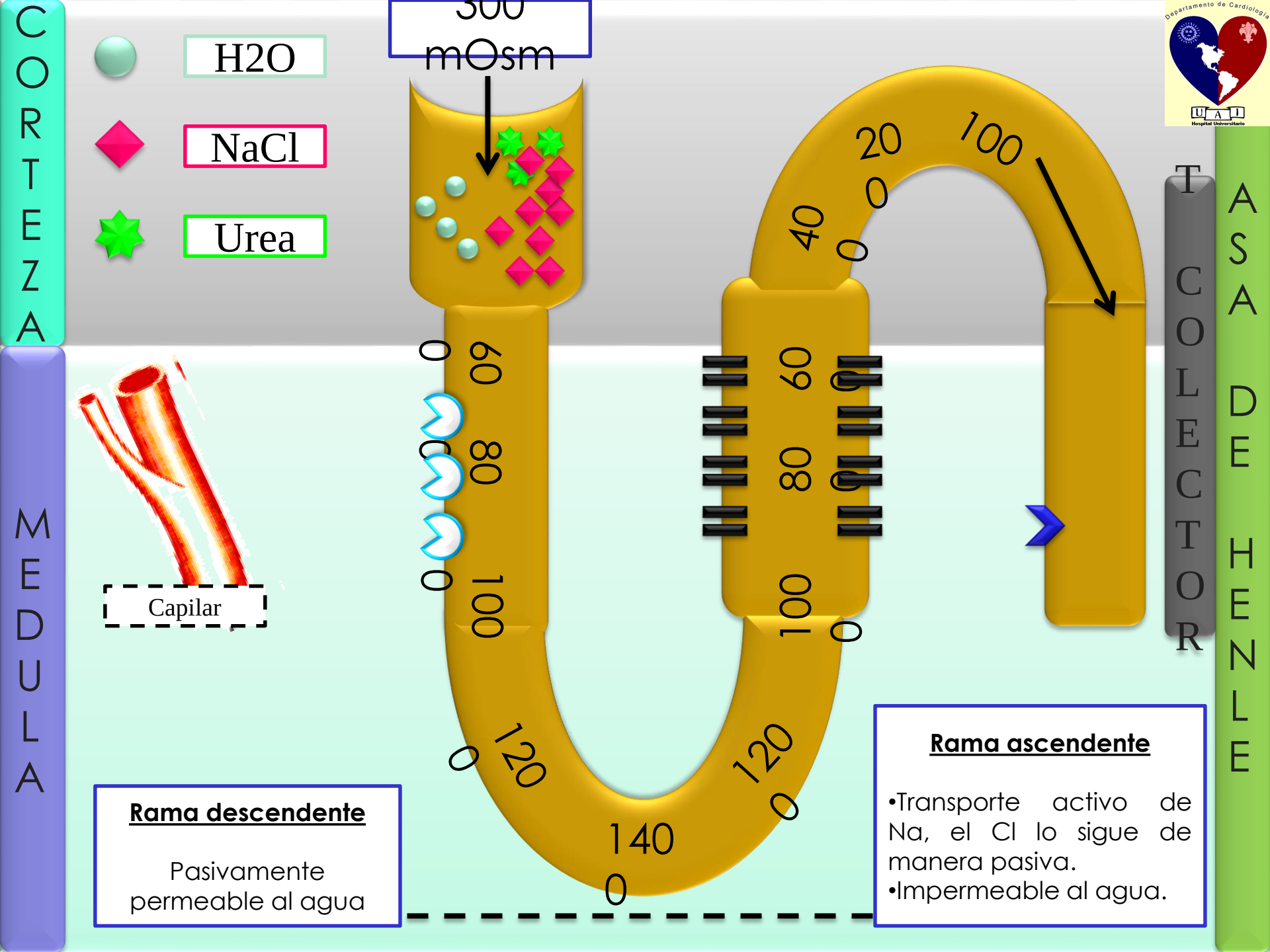
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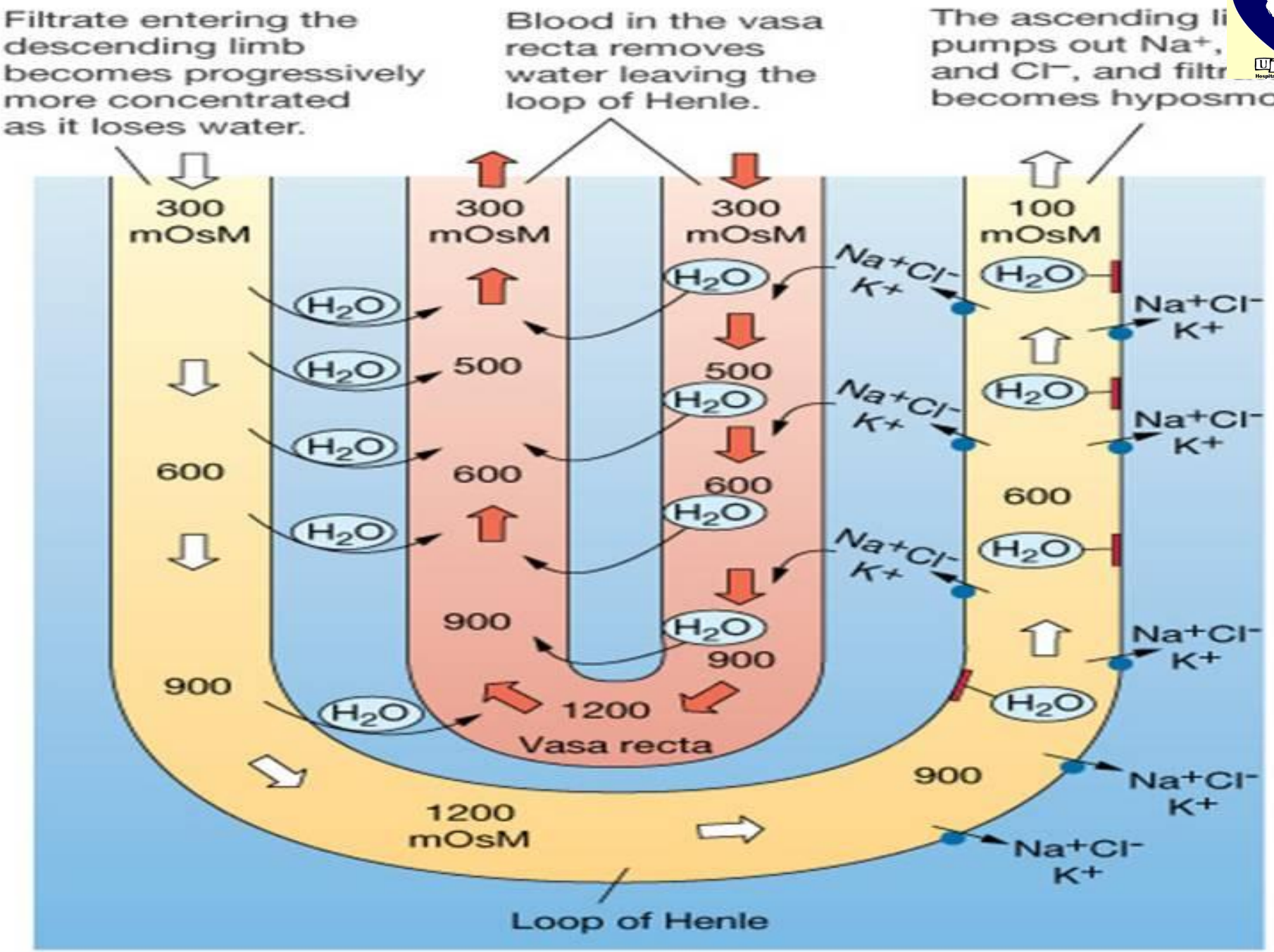
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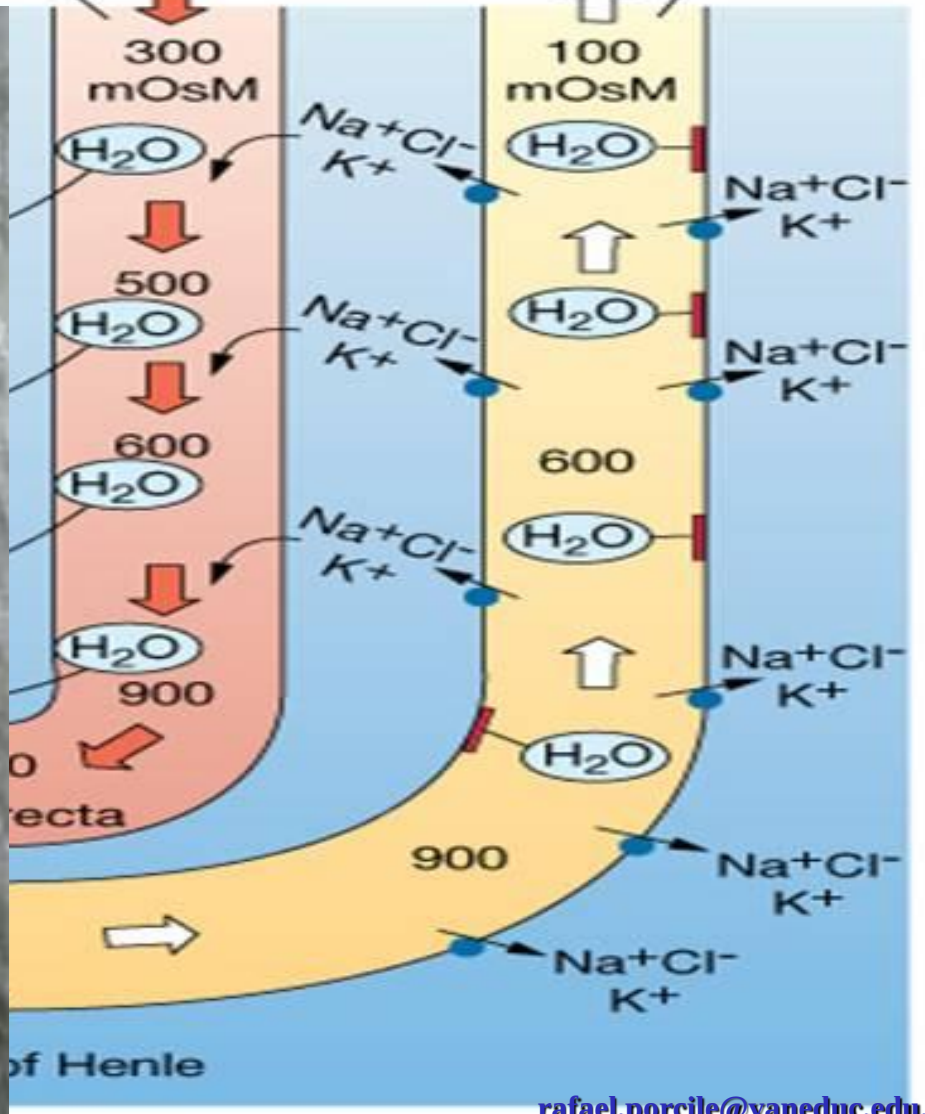

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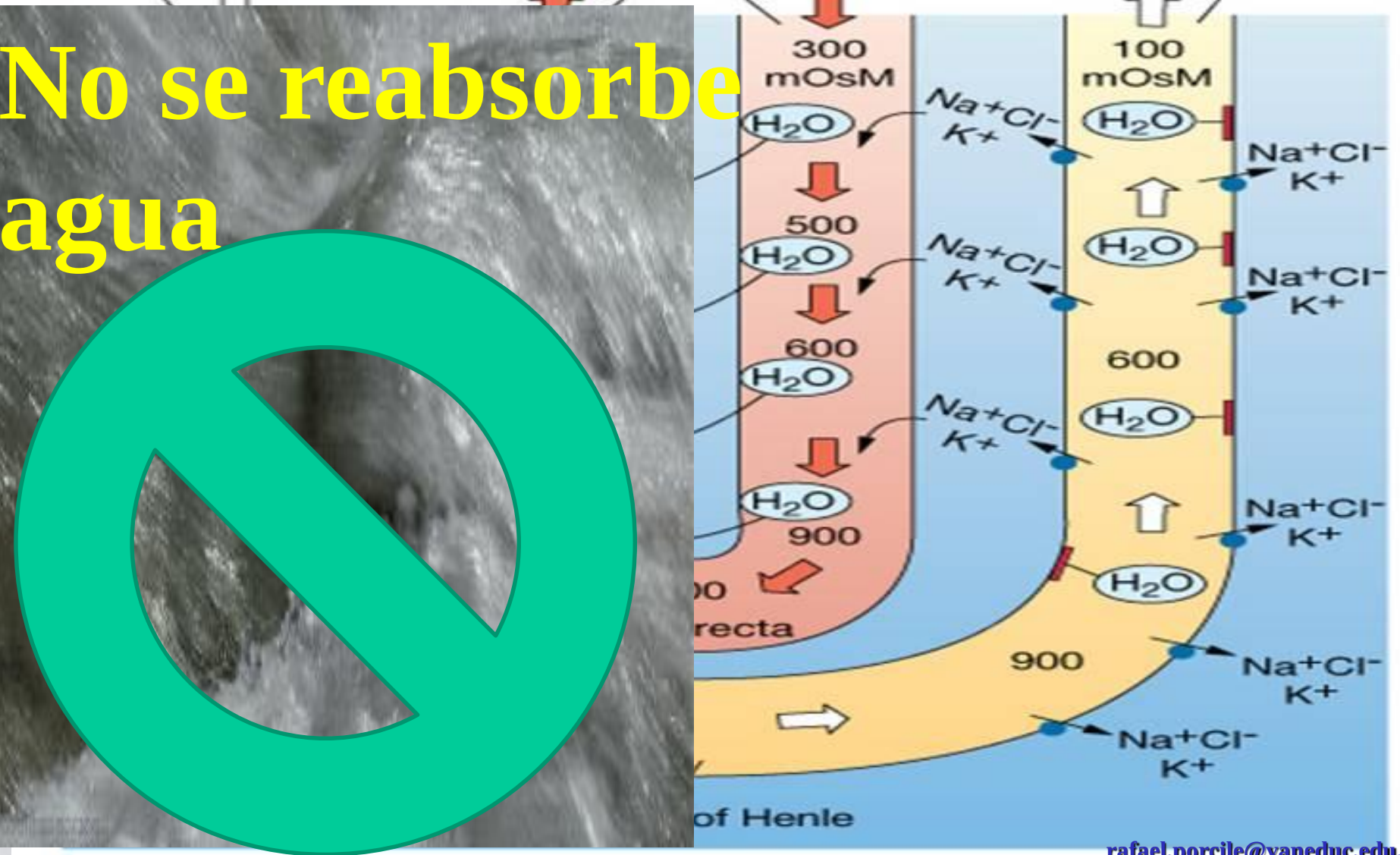
No se reabsorbe agua



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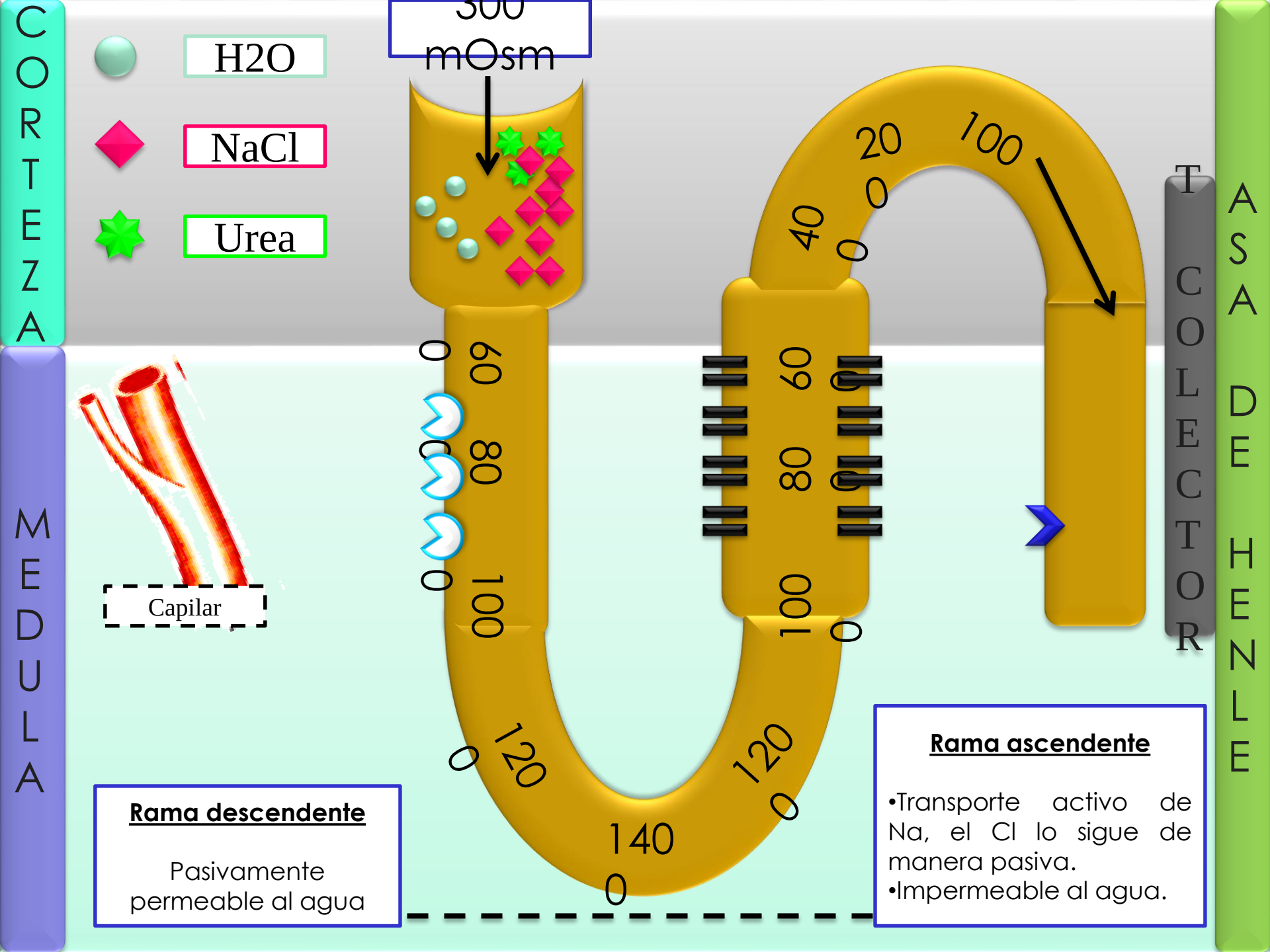
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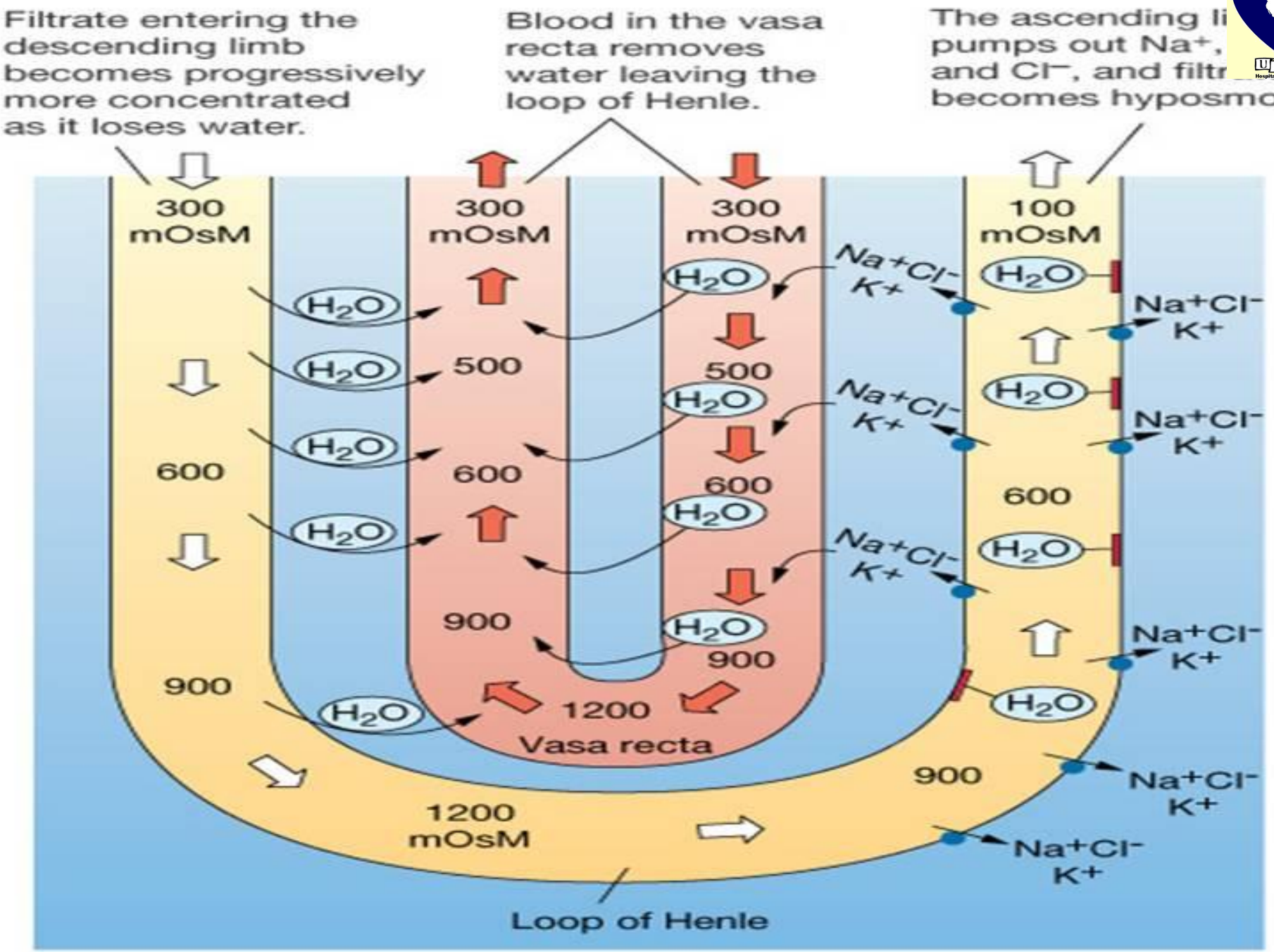
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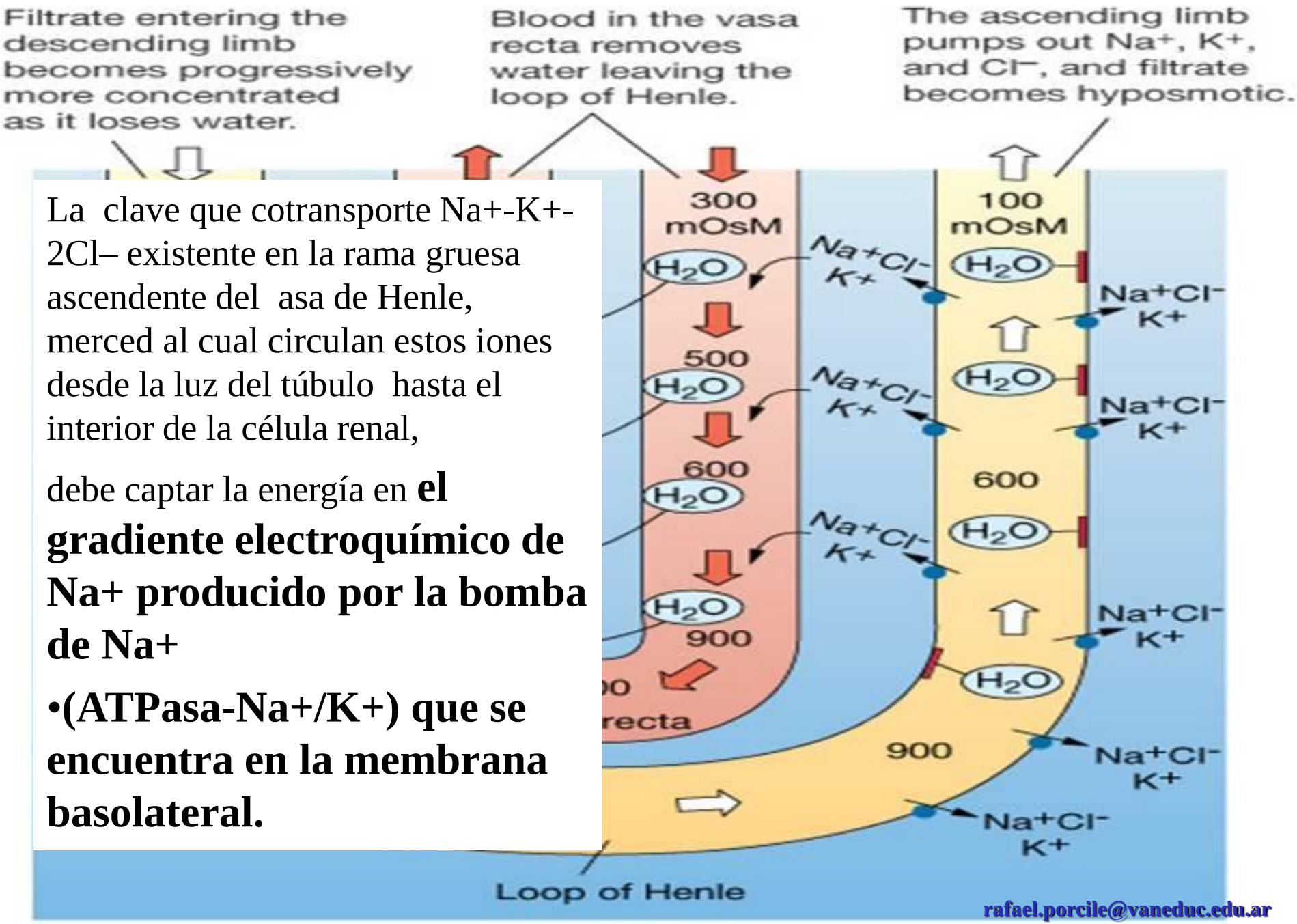
1200 mOsM
Loop of Henle



La clave que cotransporte Na+-K+-2Cl– existente en la rama gruesa ascendente del asa de Henle, merced al cual circulan estos iones desde la luz del túbulo hasta el interior de la célula renal,

debe captar la energía en **el gradiente electroquímico de Na+ producido por la bomba de Na+**

•(ATPasa-Na+/K+) que se encuentra en la membrana basolateral.

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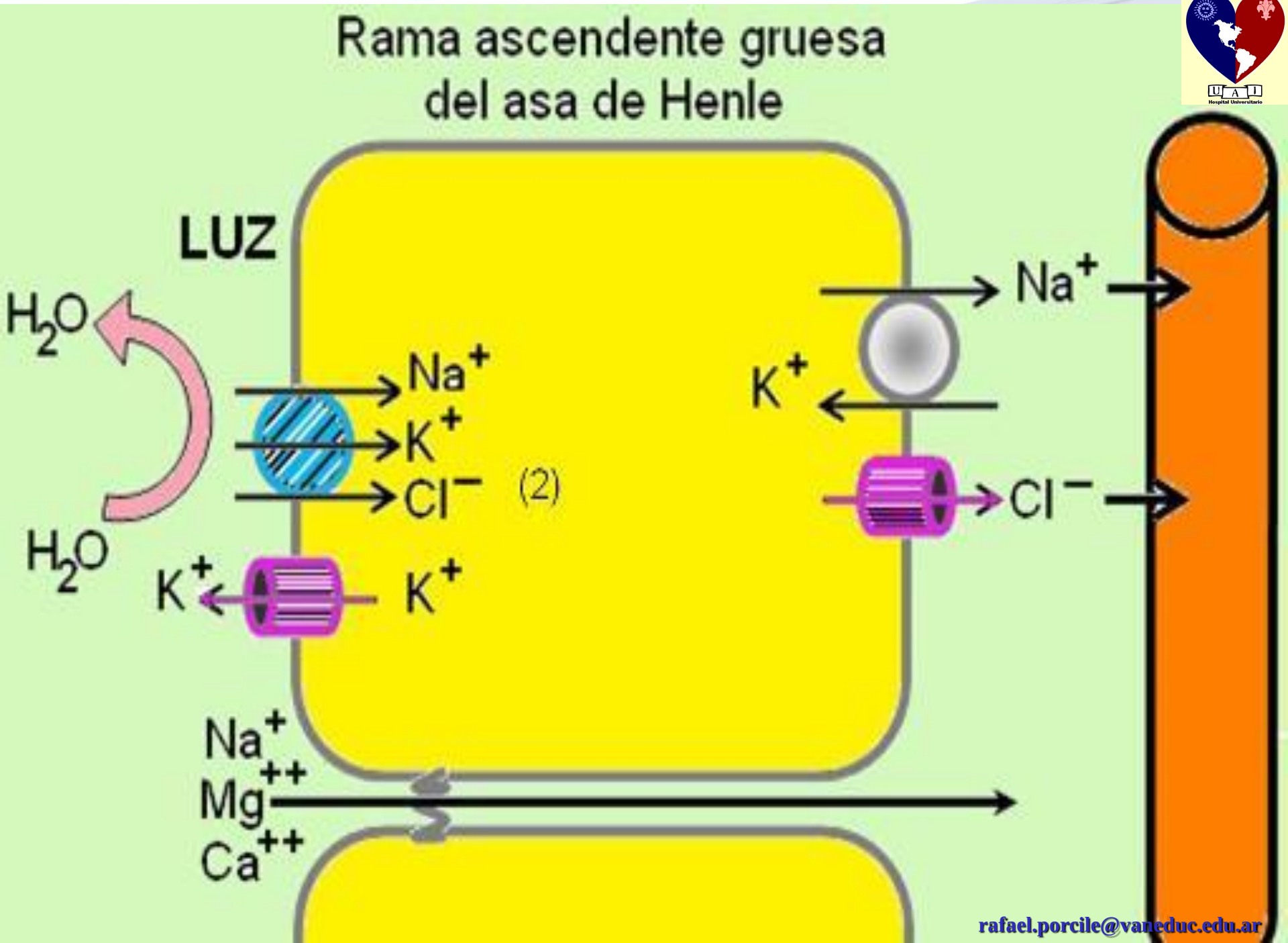

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CON GASTO ENERGETICO ESTO ES INACTIVADO EL LA ISQUEMIA RENAL Y EN LA NECROSIS TUBULAR AGUD A

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- Isquemia
- Necrosis tubular aguda
- Fase poliúrica

+

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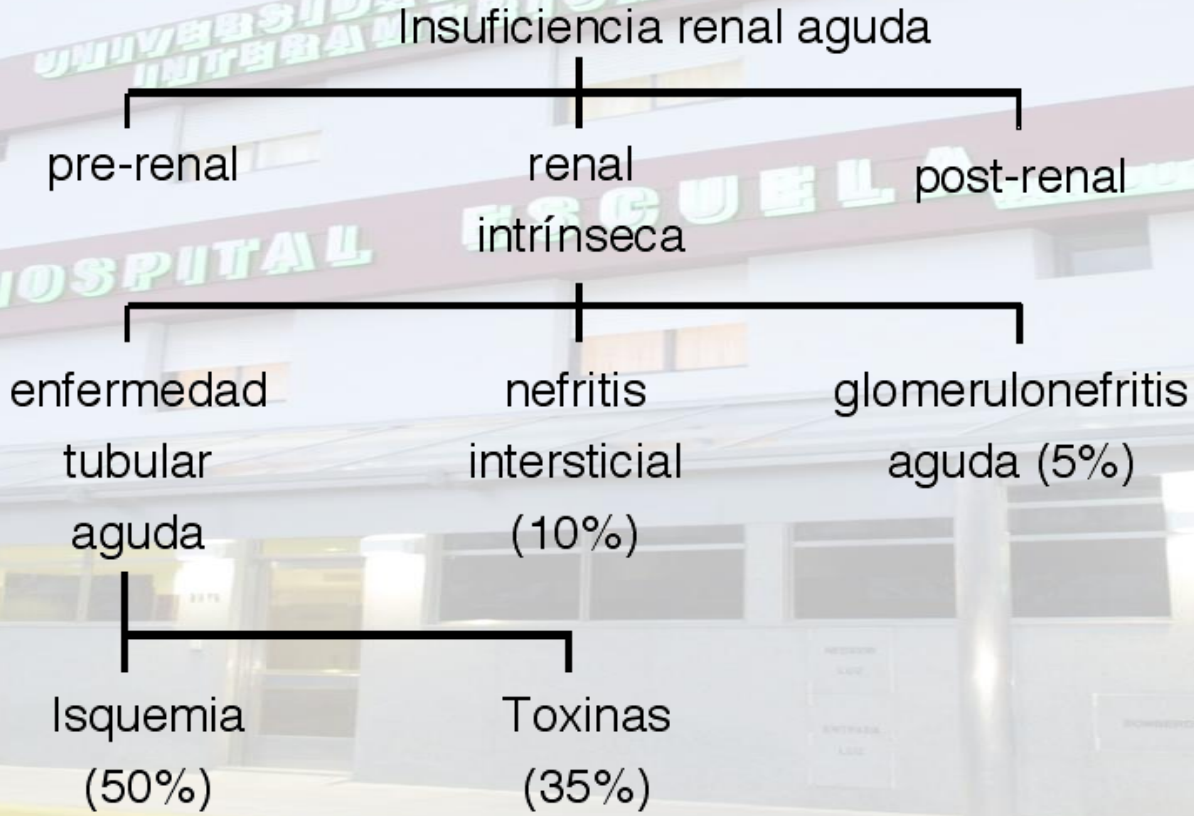
Insuficiencia renal aguda



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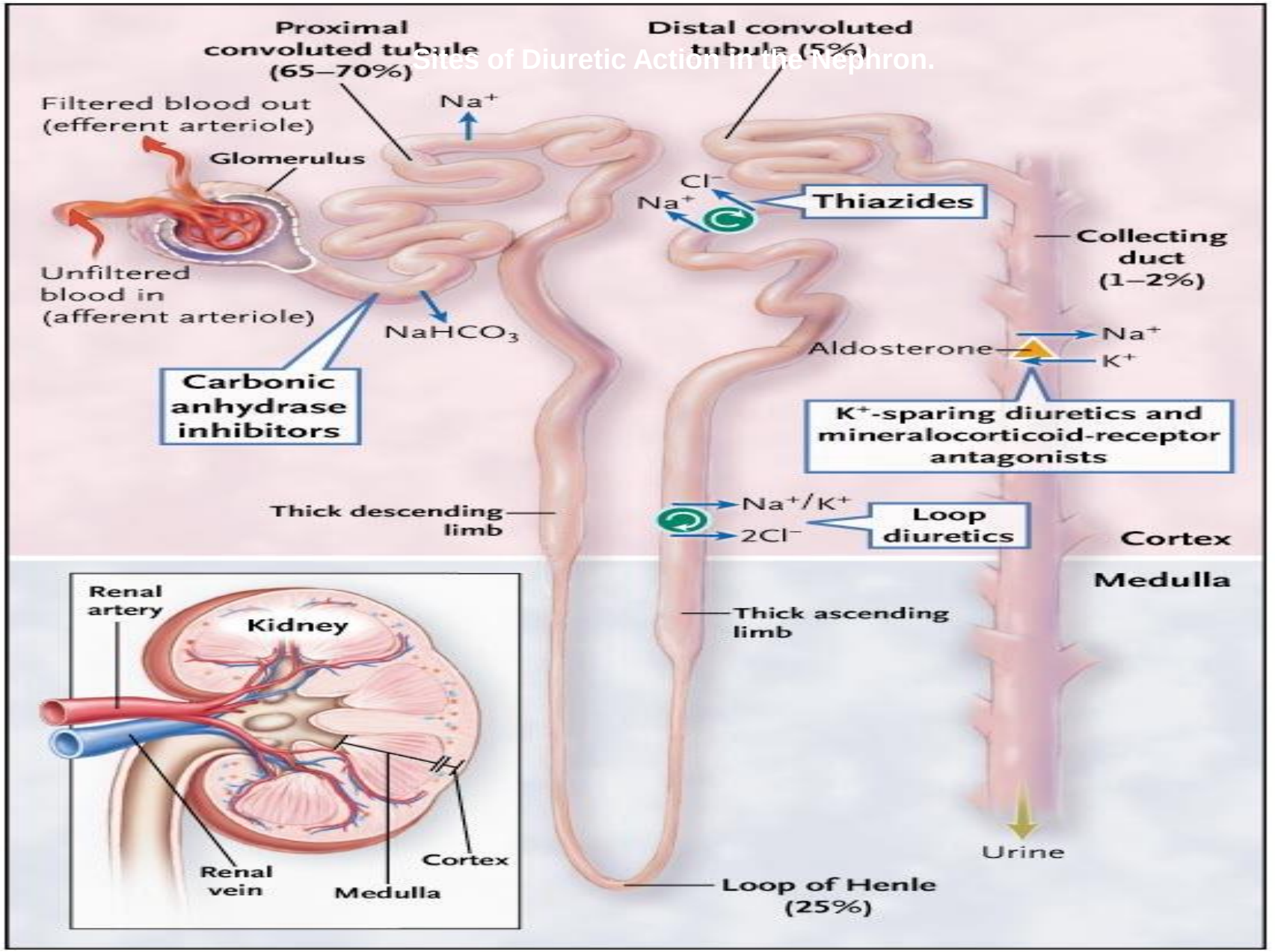
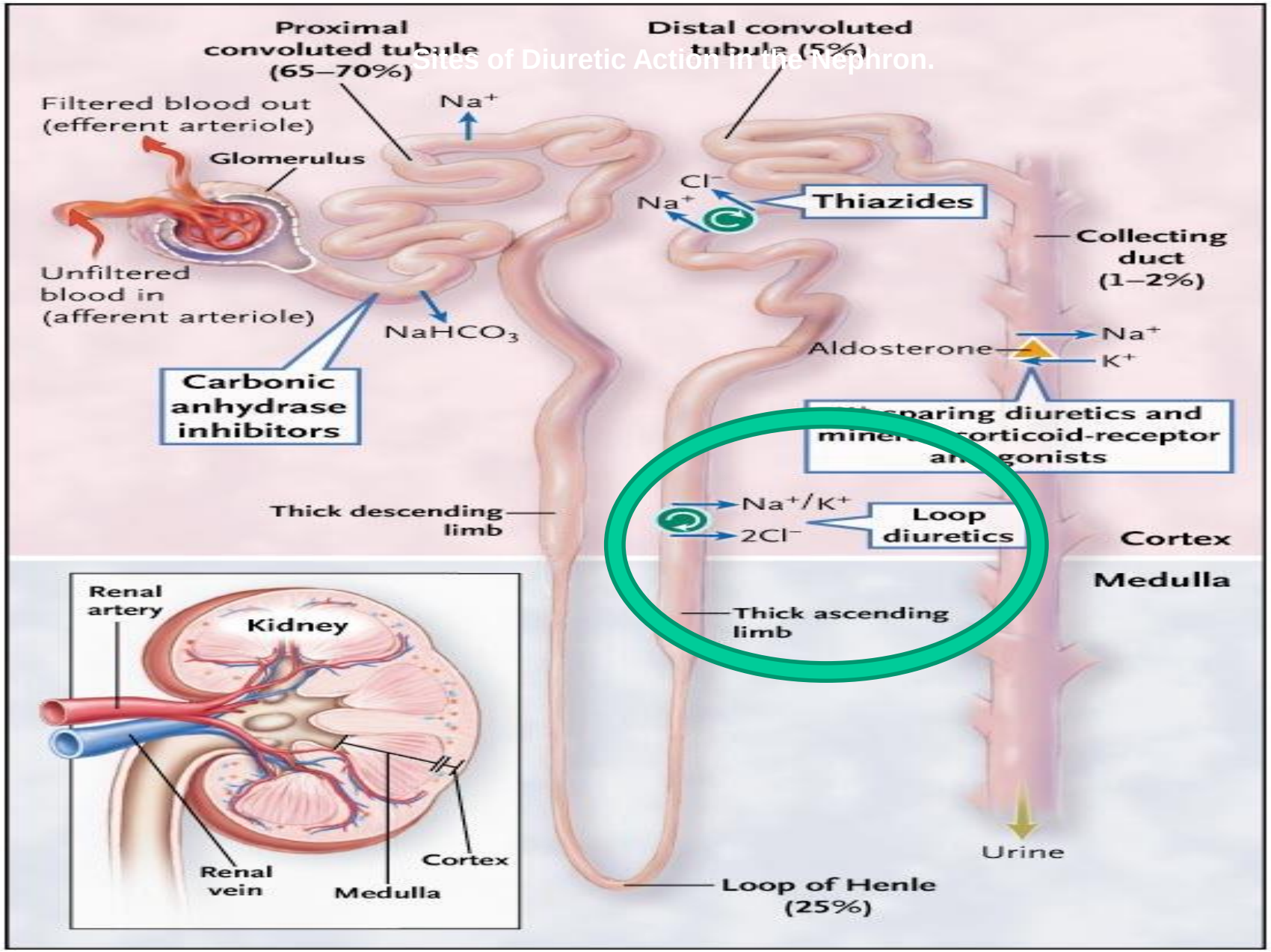


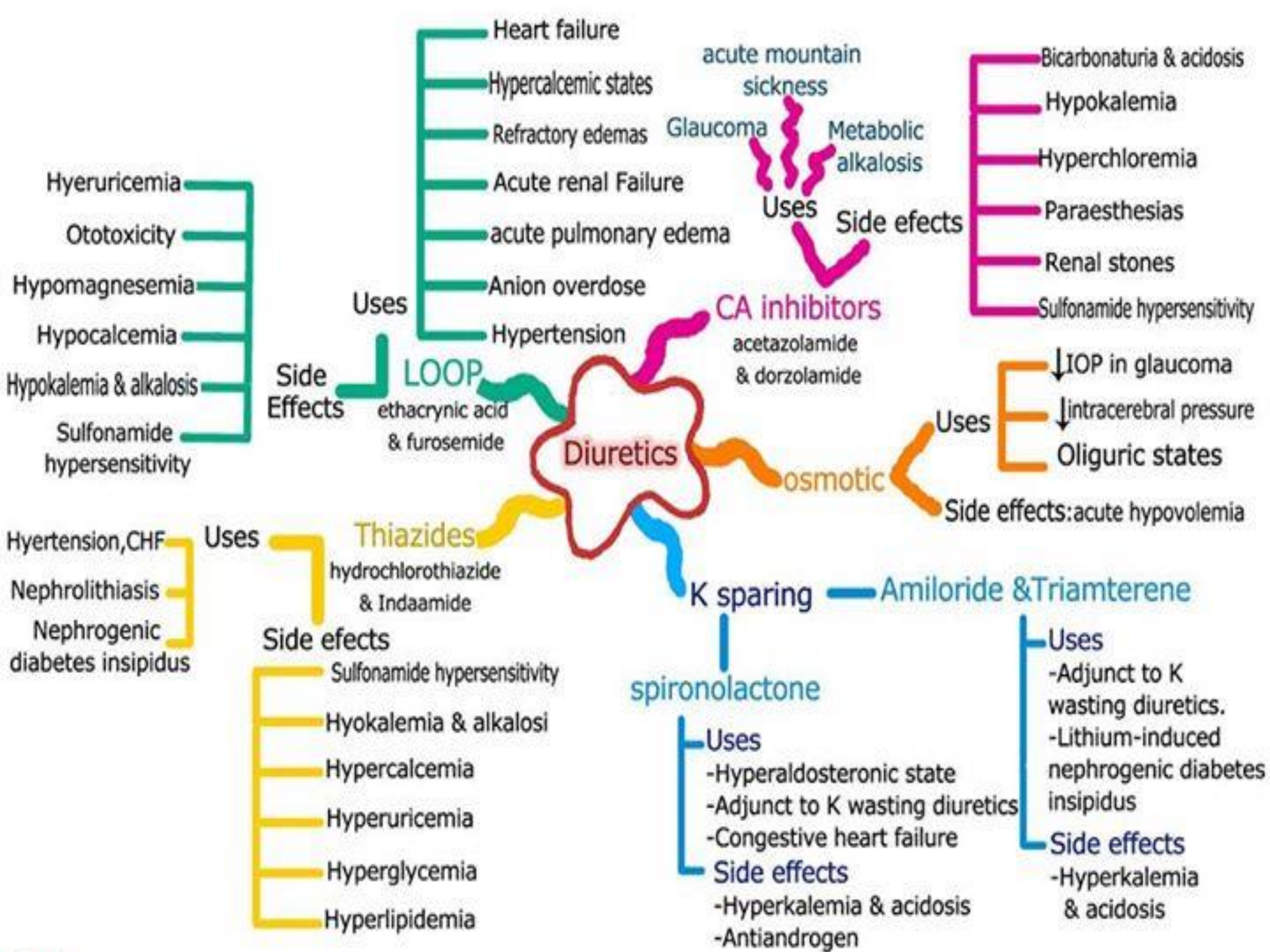
Ernst ME, Moser M. N Engl J Med 2009;361:2153-2164.

