Clinical approach to metabolic acidosis

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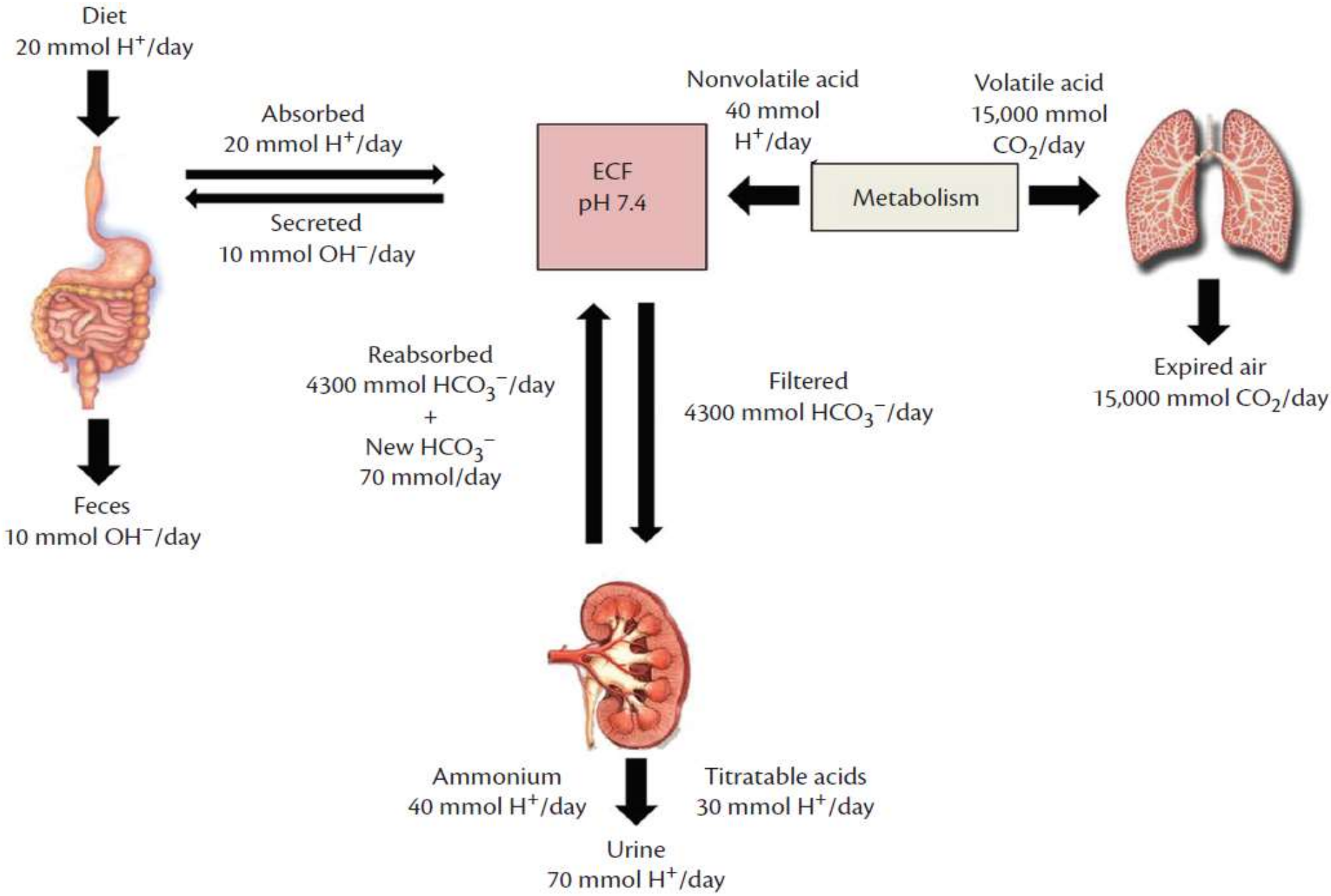
Moscow, October 2017

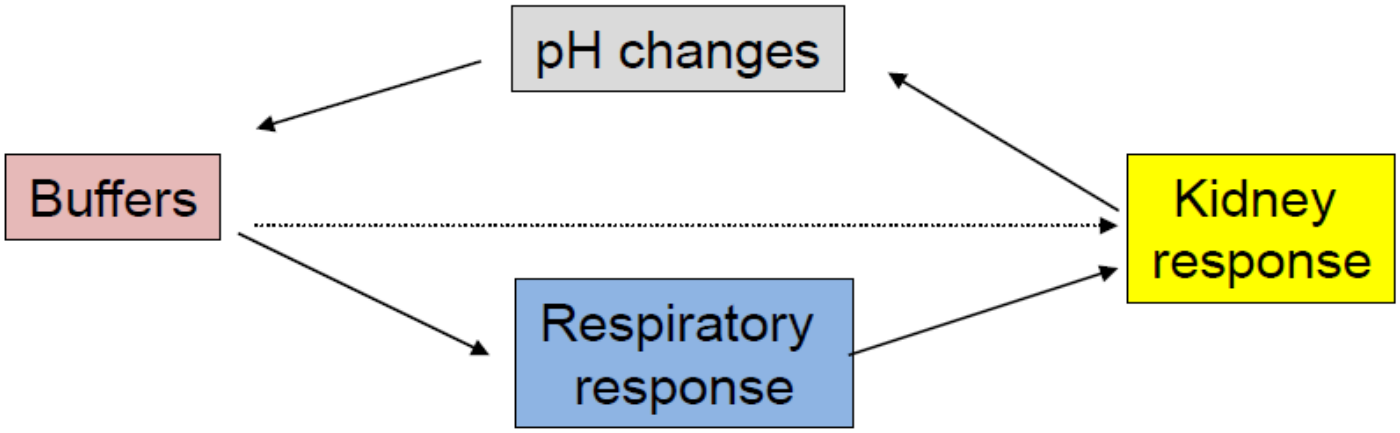
Acid base fluxes in healthy 70 kg man



The Regulation of Blood pH

- Blood pH control: essential for metabolism
  → enzymes, proteases, …

- Three lines of defense:
  1. Buffers: instantaneous response
  2. Lungs: minutes - hours
  3. Kidneys: a few days