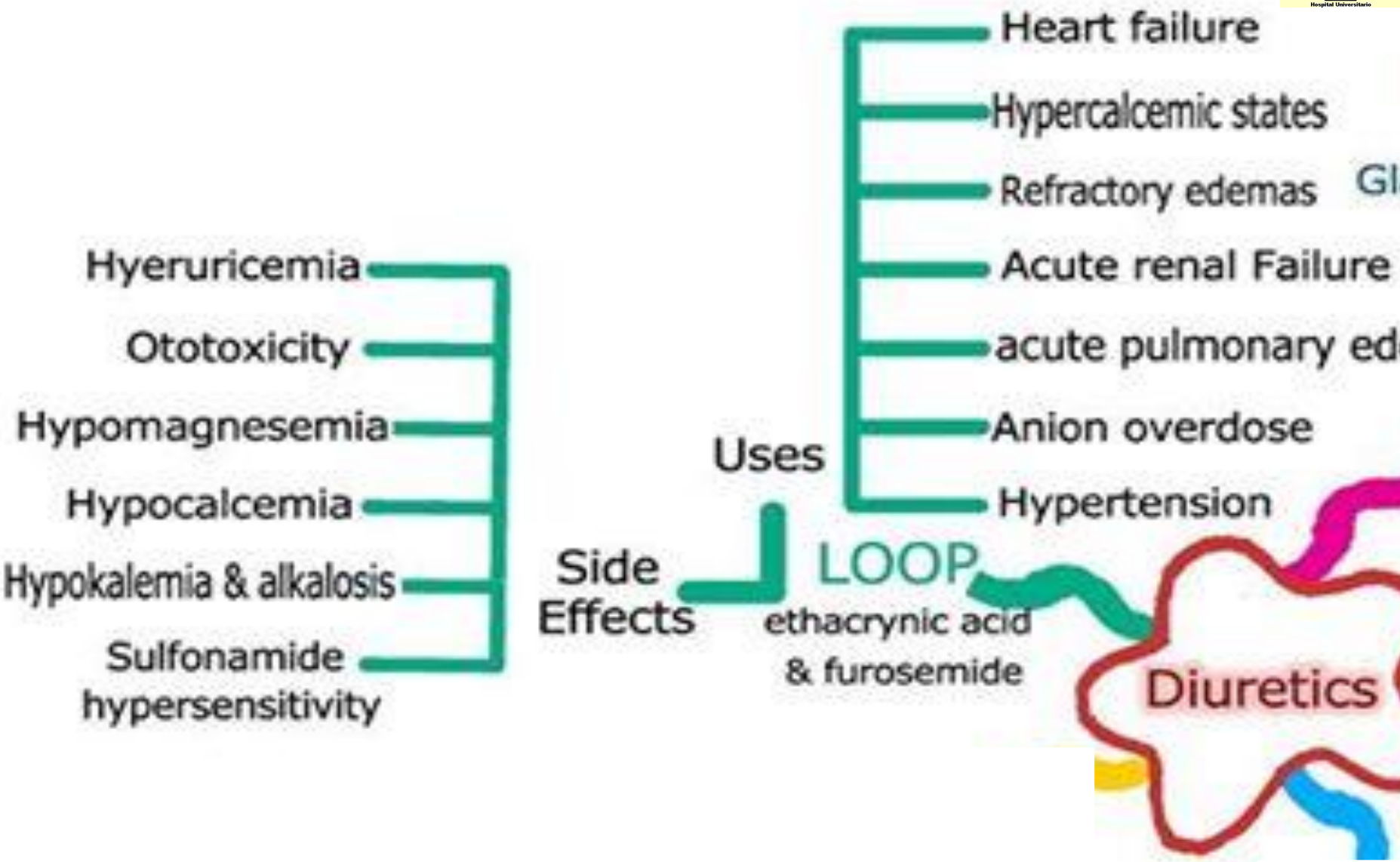
The NEW ENGLAND JOURNAL of MEDICINE



Ernst ME, Moser M. N Engl J Med 2009;361:2153-2164.

The NEW ENGLAND JOURNAL of MEDICINE


Diuretics
CA inhibitors
acetazolamide & dorzolamide
acute mountain sickness
Glaucoma
Metabolic alkalosis
Uses
Side efects
Bicarbonaturia & acidosis
Hypokalemia
Hyperchloremia
Paraesthesias
Renal stones
Sulfonamide hypersensitivity
LOOP
ethacrynic acid & furosemide
Uses
Heart failure
Hypercalcemic states
Refractory edemas
Acute renal Failure
acute pulmonary edema
Anion overdose
Hypertension
Side Effects
Hyeruricemia
Ototoxicity
Hypomagnesemia
Hypocalcemia
Hypokalemia & alkalosis
Sulfonamide hypersensitivity
osmotic
Uses
↓IOP in glaucoma
↓intracerebral pressure
Oliguric states
Side effects:acute hypovolemia
Thiazides
hydrochlorothiazide & Indaamide
Uses
Hyertension,CHF
Nephrolithiasis
Nephrogenic diabetes insipidus
Side efects
Sulfonamide hypersensitivity
Hyokalemia & alkalosi
Hypercalcemia
Hyperuricemia
Hyperglycemia
Hyperlipidemia
K sparing
Amiloride &Triamterene
Uses
-Adjunct to K wasting diuretics.
-Lithium-induced nephrogenic diabetes insipidus
Side effects
-Hyperkalemia & acidosis
spironolactone
Uses
-Hyperaldosteronic state
-Adjunct to K wasting diuretics
-Congestive heart failure
Side effects
-Hyperkalemia & acidosis
-Antiandrogen


Heart failure
Hypercalcemic states
Refractory edemas
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Anion overdose
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ethacrynic acid & furosemide
Diuretics
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Hypocalcemia
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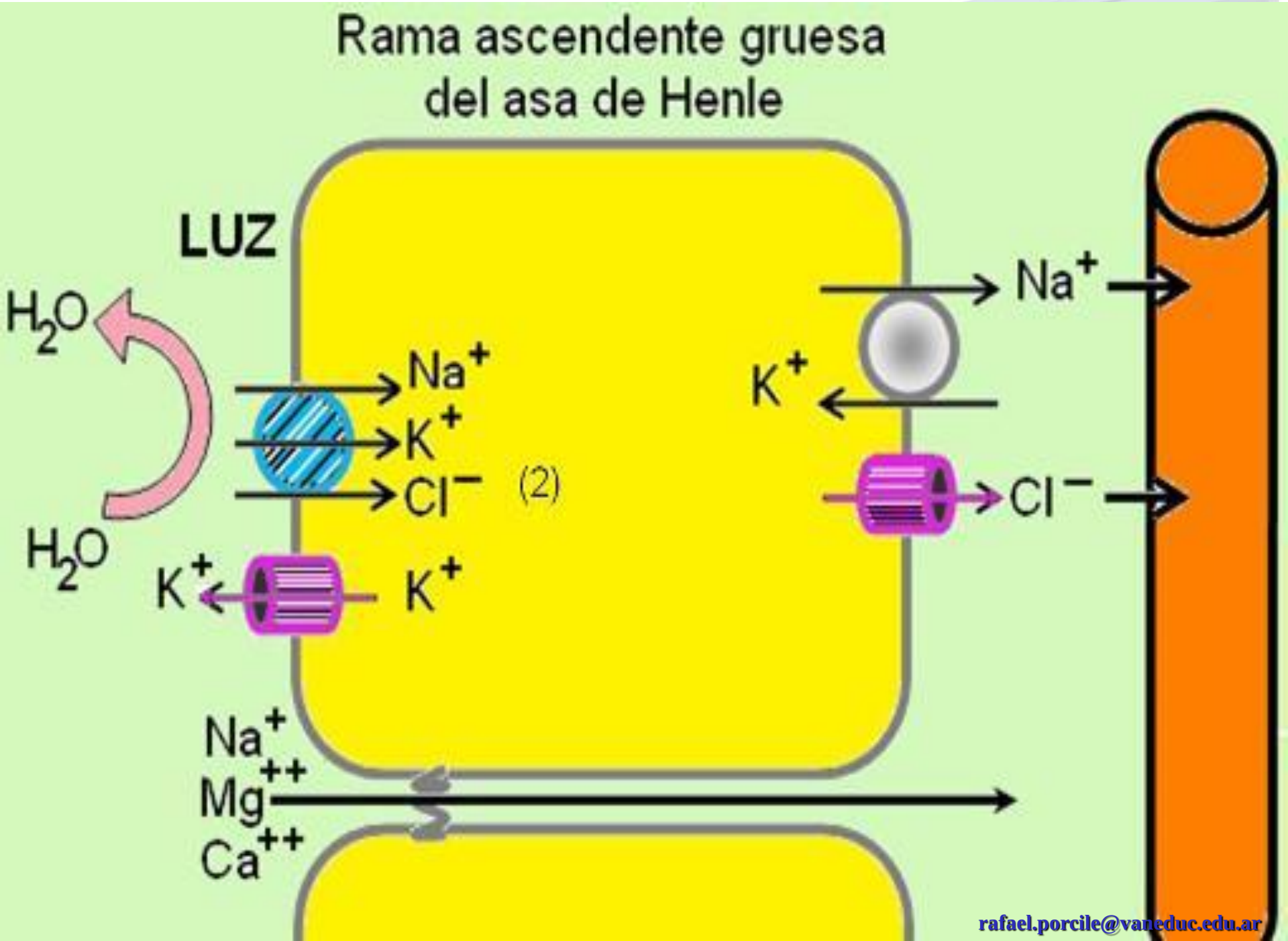
Sulfonamide hypersensitivity



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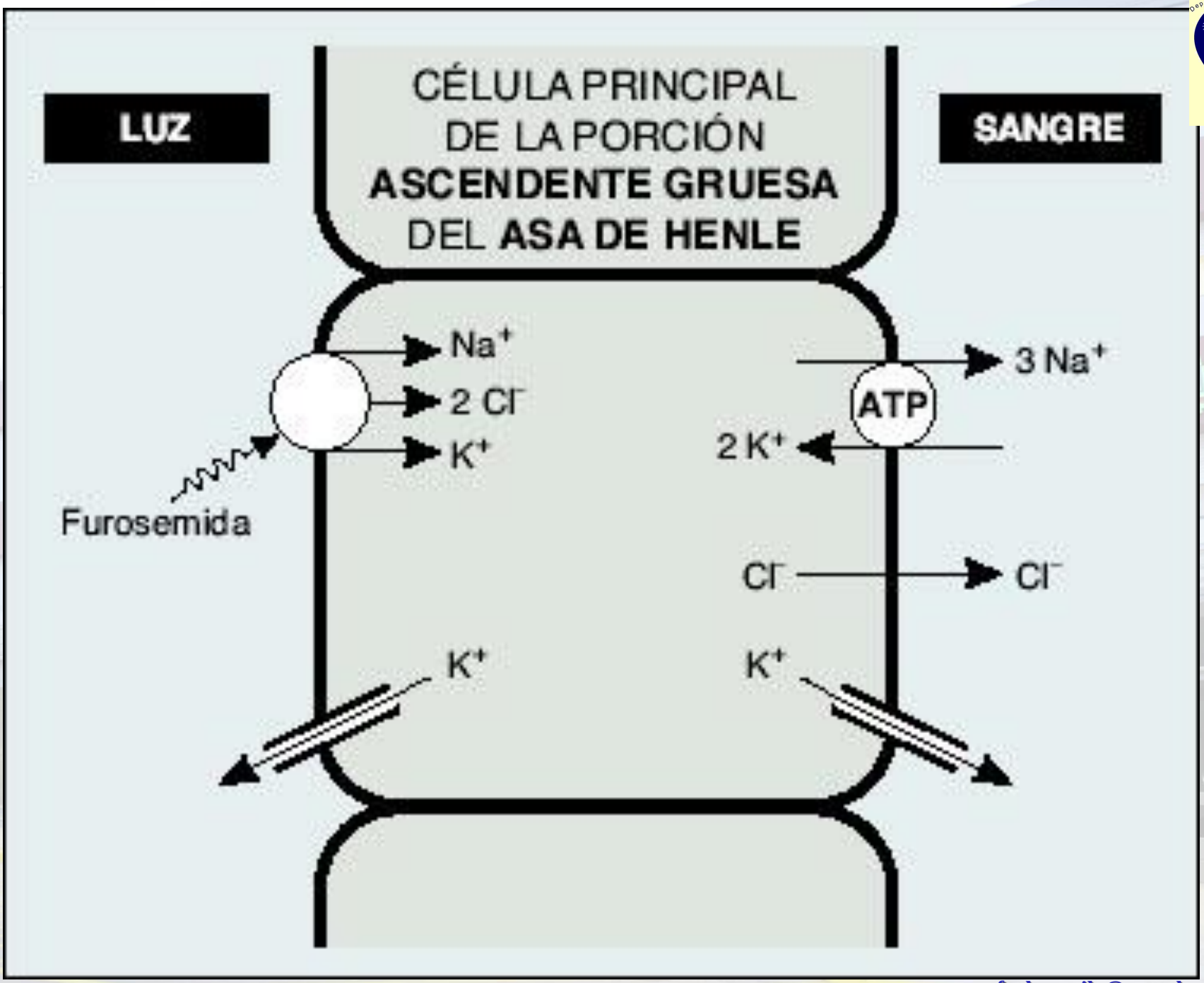

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DIURÉTICOS DEL ASA:”De alto techo”
furosemida, bumetanida, torasemida, ácido etacrínico, piretanida
- Gran potencia diurética: facilita la excreción de un 25-30% del sodio filtrado (frente a una cifra normal de 1%) da lugar a una diuresis profusa
- Lugar de acción: porción gruesa del asa de Henle

- Mecanismo de acción:

- Inhiben el cotransportador Na+/k+/2 Cl- de la membrana luminal.

- También se inhibe la reabsorción de Ca2+ y Mg+

Al tubo colector llega mayor cantidad de Na+ y Ca2+ que hace que se excrete más cantidad de H+ y K+ □ pueden dar alcalosis metabólica
- Puede producir vasodilatación venosa por la liberación de un factor renal (PG)□puede ser útil en el edema agudo de pulmón antes de iniciarse el efecto diurético.

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Capacidad de actuar en el segmento diluyente del asa de Henle

Los sulfamoilbenzoatos

Furosemida , bumetanida y la **piretanida**

Derivados fenoxiacéticos, especialmente el **ácido etacrínico**

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Loop diuretics (e.g. furosemide)

- **Used in acute hypertension (emergency cases)**
  How: by the potent hypovolemic (diuretic) effect. Furosemide is specifically used in hypertension with renal dysfunction due to its potent venodilator effect which manages hypertenion before a considerable urinary output change occurs.
- **Mainly in Pulmonary venous congestion**
  How: flurosemide has a very potent venodilator effect especially at the pulmonary area.

Furosemida endovenosa

2 minutos

Venodilatación

20 minutos

Activación adrenérgica

120 minutos

Hipereninemia

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Direct Vascular Effects of Furosemide in Humans

- Furosemide at therapeutic concentrations exerts no direct vasodilator or antivasoconstrictor effect on arterial resistance vessels in the human forearm but rather **directly dilates veins in humans.**

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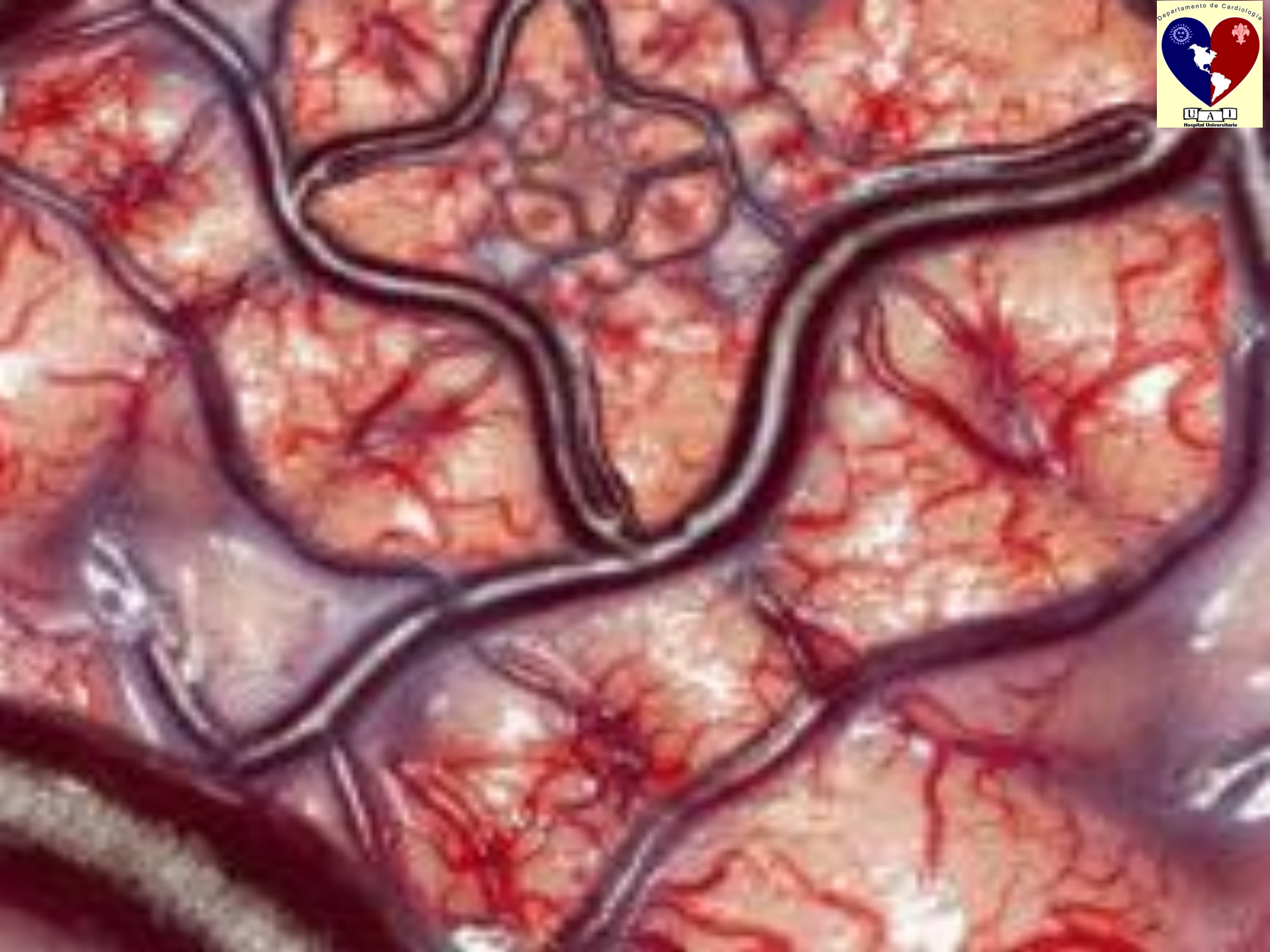

LOOP DIURETICS

- Additional non-tubular effects
    1. Renal Vasodilation and redistribution of blood flow
    2. Increase in renin release
    3. Increase in venous capacitance

These effects mediated by release of prostaglandins from the kidney.

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20 minutos después

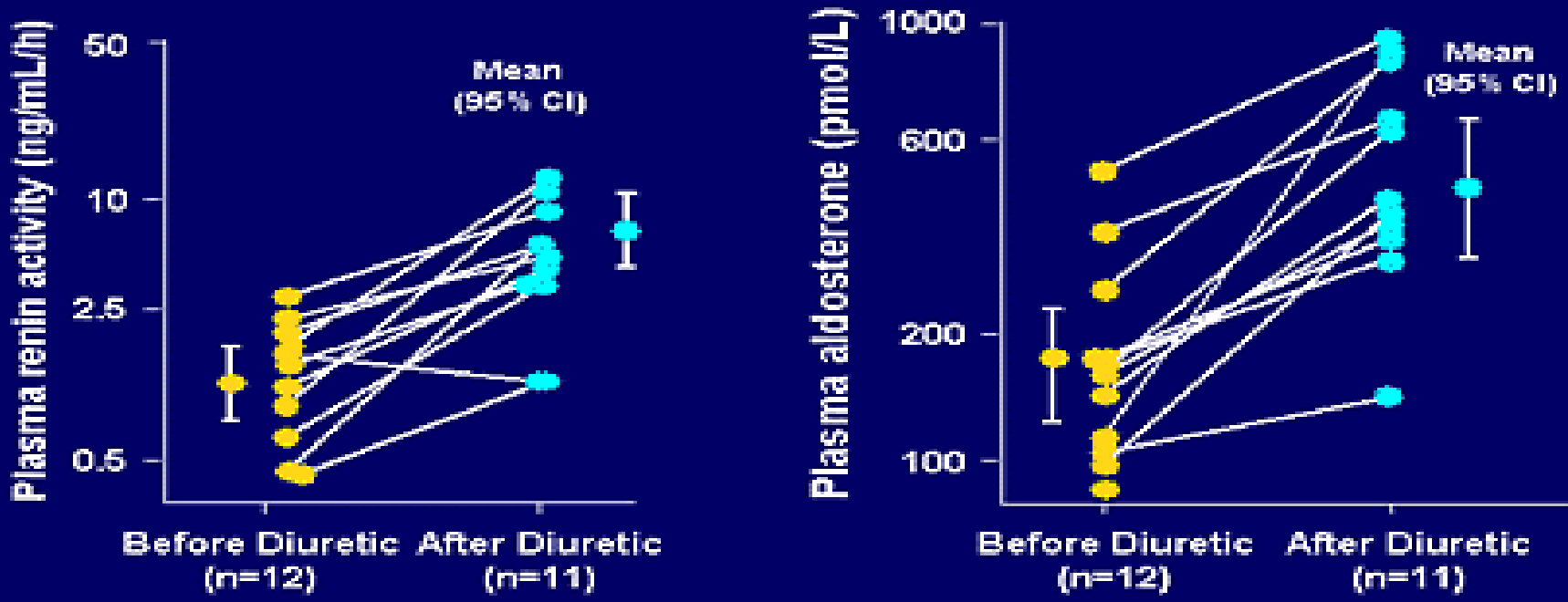
IV Diuretics Are Associated With Vasoconstriction and Neurohormonal Activation

Hemodynamic Variable	Baseline	20 mins after IV Furosemide 40 mg	P value
PAWP (mmHg)	33±9	28±7	<0.01
SVI (ml/min/m²)	27±8	24±7	<0.01
HR (bpm)	87±13	91±16	<0.01
BP (mmHg)	90±15	96±15	<0.01
SVR (dyn-s-cm⁻⁵)	1454±384	1676±415	<0.01
PRA (ng/ml)	9.9±8.5	17.8±16	<0.05
PNE (pg/ml)	667±390	839±368	<0.01

Kubo et al. *Am J Cardiol* 1987;60:1322-8

120 minutos después

Marked Activation of the Renin-Angiotensin-Aldosterone System By IV Loop Diuretics



Bayliss et al. *Br Heart J.* 1987;57:17.

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Vuelca contenido hipertónico al TCD

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Vuelca contenido hipertónico al TCD

Aumenta la excresión de sodio cloro , potasio , magnesio y calcio

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Vuelca contenido hipertónico al TCD

Aumenta la excresión de sodio cloro , potasio , magnesio y calcio

Alcalosis hipocloremica

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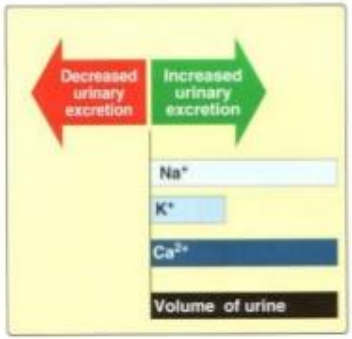
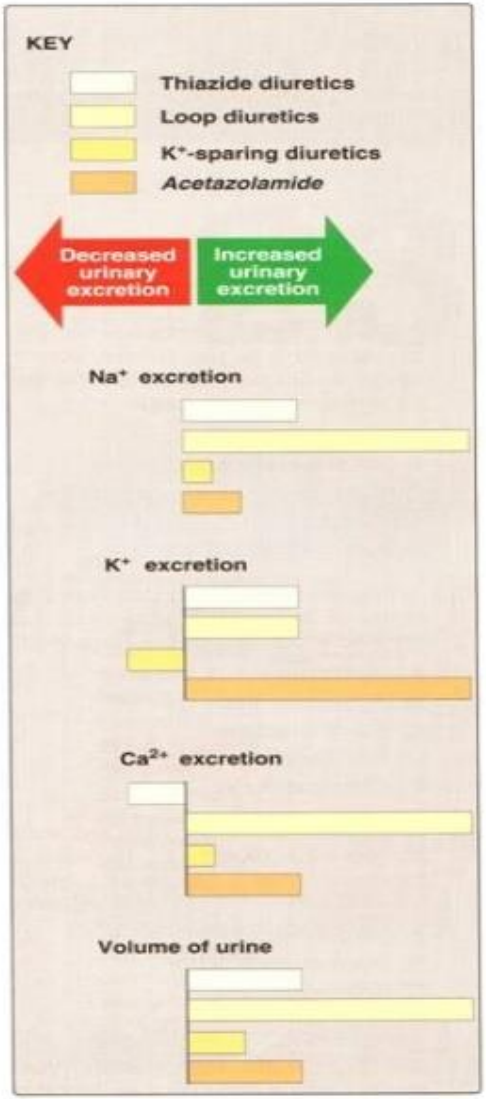
Furosemida, bumetanida: Usos

- Edema pulmonar agudo (por insuficiencia cardiaca congestiva)
- Síndrome nefrótico
- Edema refractario (resistente a otros fármacos), en combinación con tiazidas o ahorradores de K+
- Tratamiento de hipercalcemia
- Deportes, espectáculos, control de peso (uso autorizado?)

Efecto de los diuréticos del asa en la composición urinaria





Los diuréticos de asa deben ser conducidos con cuidado no hay que dejar de controlarlos

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J Clin Hypertens (Greenwich). 2011 Sep;13(9):639-43.

Thiazide and loop diuretics

Loop diuretics **should not be used as first-line therapy in hypertension** since there are no outcome data with them. They should be **reserved for conditions of clinically significant fluid overload** (eg, heart failure and significant fluid retention with vasodilator drugs, such as minoxidil) or with advanced renal failure and can be combined with thiazide-type diuretics.

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DIURETICOS DE ASA E HIPERTENSION ARTERIA

Son diuréticos fuertes pero no tienen mayor acción antihipertensiva que las tiazidas. Una dosis diaria se asocia con poliuria intensa. Son de utilidad en pacientes con insuficiencia cardíaca y renal simultáneas, en quienes las tiazidas no suelen ser eficaces.

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Ren Fail. 2014 Aug;36(7):1051-5.

Diuretics associated acute kidney injury: clinical and pathological analysis.

The combination of diuretics with other drugs such as antibiotics, contrast media, ACEI, NSAIDs, etc. would synergistically induced AKI. The pathological lesion of diuretics associated AKI may be mostly manifested vacuolar degeneration of tubular epithelial cell.

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¿QUE MAS PRODUCE LA FUROSEMIDA?

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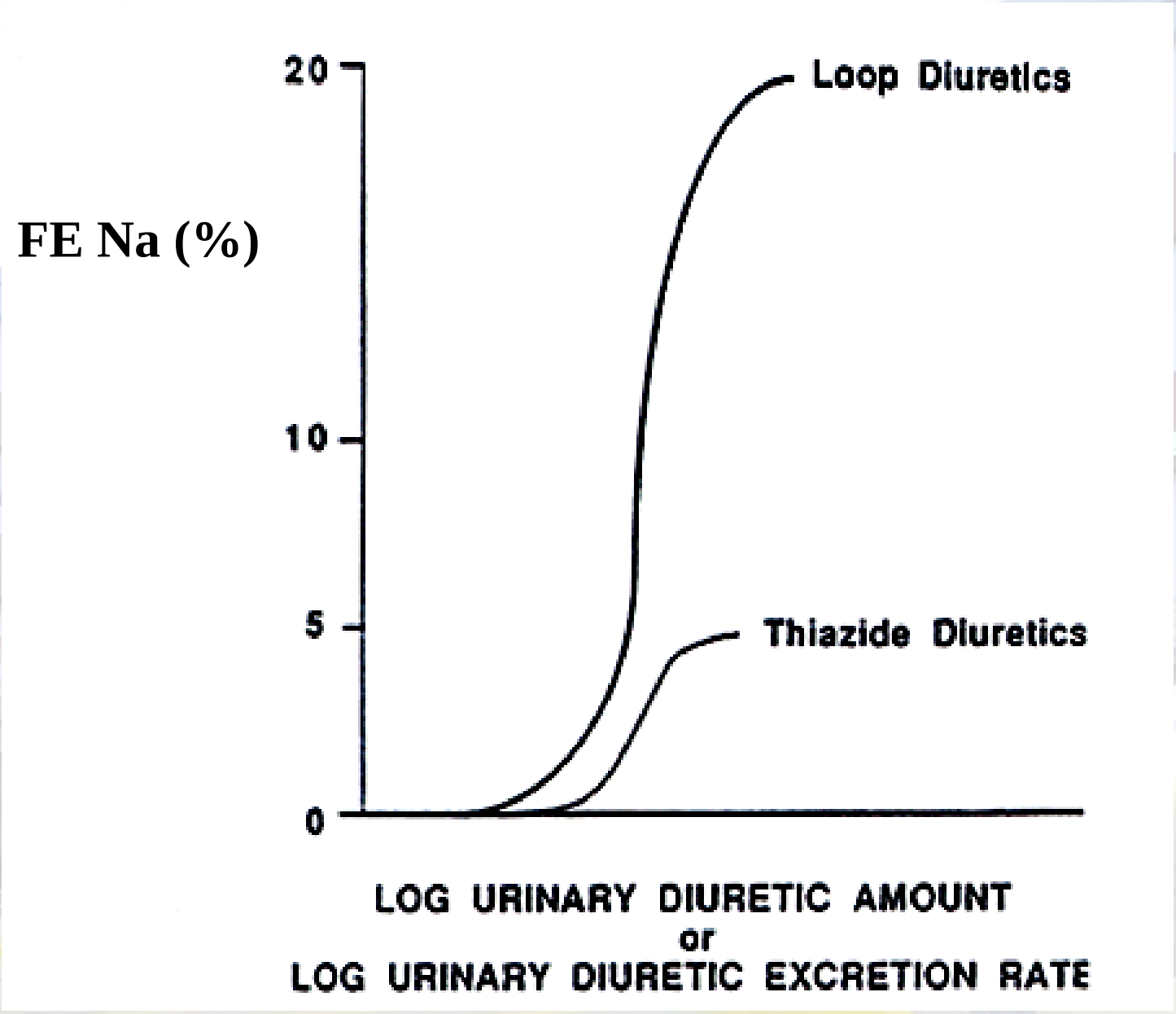
¿QUE MAS PRODUCE LA FUROSEMIDA?

Tabla 2. Ototoxidad de la administración de furosemida

	Mortalidad hospitalaria
Grupo furosemida	9/253 (3,6%)
Grupo placebo	1/255 (0,4%)
RR* (IC del 95%)	3,97 (1,00 a 15,78)
NNP* (IC 95%)	33 (19 a 134)

RR: riesgo relativo; NNP: número necesario para perjudicar.
*Calculado con técnicas metaanalíticas.



From Brater, DC. Pharmacology of Diuretics. Am. J. Med. Sci. 2000, 319:38-50.

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Diuréticos asa en isuficiencia cardíaca

- No hay estudios prospectivos randomizados en icc
- Incluidos como tratamiento asociado en todos los estudios que evalúan otras drogas
- Asa y tiazidas mas evidente impacto clinico

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INSUFICIENCIA CARDIACA ESTADIO C

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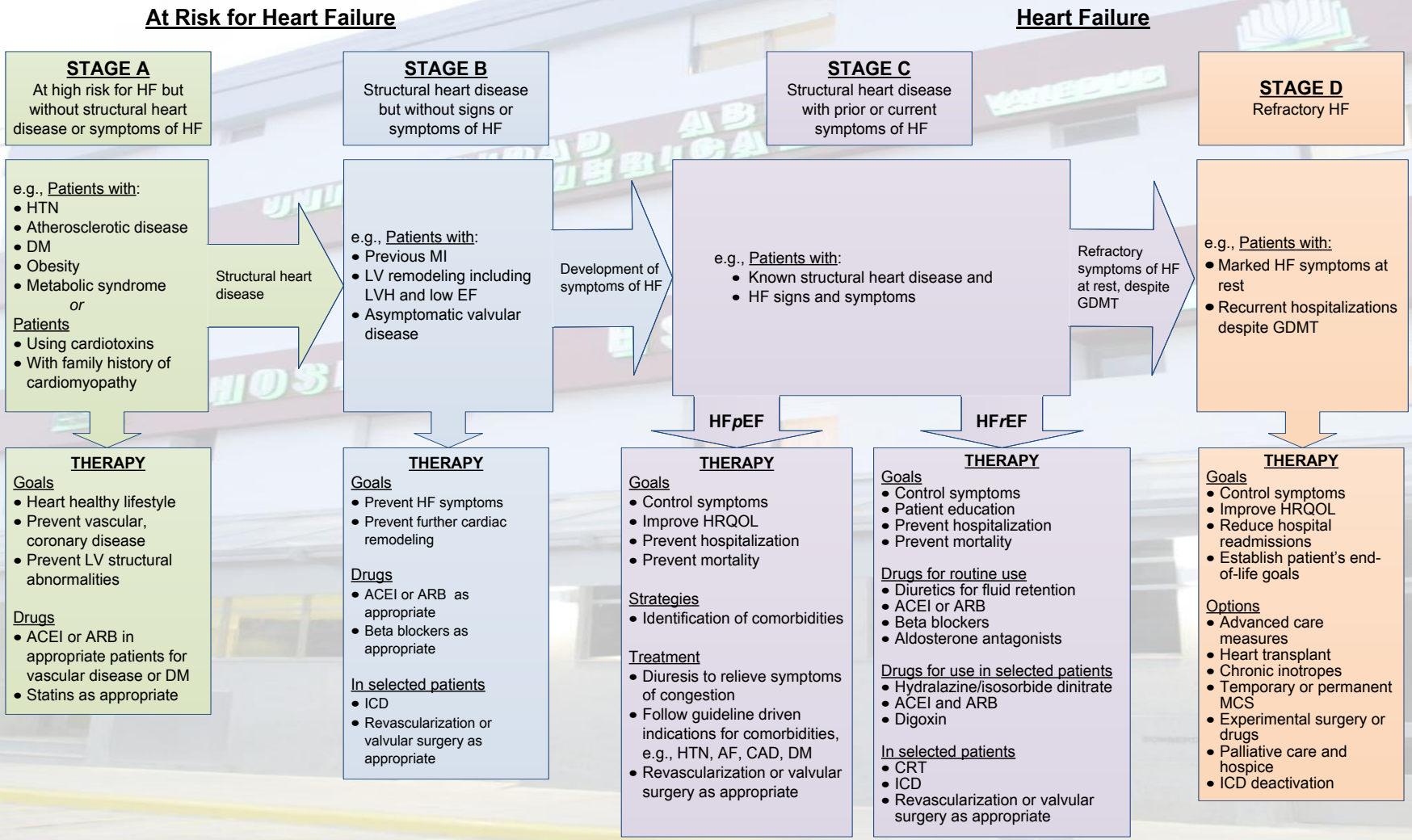
Stages, Phenotypes and Treatment of HF



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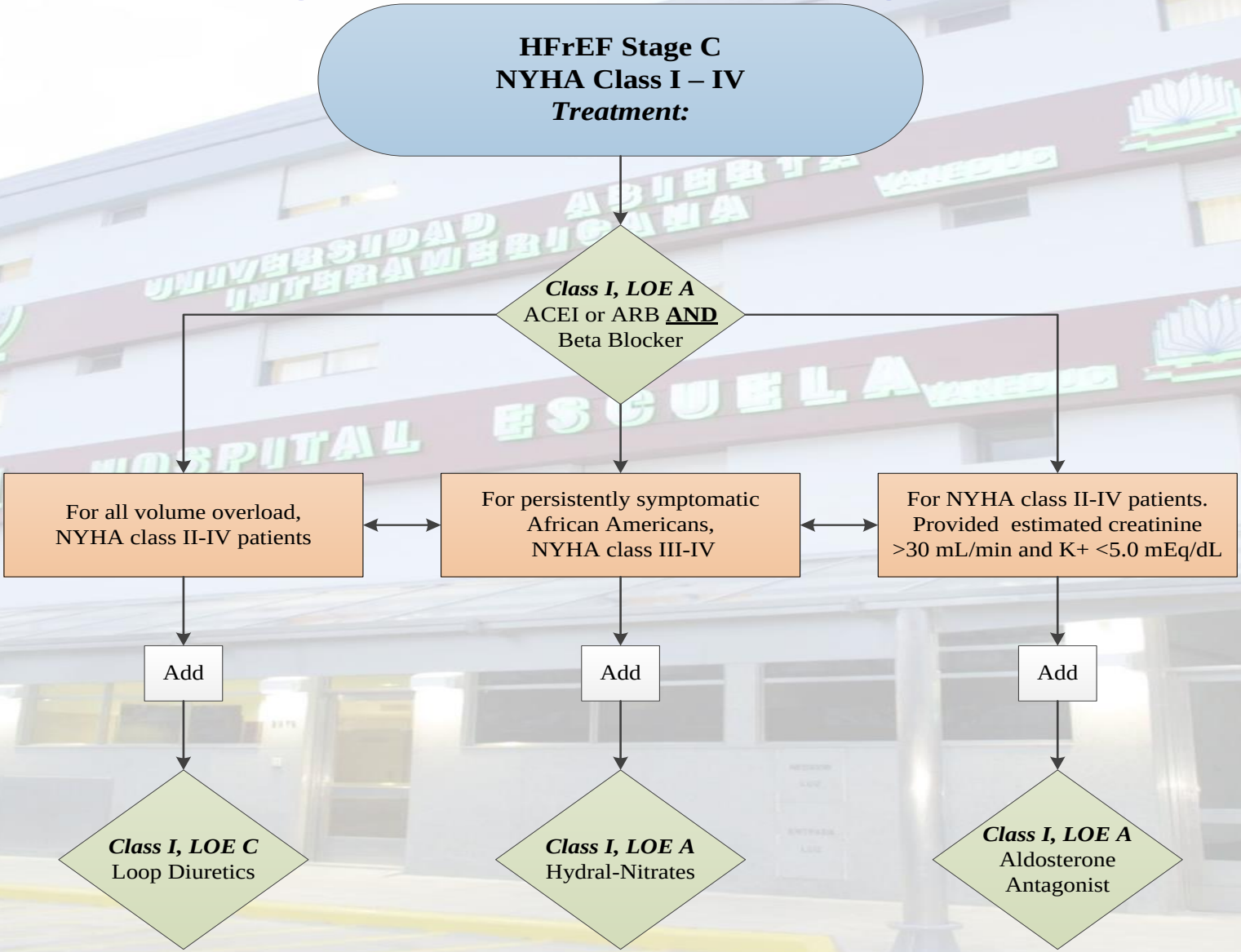
Pharmacologic Treatment for Stage C HF*r*EF