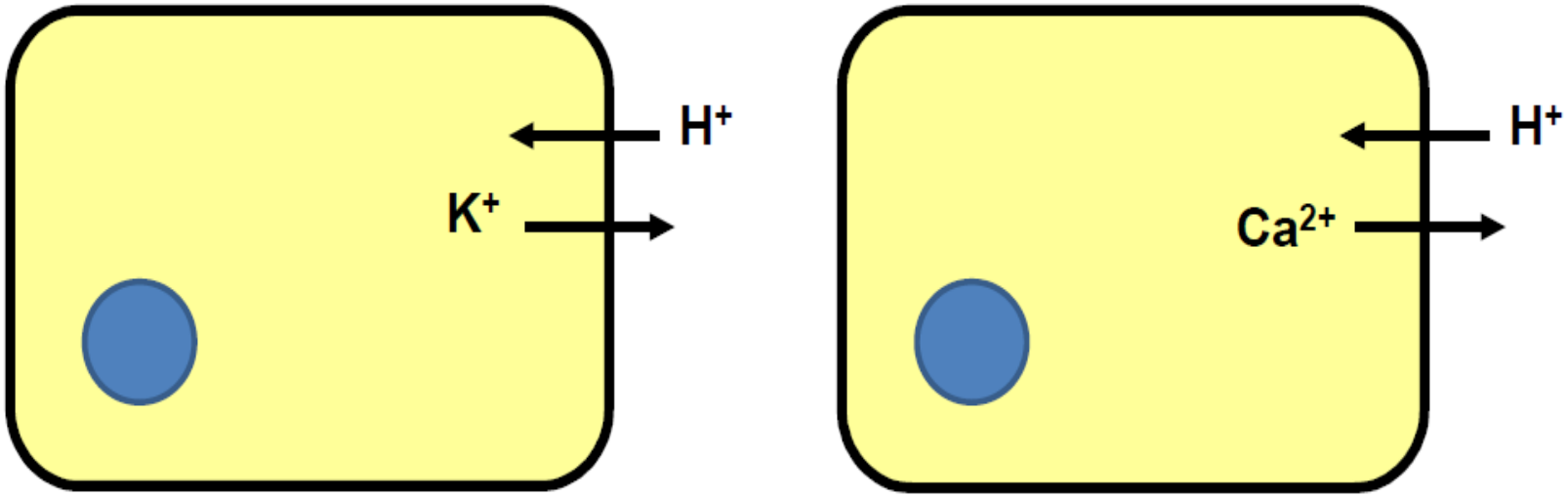


Buffer Systems (I)

- Weak acids which capture the circulating H^+

→ Intracellular buffers: proteins, hemoglobin

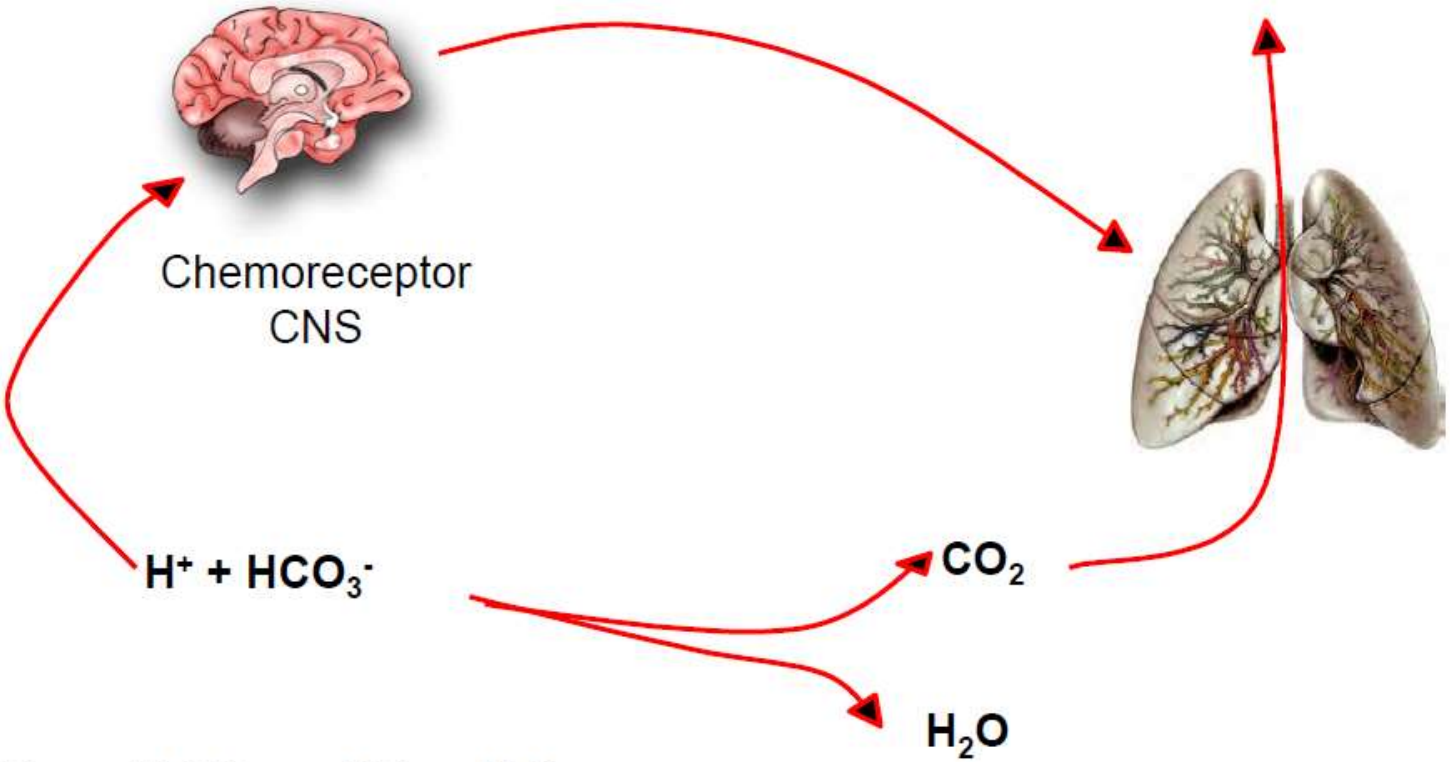
- Exchange H^+ for K^+ or Ca^{2+}



All cells *Bone cells*

Acid Stress: The Respiratory Response

- Central chemoreceptor: sense P_{CO2} & (H^+)
- Stimulation ventilation - CO_2 elimination
- Loss of CO_2 – volatile acids: reaction favours captation of H^+



$$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

Acid Stress: The Renal Response

→ ***Double role: two different nephron segments***

1. Reabsorption of filtered bicarbonate
   - Proximal tubule(+ TAL)
   - Regeneration of the main circulating buffer
2. Excretion of net acid load
   - Distal nephron: intercalated cells
   - Elimination of non-volatile acids < metabolism

Basal state: loss of 70 mEq H^+ /day in urine

→ Daily production of non-volatile acids : needs buffering !

→ Equilibrium: production H^+ = excretion H^+

→ Blood pH is stable

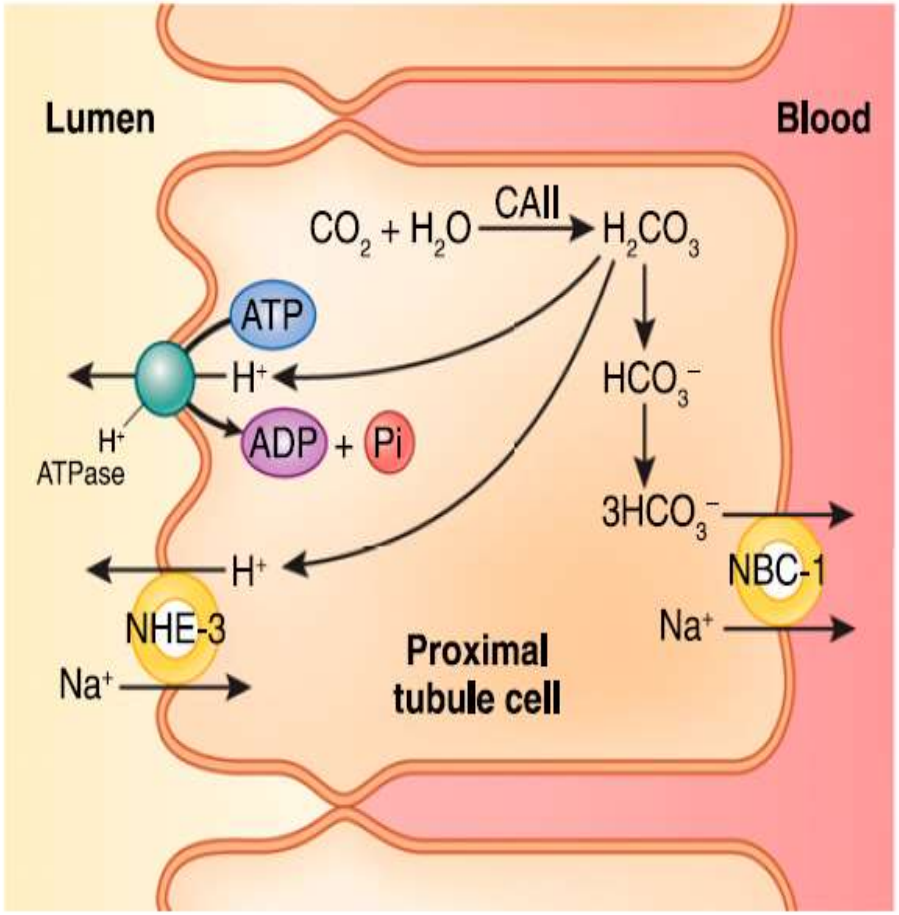
Buffers in the Urine: Phosphate, Ammonia