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Evolucion de la clase funsional

NORMAL

Disfuncion sin sintomas

Sin sintomas
Ejerc normal
Depresion vi

Ins card compensada

No sintomas
⬇ Ejercicio
FSVI DEPRIMIDA

Ins Card Descopmpensada

Sintomas reposo
⬇⬇ Ejercicio
Fsvi deprimida

Ins card Refractaria

Sintomas no controlados
Con medicación

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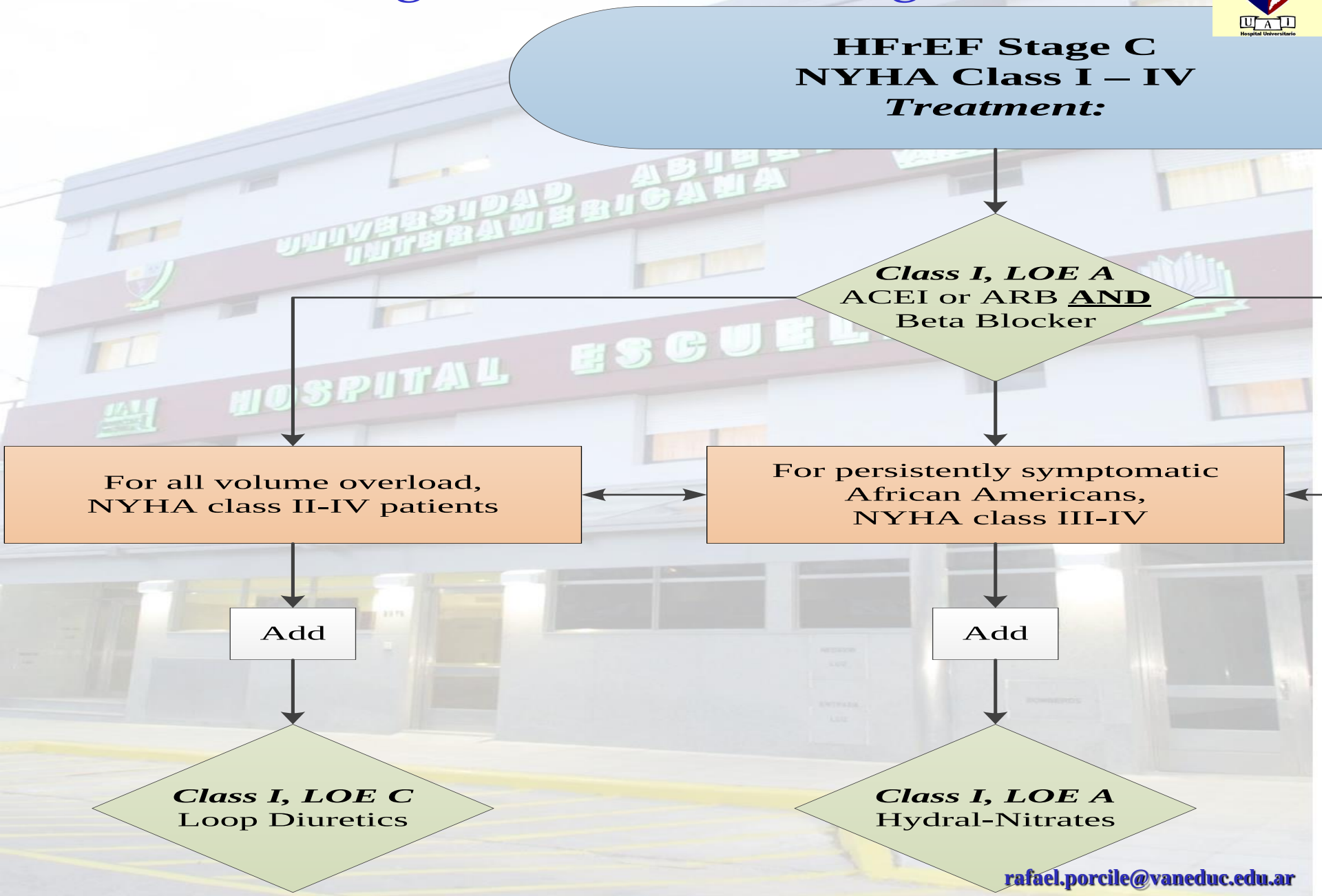
Pharmacologic Treatment for Stage C HF*r*EF



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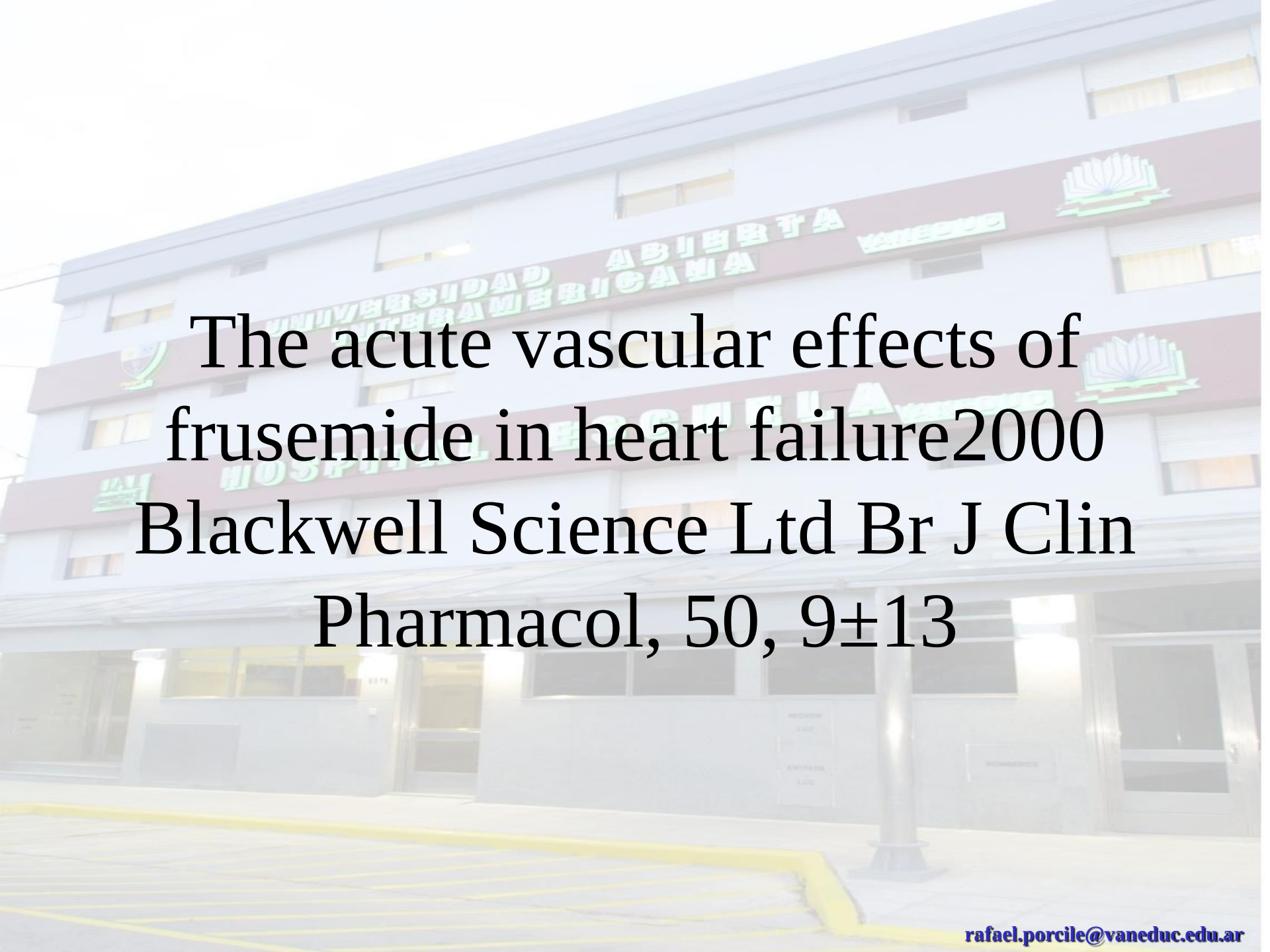

The acute vascular effects of frusemide in heart failure2000 Blackwell Science Ltd Br J Clin Pharmacol, 50, 9±13

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Venous capacitance and blood flow in the calf hadincreased in just 5 min following the injection of frusemide. At this time, the mean urinary output was only 20 ml, and peak urine Flow did not occur until 30 min after the patients had been given frusemideº

The natiuretic effect of frusemide was dose dependent but its venodilatory effect did not seem to show the same dose± dependency . A dose greater than 20 mg did not result in a further increase in venous capacitance.

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SECUESTRO DE VOLEMIA A NIVEL VENOSOS POR VENODILATACIÓN

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Johnston GD, Nicholls DP, Leahey WJ. The dose±response characteristics of the acute non-diuretic peripheral vascular effects of furosemide in normal subjects. Br J Clin Pharmacology 1984; 18: 75±81.

Plasma renin activity has been consistently noted to rise in the minutes following the administration of furosemide irrespective of whether venodilatation or arterial constricción predominantes

Plasma renin activity but not the vasodilator effect increases with dose

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Johnston GD, Nicholls DP, Leahey WJ. The dose±response characteristics of the acute non-diuretic peripheral vascular
effects of furosemide in normal subjects. Br J Clin Pharmacology
1984; 18: 75±81.

As the mechanism of action of frusemide involves the activation of the renin±angiotensin system and prostaglandin
production it is possible that other drugs used in the treatment of heart failure may augment or attenuate any acute venodilatory effect produced by frusemide. The
potential for pharmacological interaction is enormous.

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TORASEMIDA

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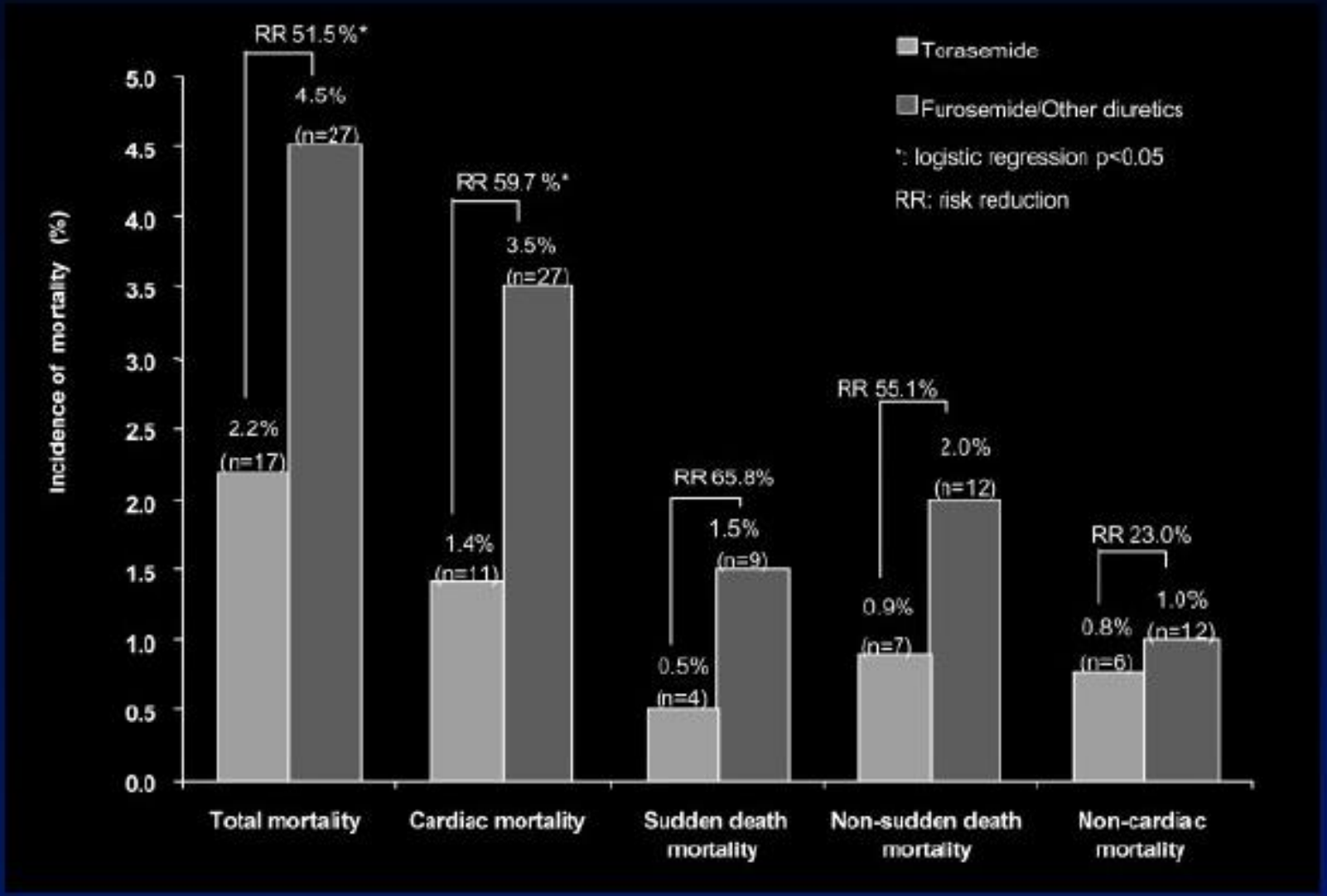
Torsemida en IC



Cosín J, et al. Eur J of Heart Fail 2002:4:507-13

Torasemida

A diferencia de la furosemida, la torasemida posee la capacidad de inhibir la secreción adrenal de aldosterona y su unión al receptor mineralocorticoide, así como de disminuir la extracción cardiaca de aldosterona en los pacientes con insuficiencia cardiaca

La torasemida, al igual que la furosemida, es un diurético de asa, pero tiene una vida media de eliminación más prolongada, una duración de acción más larga y mayor biodisponibilidad en comparación con esta última.

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Torasemida Phoenix 5 Mg
Torasemida Phoenix 2.5 Mg
Torasemida Phoenix 10 Mg
Torasemida Phoenix 20 Mg
Flugerol
Torasemida Bristol 5 Mg
Torasemida Bristol 10 Mg
Torasemida Bristol 20 Mg
Torasemida Bristol 100 Mg
Torem 5 Mg
Torem 10 Mg
Butadif

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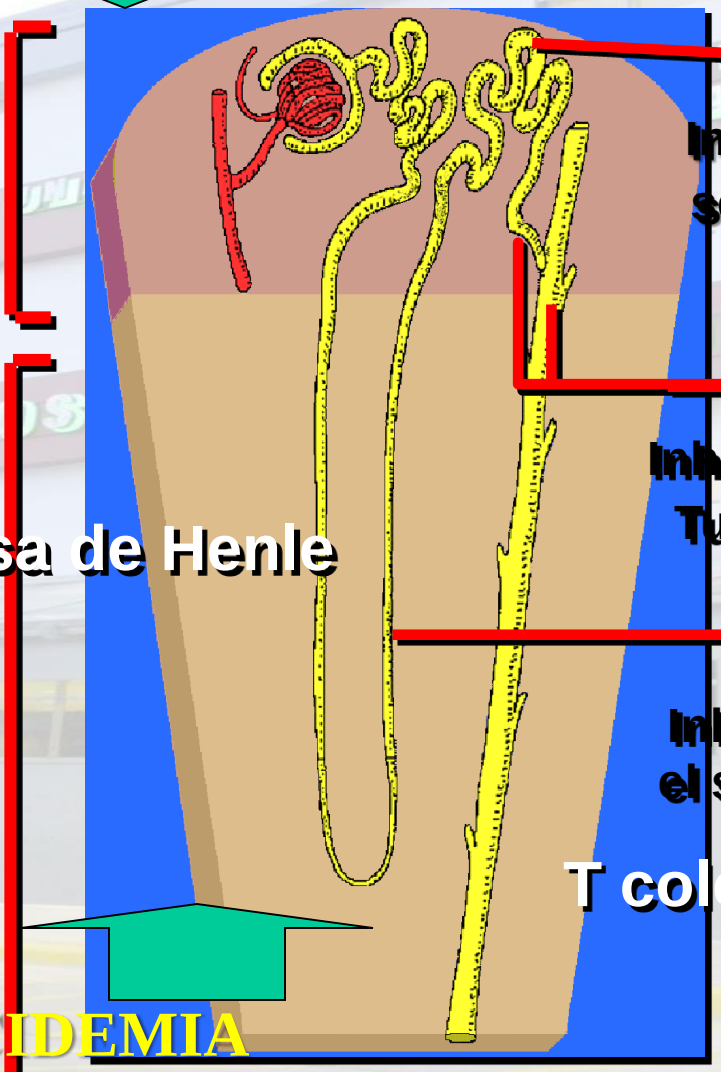
ISQUEMIA



Cortex

Asa de Henle

Medula

T colectores

ACIDEMIA
HIPONATREMIA

Tiazidas

Inhiben la reabsorción de Cl y Na segmento de dilucion cortical de Asa de Henle

Ahorradores de K

Inhiben la reabsorción de k en los Tubulos contorneados distales

Diureticos de asa

Inhiben el intercambio Na –Cl-K en el segmento delgado ascendente del asa

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5 minutos …

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INHIBIDORES DE LA REABSORCIÓN DE SODIO

DIURETICOS OSMOTICOS
- Manitol

DIURETISO INHIBIDORES DE LA ANIDRASA CARBONICA
-Acetazolamida

DIURÉTICOS DEL ASA
- Furosemida
-Bumetanida
-Torasemida

TIAZÍDICOS:
- Bendroflumetiacida
- Hidroclorotiazida
- Clortalidona
- Indapamida

AHORRADORES DE POTASIO
- Espironolactona
- Amilorida
- Triamtereno

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TIAZÍDICOS:
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- **Clortalidona**
- **Indapamida**

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Túbulo contorneado distal

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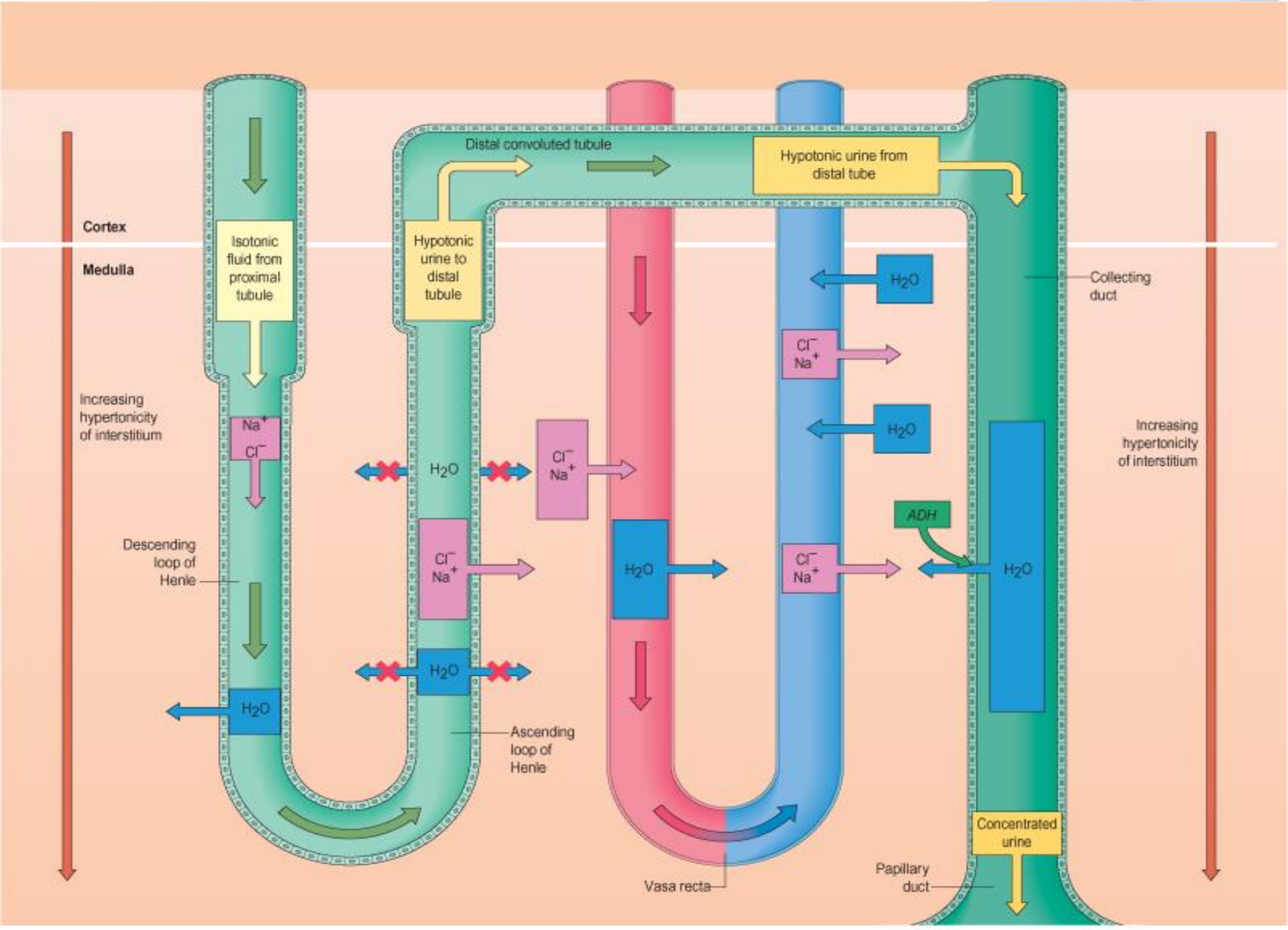


PROXIMAL CONVOLUTED TUBULE

Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium-potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
Glucose	100% (symporters and facilitated diffusion)
Amino acids	100% (symporters and facilitated diffusion)
Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
Urea	50% (diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
Creatinine	small amount

At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).

LOOP OF HENLE

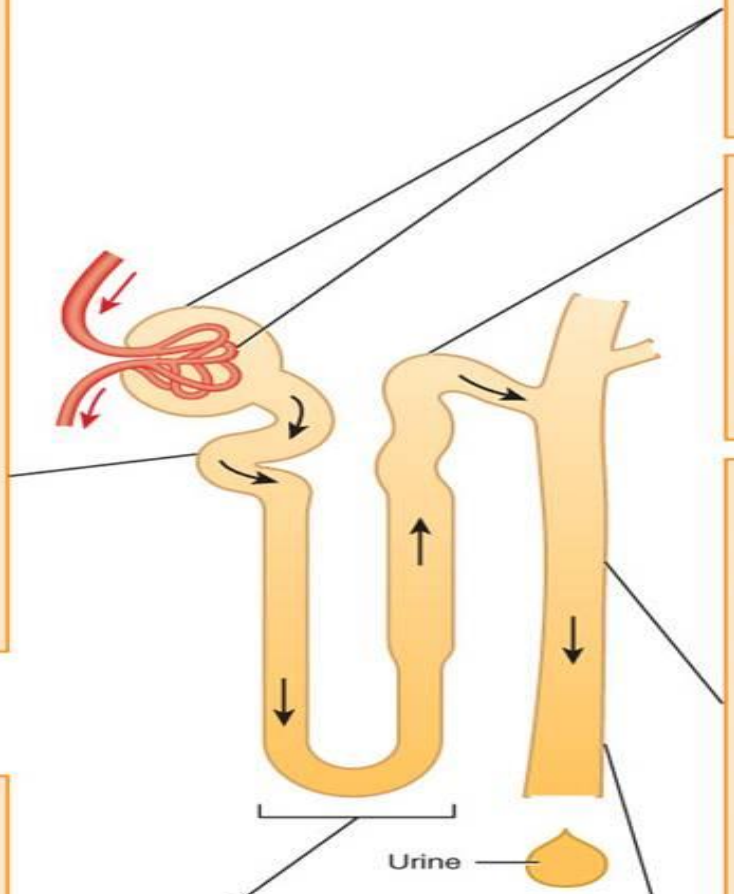
Reabsorption (into blood) of:

Water	15% (osmosis in descending limb)
Na^+	20–30% (symporters in ascending limb)
K^+	20–30% (symporters in ascending limb)
Cl^-	35% (symporters in ascending limb)
HCO_3^-	10–20% (facilitated diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

Urea	variable (recycling from collecting duct)

At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).



RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid

DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

PRINCIPAL CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

Water	5–9% (insertion of water channels stimulated by ADH)
Na^+	1–4% (sodium-potassium pumps)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

K^+	variable amount to adjust for dietary intake (leakage channels)

Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.

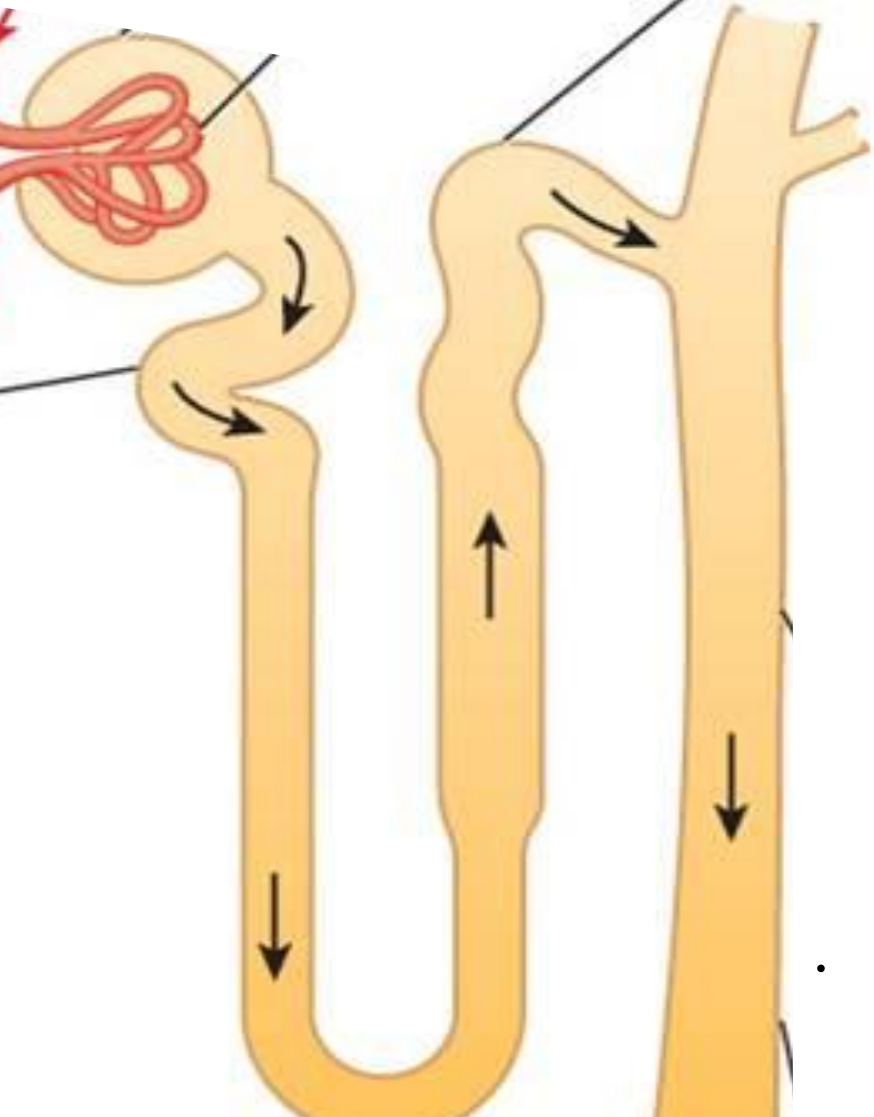
INTERCALATED CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

HCO_3^- (new)	varible amount, depends on H^+ secretion (antiporters)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

H^+	variable amounts to maintain acid-base homeostasis (H^+ pumps)



DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

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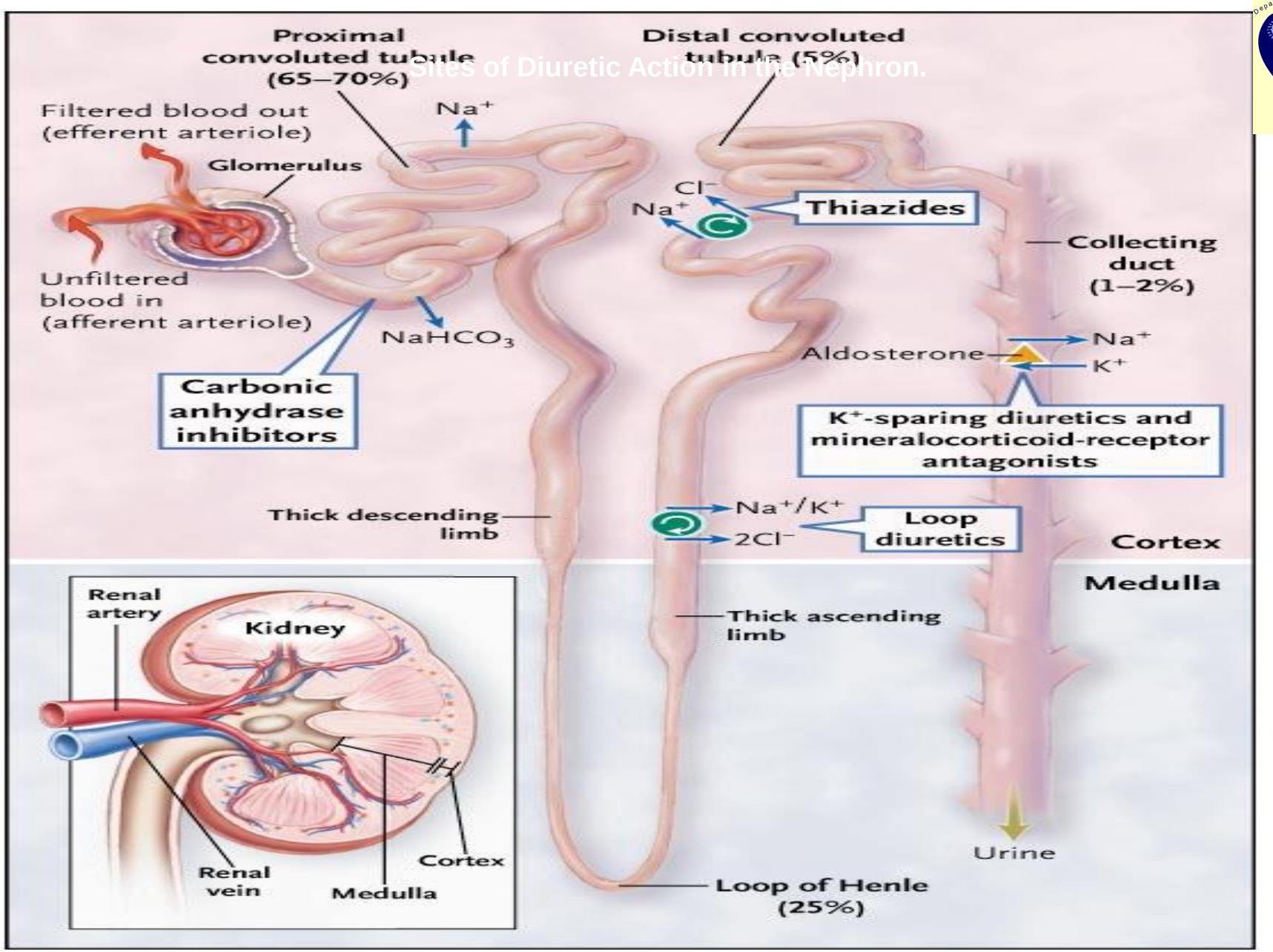
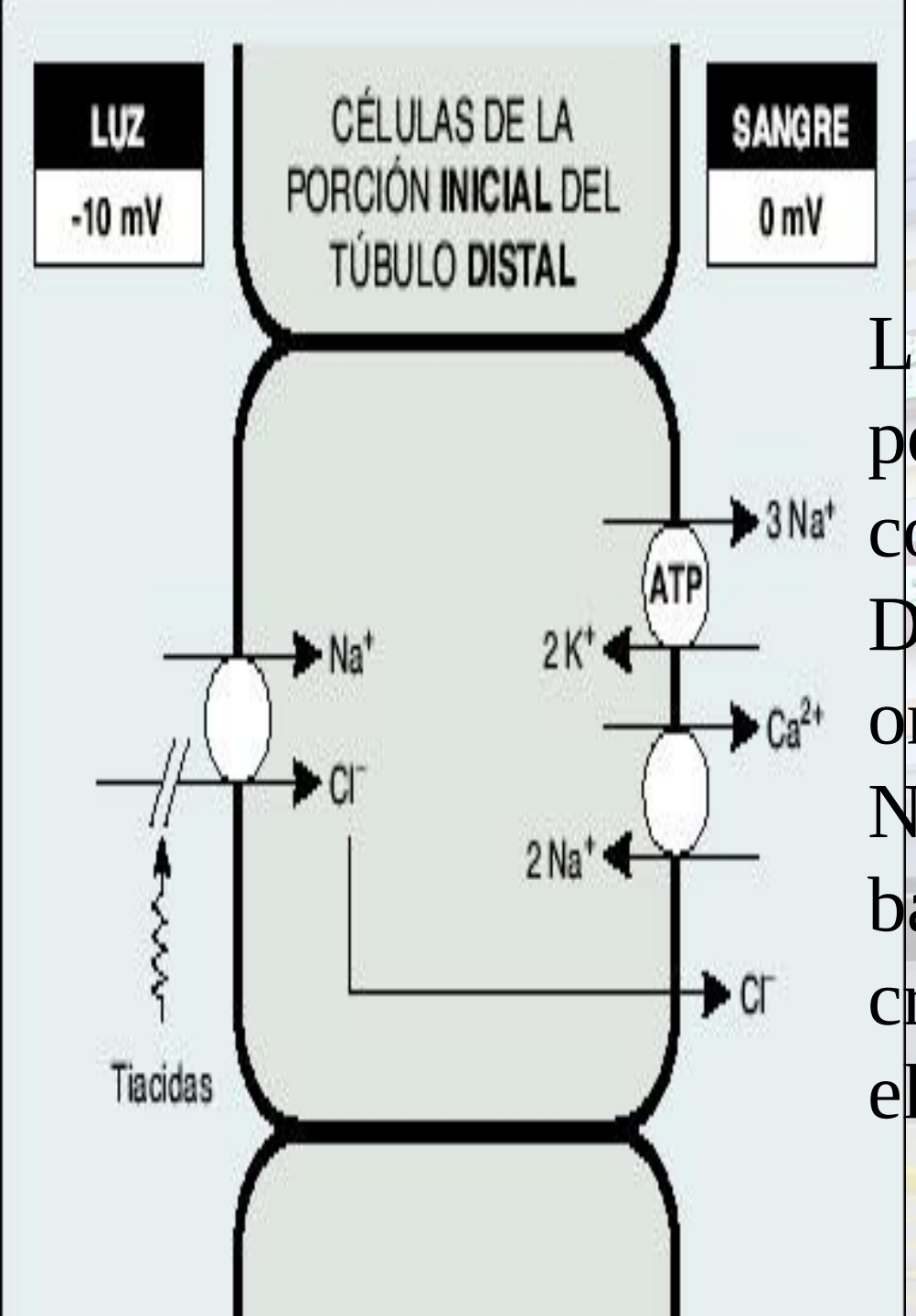


Ernst ME, Moser M. N Engl J Med 2009;361:2153-2164.

The NEW ENGLAND JOURNAL of MEDICINE



La membrana luminal posee también un cotransportador Cl–-K+.
D) utiliza la energía originada por la bomba de Na+ de la membrana basolateral, que es la que crea el gradiente electroquímico para el Na

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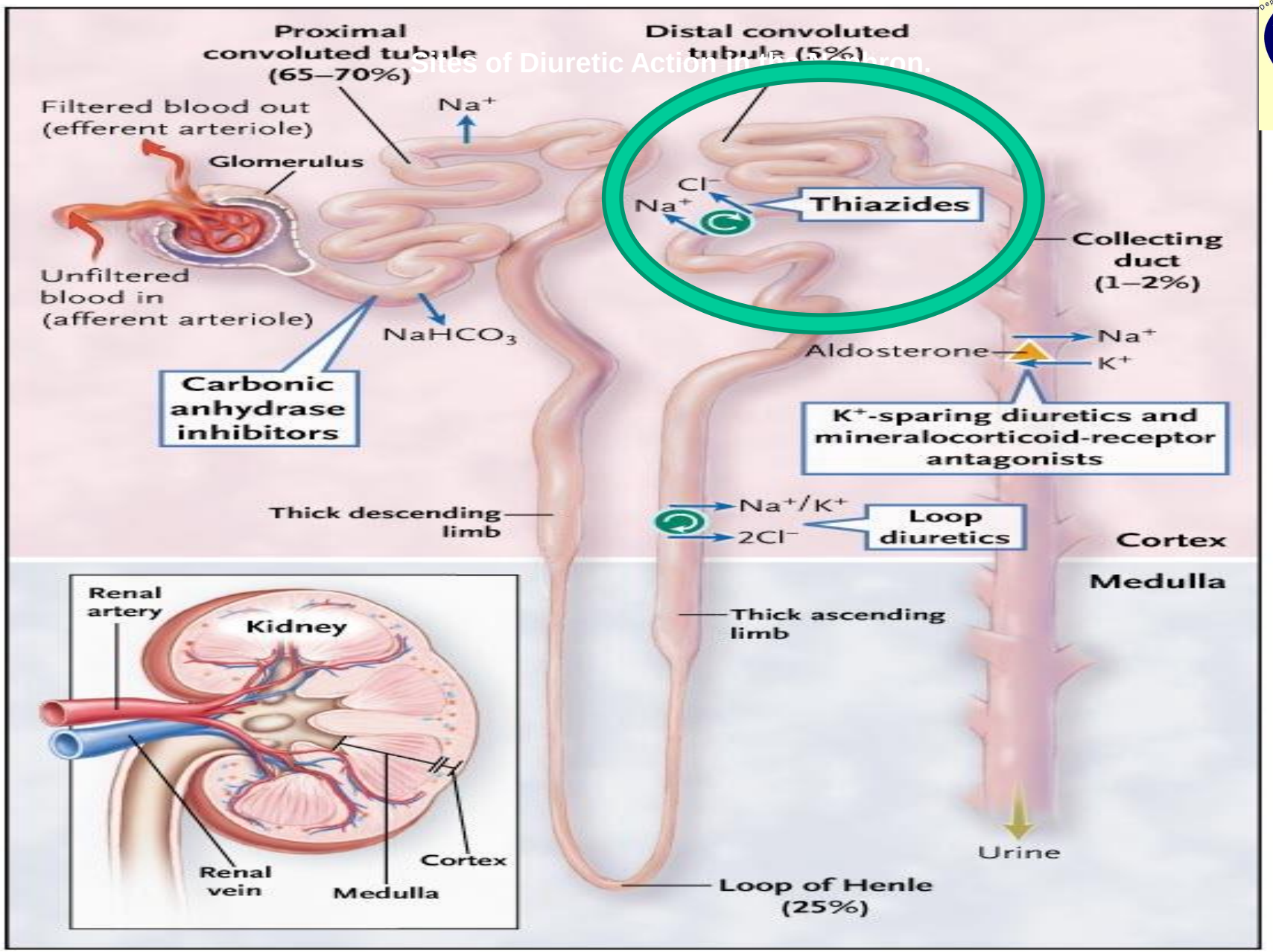

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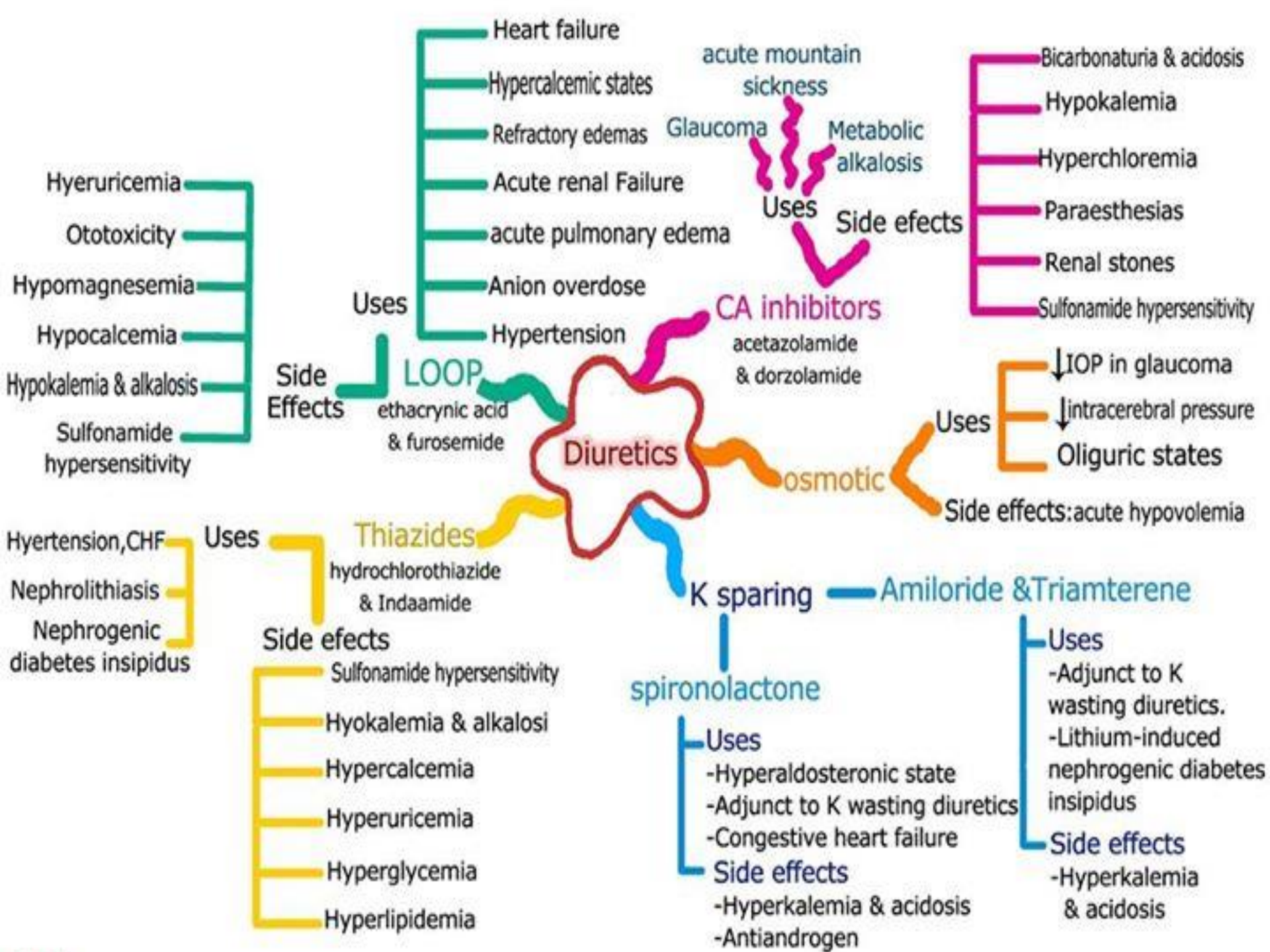
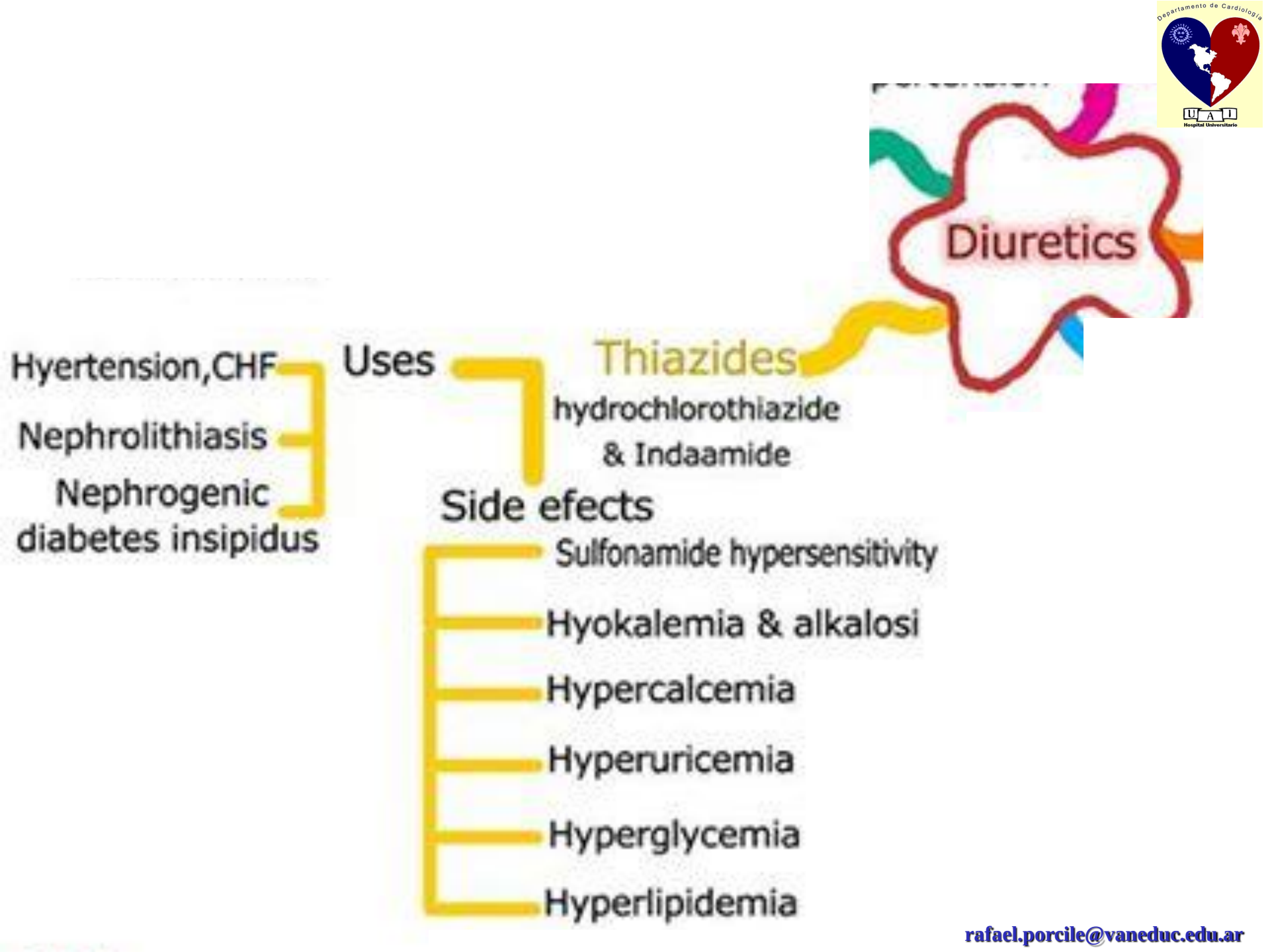

Diuretics
CA inhibitors
acetazolamide & dorzolamide
acute mountain sickness
Glaucoma
Metabolic alkalosis
Uses
Side efects
Bicarbonaturia & acidosis
Hypokalemia
Hyperchloremia
Paraesthesias
Renal stones
Sulfonamide hypersensitivity
LOOP
ethacrynic acid & furosemide
Uses
Heart failure
Hypercalcemic states
Refractory edemas
Acute renal Failure
acute pulmonary edema
Anion overdose
Hypertension
Side Effects
Hyeruricemia
Ototoxicity
Hypomagnesemia
Hypocalcemia
Hypokalemia & alkalosis
Sulfonamide hypersensitivity
osmotic
Uses
↓IOP in glaucoma
↓intracerebral pressure
Oliguric states
Side effects:acute hypovolemia
Thiazides
hydrochlorothiazide & Indaamide
Uses
Hyertension,CHF
Nephrolithiasis
Nephrogenic diabetes insipidus
Side efects
Sulfonamide hypersensitivity
Hyokalemia & alkalosi
Hypercalcemia
Hyperuricemia
Hyperglycemia
Hyperlipidemia
K sparing
Amiloride &Triamterene
Uses
-Adjunct to K wasting diuretics.
-Lithium-induced nephrogenic diabetes insipidus
Side effects
-Hyperkalemia & acidosis
spironolactone
Uses
-Hyperaldosteronic state
-Adjunct to K wasting diuretics
-Congestive heart failure
Side effects
-Hyperkalemia & acidosis
-Antiandrogen



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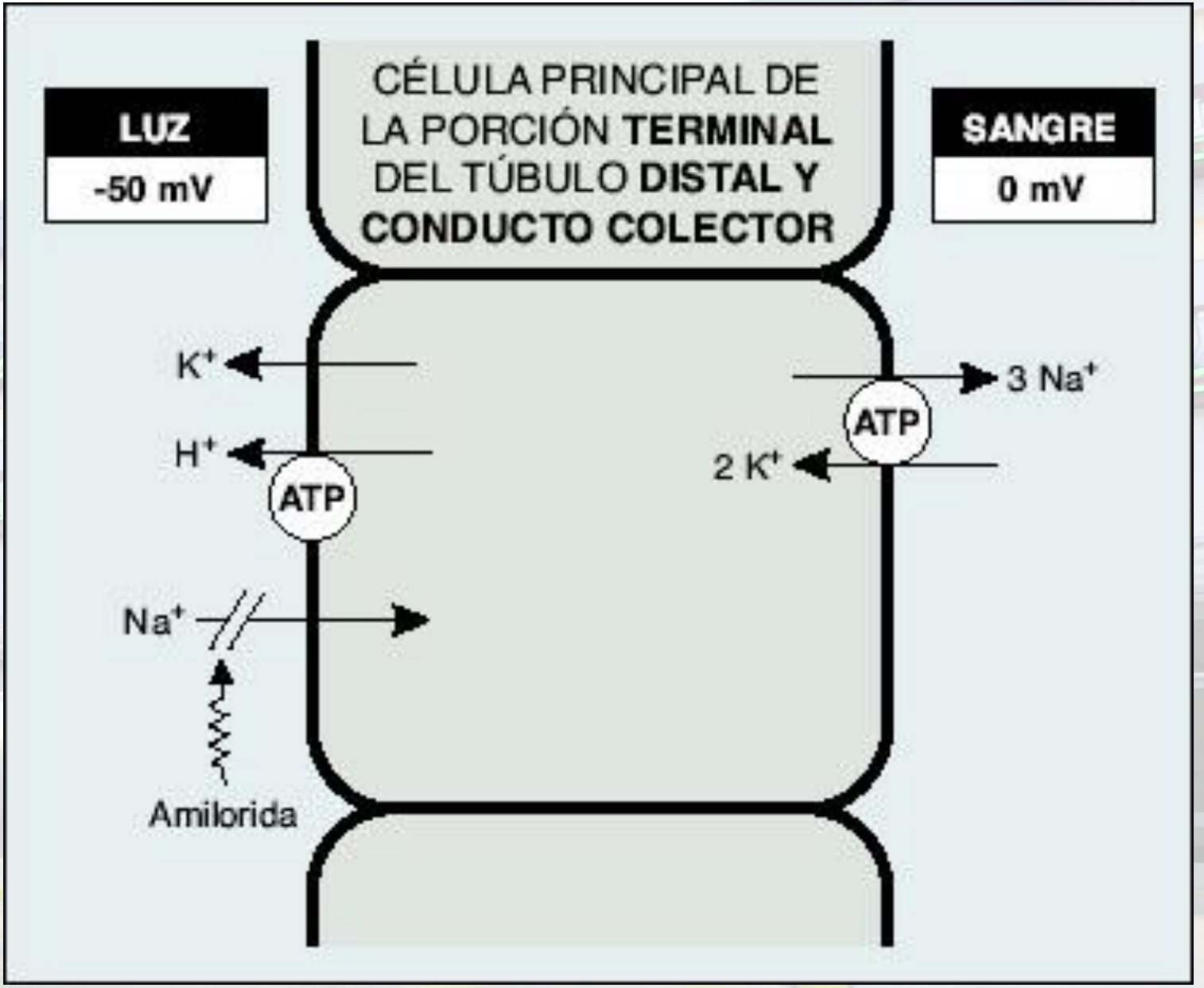

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DIURÉTICOS TIAZÍDICOS

De acción corta: clorotiazida, hidroclorotiazida

De acción intermedia: indapamida

De accion prolongada: clortalidona (adm cada 2 o 3 días)

- Potencia diurética: moderada.”de bajo techo”: facilita la
excreción de un 5-10% del sodio filtrado (frente a una cifra
normal de 1%)

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Table 1. Pharmacokinetic Characteristics of the Thiazide Diuretics Approved for Use in the United States.*

Diuretic†	Relative Carbonic Anhydrase Inhibition‡	Oral Bioavailability	Volume of Distribution	Protein Binding	Route of Elimination	Elimination Half-Life
		percent	*liters per kilogram*	*percent*		*hr*
Thiazide-type						
Chlorothiazide	++	15–30	1	70	100% Renal	1.5–2.5
Hydrochlorothiazide	+	60–70	2.5	40	95% Renal	9–10
Methychlothiazide	—	—	—	—	Hepatically metabolized	—
Polythiazide	+	—	—	—	25% Renal	26
Bendroflumethiazide	0	90	1.0–1.5	94	30% Renal	9
Thiazide-like						
Chlorthalidone	+++	65	3–13	99	65% Renal	50–60
Metolazone	+	65	113 (total)§	95	80% Renal	8–14
Indapamide	++	93	25 (total)§	75	Hepatically metabolized	14

* All the diuretics listed are available in generic form in the United States as monotherapy, except polythiazide (not currently available) and bendroflumethiazide (available only in combination with nadolol). Dashes indicate an absence of data.

† The terms thiazide-type and thiazide-like are used to group thiazides on the basis of the presence of a benzothiadiazine molecular structure. Thiazide-like diuretics lack the benzothiadiazine structure but have a mechanism of action similar to that of thiazide-type diuretics, which have the benzothiadiazine structure.

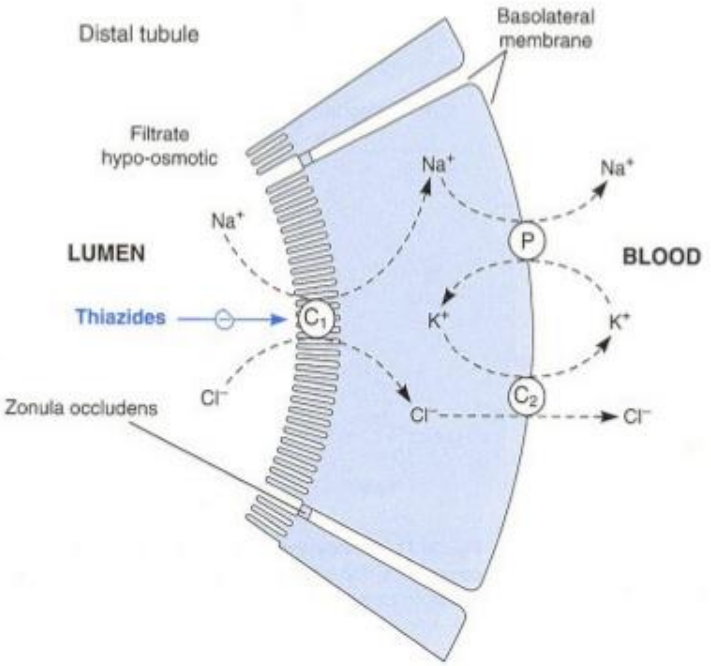
‡ Plus signs indicate inhibition, with greater numbers of plus signs reflecting increased inhibition (lower inhibition constants); the zero indicates an inhibition constant of 0.

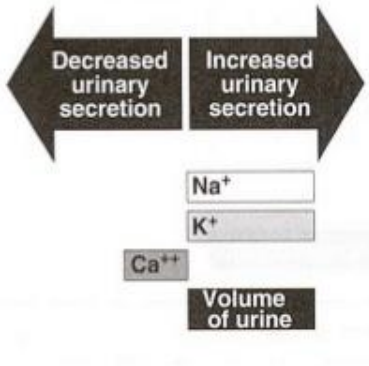
§ The volumes of distribution of metolozone and indapamide are given for the total volume, in liters; data on liters per kilogram were not available.

Ernst ME, Moser M. N Engl J Med 2009;361:2153-2164.

Tiazidas: *Hidroclorotiazida,clortalidona*

- Inhiben al cotransportador Na^+/Cl^- del túbulo c. distal
  - ↓ reabsorción de Na^+
  - ↑ excreción de Na^+ y Cl^-
  - Pérdida de K^+
- Excreción de orina hiperosmolar
- ↓ volumen sanguíneo

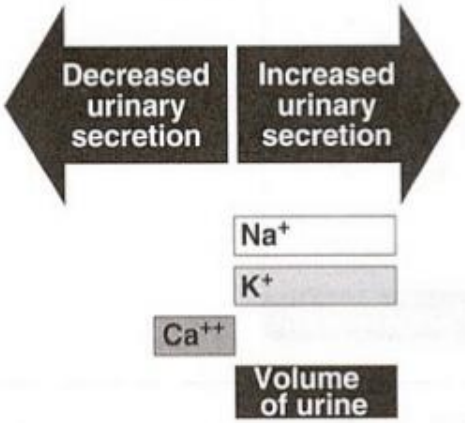


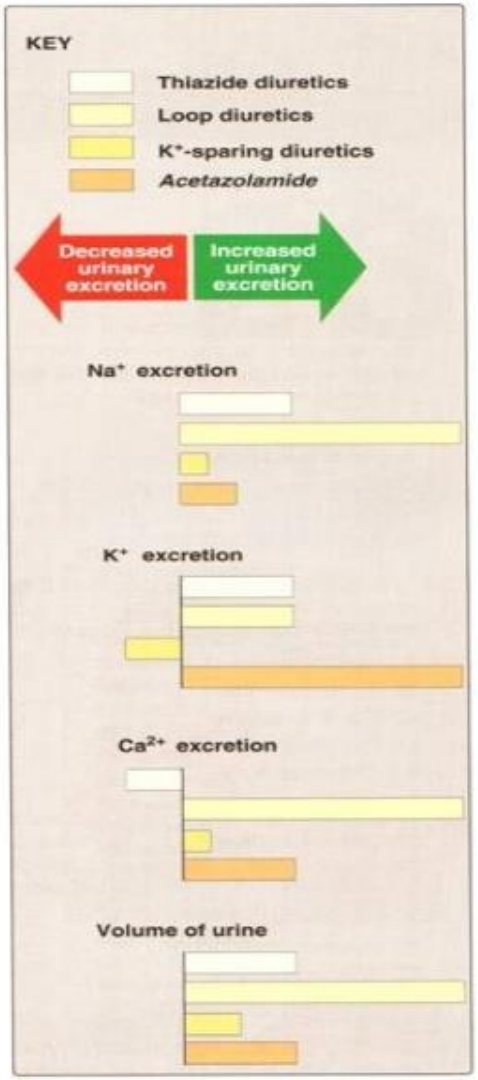


Tiazidas: Usos

1. Hipertensión.
2. Enfermedad cardiaca congestiva.
3. Síndrome nefrótico con edema.

Efecto de las tiazidas en la composición urinaria





Excreción de orina hiperosmolar

Son los fármacos más utilizados; se los recomienda como drogas de **primera línea en pacientes con hipertensión leve a moderada, especialmente en individuos de edad avanzada y de raza negra**.

Se los prefiere a los diuréticos de asa por su efecto más lento y prolongado.

Son mucho más eficaces cuando se los combina con restricción de sodio en la dieta.

La respuesta a la terapia depende de varios factores edad

raza

función renal.

Cuando el efecto no es el deseado se prefiere agregar otra droga antes que aumentar la dosis

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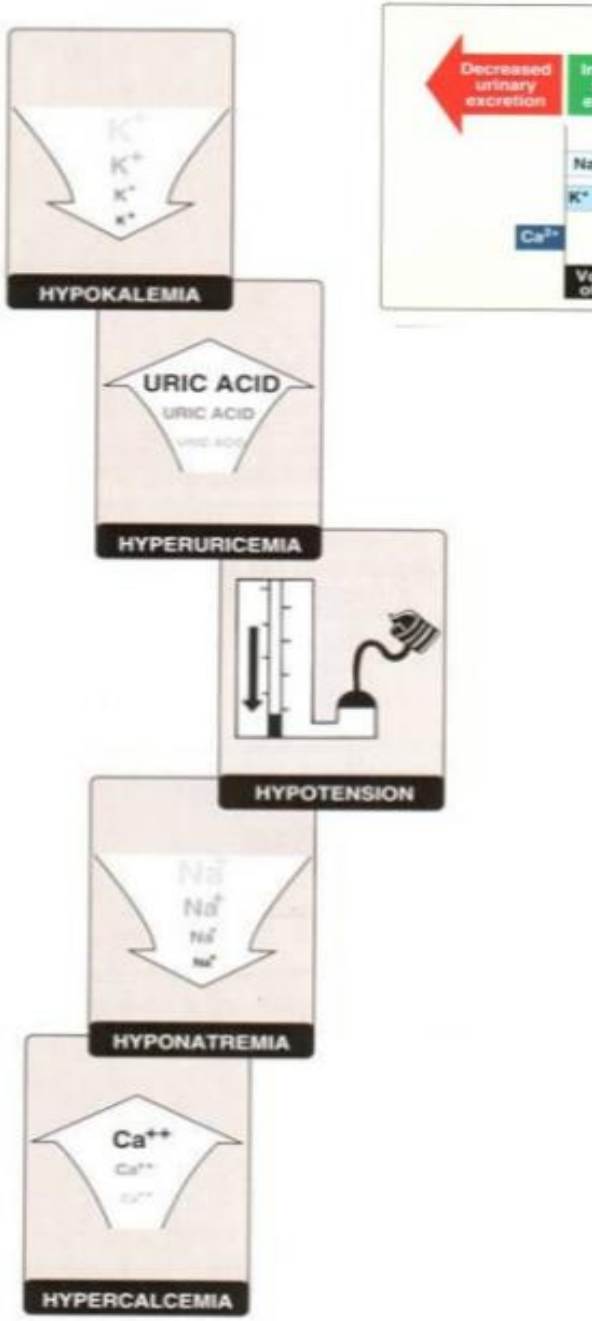
Efectos adversos de las tiazidas:

- Consecuencia de sus acciones renales y en dosis con diuresis marcada (>12.5 mg/día): Hiperglucemia
- Sin embargo, para el control de la hipertensión basta con dosis menores
  - Clortalidona 1 vez al día (HIGROTON 50, HIDROPHARM, TENORETIC, ésta combinada con atenolol)
  - Hidroclorotiazida: en combinación con otros fármacos (Solo en ROFUCAL, o combinado en ATACAND PLUS, COAPROVEL, etc)



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ADVERSE EFFECTS OF THIAZIDES-2

- **HYPERLIPIDEMIA**; mechanism unknown but cholesterol increases usually trivial (1% increase)
- **IMPOTENCE**
- **HYPONATREMIA** due to thirst, sodium losloss, inappropriate ADH secretion (can cause confusion in the elderly), usually after prolonged use

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Tiazidas y el Calcio

- Thiazide increase calcium reabsorption at the distal tubule.

By lowering the sodium concentration within the epithelial cells, thiazides increase the activity of the Na^+/Ca^{2+} antiporter on the basolateral membrane to transport more Ca^{2+} into the interstitium. This, in turn, lowers the intracellular Ca^{2+} concentration so that more Ca^{2+} may diffuse into the cell via apical Ca^{2+}-selective channels (TRPV5). In other words, less Ca^{2+} in the cell increases the driving force for reabsorption from the lumen.

Some of this response is due to augmentation of the action of parathyroid hormone.

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Hyponatremia

La hiponatremia hipotónica genera movimiento de agua hacia las células, con tumefacción celular. La tumefacción de las células encefálicas origina edema cerebral que conduce a los síntomas neurológicos de la hiponatremia: cefalea, náuseas, vómitos, calambres musculares, letargia, sedación, desorientación y reflejos disminuidos. Los síntomas de la hiponatremia guardan una estrecha correlación con la intensidad y rapidez del descenso de las concentraciones de sodio[1]

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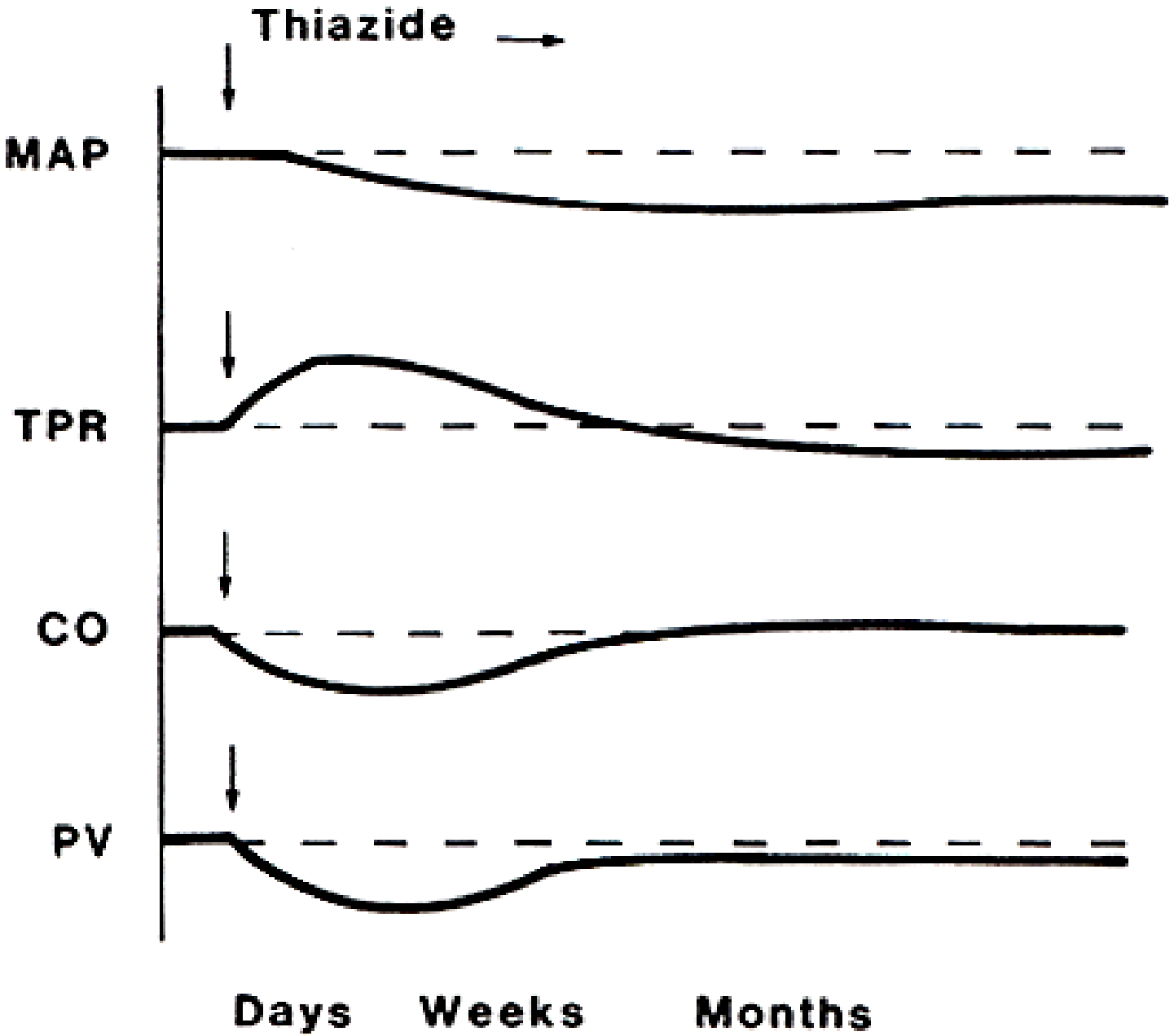
Las causas más frecuentes de hiponatremia severa en adultos son:
-el tratamiento diurético con tiazidas,
-los estados postoperatorios
-secreción inapropiada de hormona antidiurética,
-polidipsia en pacientes psiquiátricos y prostatectomía transuretral

- **El tratamiento diurético está presente en más de la mitad de las hospitalizaciones por hiponatremia crónica grave, y afecta sobre todo a pacientes ancianos.**

Hyponatremia



From Birkenhäger, WH: Diuretics and blood pressure reduction: physiological aspects. J. Hyperten. 1990, 8 (Suppl 2) S3-S7.

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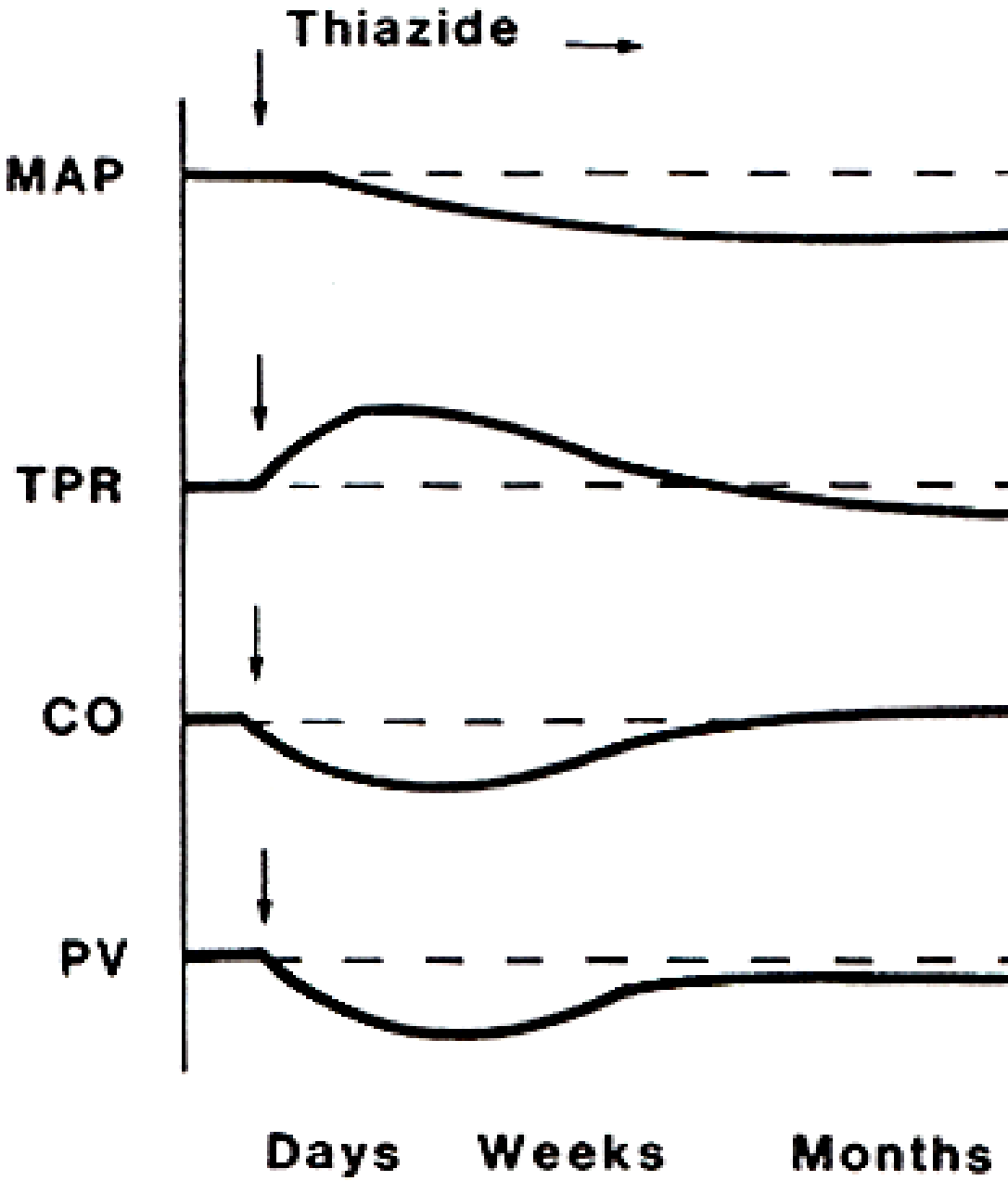

Reducción de la presión arterial media

Aumento y luego reducción de las Resistencias vasculares

Reducción inicial del volumen minuto cardíaco

Reducción y posterior estabilización de la volemia

From Birkenhäger, WH: Diuretics and blood pressure reduction: physiological aspects. J. Hyperten. 1990, 8 (Suppl 2) S3-S7.

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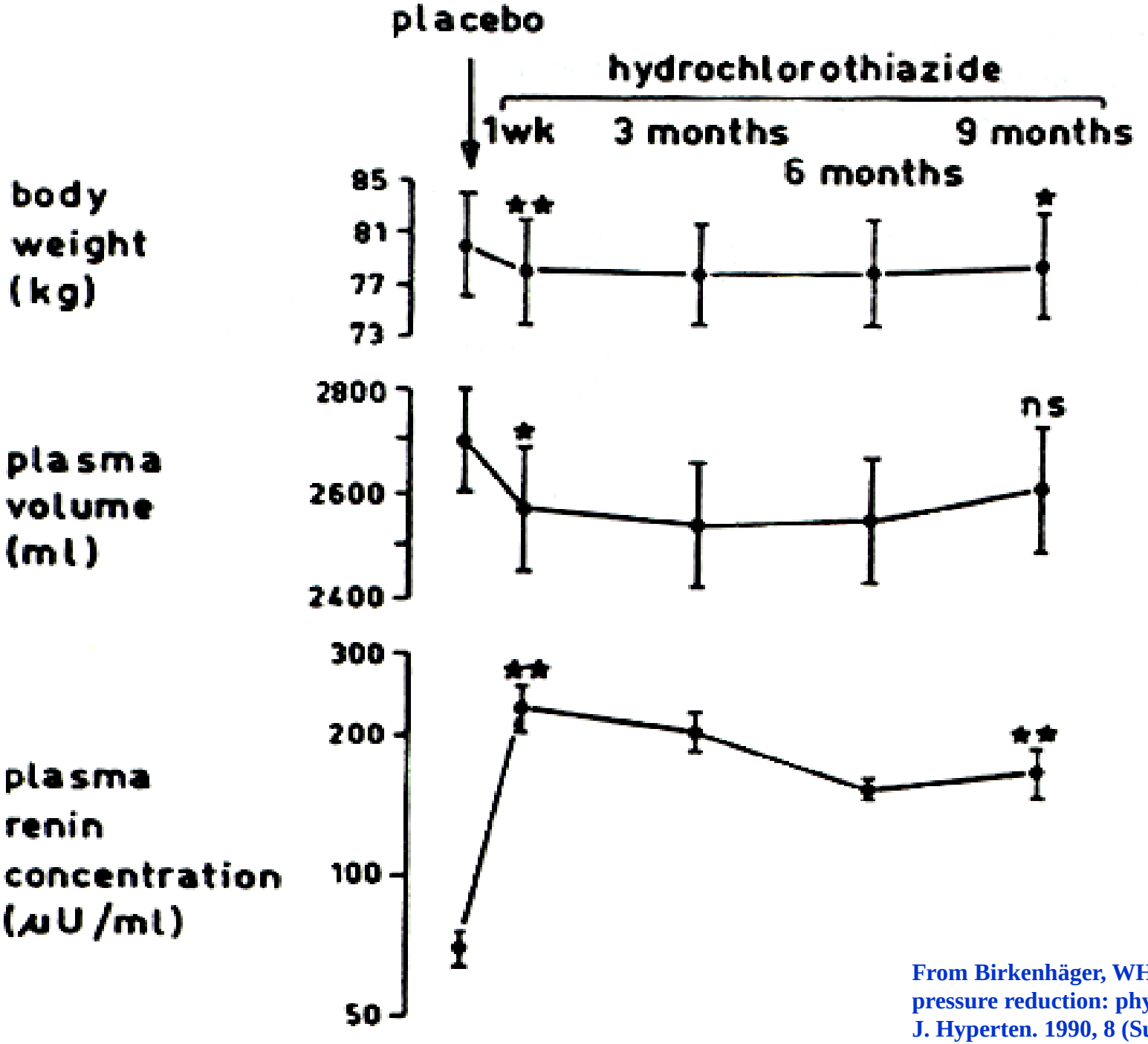

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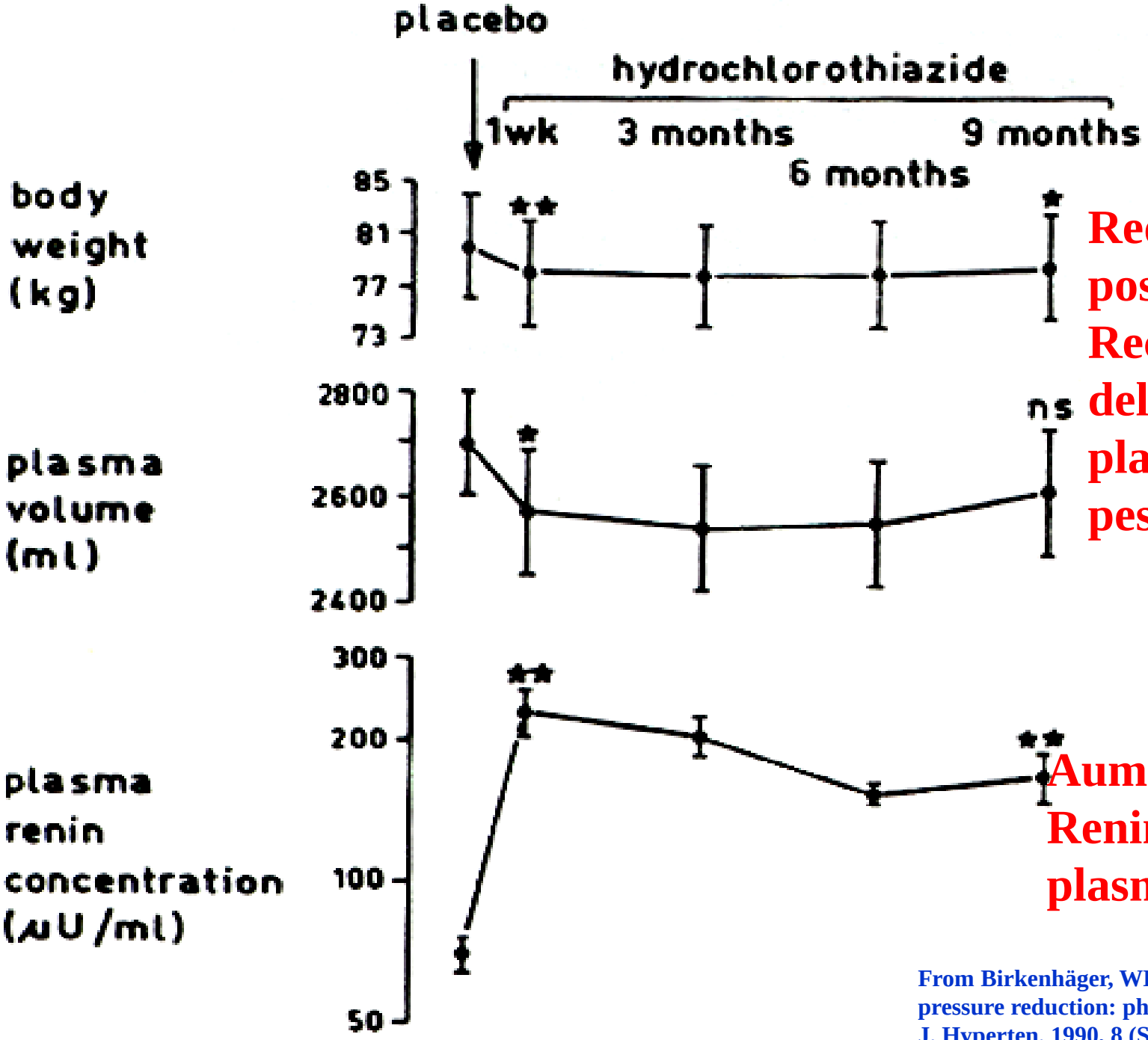

Reducción y posterior Recuperación del volumen plasmático y peso corporal

Aumento de la Renina plasmática

From Birkenhäger, WH: Diuretics and blood pressure reduction: physiological aspects. J. Hyperten. 1990, 8 (Suppl 2) S3-S7.

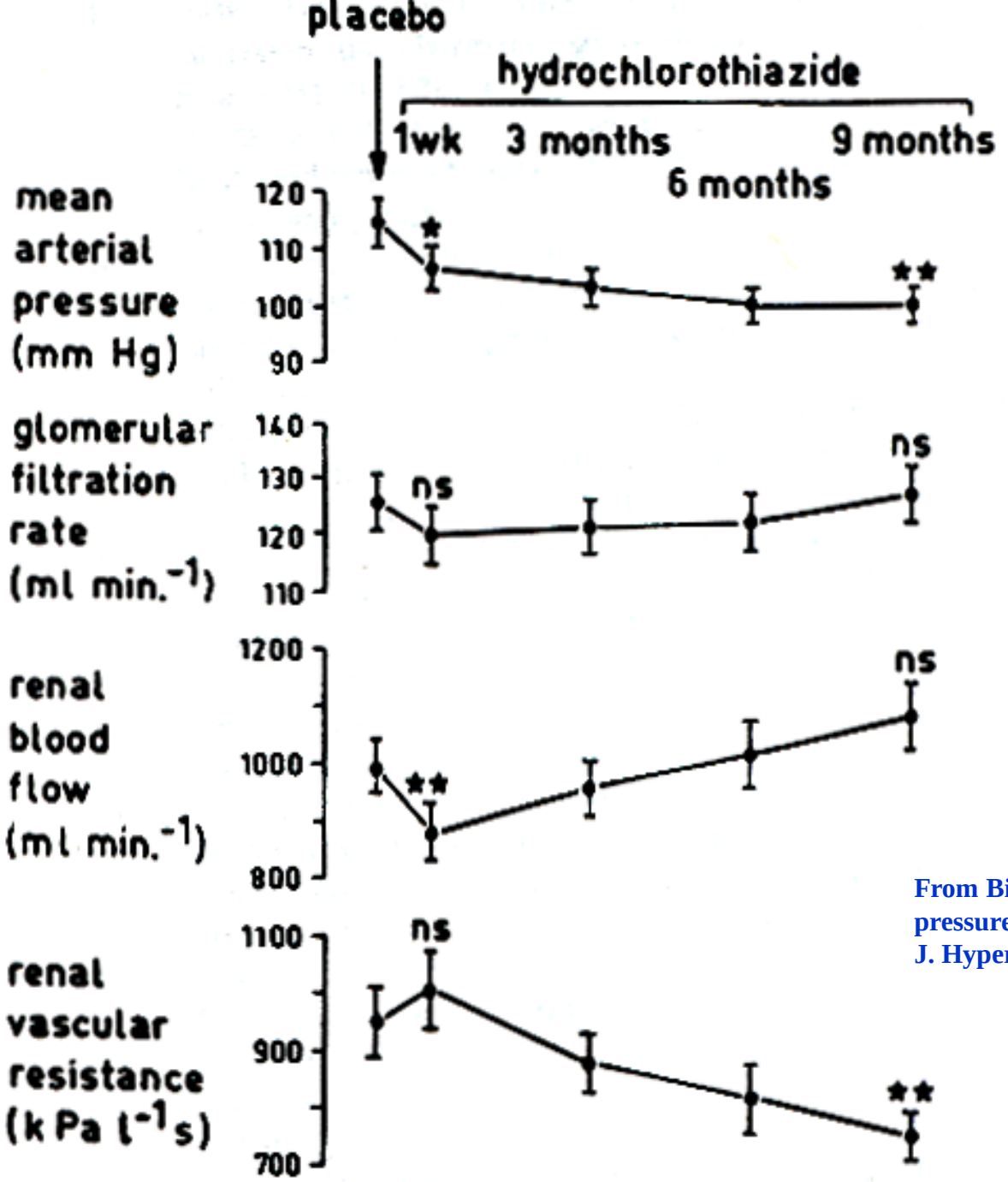

Fig. 3. Biphasic changes in renal hemodynamics during hydro-

From Birkenhäger, WH: Diuretics and blood pressure reduction: physiological aspects. J. Hyperten. 1990, 8 (Suppl 2) S3-S7.