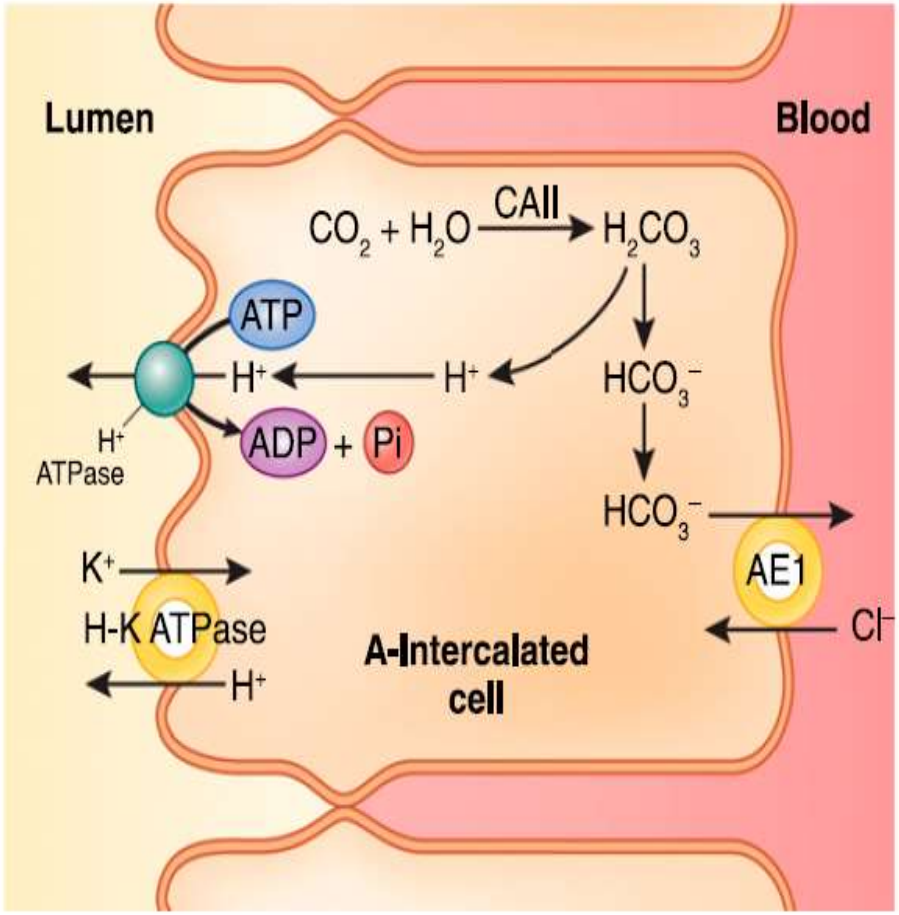
To buffer the large amounts (70-80 mM/day) of free H^+

- NHE_3 - NH_4^+ (ammonia/ammonium - 2/3 acid excretion - 40 mmol/d)
- HPO_4^{2-} - $H_2PO_4^-$ (phosphate - 1/3 acid excretion - 20 mmol/d)
- HCO_3^- (filtered but > 95% reabsorbed in PT + TAL)

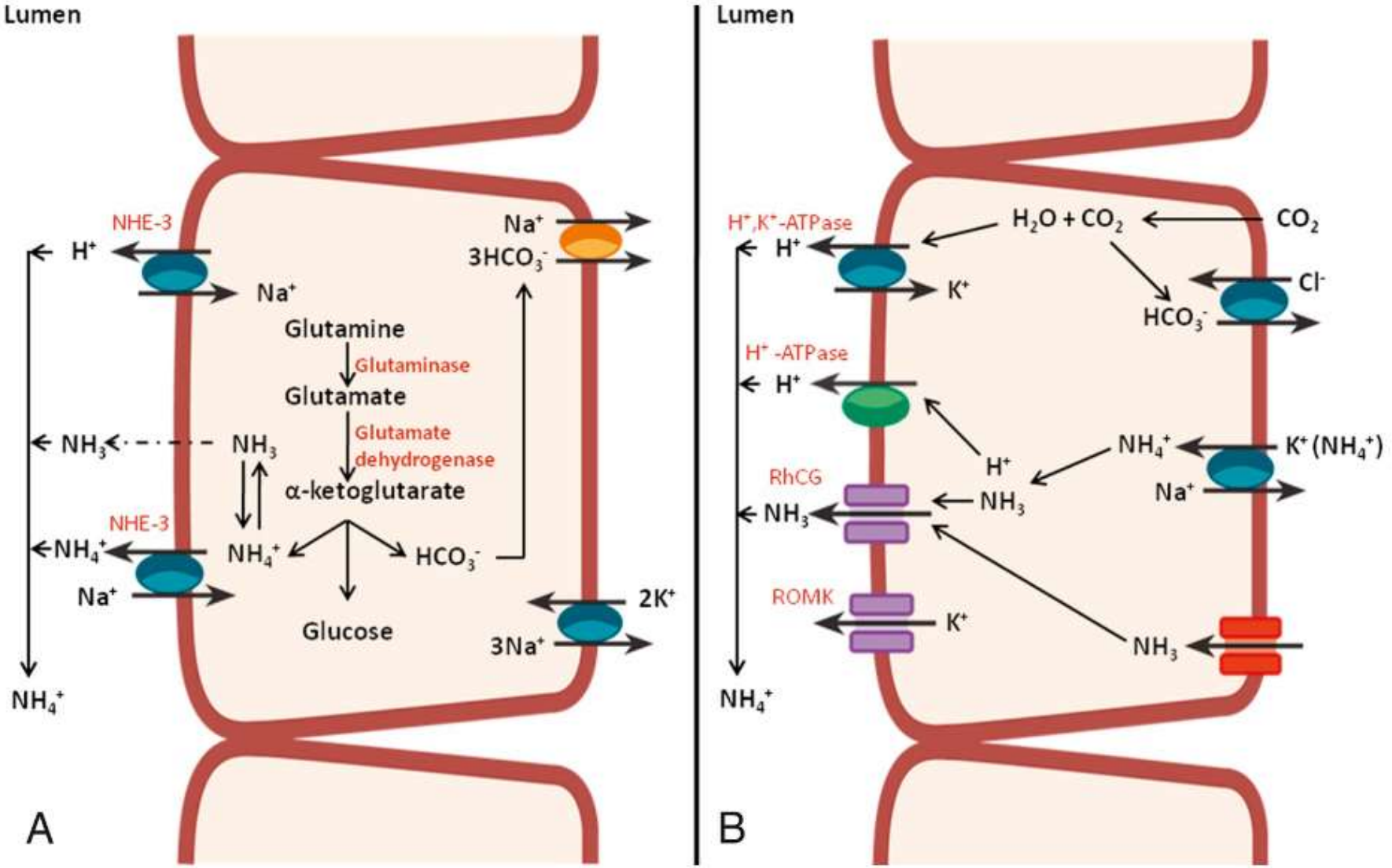
! Urine pH : indicative value but quantitatively negligible (nEq/L)