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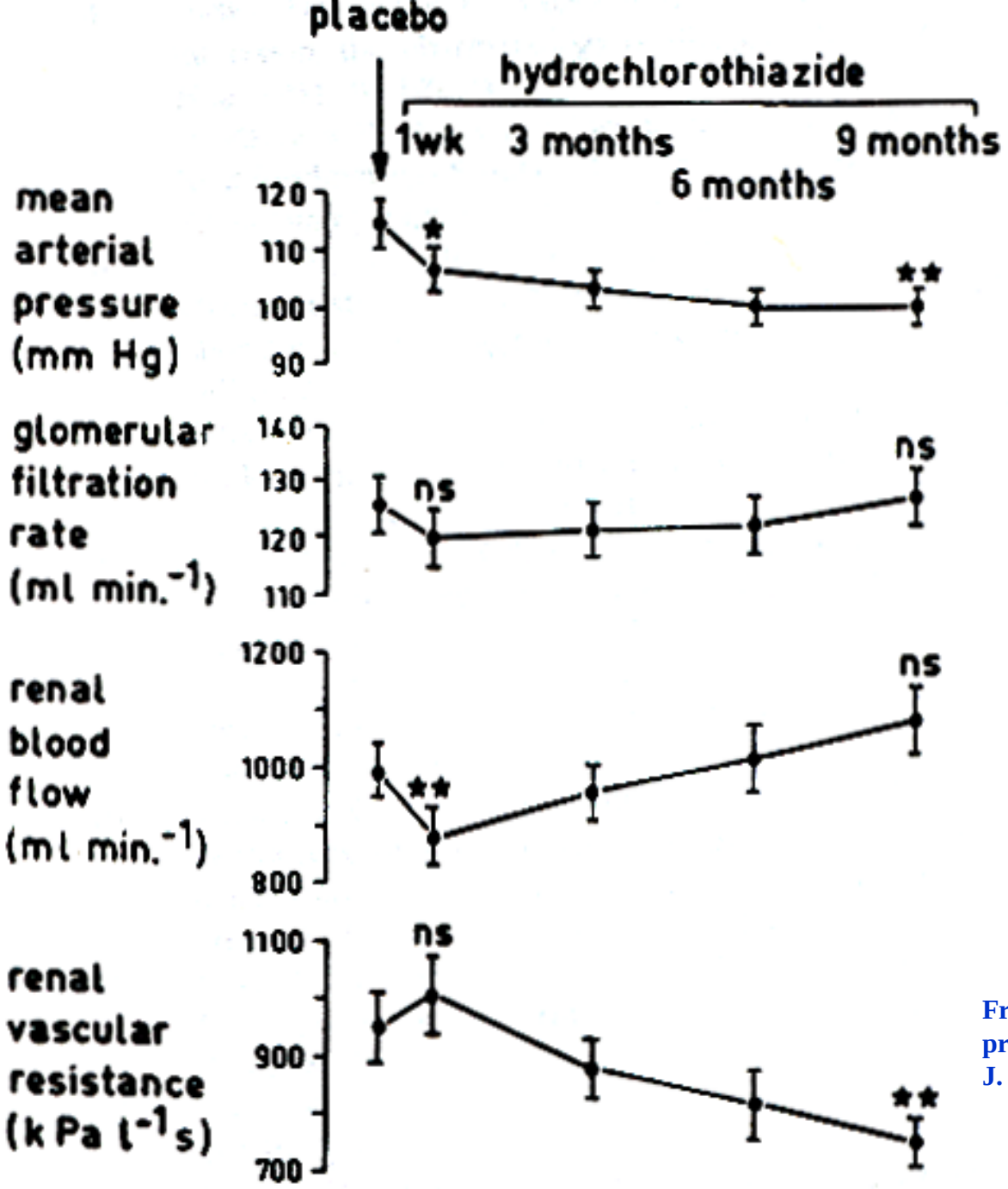

Fig. 3. Biphasic changes in renal hemodynamics during hydro-

A medida que cae la presión arterial las resistencias renales caen aumenta el volumen del flujo renal y el volumen de filtrado glomerular

From Birkenhäger, WH: Diuretics and blood pressure reduction: physiological aspects. J. Hyperten. 1990, 8 (Suppl 2) S3-S7.

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INSUFICIENCIA CARDIACA ESTADIO C

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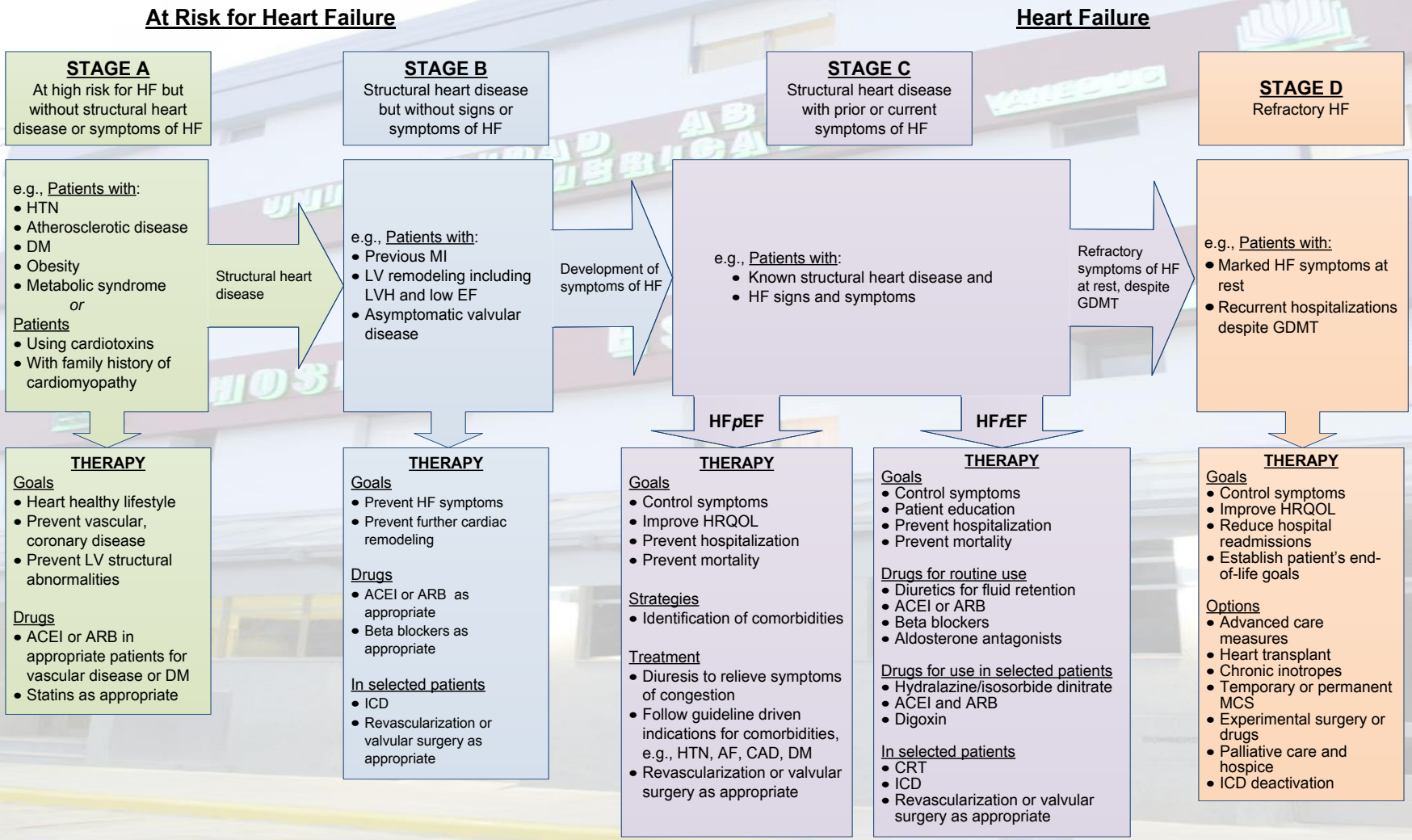
Stages, Phenotypes and Treatment of HF



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NO deben indicarse

diuréticos sin signos de congestión o disnea

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Si comienza
con ingurgitación yugular y edema periférico en clase I/II de disnea a pesar de la restricción de sal en la dieta, se podrá iniciar
el tratamiento diurético con tiazidas; éstas deben
usarse con sumo cuidado, requiriendo monitorización de los niveles de sodio al inicio del
tratamiento en pacientes ancianos, y con antecedente
de hiponatremia.

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De :

*Fracasar las tiazidas

*Estar el paciente en CF III/IV

Diuréticos de asa

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FRACASO DIURETICO EN INSUFICIENCIA CARDÍACA

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Eur Heart J. 2014 May 14;35(19):1284-93.

Diuretic response in acute heart failure: clinical characteristics and prognostic significance

Worse diuretic response was associated with more advanced heart failure, renal impairment, diabetes, atherosclerotic disease and in-hospital worsening heart failure, and predicts mortality and heart failure rehospitalization in this post hoc, hypothesis-generating study.

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5 minutos …

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Fármacos diuréticos y antidiuréticos

Tercera parte

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DEPARTAMENTO DE CARDIOLOGIA

CATEDRA DE FISIOLOGÍA

Universidad Abierta Interamericana

INHIBIDORES DE LA REABSORCIÓN DE SODIO

DIURETICOS OSMOTICOS
- Manitol

DIURETISO INHIBIDORES DE LA ANIDRASA CARBONICA
-Acetazolamida

DIURÉTICOS DEL ASA
- Furosemida
-Bumetanida
-Torasemida

TIAZÍDICOS:
- Bendroflumetiacida
- Hidroclorotiazida
- Clortalidona
- Indapamida

AHORRADORES DE POTASIO
- Espironolactona
- Amilorida
- Triamtereno

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El tubo colector

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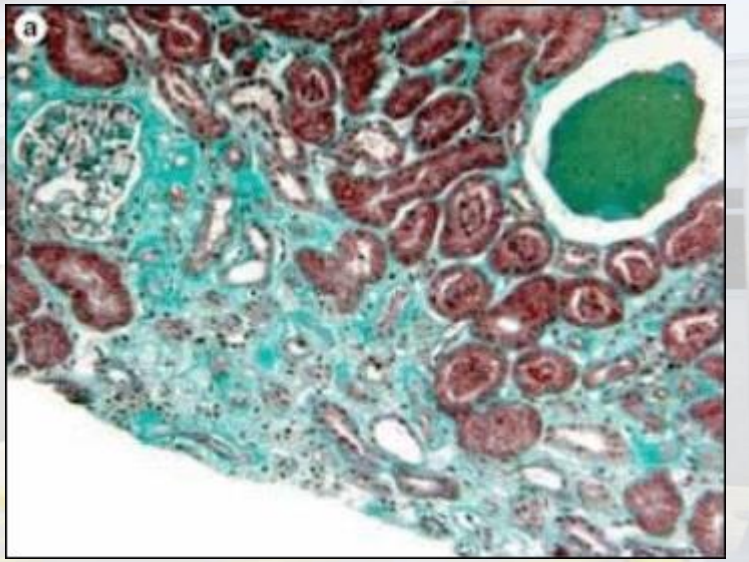
ES UN EFECTOR NEFROENDOCRINO



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PROXIMAL CONVOLUTED TUBULE

Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium-potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
Glucose	100% (symporters and facilitated diffusion)
Amino acids	100% (symporters and facilitated diffusion)
Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
Urea	50% (diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
Creatinine	small amount

At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).

LOOP OF HENLE

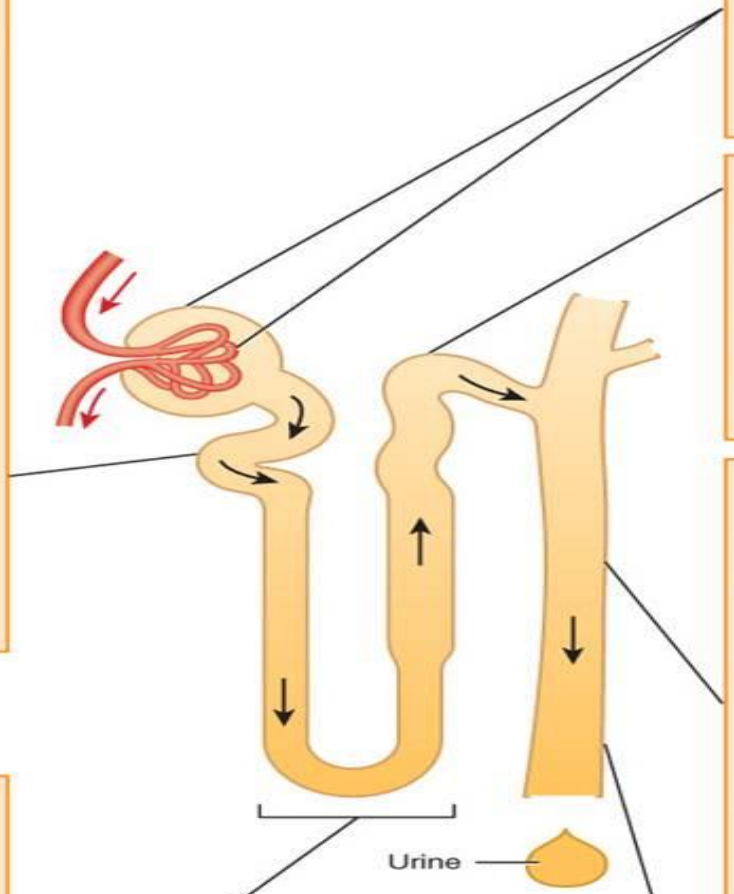
Reabsorption (into blood) of:

Water	15% (osmosis in descending limb)
Na^+	20–30% (symporters in ascending limb)
K^+	20–30% (symporters in ascending limb)
Cl^-	35% (symporters in ascending limb)
HCO_3^-	10–20% (facilitated diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

Urea	variable (recycling from collecting duct)

At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).



RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid

DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

PRINCIPAL CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

Water	5–9% (insertion of water channels stimulated by ADH)
Na^+	1–4% (sodium-potassium pumps)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

K^+	variable amount to adjust for dietary intake (leakage channels)

Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.

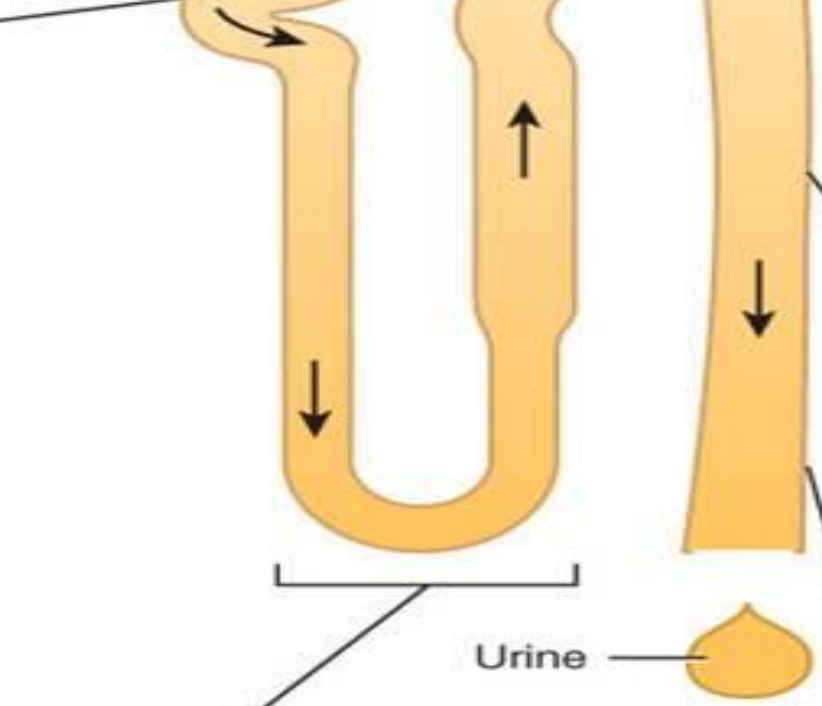
INTERCALATED CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

HCO_3^- (new)	varible amount, depends on H^+ secretion (antiporters)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

H^+	variable amounts to maintain acid-base homeostasis (H^+ pumps)



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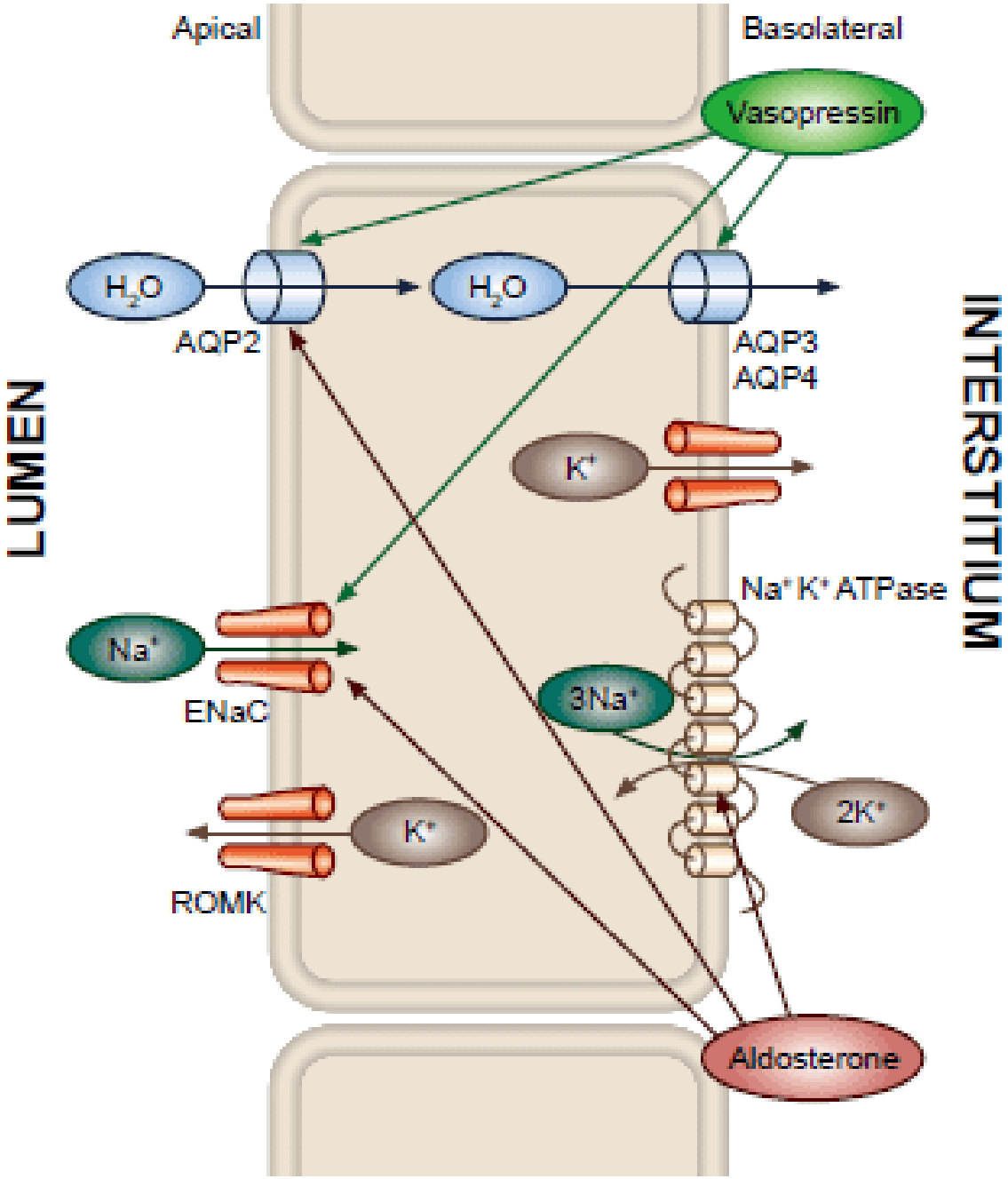
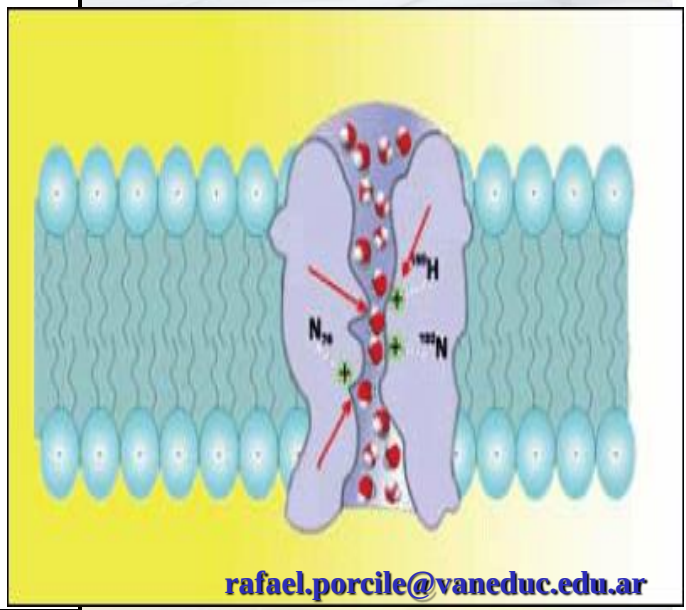


ACUO PORINAS



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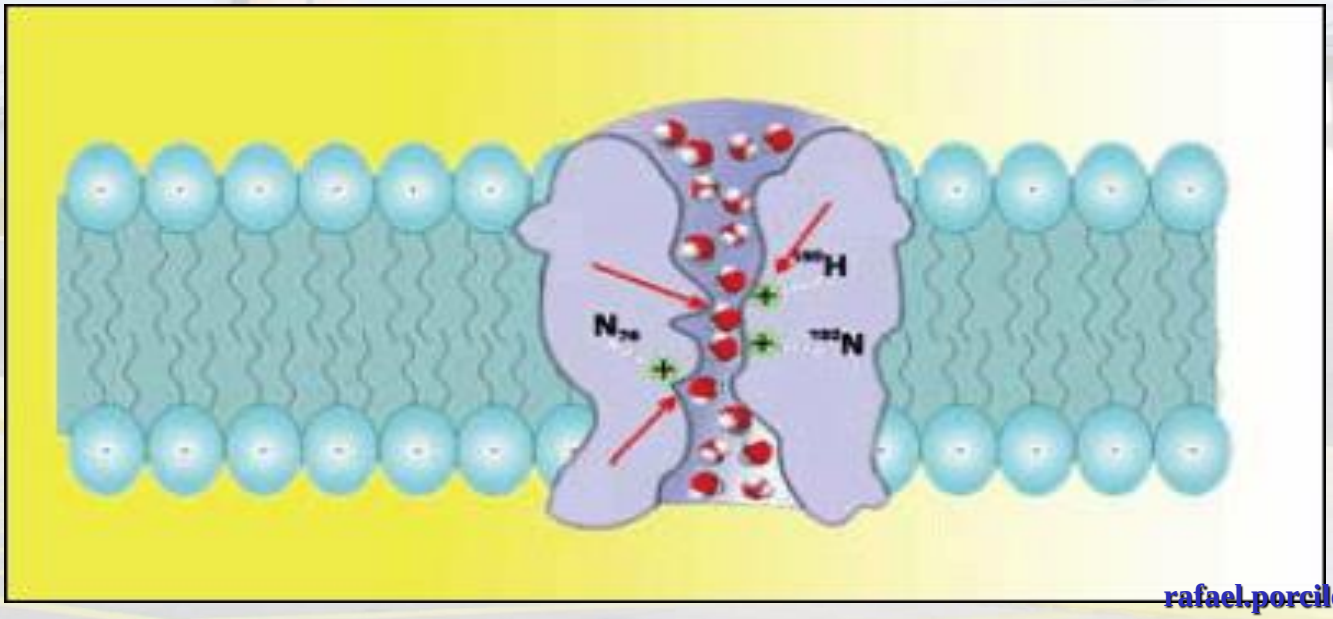
La **acuaporina** es una proteína transmembrana, encargada de transportar el agua a través de los compartimientos celulares. Dejan una estrecha abertura en su interior por la que pueden pasar moléculas de agua.

Estas proteínas transmembrana son especializadas, no permiten que los aniones y la mayoría de los cationes grandes puedan atravesarla. Además hay un par de aminoácidos catiónicos que actúan como "puerta", impidiendo el paso de cationes pequeños como el ion H3O+.



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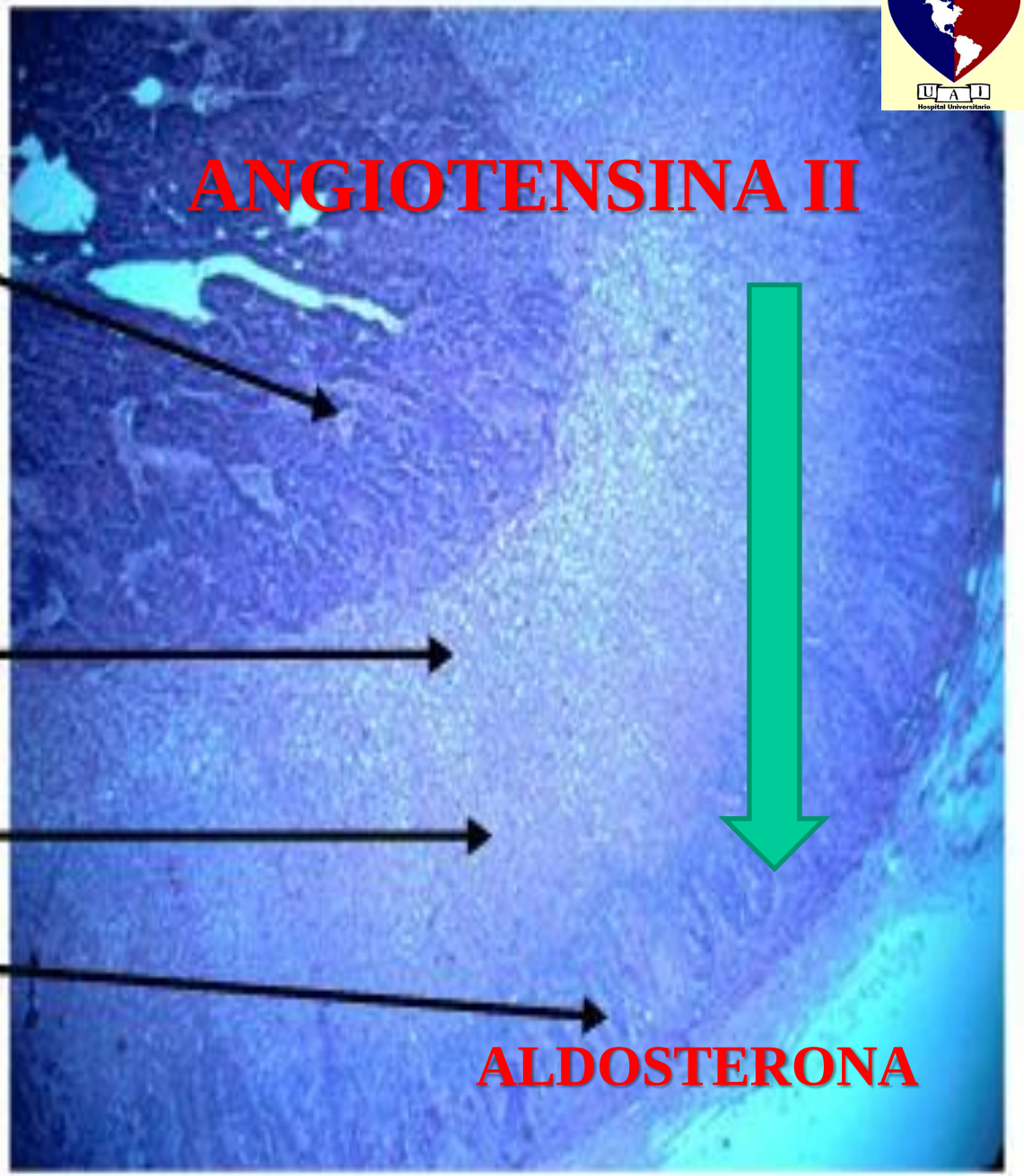
Médula adrenal -
. Noradrenalina
. Adrenalina

Corteza adrenal -
Zona reticular:
. *Esteroides sexuales*
Zona fasciculada:
. *Glucocorticoides*
Zona glomerulosa:
. *Mineralocorticoides*



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ALDOSTERONA

- Retencion Na^+
- Retencion H_2O

→ **Edema**

- Excrecion K^+
- Excrecion Mg^{2+}

→ **Arritmias**

- Deposito de colageno

→ **Fibrosis**

- miocardica
- vascular

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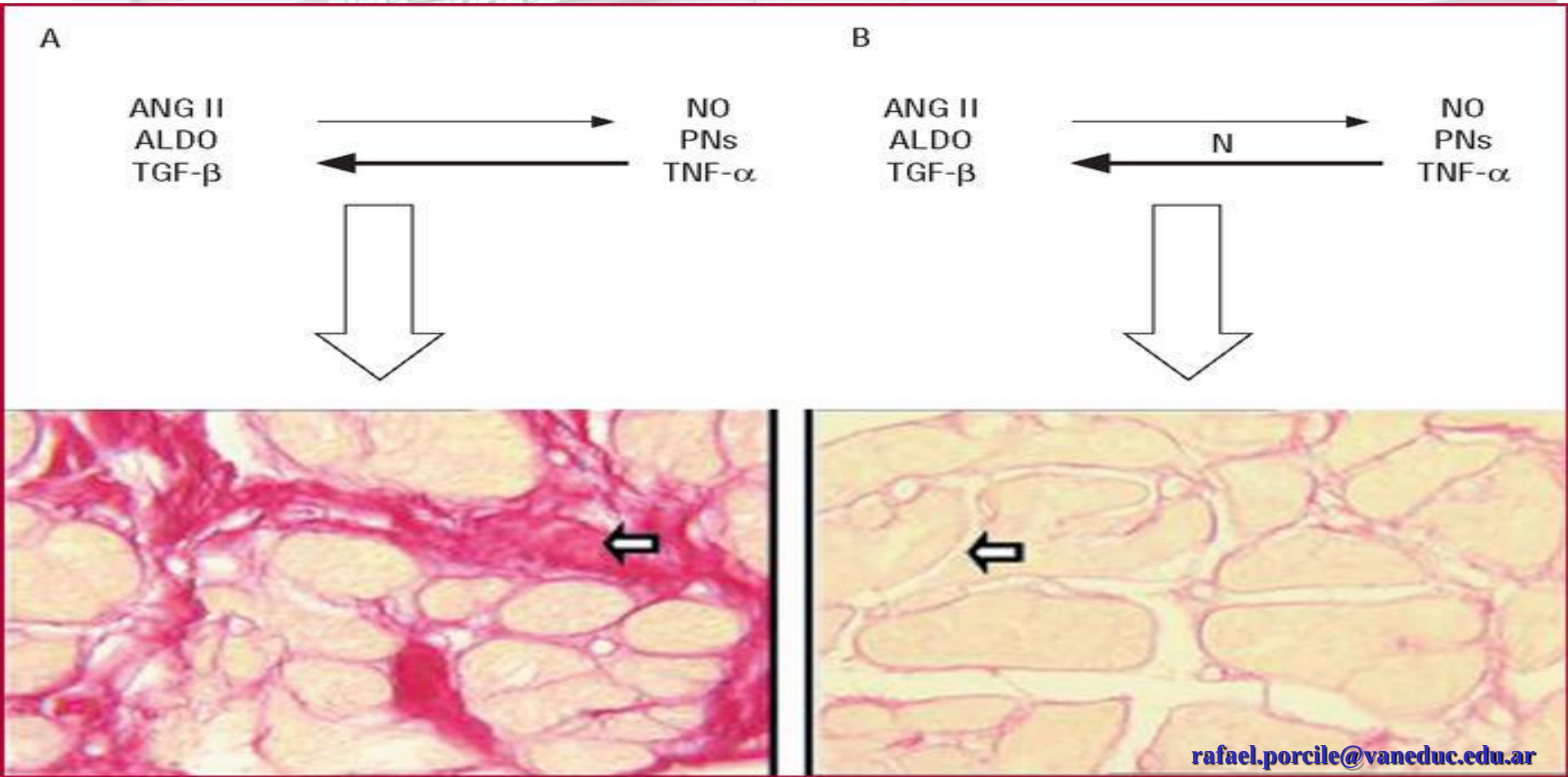
Proliferación colágeno



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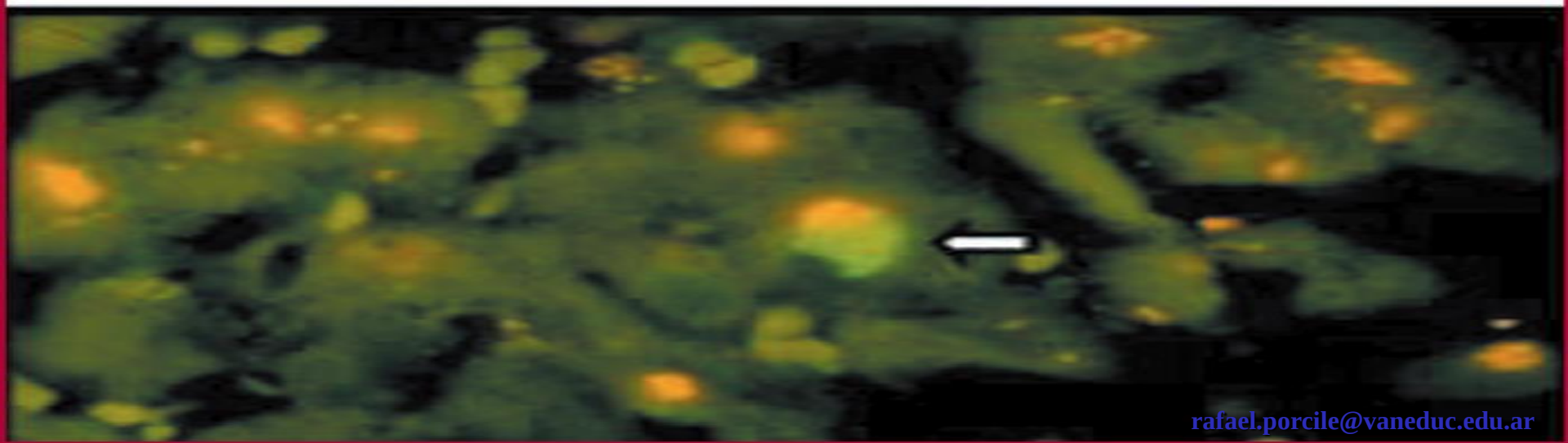
APOPTOSIS

ANG II
NE
$\bullet O_2^-$
IL-1,2,8

CT-I
IGF-1
LIF
NG
IL-6



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FIBROSIS

+apoptosis

+hipertrofia

Remodelación

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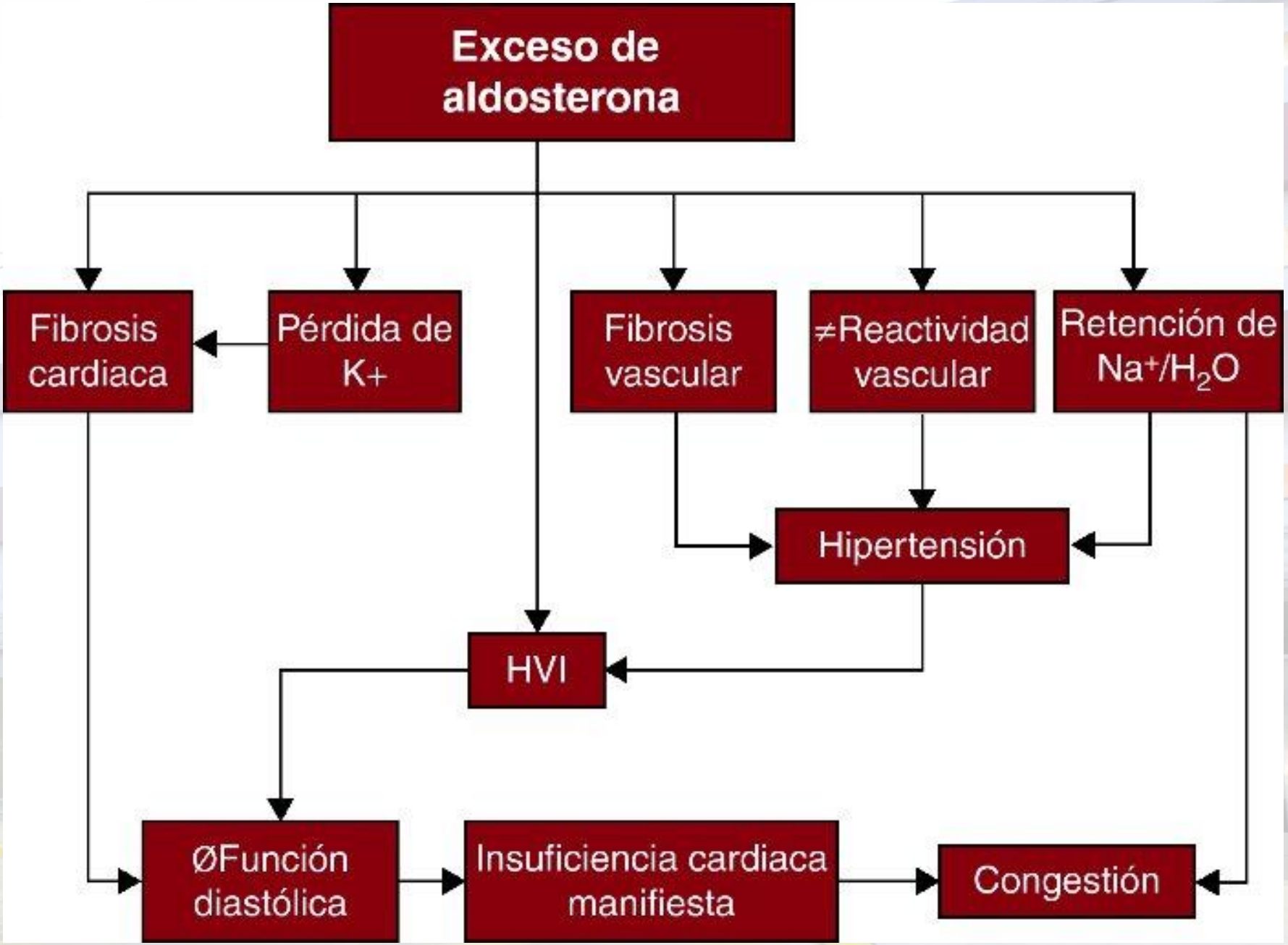

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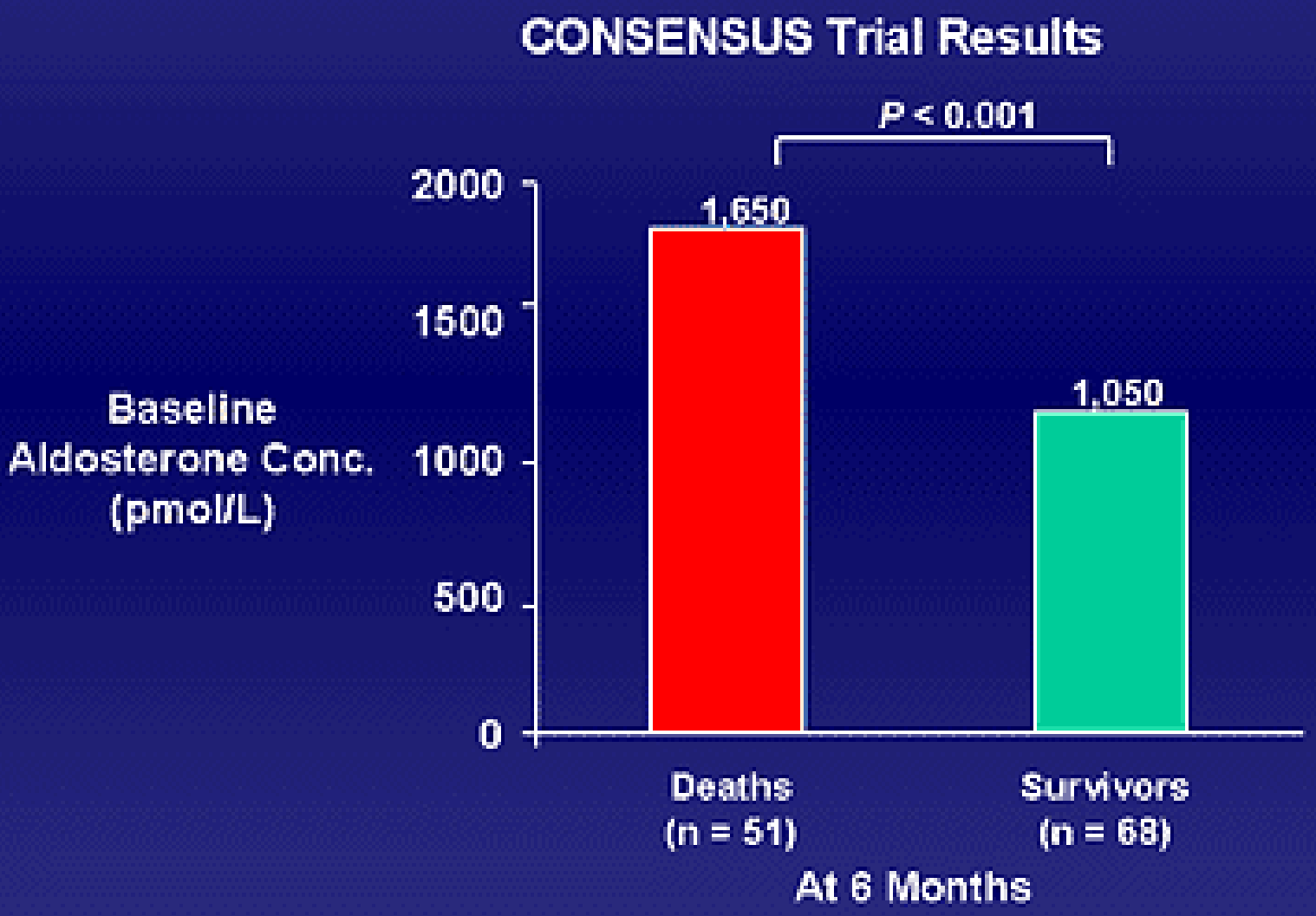
Aldosterone Correlates with Increased Mortality in Heart Failure



Swedberg K et al. *Circulation.* 1990;82(5):1730-6.

Cardiovascular Effects of Aldosterone

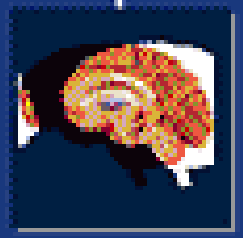
Aldosterone + Na^+

Oxidative Stress

Blood vessels

Endothelial dysfunction
Vascular inflammation
Vascular remodeling
Perivascular fibrosis

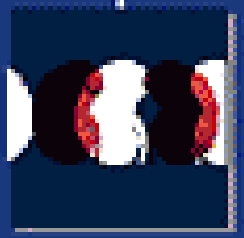
Hypertension
Atherosclerosis
Ischemia
Infarction



Brain

Vascular damage
Baroreceptor dysfunction

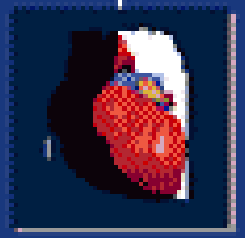
Hypertension
Stroke



Kidneys
(and other epithelial tissues)

Vascular inflammation
Renal fibrosis

Hypertension
Renal failure
Heart failure

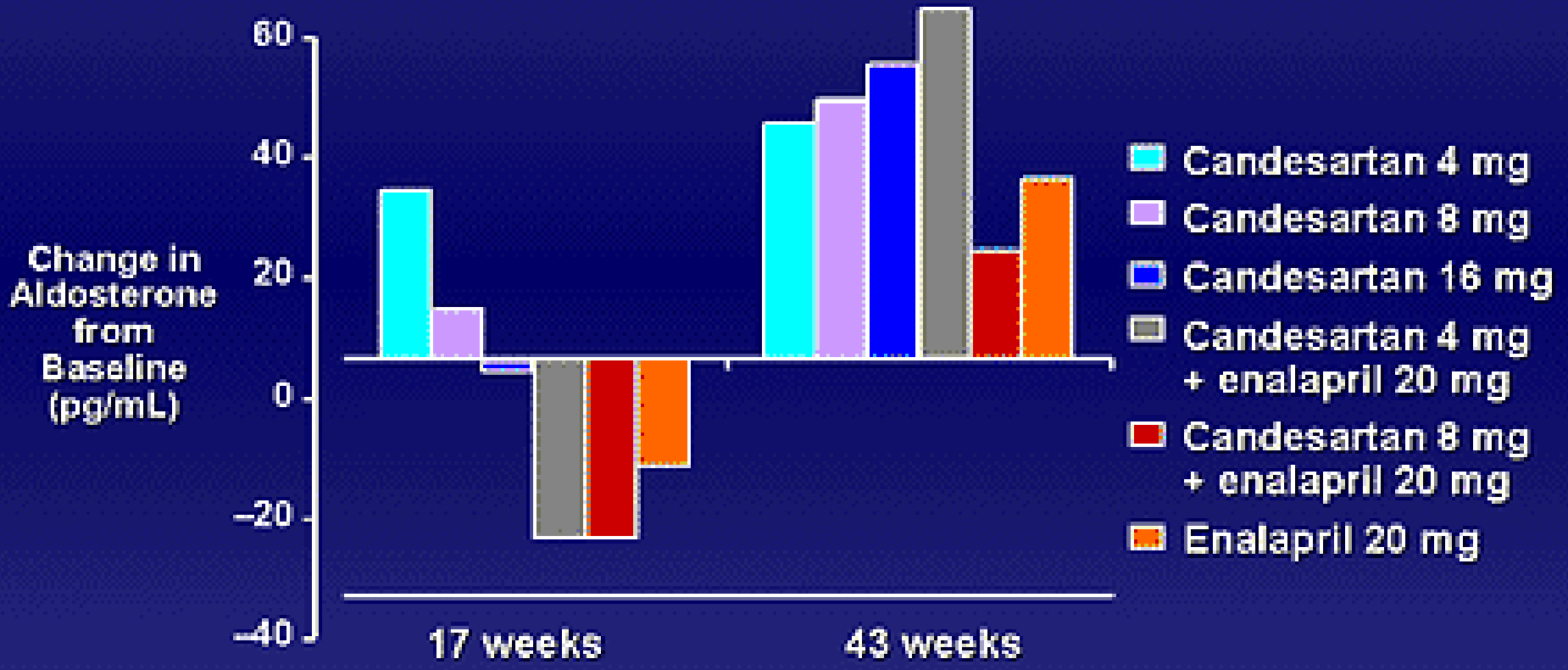


Heart

Ventricular hypertrophy
Myocardial fibrosis
Ventricular remodeling
Sympathomimetic activation

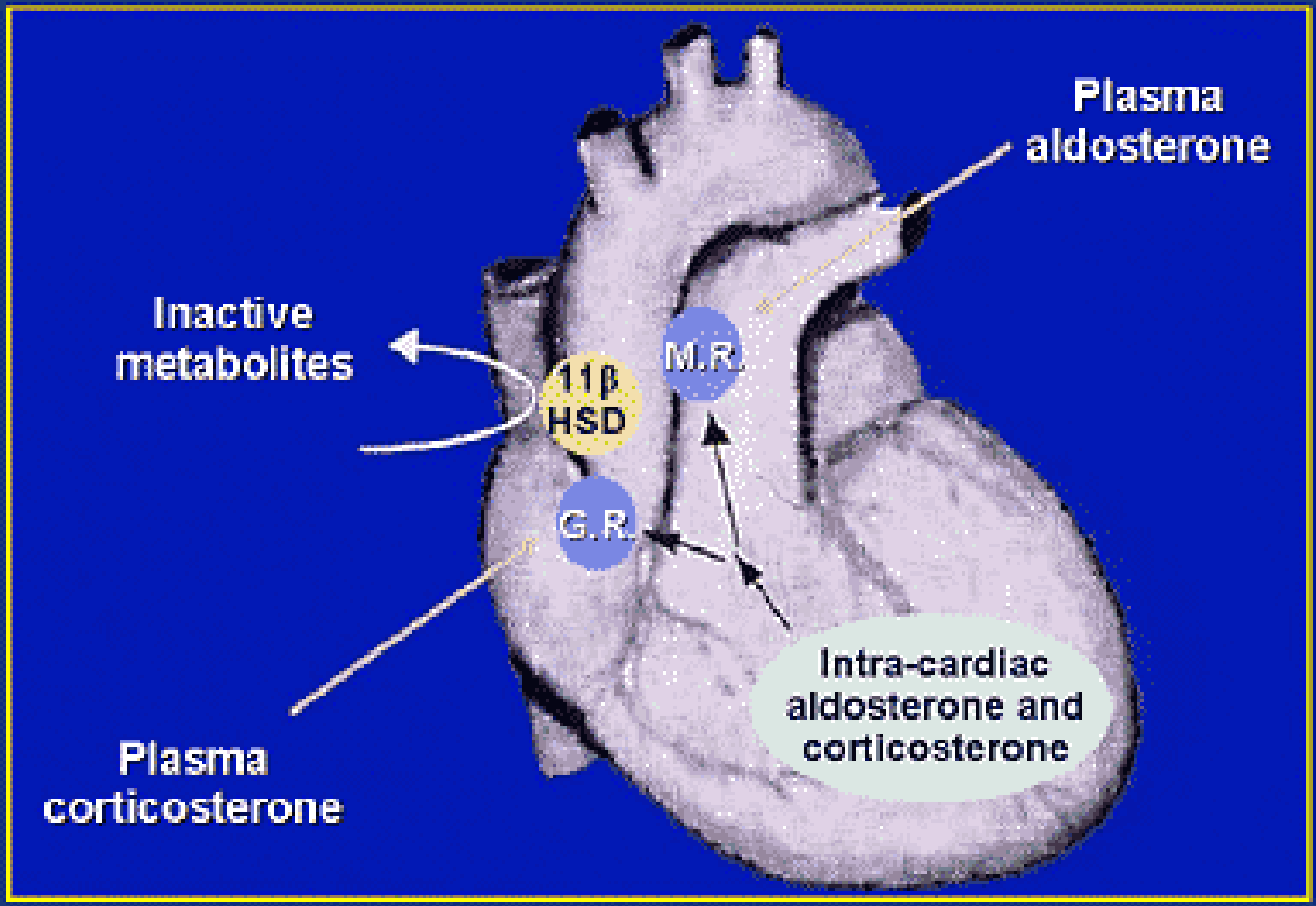
Heart failure
Sudden death, MI

Aldosterone "Escape" Despite Angiotensin II Blockade



RESOLVD Investigators. American College of Cardiology. 1998.

Synthesis of Steroids in the Heart



Delcayre and Silverstre. *Cardiovasc Res.* 1998;43:7-12.

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DIURETICOS AHORRADORES DE POTASIO

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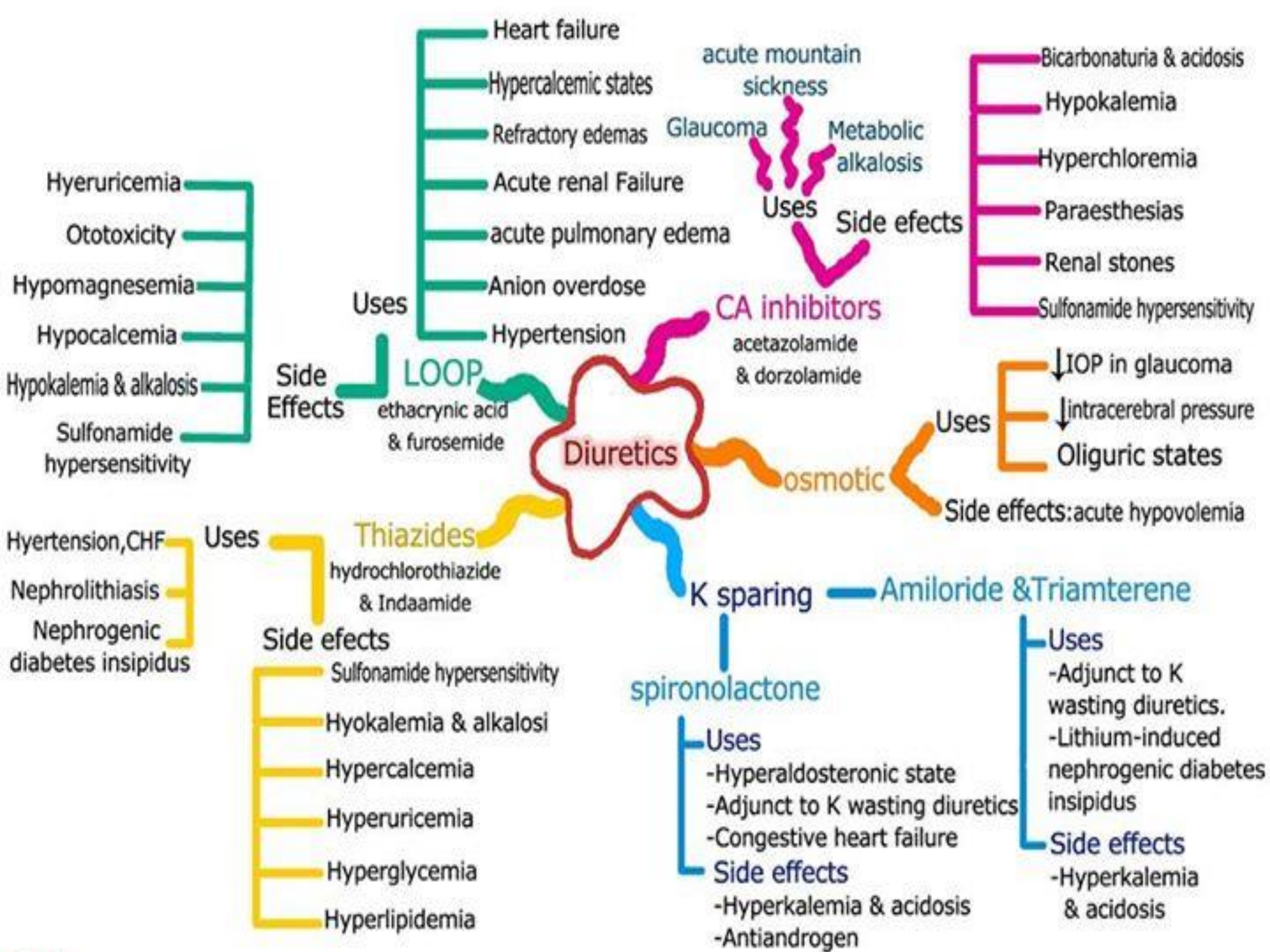
Diuretics
CA inhibitors
acetazolamide & dorzolamide
acute mountain sickness
Glaucoma
Metabolic alkalosis
Uses
Side efects
Bicarbonaturia & acidosis
Hypokalemia
Hyperchloremia
Paraesthesias
Renal stones
Sulfonamide hypersensitivity
LOOP
ethacrynic acid & furosemide
Uses
Heart failure
Hypercalcemic states
Refractory edemas
Acute renal Failure
acute pulmonary edema
Anion overdose
Hypertension
Side Effects
Hyeruricemia
Ototoxicity
Hypomagnesemia
Hypocalcemia
Hypokalemia & alkalosis
Sulfonamide hypersensitivity
osmotic
Uses
↓IOP in glaucoma
↓intracerebral pressure
Oliguric states
Side effects:acute hypovolemia
Thiazides
hydrochlorothiazide & Indaamide
Uses
Hyertension,CHF
Nephrolithiasis
Nephrogenic diabetes insipidus
Side efects
Sulfonamide hypersensitivity
Hyokalemia & alkalosi
Hypercalcemia
Hyperuricemia
Hyperglycemia
Hyperlipidemia
K sparing
Amiloride &Triamterene
Uses
-Adjunct to K wasting diuretics.
-Lithium-induced nephrogenic diabetes insipidus
Side effects
-Hyperkalemia & acidosis
spironolactone
Uses
-Hyperaldosteronic state
-Adjunct to K wasting diuretics
-Congestive heart failure
Side effects
-Hyperkalemia & acidosis
-Antiandrogen

Diuretics

K sparing

Amiloride &Triamterene

Uses
- -Adjunct to K wasting diuretics.
- -Lithium-induced nephrogenic diabetes insipidus

Side effects
- -Hyperkalemia & acidosis

spironolactone

Uses
- -Hyperaldosteronic state
- -Adjunct to K wasting diuretics
- -Congestive heart failure

Side effects
- -Hyperkalemia & acidosis
- -Antiandrogen

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- Muchos de los metabolitos de la espironolactona son farmacológicamente activos, incluyendo el canreonato de potasio (canrenona) que se usa por vía parenteral cuando se necesita un efecto más rápido.
- La vida media de la canrenona es de 85 minutos, pero el de la espironolactona está entre 10 y 35 horas, dependiendo de la dosis.
- La vía de eliminación principal es en la orina, aunque algo se elimina por la vía biliar.

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Los efectos secundarios ginecomastia, irregularidades menstruales y atrofia testicular.

Otros efectos adversos incluyen ataxia, disfunción eréctil, somnolencia y rash en la piel.

Se ha demostrado un efecto carcinógeno en ratas experimentales. La espironolactona tiende a ser inmunosupresor en el tratamiento de la sarcoidosis.

Quienes tomen espironolactona deben evitar consumir sustitutos de la sal de mesa que contengan potasio.

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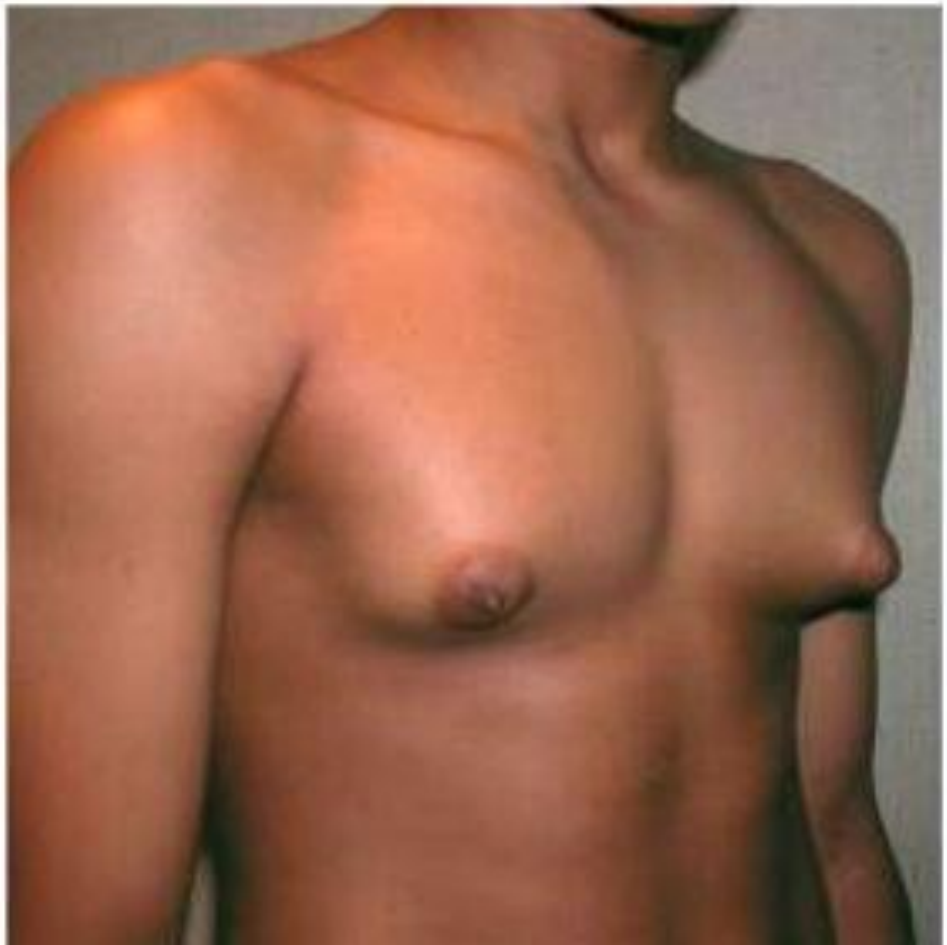
Ginecomastia por inhibición androgénica



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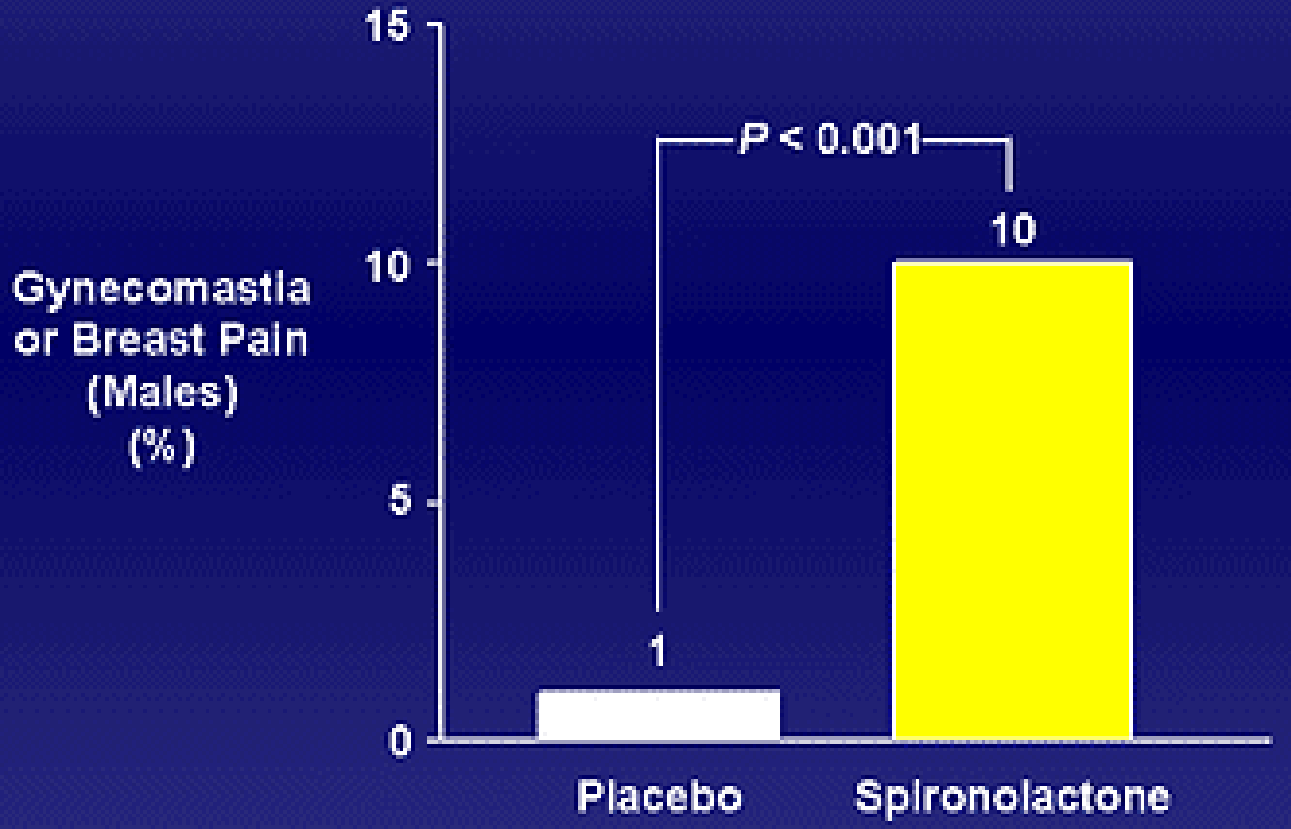
Spironolactone Induces Gynecomastia in Heart Failure Patients



Pitt B et al. *N Engl J Med.* 1999;341:709-17.

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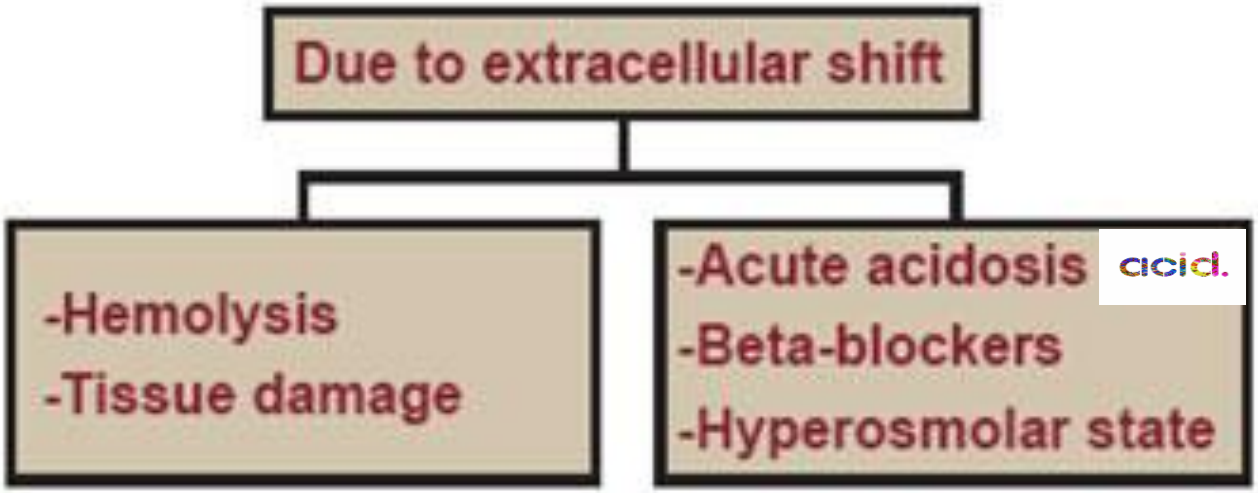
Figure 1.

Hyperkalemia



-Hemolysis and tissue damage will usually only cause hyperkalemia if it is accompanied by renal failure.[2]

-Acidosis can be caused by a decrease in insulin or an overdose of digoxin (decreases ATPase activity). Beta-blockers decrease ATPase activity. Hyperosmolar states, such as diabetes, decrease potassium entering the cell.[2]

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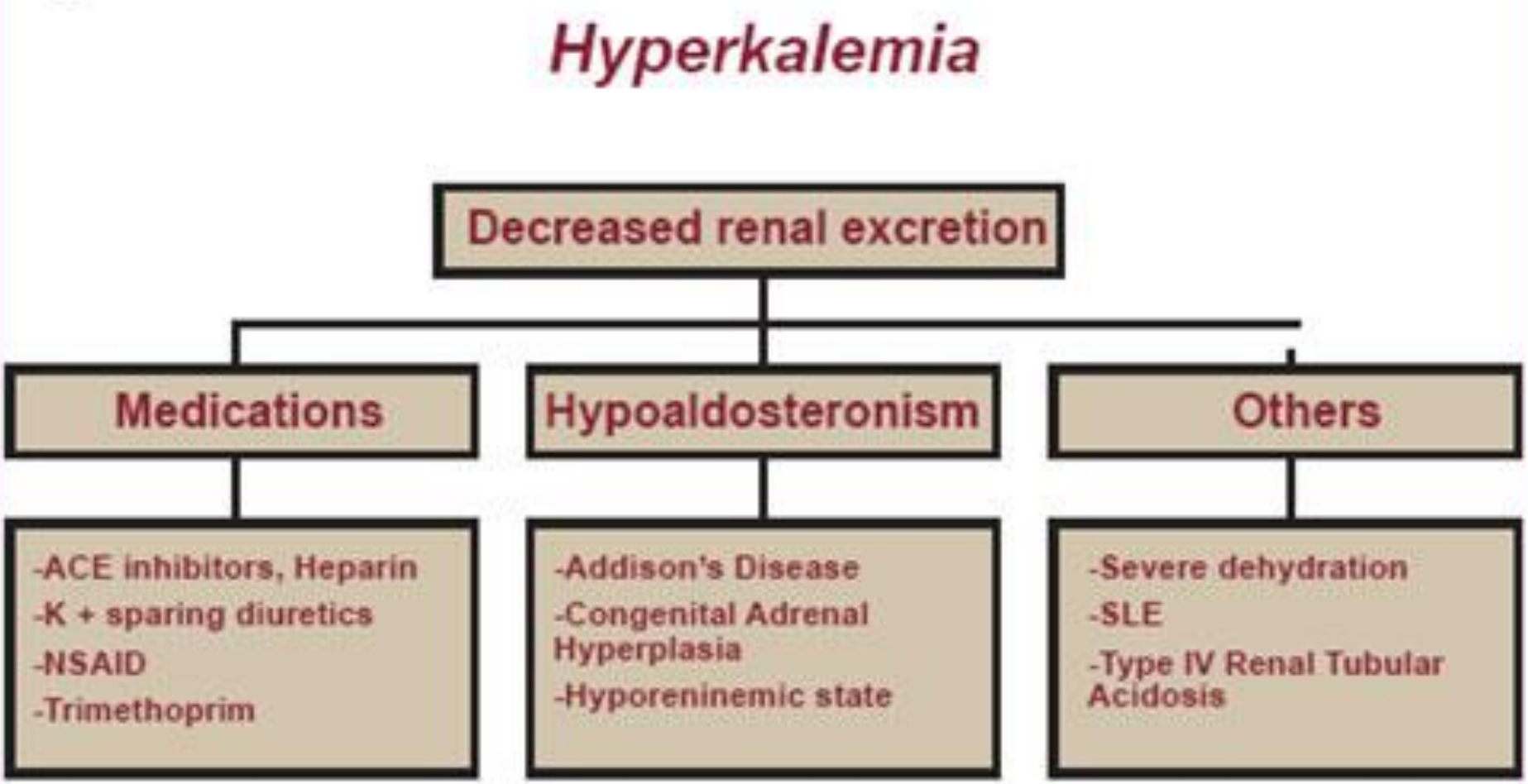
Figure 3.



-ACE inhibitors decrease aldosterone. NSAID's decrease prostaglandin production that leads to decreased arteriolar flow. It also suppresses renin and aldosterone secretion. Trimethoprim reduces the cellular electrical gradient.[2]

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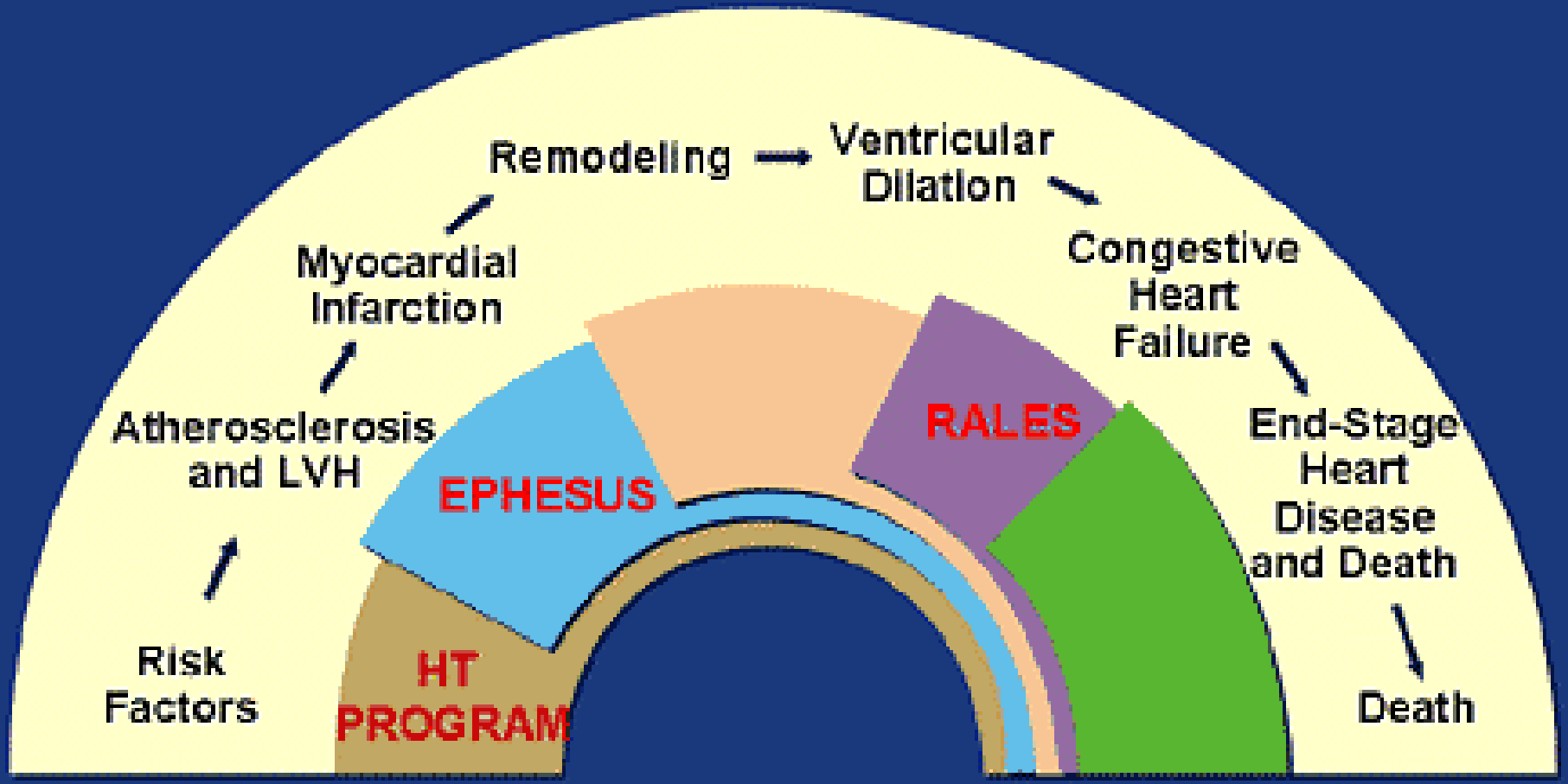
The Action of Aldosterone Antagonists on the Cardiovascular Continuum: "Therapeutic Convergence"



RALES 11% REDUCCIÓN MORTALIDAD

RALES: Randomized Aldactone Evaluation Study
- RESULTS continued -

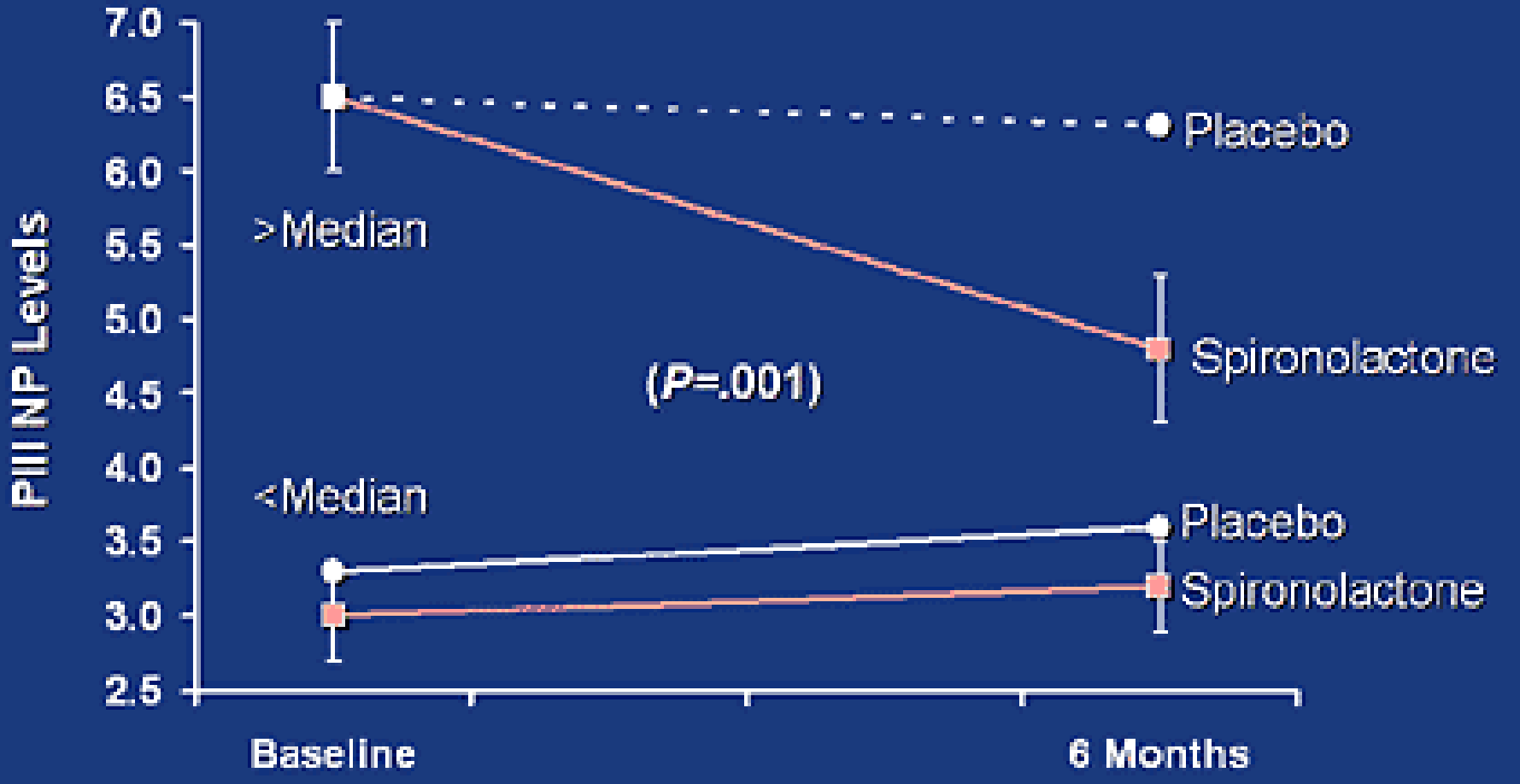
Adverse events

	Placebo n=841 No. (%)	Spironolactone n=822 No. (%)	P
Discontinuation because of adverse event	40 (5)	62 (8)	
Cardiovascular disorders	251 (30)	248 (30)	
Angina	83 (10)	103 (13)	
Heart failure	80 (10)	52 (6)	
Endocrine disorders*			
Gynecomastia in men	8 (1)	55 (9)	<0.001
Breast pain in men	1 (0.1)	10 (2)	0.006

*614 men in placebo group; 603 in spironolactone group.

Pitt et al. *N Eng J Med* 1999; **341**: 709–17.

RALES: Changes in PIII NP Levels According to Baseline



Zannad et al. *Circulation*. 2001;103:476.