Cell transport models of a bicarbonate reabsorbing proximal tubule cell (left) and an acid secreting α-intercalated cell (right)

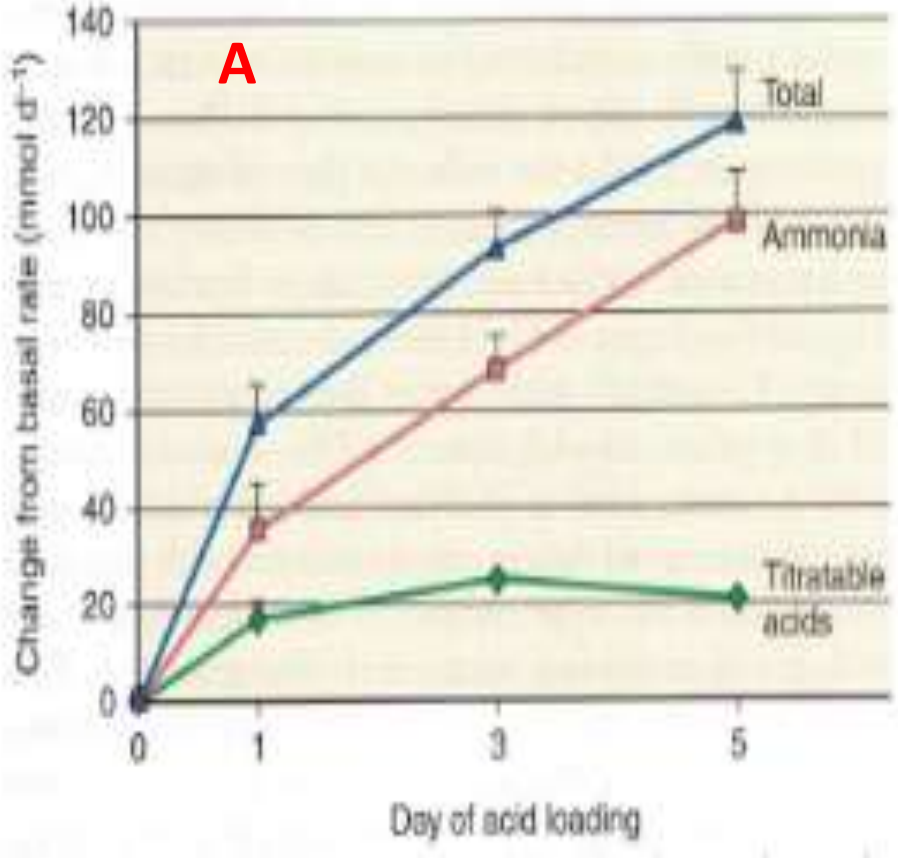


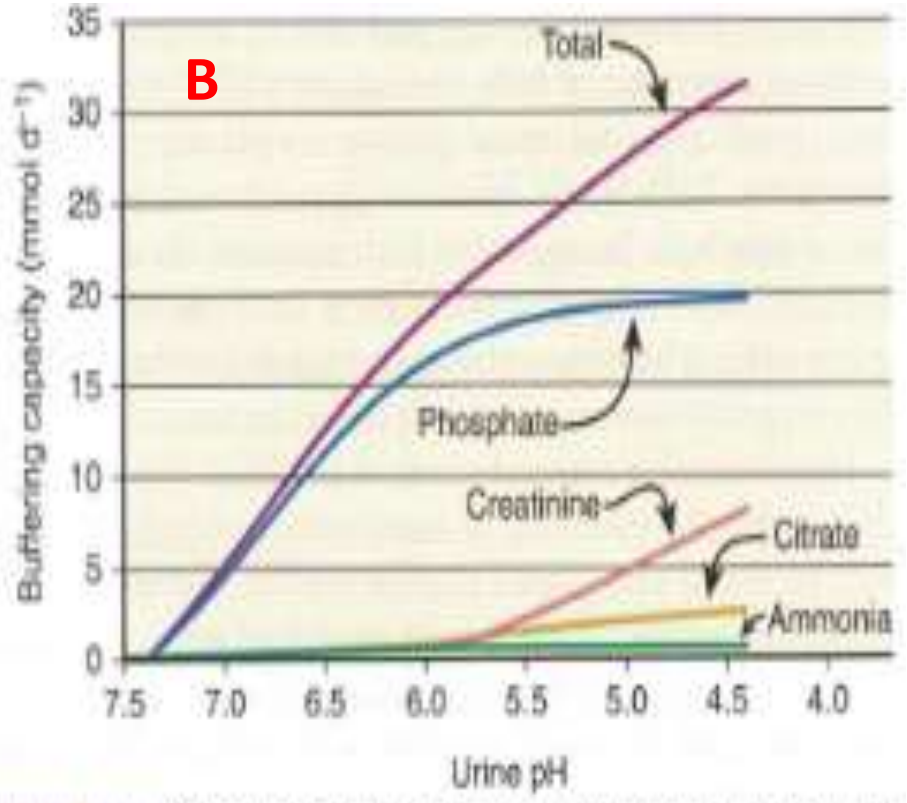


Cell models of ammonia synthesis and excretion pathways-panel A: Proximal convoluted tubule panel B: Type A intercalated cell in collecting tubule



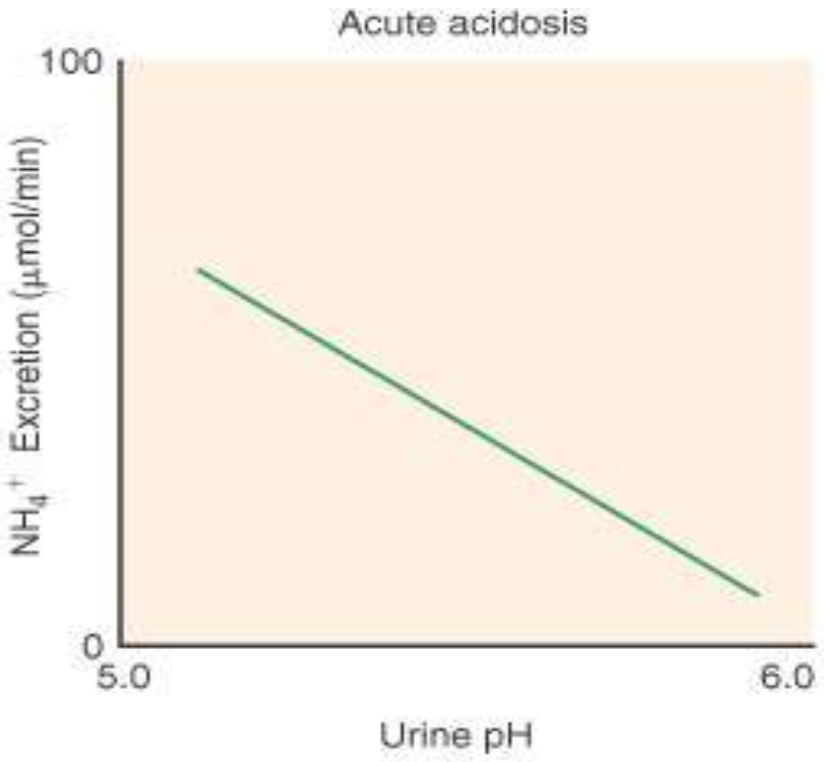
Relative responses of TA and ammonia excretion in the response to metabolic acidosis (panel A) Relative contribution of urinary buffers to TA excretion (panel B)

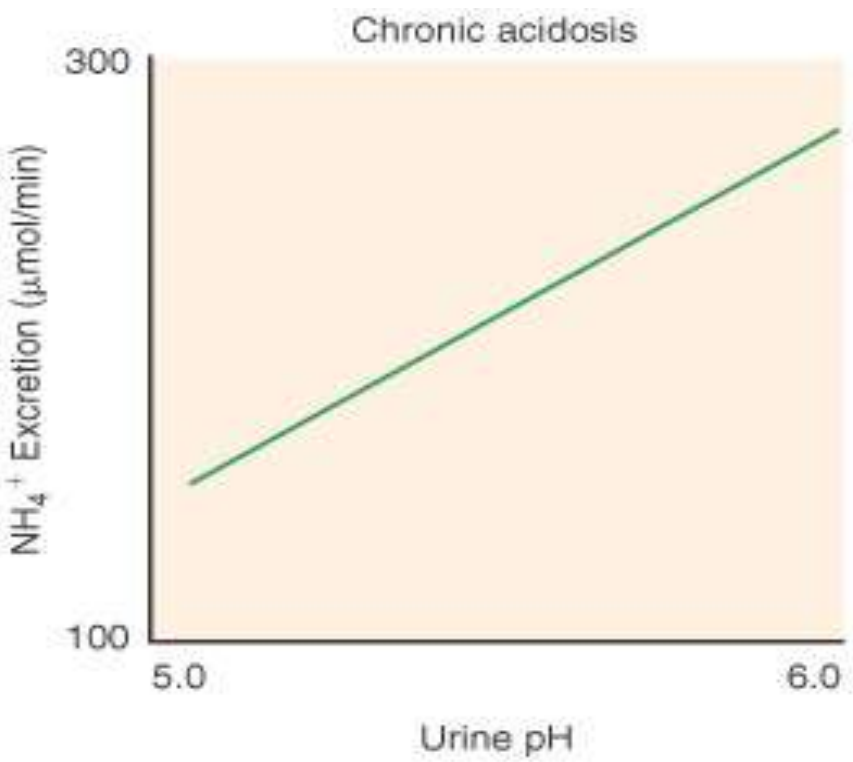




Net UAE= (UNH_4^+ x V) + (UTA x V) – ($UHCO_3^-$ x V)

Urine pH and the excretion of NH_4^+





$$H^+ + NH_3 \longrightarrow NH_4^+$$

$$H^+ + NH_3 \longrightarrow NH_4^+$$

Acidification of the urine by the A intercalated cell

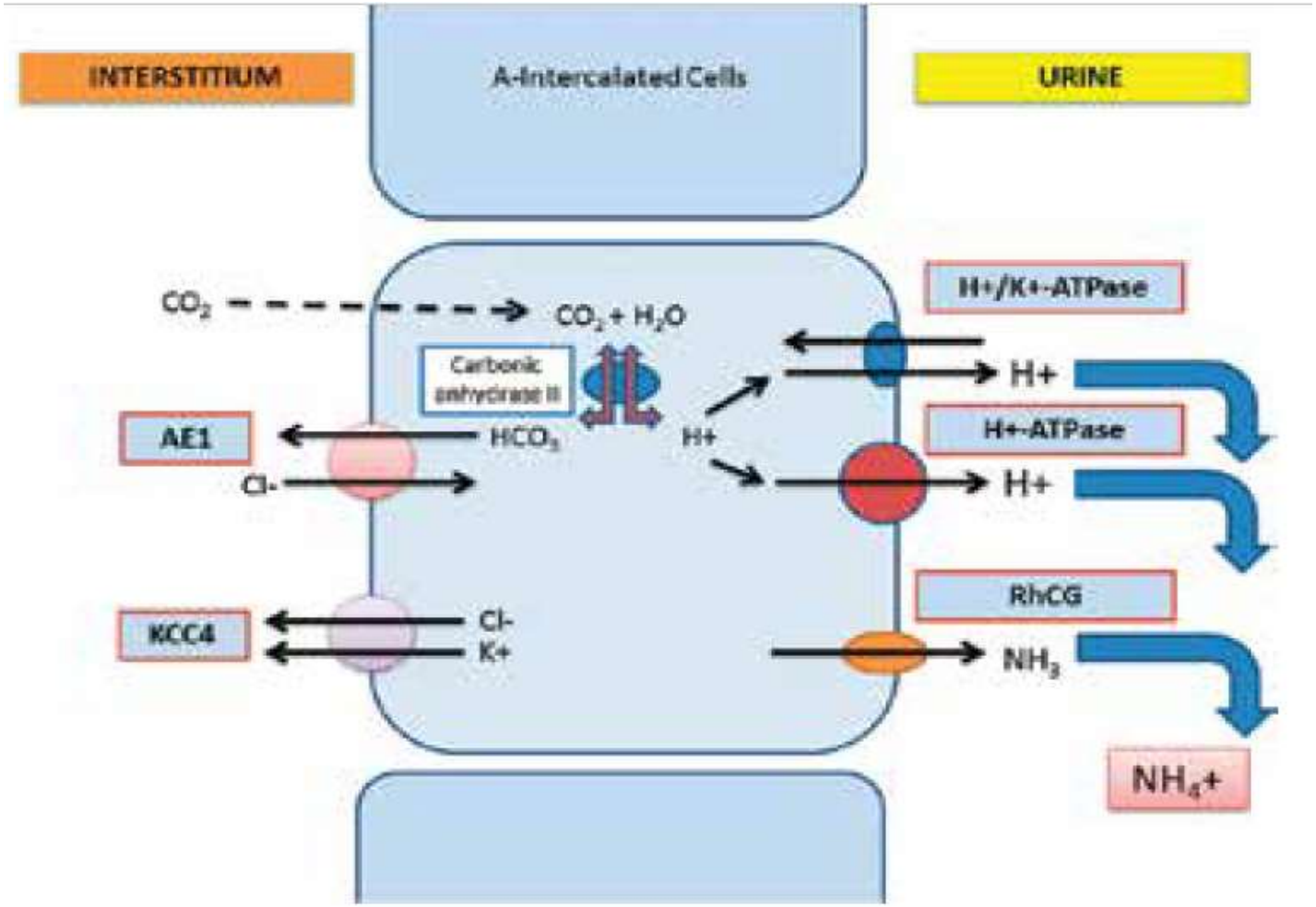
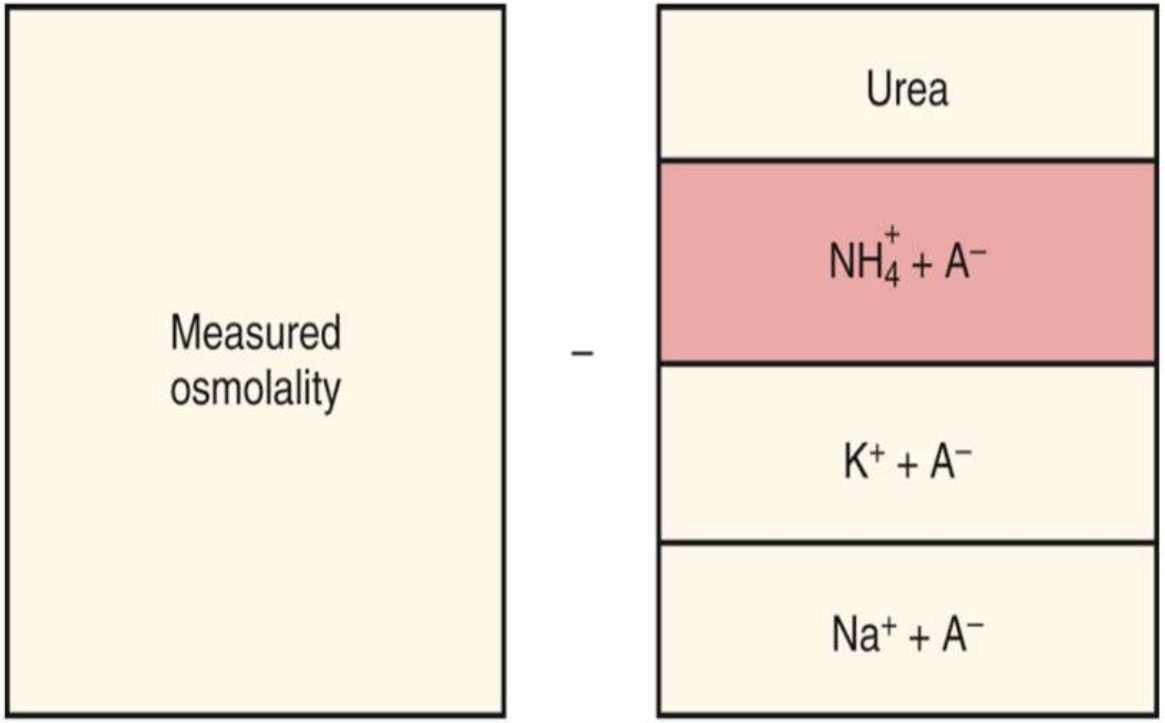