Espironolactone - Recomendaciones

- Usar en todos los pacientes con Clase III-IV
- Baja Dosis (subterapeutica) 25 mg QD
- Chequear K y Cr en 1 y 2 semanas
- 12.5 mg si ginecomastia o hiperkalemia leve (12.5 QOD)
- Eplerenone solo alternativo

Eplerenone: A Selective Aldosterone Blocker

- Novel mechanism of action different from commonly used antihypertensive agents
- Mineralocorticoid antagonist with 9,11-epoxide substitution
- Minimal affinity for androgen and progesterone receptors
- Substantial target end-organ protection in the kidney, heart, vasculature, and brain in preclinical models of CV disease

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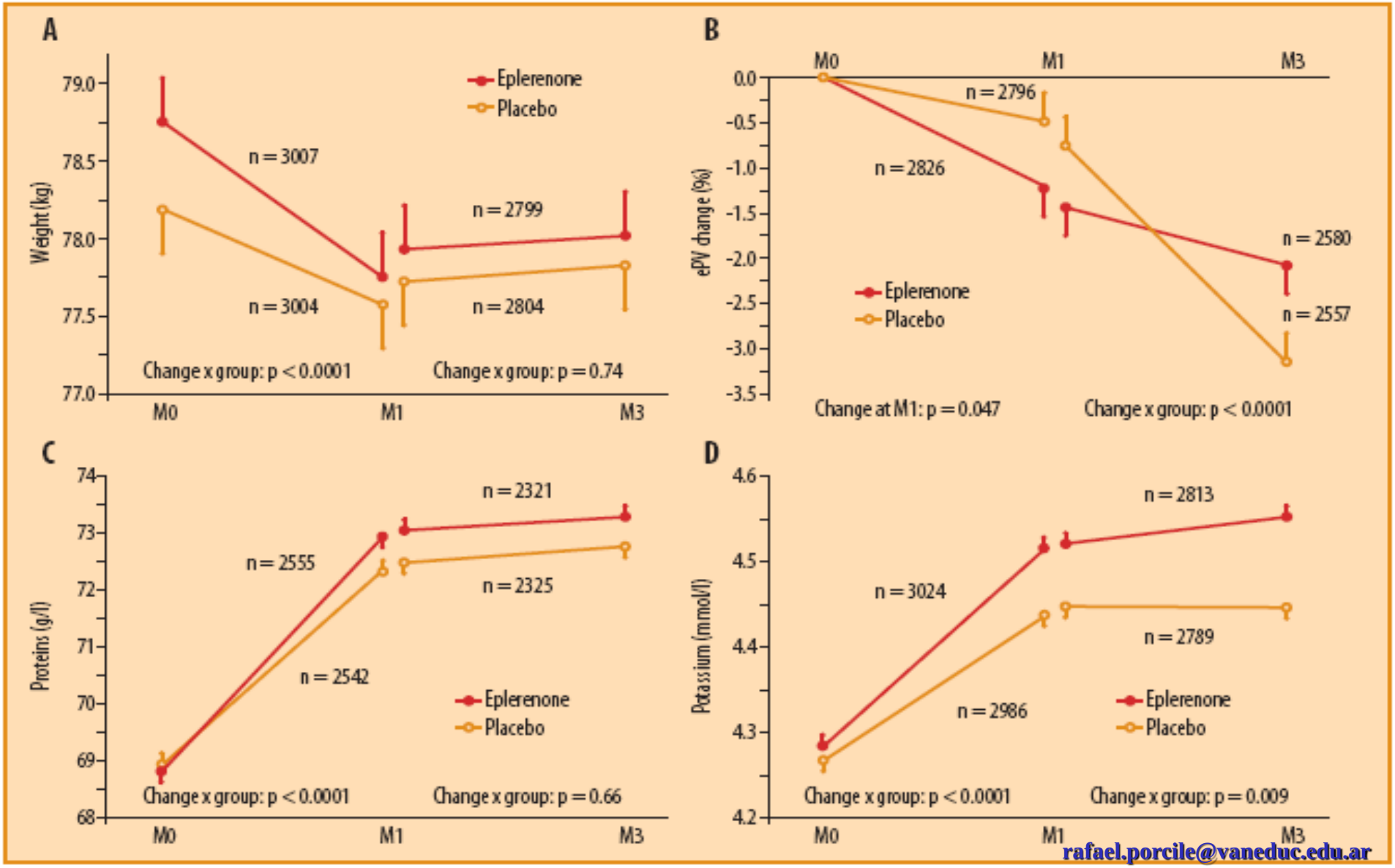
Eplerenona proporciona protección cardiovascular más allá de su efecto diurético y ahorrador de potasio



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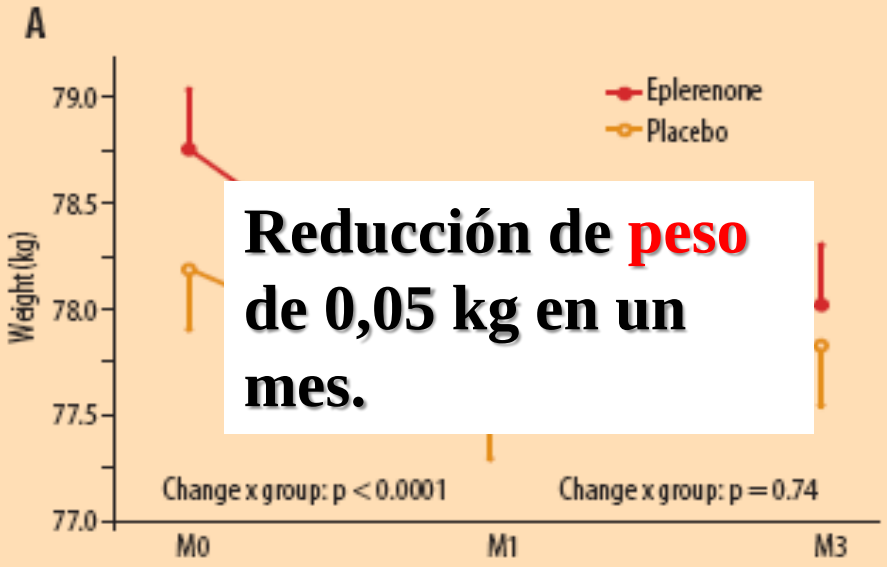
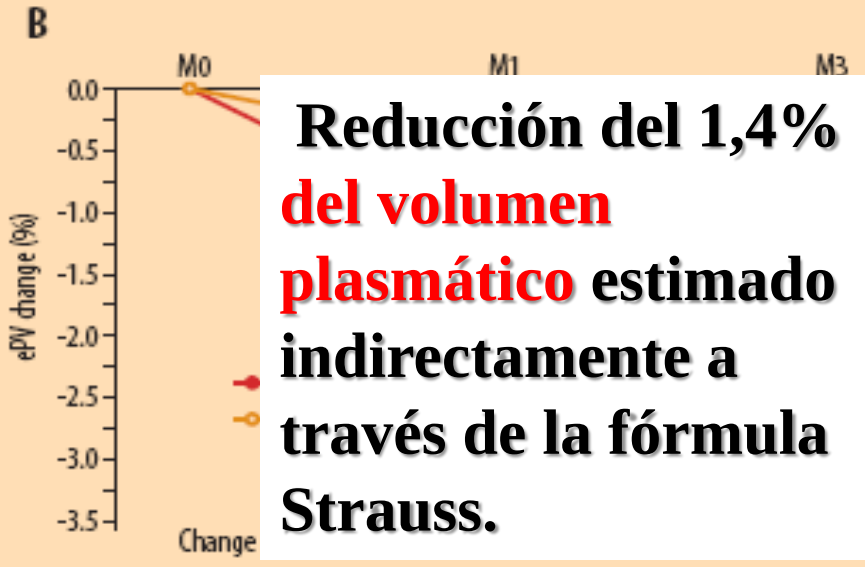
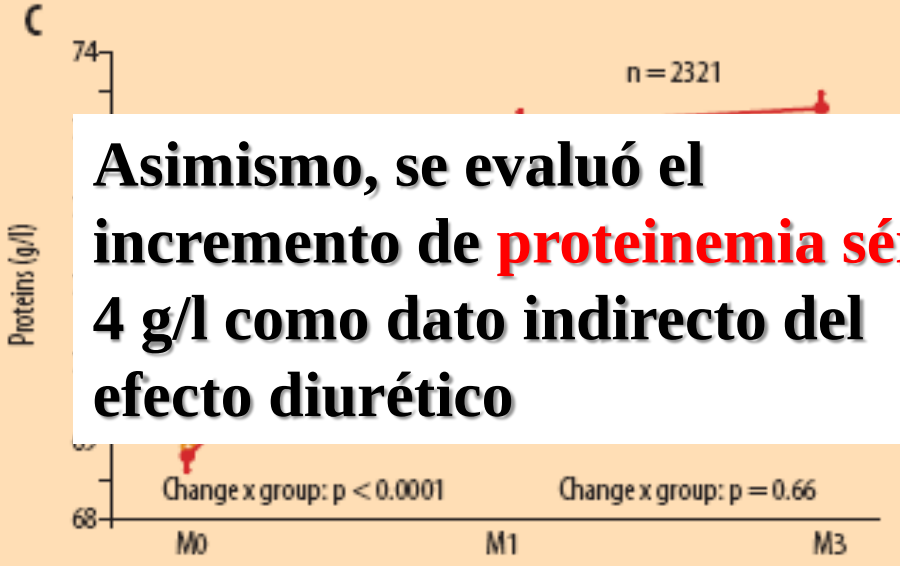
Eplerenona proporciona protección cardiovascular más allá de su efecto diurético y ahorrador de potasio



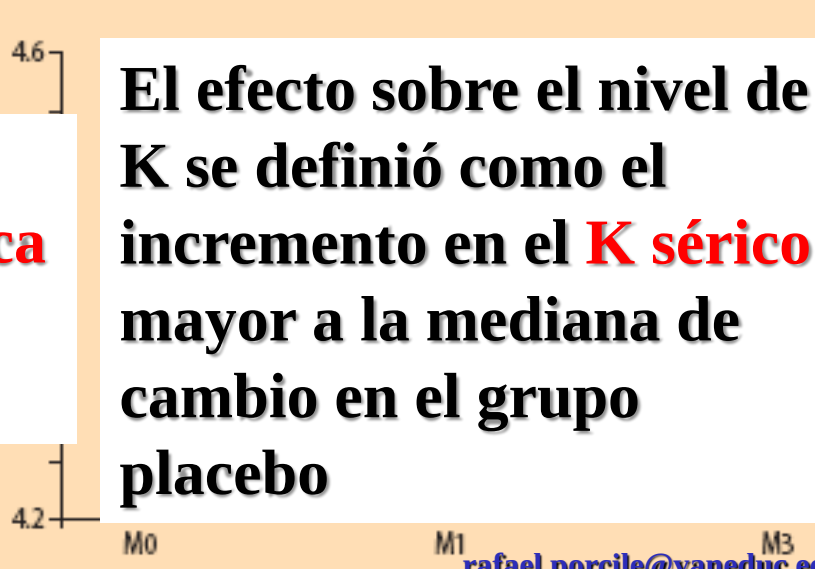
Reducción de peso de 0,05 kg en un mes.



Reducción del 1,4% del volumen plasmático estimado indirectamente a través de la fórmula Strauss.



Asimismo, se evaluó el incremento de proteinemia sérica 4 g/l como dato indirecto del efecto diurético



El efecto sobre el nivel de K se definió como el incremento en el K sérico mayor a la mediana de cambio en el grupo placebo

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La mortalidad global en el grupo asignado a eplerenona se redujo un 15% (p = 0,008)

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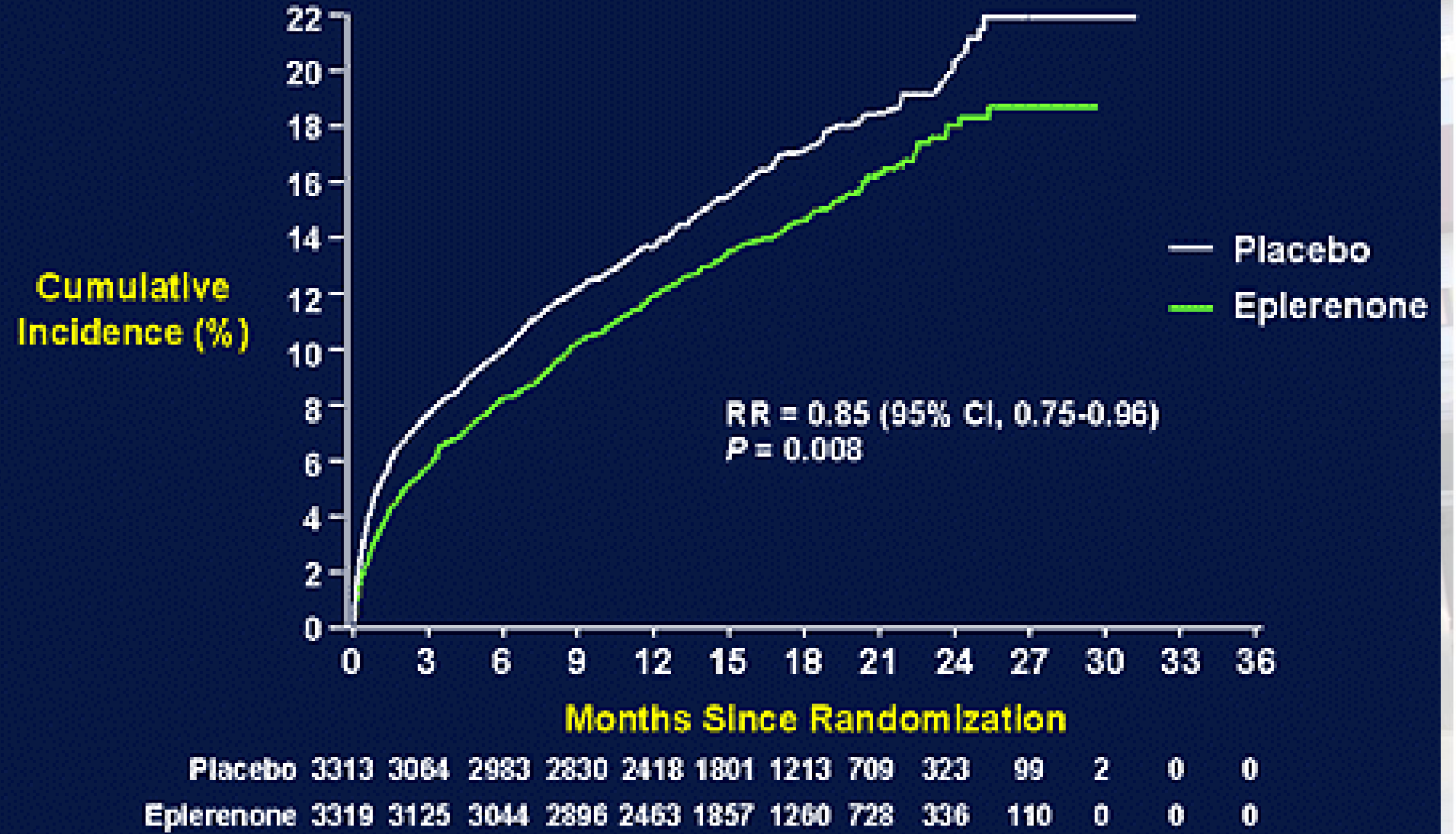
EPHESUS

Relative Risk of Total Mortality



EPHESUS Summary

Eplerenone at a mean dose of 43 mg once daily reduced:

- Total mortality 15% ($P = 0.008$)
- CV mortality/CV hospitalization 13% ($P = 0.002$)
- CV mortality 17% ($P = 0.005$)
- Sudden cardiac death 21% ($P = 0.03$)
- Total mortality/total hospitalization 8% ($P = 0.02$)
- Patients hospitalized for HF 15% ($P = 0.03$), episodes of hospitalization for HF 23% ($P = 0.02$)
- These effects were relatively consistent across pre-defined sub-groups

¿Espleronone o espironalactona parecidas o diferentes ?

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Differential Actions of Eplerenone and Spironolactone on the Protective Effect of Testosterone Against Cardiomyocyte Apoptosis

This study showed that treatment with testosterone protects the H9c2 embryonic cardiac cell line from the apoptosis induced by hyperosmotic stress, by non-genomic means independent of the androgen receptor in which at least SAPK/JNK and ERK1/2 are involved. **Furthermore, this beneficial effect of testosterone is blocked by spironolactone but not by eplerenone, which suggests a differential action of the two drugs and a possible additional benefit of eplerenone compared with spironolactone**

Rev Esp Cardiol. 2010;63:779-87 - Vol. 63

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2013 ACCF/AHA Guideline for the Management of Heart Failure

Developed in Collaboration With the American Academy of Family Physicians, American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

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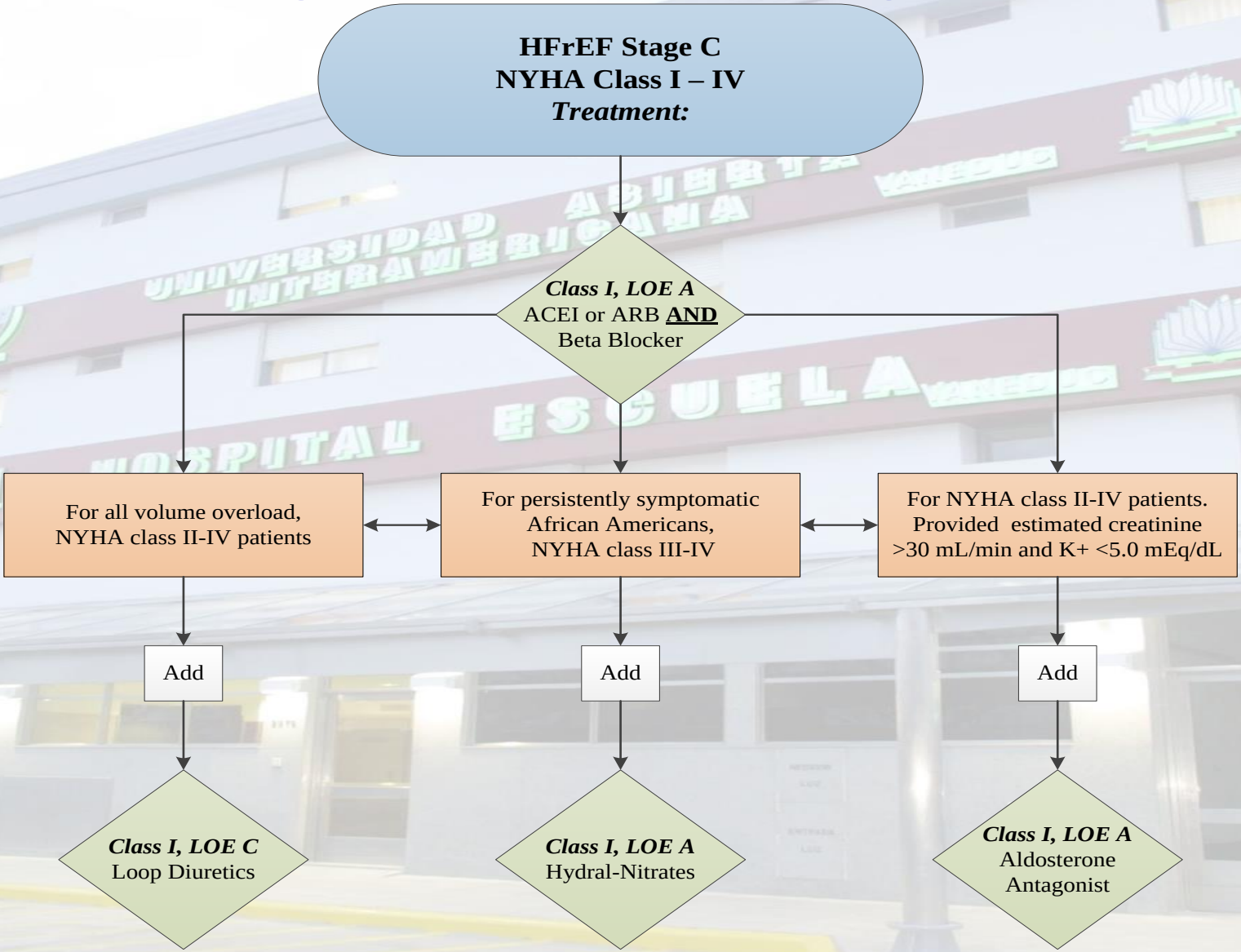
Pharmacologic Treatment for Stage C HF*r*EF



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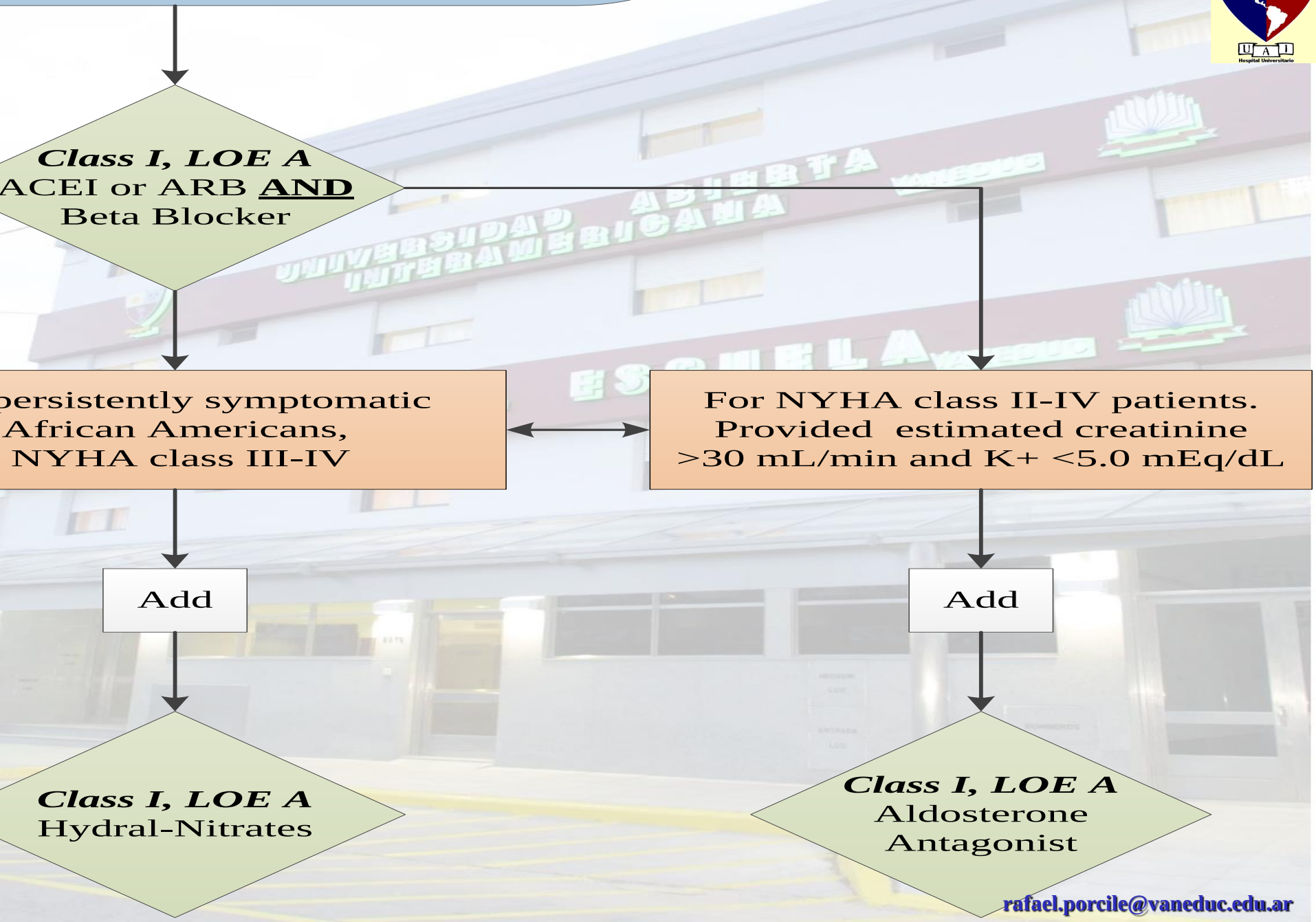
Treatment:



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Pharmacological Treatment for Stage C HF*r*EF (cont.)

Aldosterone receptor antagonists [or mineralocorticoid receptor antagonists (MRA)] are recommended in patients with **NYHA class II-IV and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality.** Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists**. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73m2) and potassium should be less than 5.0 mEq/L**. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency.

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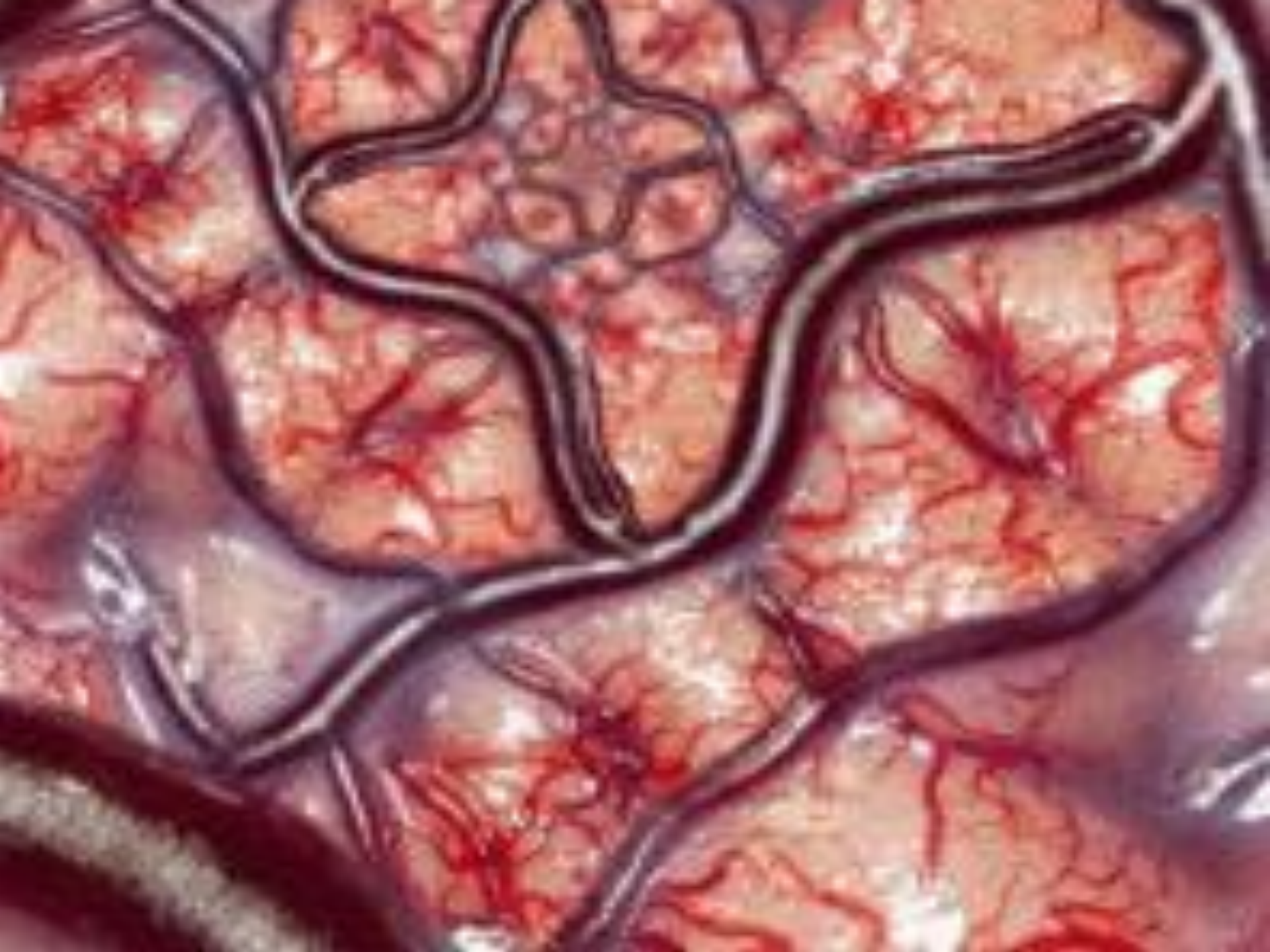

HORMONA ANTIDIURETICA

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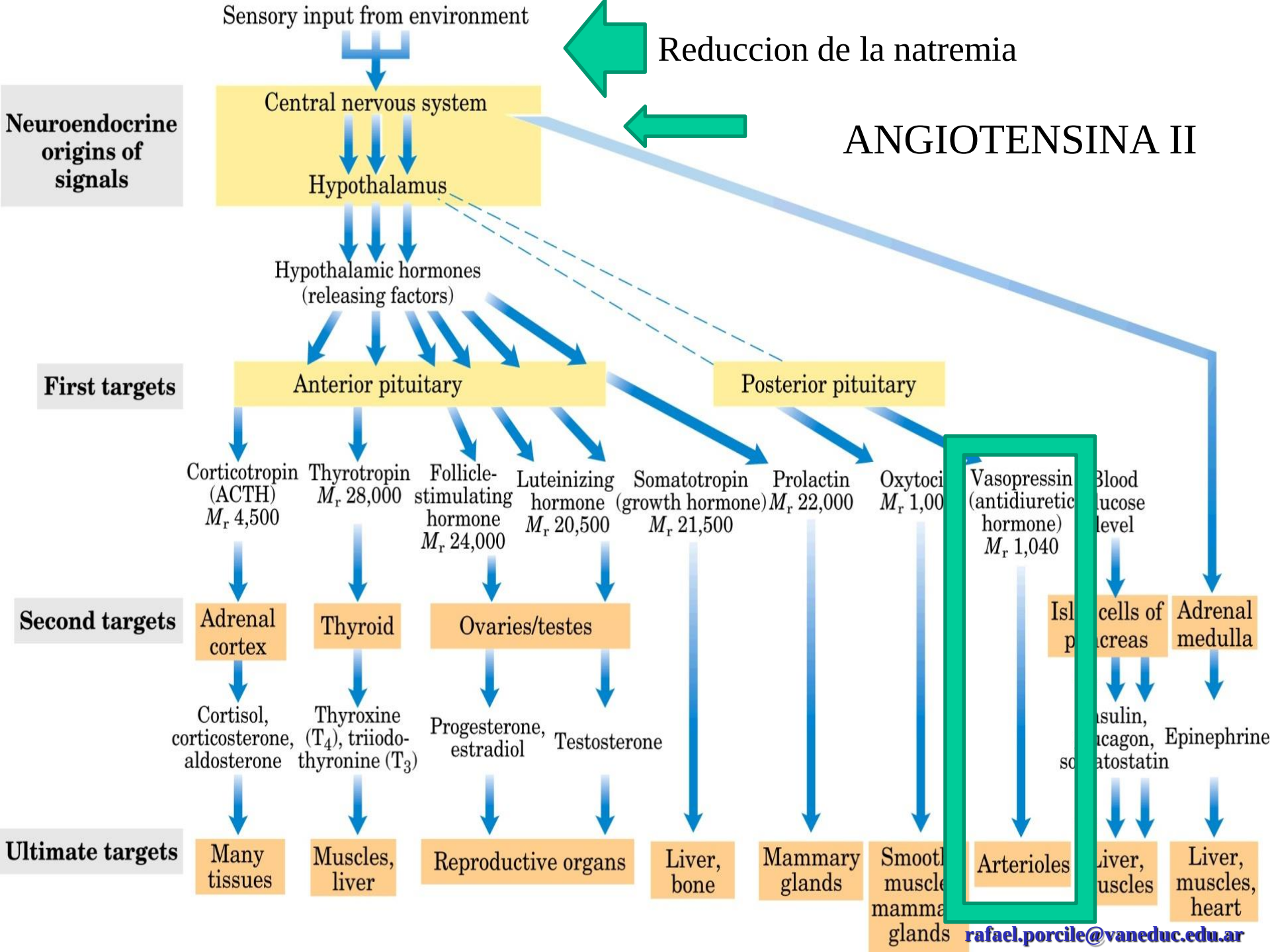

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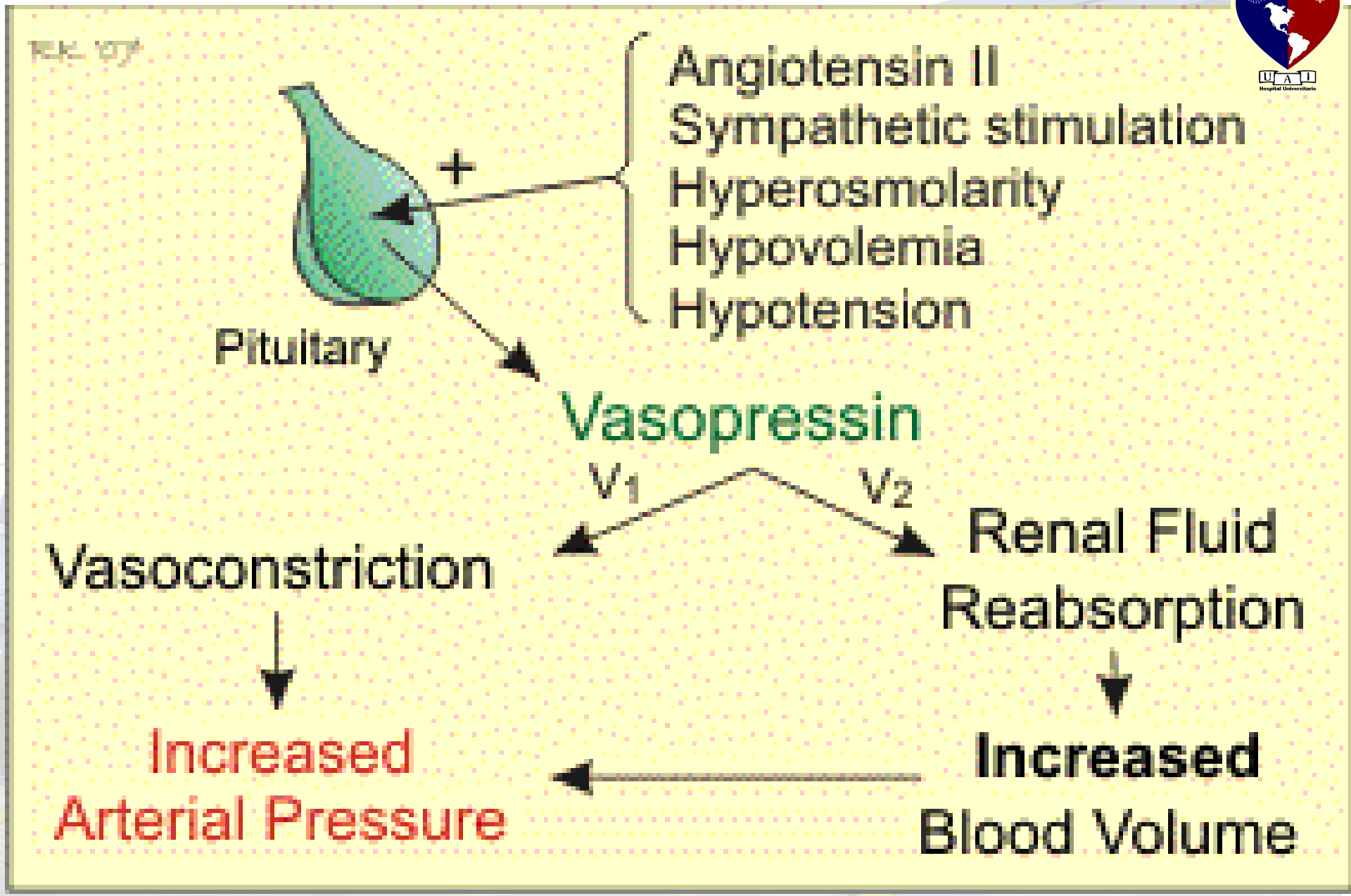

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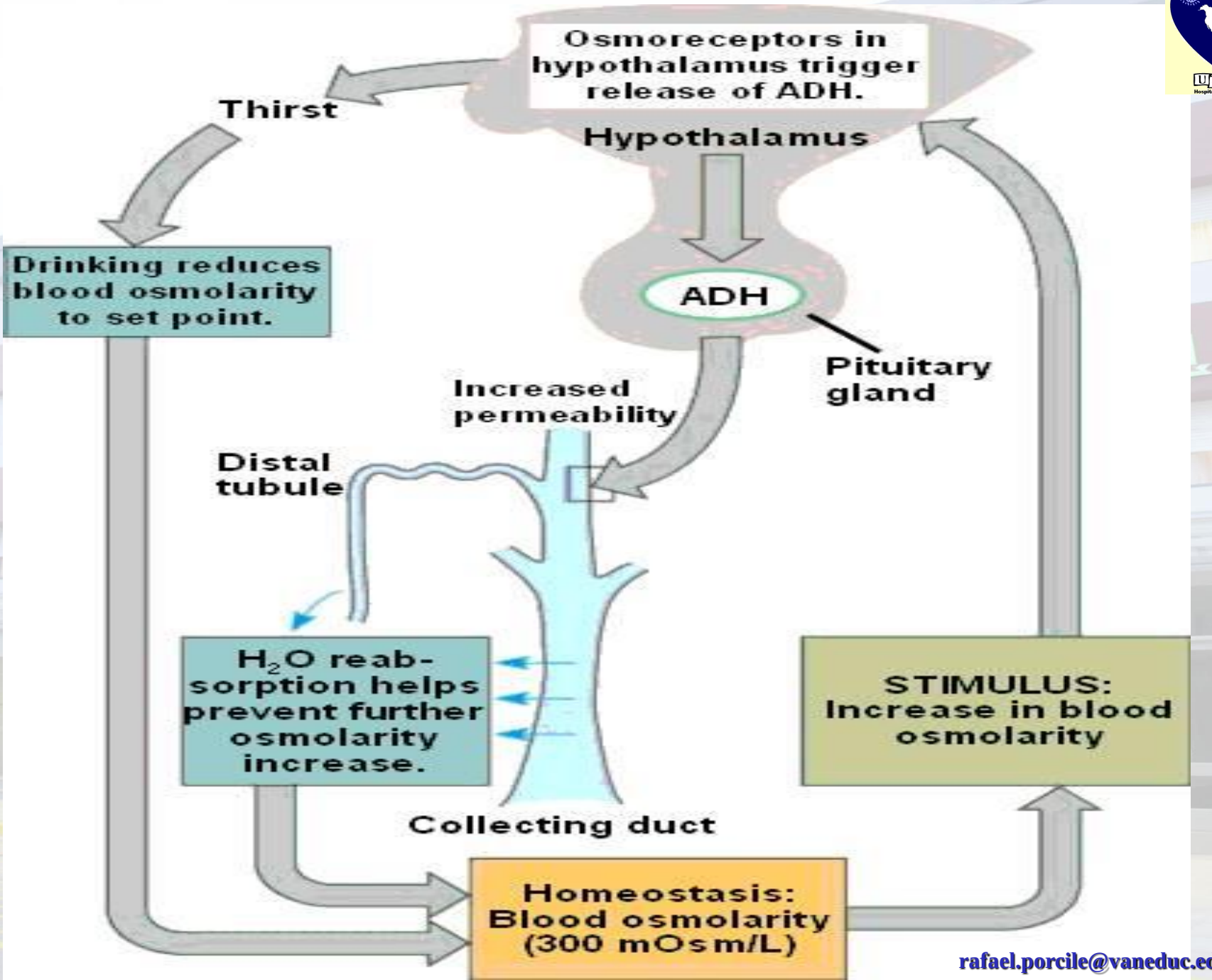

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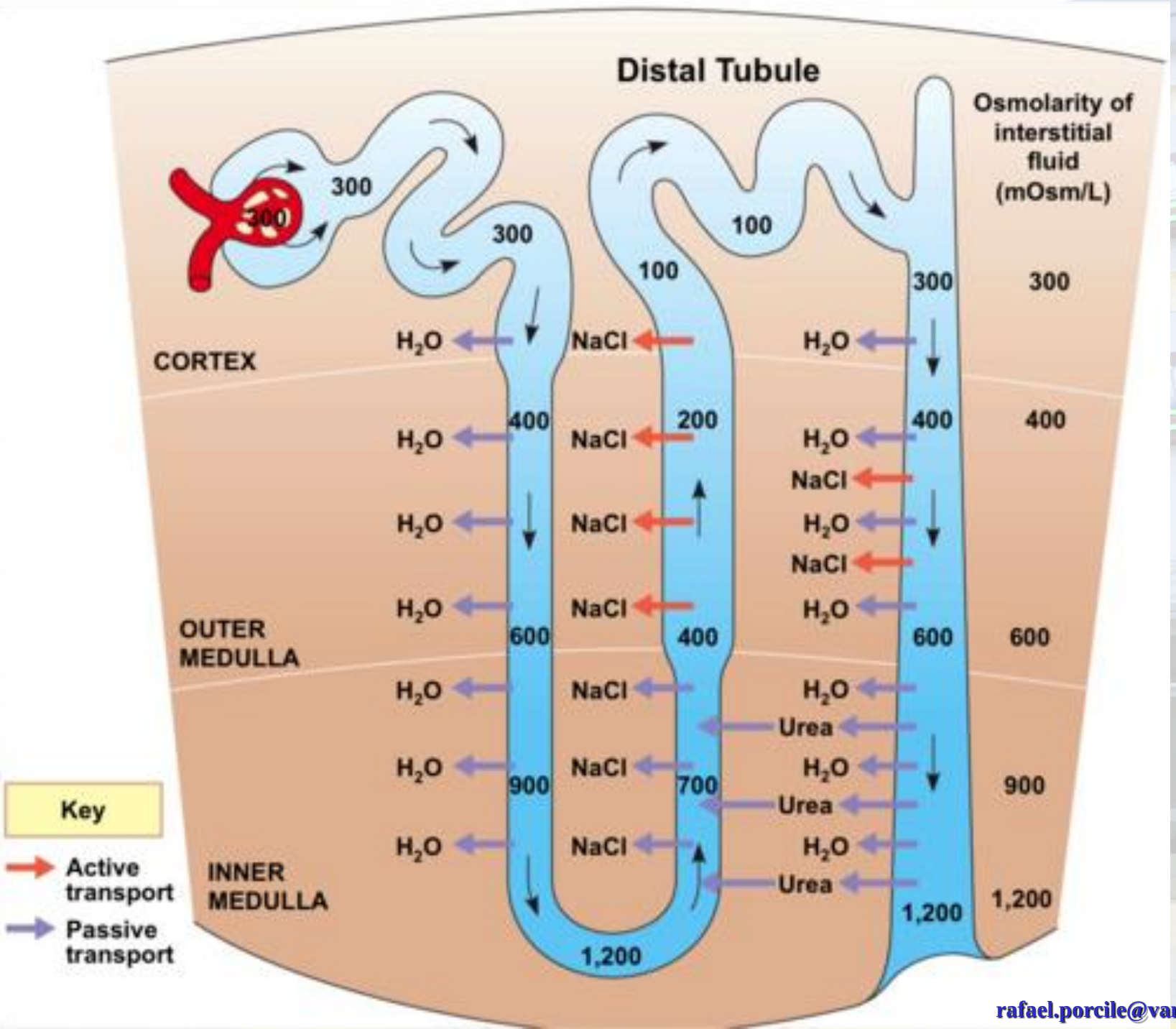

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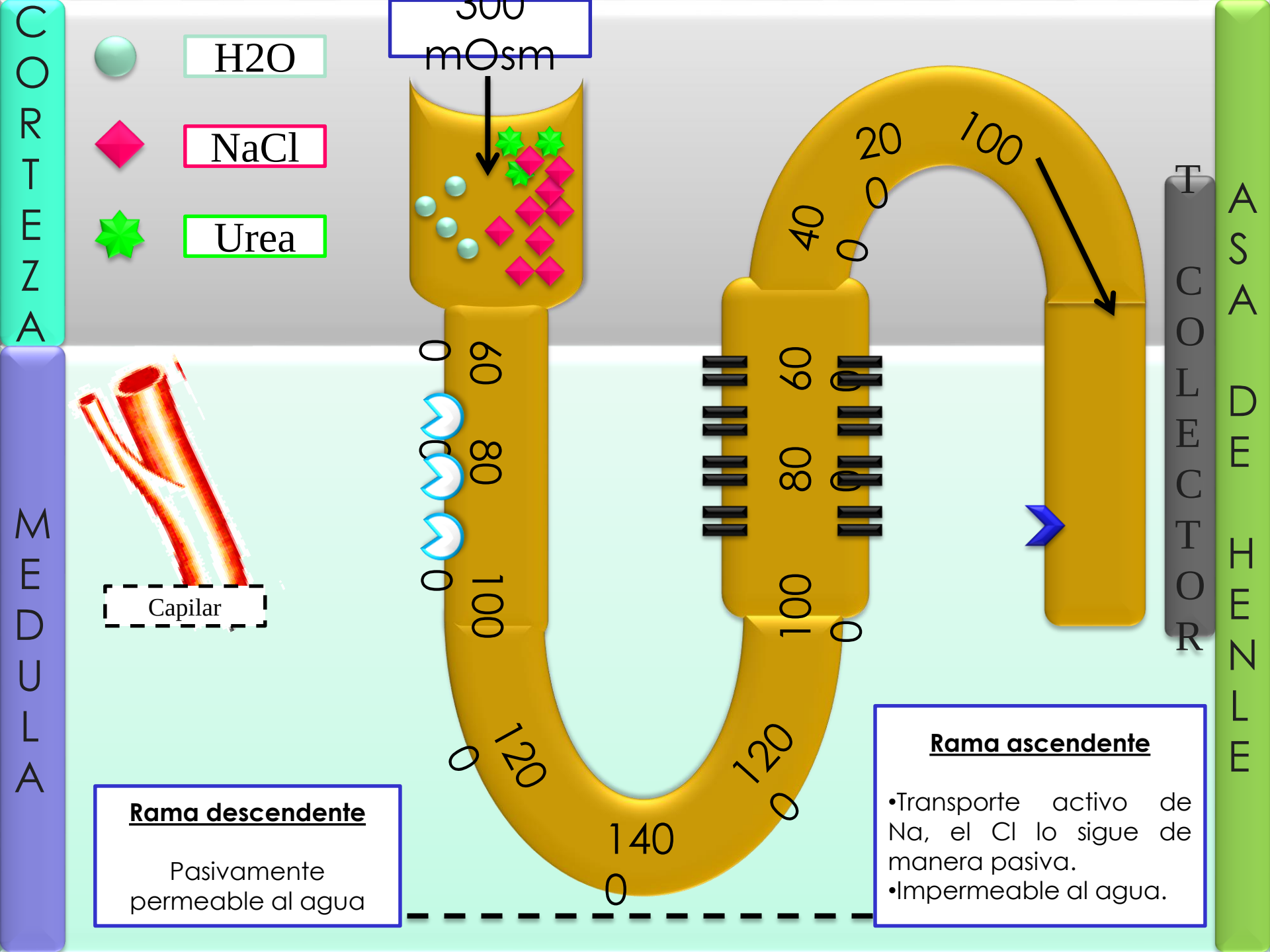
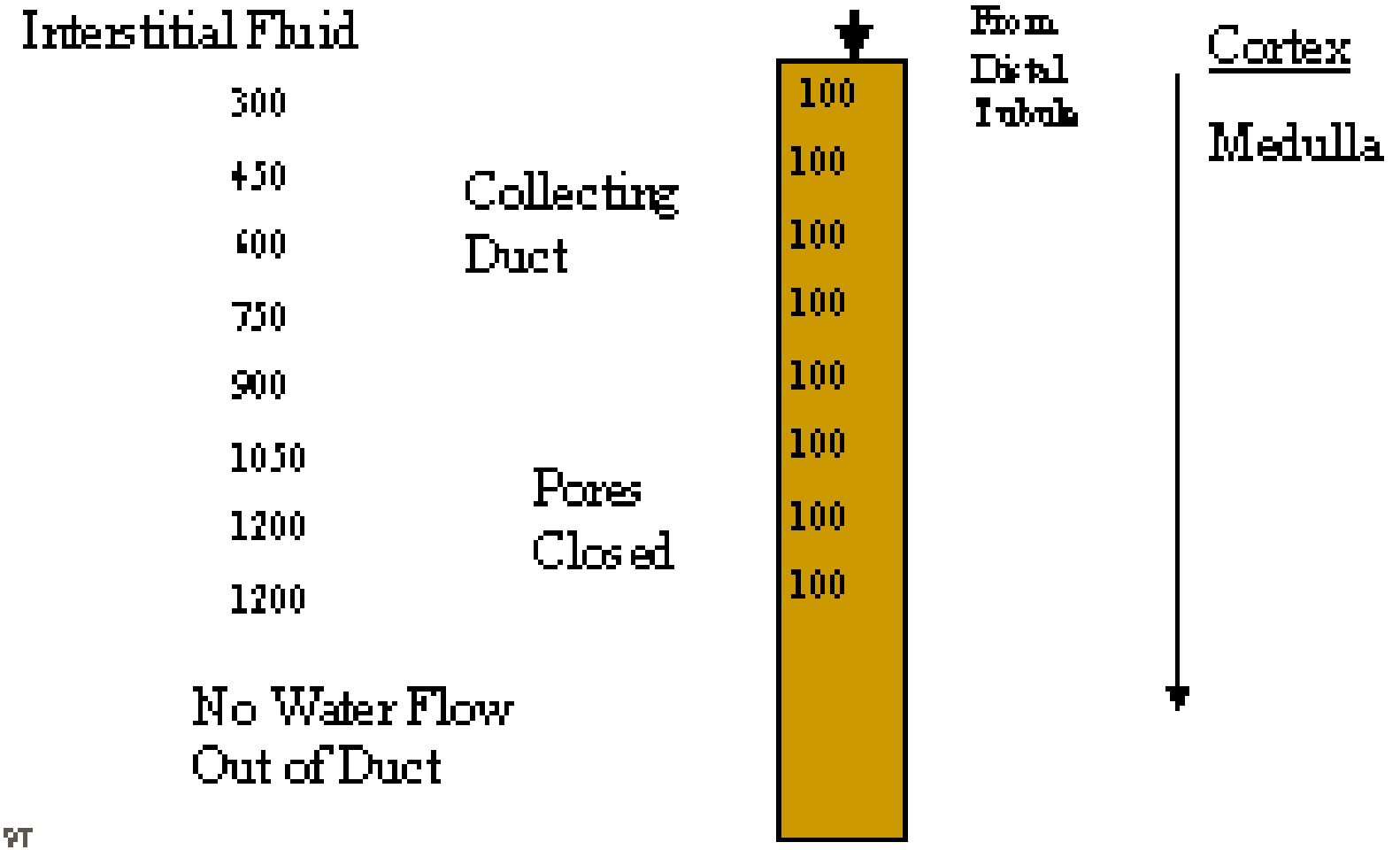

CORTEZA
MEDULA
ASA DE HENLE
TUBO COLECTOR
H2O
NaCl
Urea
300 mOsm
Capilar
0
60
80
100
120
140
20
40
Rama descendente
Pasivamente permeable al agua
Rama ascendente
•Transporte activo de Na, el Cl lo sigue de manera pasiva.
•Impermeable al agua.