Figure 5. | The α-intercalated cell and handling of acid balance in the distal tubule. Acidification of the urine depends on the entry of CO_2 into the cell and its reaction with water to create bicarbonate and H+ ions. This reaction is catalyzed by carbonic anhydrase II (CAII). The bicarbonate is reabsorbed *via* cellular exit through the anion exchanger 1 (AE1). The H+ is excreted *via* H+/K+-ATPase or H+-ATPase. Lastly, ammonia is transported into the tubule *via* the Rh C glycoprotein (RhCG) channel. Defects in H+ ion secretion, backflow of H+ ions into the cell, defects in AE1 or CAII or in ammonia production or transport can all lead to forms of distal RTA.

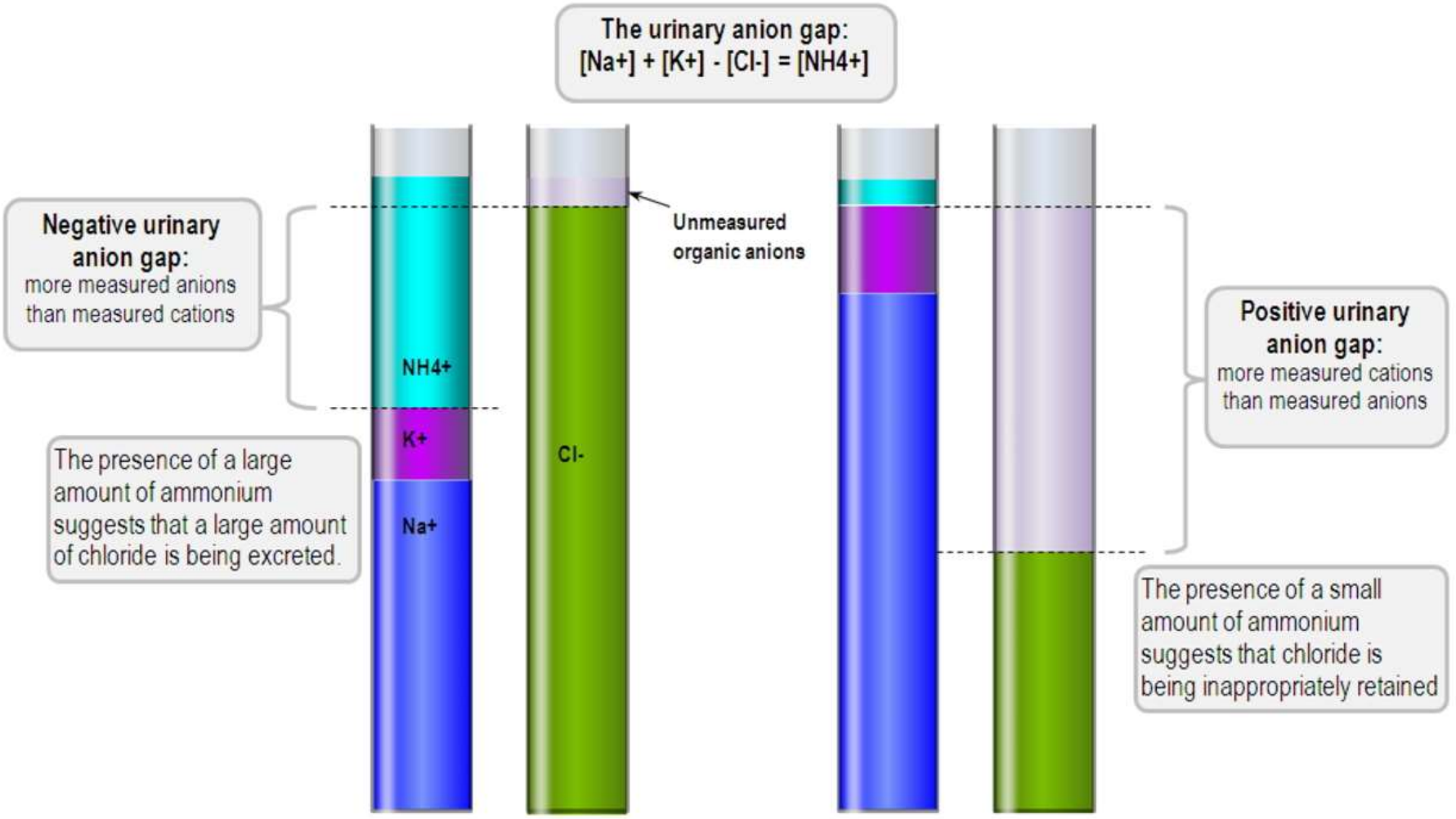
Estimation of the U_{NH4}+ concentration by calculation of the urine osmolality gap



$$U_{NH_4^+} = 0.5 \left(U_{osm} - \left[2\,Na^+ + K^+ \right]_u + urea_u + glucose_u \right)$$

Urinary ammonium concentrations of 75 mEq/L or more would be anticipated if renal tubular function is intact and the kidney is responding to the prevailing metabolic acidosis by increasing ammonium production and excretion. Conversely, values below 25 mEq/L denote inappropriately low urinary ammonium concentrations.

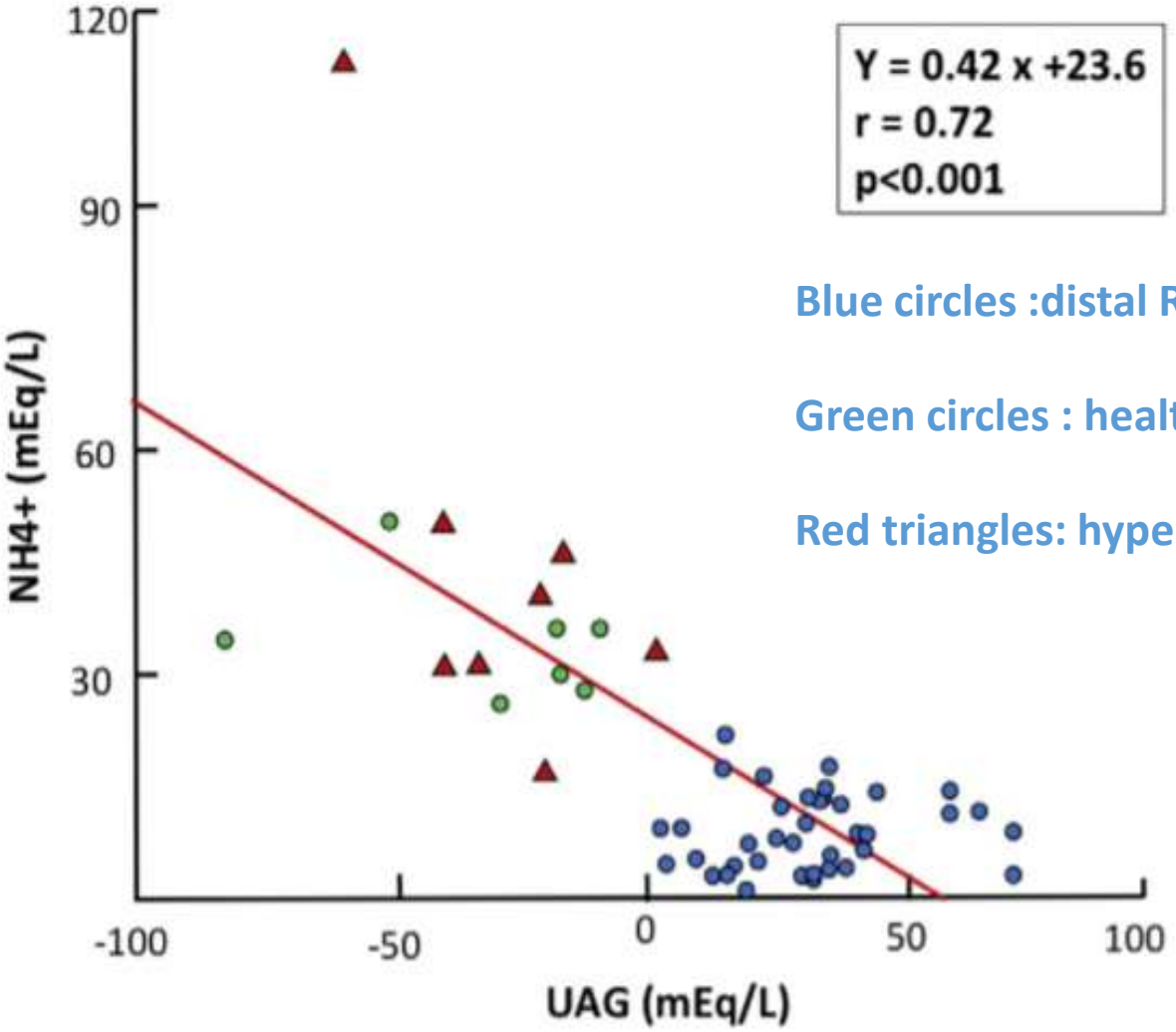
The urinary anion gap in metabolic acidosis



Mostly chronic metabolic acidosis or
Diarrhea induced hypercloremic acidosis

CKD, Distal RTA or
Renal adaptation of chonic respiratory alkalosis where NH4+ is suppressed

Urinary ammonium (NH4+) excretion in relation to urinary anion gap (UAG)