WHEN VASOPRESSIN (ANTI DIURETIC HORMONE [ADH]) IS ABSENT A DILUTE URINE IS PRODUCE



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FÁRMACOS ANTIDIURÉTICOS

VASOPRESINA hormona antidiurética (HAD) y análogos :DESMOPRESINA

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DESMOPRESINA

- Análogo estructural de la hormona natural argininavasopresina

.

-La desmopresina induce la secreción de factor VIII y de factor de Von Willebrand. Al mismo tiempo produce una liberación del activador del plasminógeno (t-PA).

La desmopresina está relacionada con la disminución o normalización del tiempo de hemorragia en pacientes con tiempo de hemorragia prolongado:caso de uremia, cirrosis hepática, insuficiencia trombocitaria congénita

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Se emplea en medicina para el tratamiento de la diabetes insípida, la hemofilia y la enuresis nocturna. Su acción se diferencia de la hormona antidiuretica natural o vasopresina, en que no actúa sobre los receptores V1, responsables de la acción vasoconstrictora de la vasopresina, por tanto su efecto vasoconstrictor es prácticamente despreciable

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La desmopresina tiene la propiedad de elevar entre 2 y 5 veces el nivel de factor de coagulación VIII en sangre, muy probablemente por favorecer su liberación desde los lugares que el organismo utiliza para almacenar esta sustancia. Por ello se utiliza tanto en el tratamiento de la hemofilia A, como en la enfermedad de von Willebrand

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•Comprimidos; aerosol y gotas
- [DIABETES INSIPIDA] central.
- [ENURESIS NOCTURNA] en niños mayores de 5 años.
Parenteral:
-[DIABETES INSIPIDA].
-Prueba de la capacidad de concentración renal, especialmente en el diagnóstico diferencial de infecciones urinarias (cistitis, pielonefritis).
- Tratamiento corrector y preventivo de accidentes hemorrágicos en: [HEMOFILIA A] y [ENFERMEDAD DE VON WILLEBRAND] (Mantenimiento de la hemostasis antes de una intervención quirúrgica.

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Otros fármacos antidiuréticos

•BENZOTIAZIDAS (diuréticos)

Reducen la poliuria de la diabetes insípida de naturaleza nefrógena

Mecanismo desconocido

•CLOFIBRATO (hipolipemiante)

Reducen la poliuria de la diabetes insípida de origen central leve:

Actua a nivel central y facilita la secreción de la hormona antidiurética (ADH)

•CLORPROPAMIDA(hipoglucemiante)

Util en la diabetes insípida de origen central moderada

Actua a nivel central y facilita la secreción de la hormona antidiurética (ADH)

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Hipertensión arterial

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				Inicio Terapia	
Clasificación PA	PAS* mmHg	PAD* mmHg	Estilos de Vida	Sin indicación clara	Con indicación clara (ver Tabla 8)
Normal	**<120**	y < 80	Estimular	No indicado tratamiento farmacológico	Tratamiento Indicado***
Prehipertensión	**120-139**	ó 80-89	Si		
HTA: Estadío 1	**140-159**	ó 90-99	Sí	Tiazidas en la mayoría. Considerar IECAs, ARA II, BBs, BCC ó combinaciones	Fármacos según las indicaciones presentes***. Otros antihipertensivos (diuréticos, IECAs, ARA II, BBs, BCC) según sea necesario
HTA: Estadío 2	**>160**	ó >100	Sí	Combinación dos fármacos en la mayoría** (usualmente tiazídicos, IECAs, o ARA II, BBs ó BCC)	

* Tratamiento determinado por la elevación de la PA

** La terapia combinada inicial debe usarse con precaución cuando exista riesgo de hipotensión ortostática

***Tratamiento en enfermedad renal crónica o diabetes con objetivo PA <130/80 mmHg

	JNC 7 (2003)	JNC 8 (2014)
Métodos	No hubo sistema en repaso de literatura. Recomendaciones basadas en consenso.	Basado en estudios clínicos aleatorios con un protocolo estandarizado.
Métodos en tratamientos	Separados para hipertensión no complicada o complicada con diabetes o enfermedad renal.	Definiciones para la población hipertensa, excepto para subpoblaciónes ya evidenciadas.
Estilo de vida	Basado en repaso de literatura u opinión.	Endosa las recomendaciones del grupo de 'Estilos de vida'.
Terapia con fármacos	Recomienda 5 clases como terapias iniciales pero con diuréticos para la mayoría. Especifica agentes preferidos en condiciones mórbidas.	Recomienda 4 clases (ACE, ARB, CCB, diuréticos). Condiciones como la raza, renal y diabéticos requieren ciertas clases de medicamentos.
Proceso de revisión	Revisado por el Comité Coordinador de Educación en Hipertensión.	Revisado por el panel de expertos. No hubo auspicio por el Gobierno.

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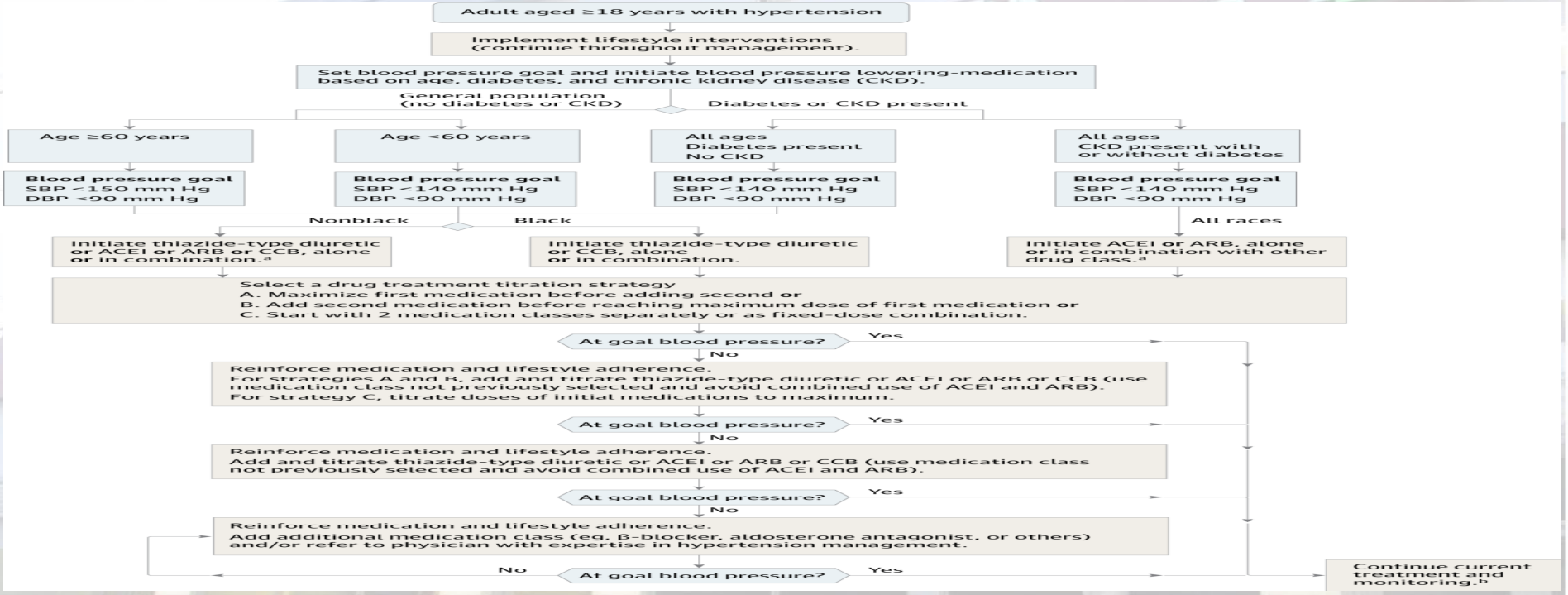

Figure Legend:

2014 Hypertension Guideline Management AlgorithmSBP indicates systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.[a]ACEIs and ARBs should not be used in combination.[b]If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

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Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

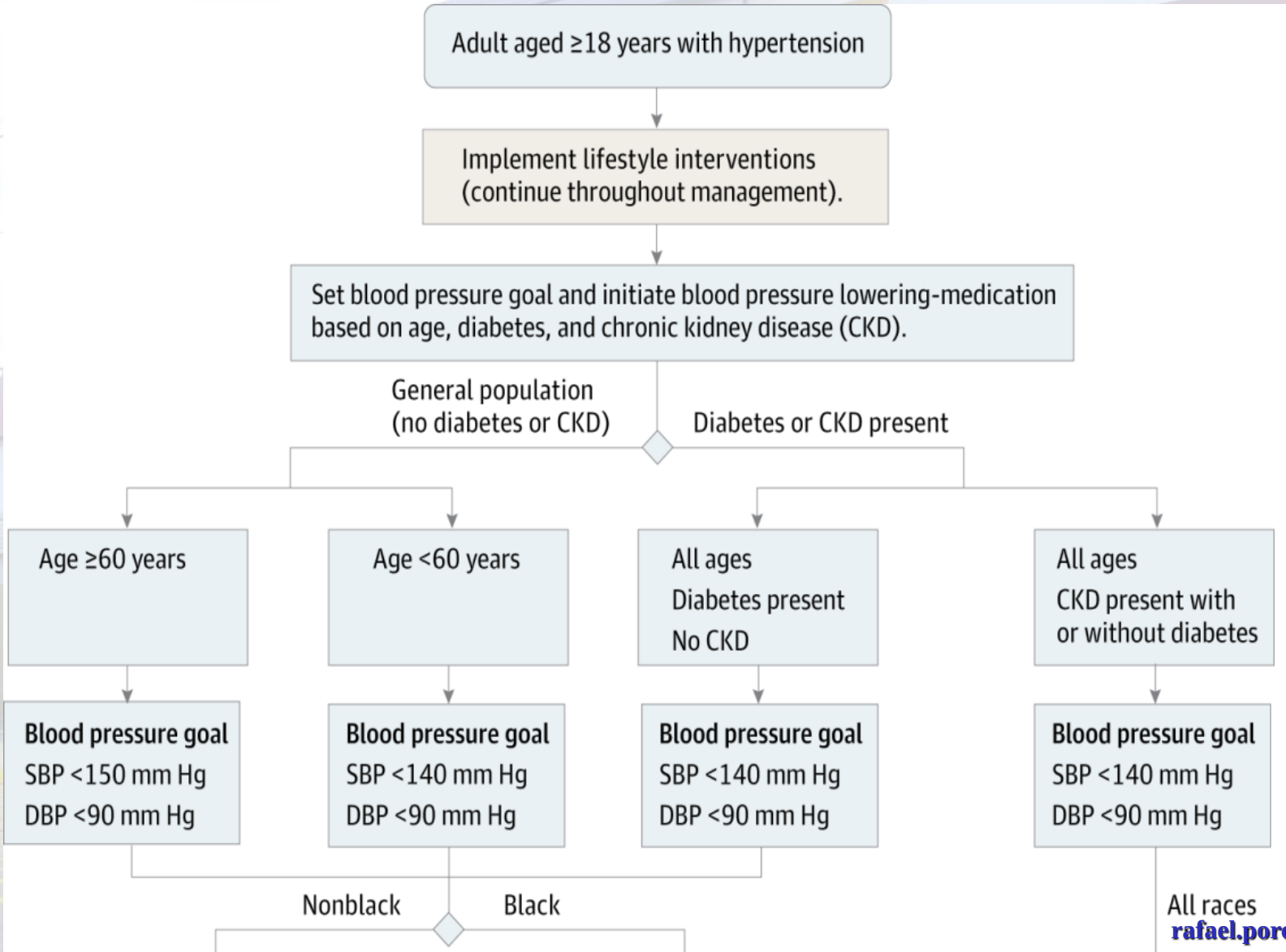

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Table 6. Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB
	General <60 y	<140/90	
	Diabetes	<140/90	
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013[37]	General nonelderly	<140/90	Diuretic, β-blocker, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
CHEP 2013[38]	General <80 y	<140/90	Thiazide, β-blocker (age <60y), ACEI (nonblack), or ARB
	General ≥80 y	<150/90	
	Diabetes	<130/80	ACEI or ARB with additional CVD risk ACEI, ARB, thiazide, or DHPCCB without additional CVD risk
	CKD	<140/90	ACEI or ARB
ADA 2013[39]	Diabetes	<140/80	ACEI or ARB
KDIGO 2012[40]	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
NICE 2011[41]	General <80 y	<140/90	<55 y: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
ISHIB 2010[42]	Black, lower risk	<135/85	Diuretic or CCB
	Target organ damage or CVD risk	<130/80	

Abbreviations: ADA, American Diabetes Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPCCB, dihydropyridine calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence.

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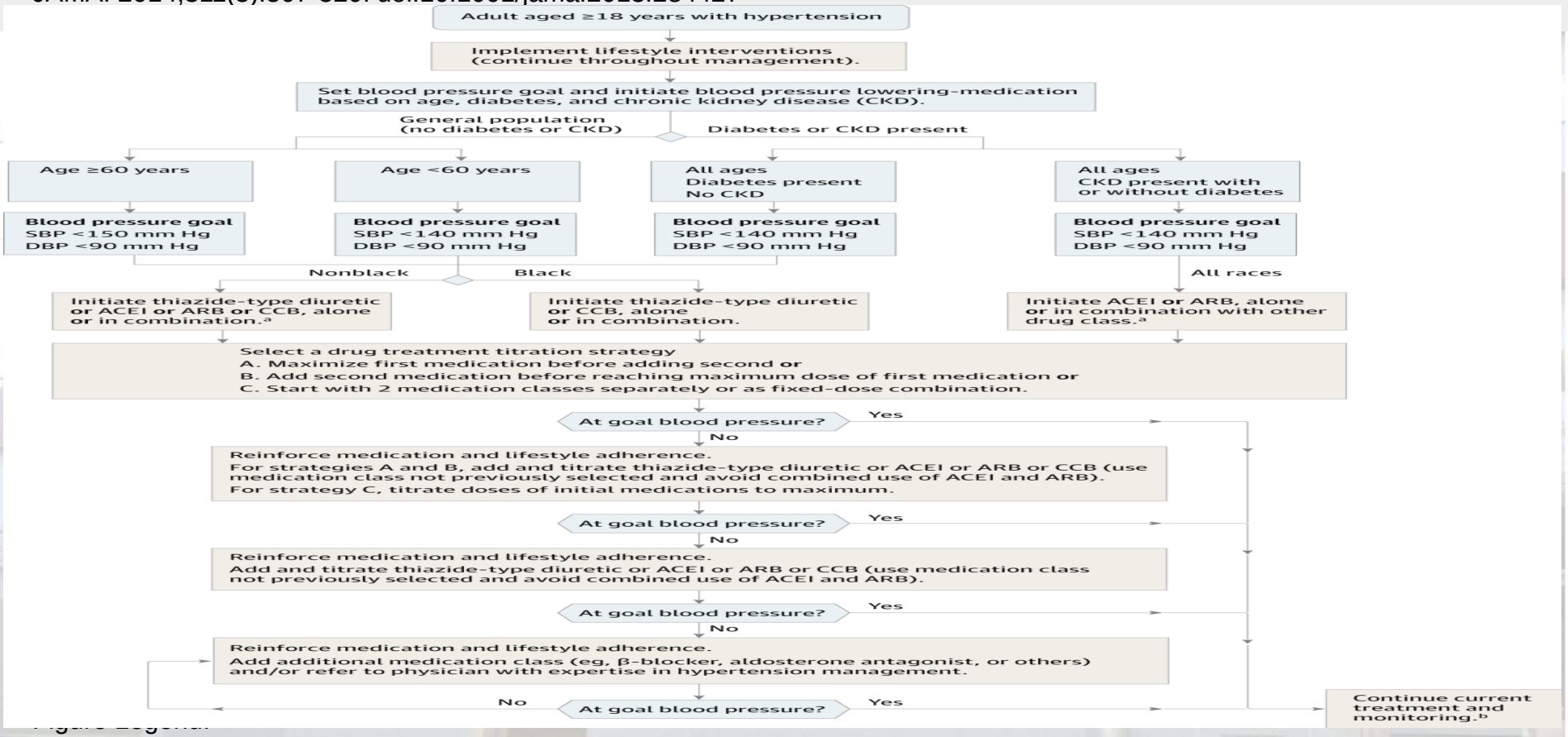

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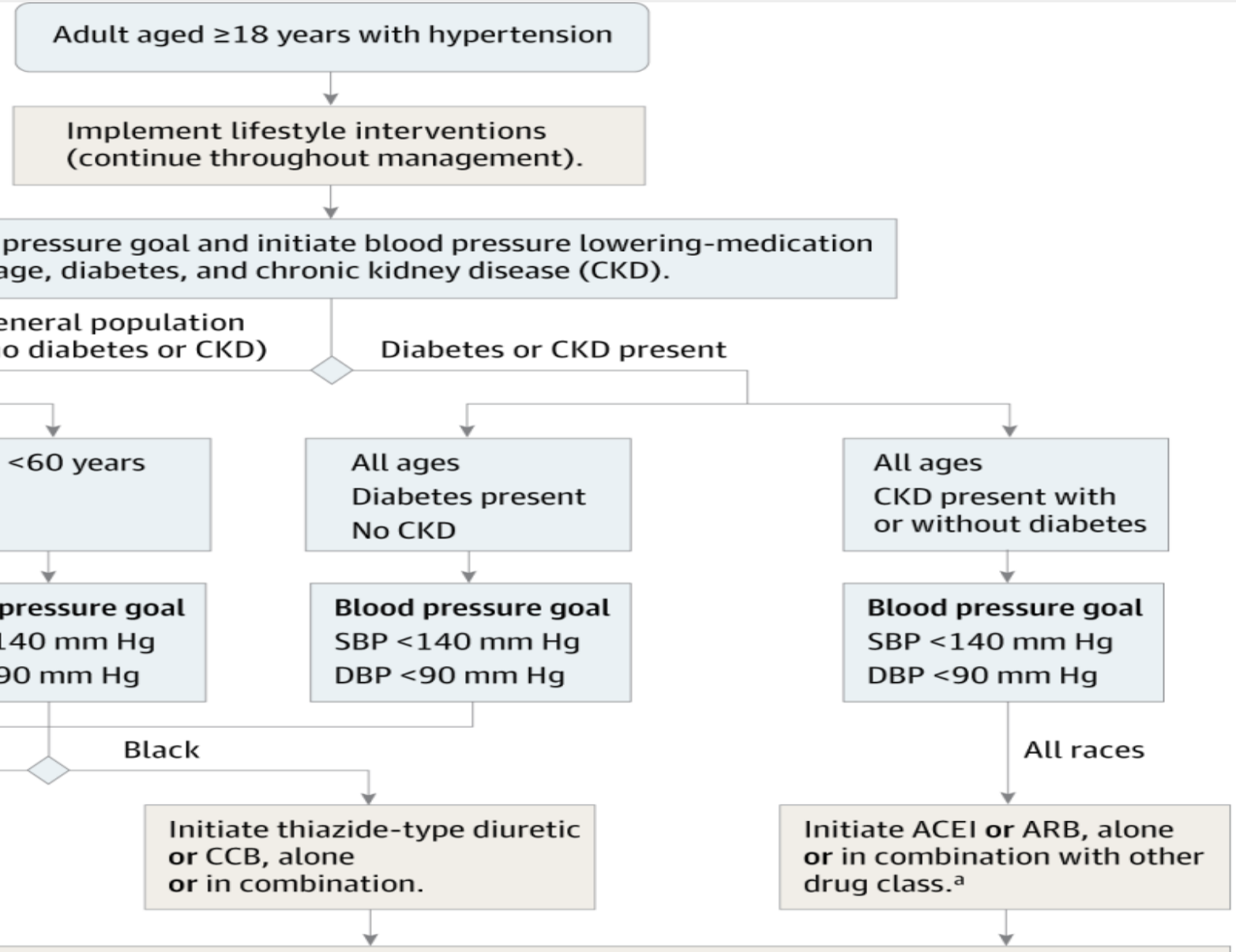

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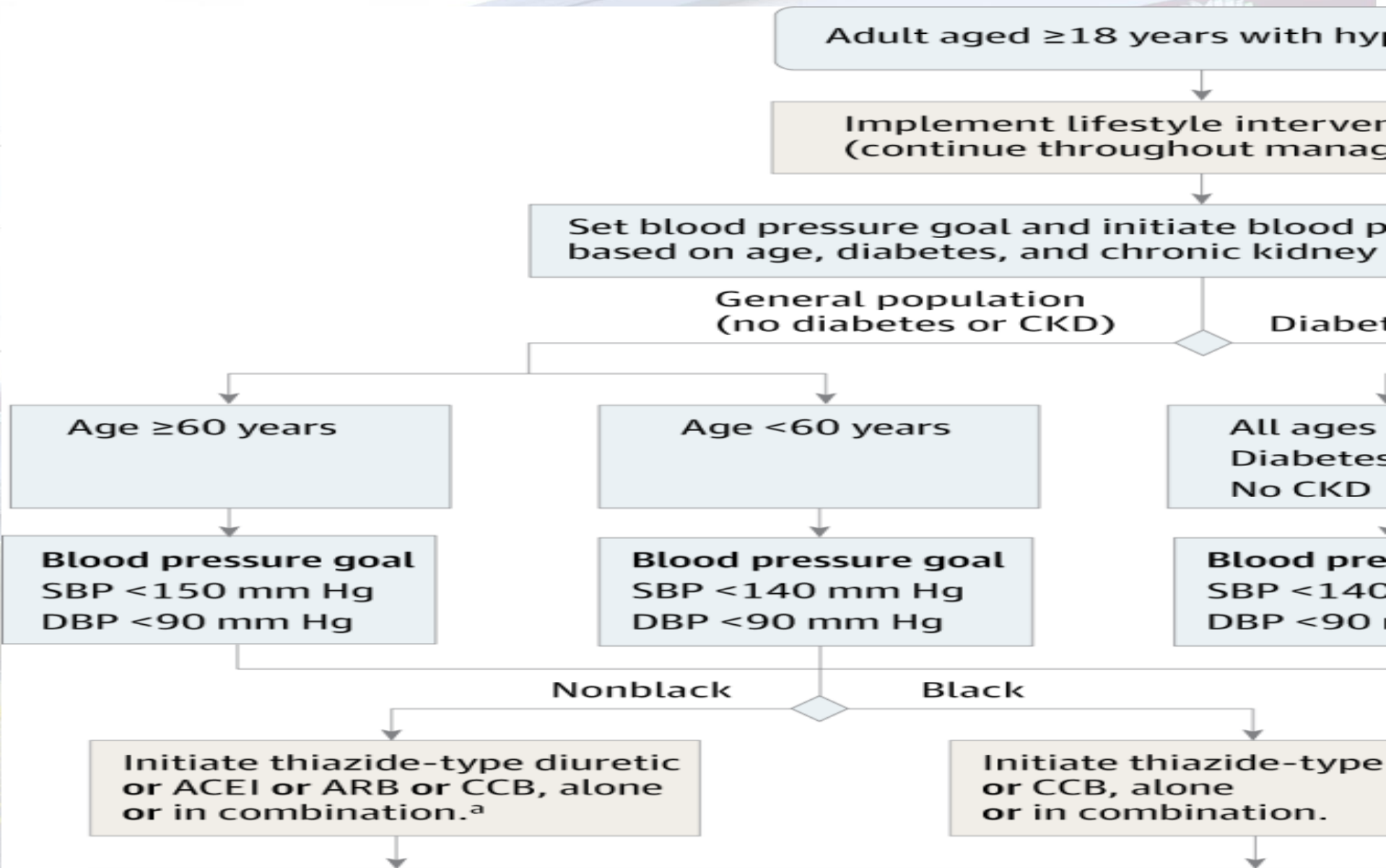

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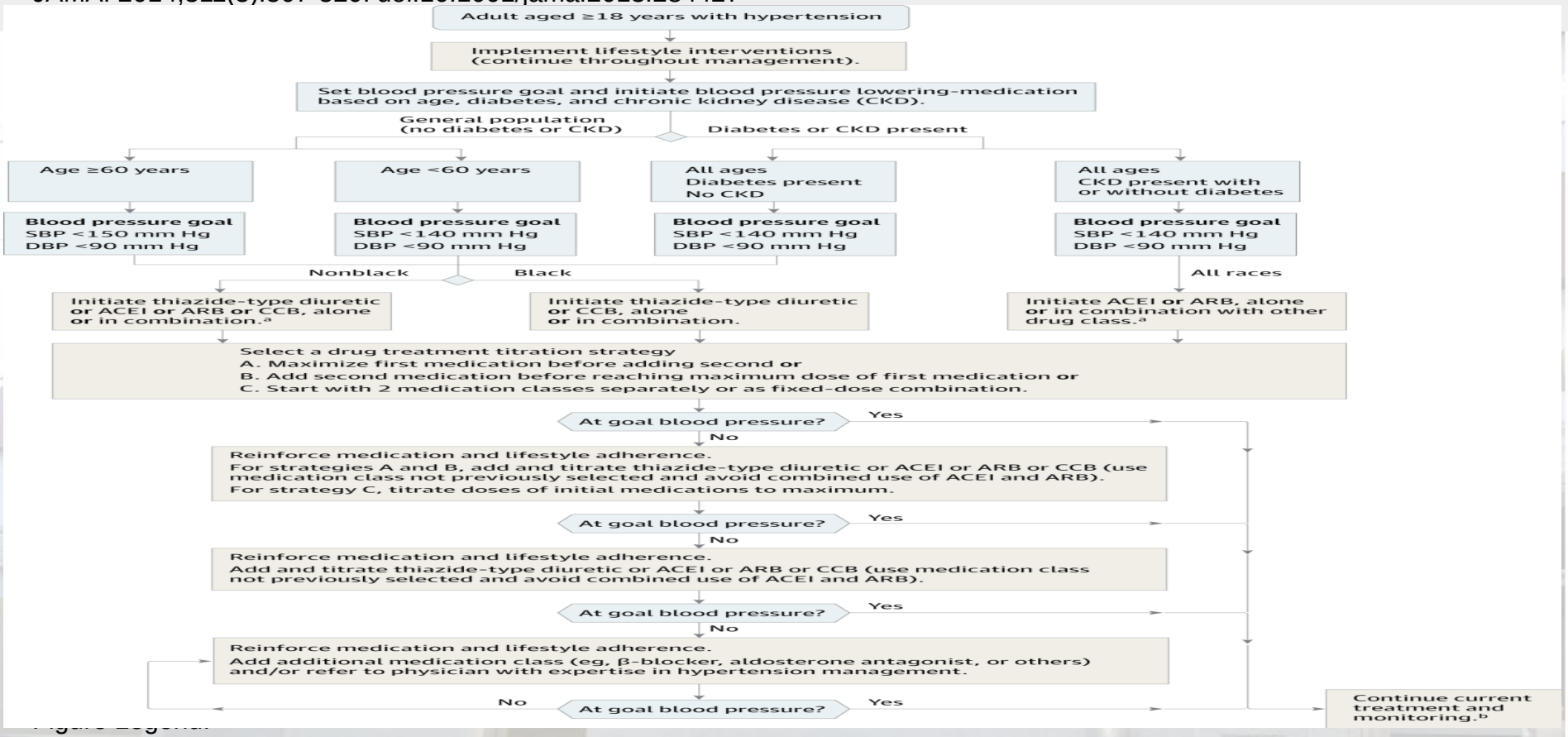

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Objetivos terapéuticos

JNC 8 Recommendations

Patient Subgroup	Target SBP (mm Hg)	Target DBP (mm Hg)
≥ 60 years	<150	< 90
< 60 years	<140	< 90
> 18 years with CKD	<140	<90
> 18 years with diabetes	<140	<90

CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure

James PA, et al. *JAMA*. 2013 Dec 18. [Epub ahead of print]

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Table 5. Strategies to Dose Antihypertensive Drugs[a]

Strategy	Description	Details
A	Start one drug, titrate to maximum dose, and then add a second drug	If goal BP is not achieved with the initial drug, titrate the dose of the initial drug up to the maximum recommended dose to achieve goal BP If goal BP is not achieved with the use of one drug despite titration to the maximum recommended dose, add a second drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB) and titrate up to the maximum recommended dose of the second drug to achieve goal BP If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP
B	Start one drug and then add a second drug before achieving maximum dose of the initial drug	Start with one drug then add a second drug before achieving the maximum recommended dose of the initial drug, then titrate both drugs up to the maximum recommended doses of both to achieve goal BP If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP
C	Begin with 2 drugs at the same time, either as 2 separate pills or as a single pill combination	Initiate therapy with 2 drugs simultaneously, either as 2 separate drugs or as a single pill combination. Some committee members recommend starting therapy with ≥2 drugs when SBP is >160 mm Hg and/or DBP is >100 mm Hg, or if SBP is >20 mm Hg above goal and/or DBP is >10 mm Hg above goal. If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose.

Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]This table is not meant to exclude other agents within the classes of antihypertensive medications that have been recommended but reflects those agents and dosing used in randomized controlled trials that demonstrated improved outcomes.

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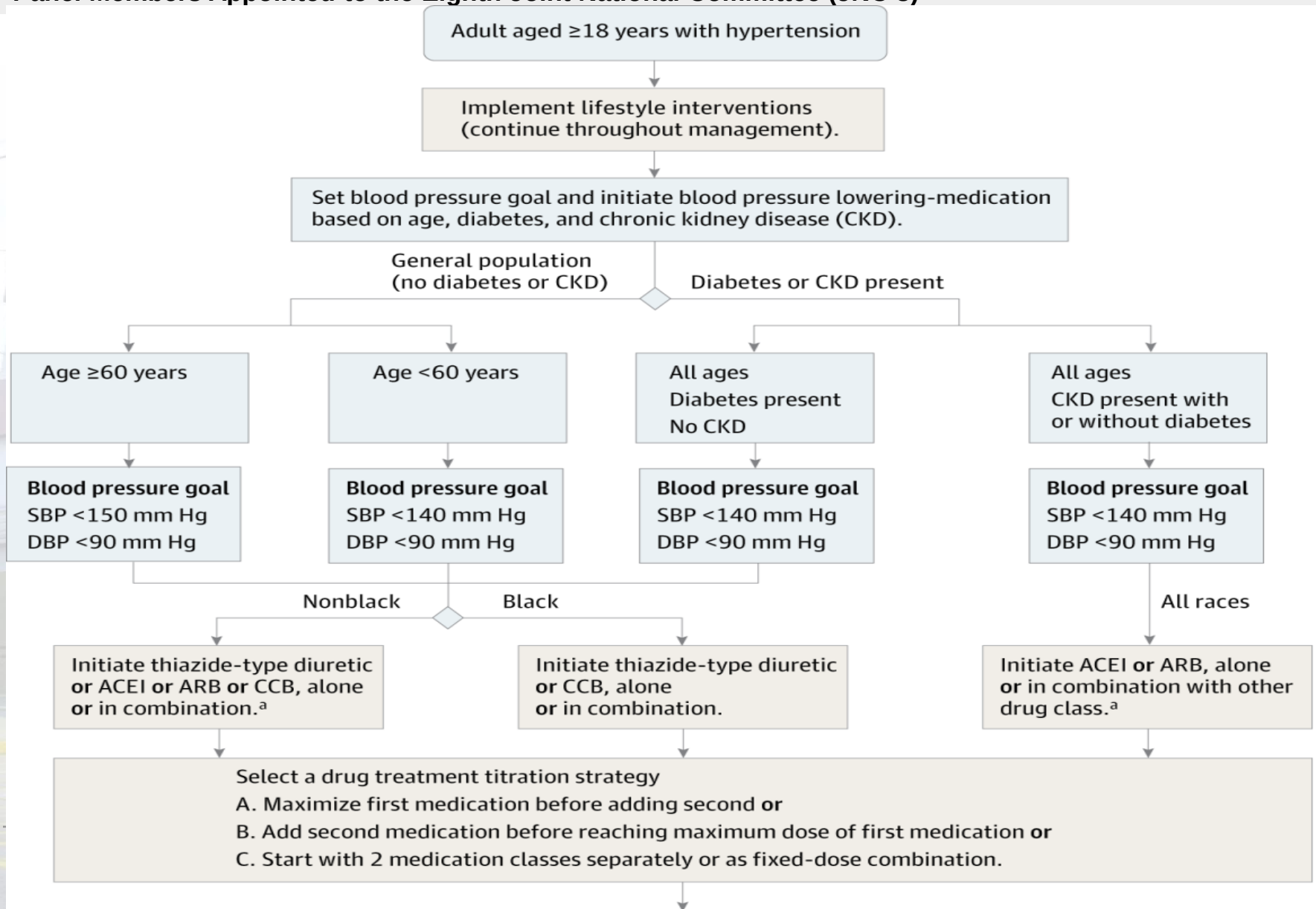

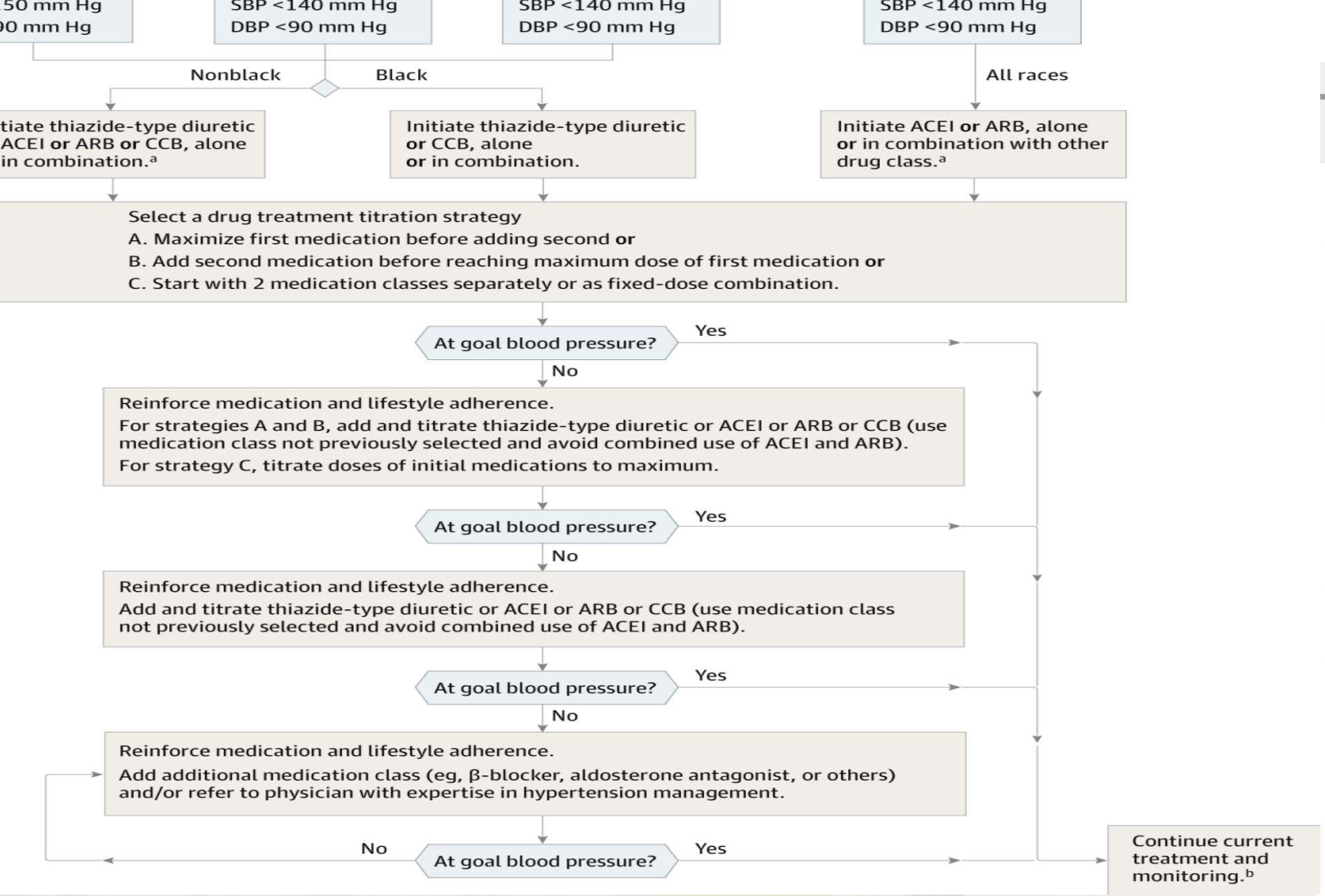

Gracias por su atención

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