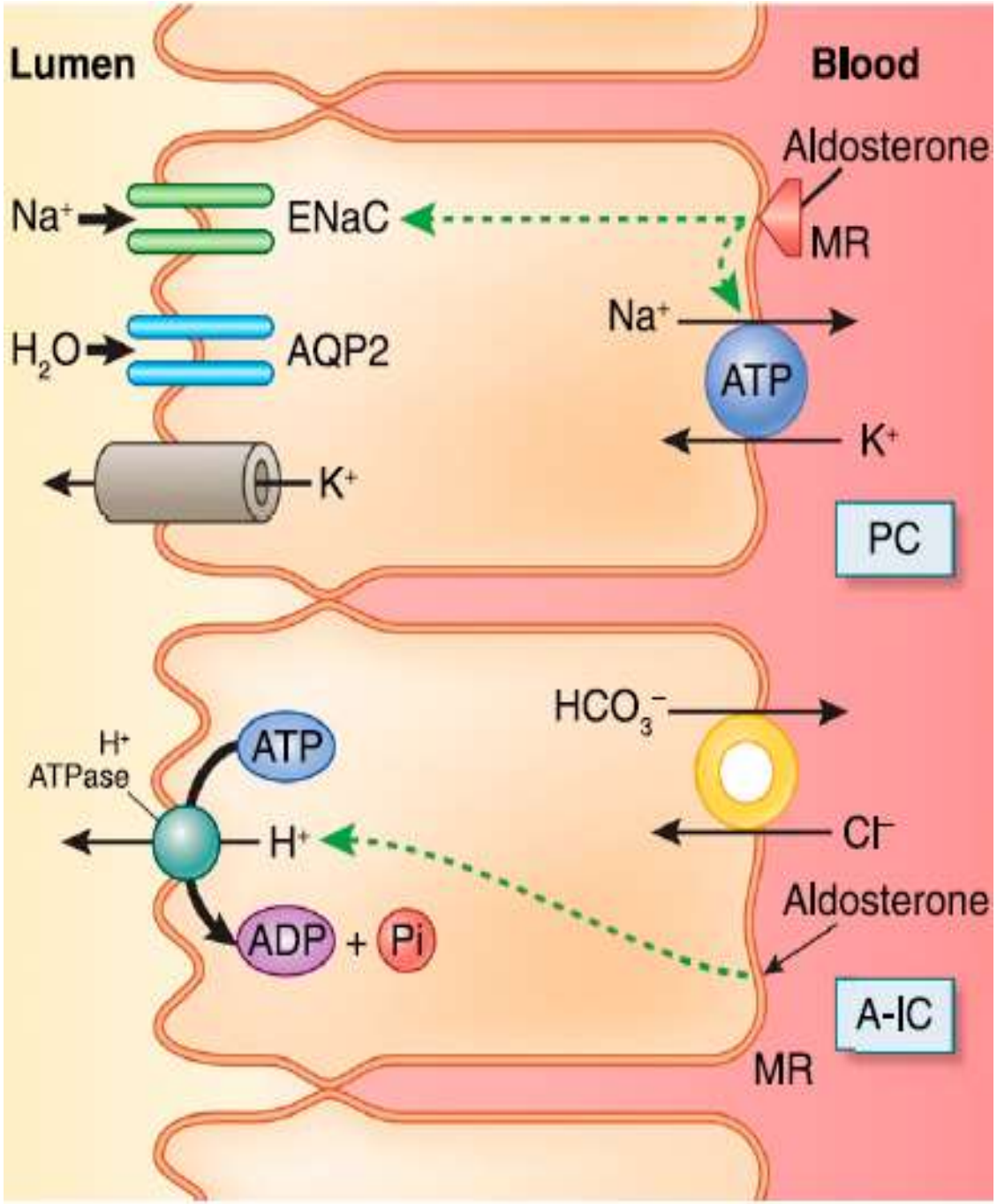


Blue circles :distal RTA

Green circles : healthy after NH4Cl

Red triangles: hyperchloremic acidosis with diarrhea

Battle et al, Am J Kidney Dis. 70:440-444, 2017



Effect of aldosterone on Na,K and H transport in the CD

Steps in evaluation of acid-base status

$$pH = pK_{\alpha} + \log \frac{[A^-]}{[HA^-]}$$

HCO_3^-

H_2CO_3 (pCO_2)

1. What is blood pH?
2. Which one (HCO_3^- or pCO_2) has moved in the direction of pH?
3. Is compensation appropriate?
4. Are there more primary abnormalities?
5. What is anion gap? **$AG = Na^+ - (Cl^- + CO_2)$**

Expected respiratory compensatory responses

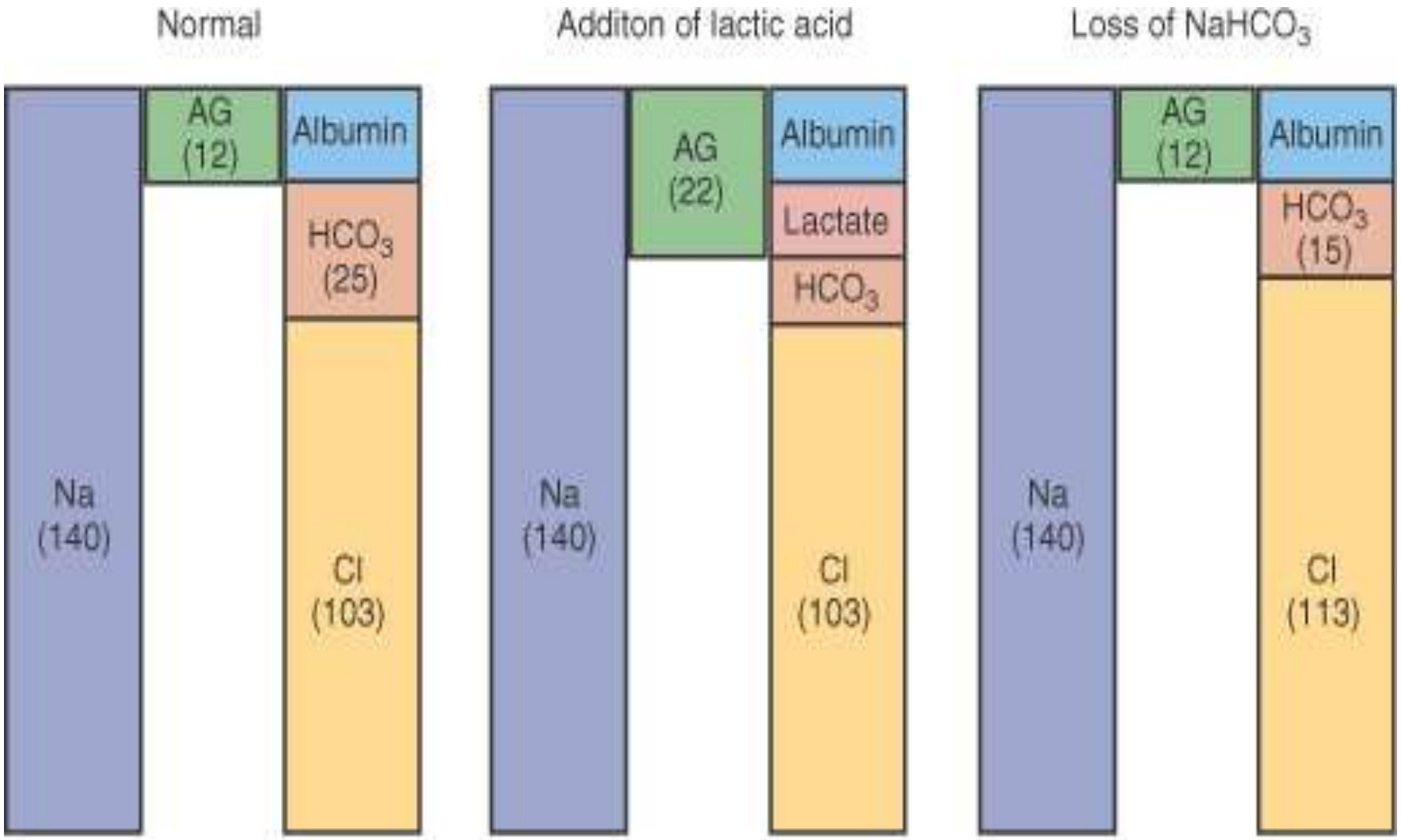
Disorder	Compensation	Limits
Metabolic Acidosis	Expected pCO_2 = (1.5 x HCO_3-) + 8 ± 2 Expected pCO_2 = last 2 digits of pH Δ pCO_2 = 1.2 x Δ HCO_3-	pCO_2 cannot go < 10 mmHg
Metabolic Alkalosis	Δ pCO_2 = 0.7 x Δ HCO_3- HCO_3- + 15 = pCO_2 = last two digits of pH	pCO_2 cannot go > 55 mmHg
Respiratory Acidosis	Acute: Δ HCO_3- = 0.2 x Δ pCO_2 Chronic: Δ HCO_3- = 0.4 x Δ pCO_2	HCO_3- cannot go > 30 mmHg HCO_3- cannot go > 45 mmHg
Respiratory Alkalosis	Acute: Δ HCO_3- = 0.2 x pCO_2 Chronic: Δ HCO_3- = 0.5 x pCO_2	HCO_3- cannot go < 17-18 mmHg HCO_3- cannot go < 12-15 mmHg

Arterial and central venous blood acid-base parameters

Condition	pH	pH	$[HCO_3^-]$		PCO_2 mmHg	PCO_2 mmHg
	A	CVB	A	CVB	A	CVB
Control	7.40	7.38	24	24	40	41
Acidosis without poor tissue perfusion	7.37	7.34	22	22	38	42
Severe CHF with decreased tissue perfusion	7.31	7.21	19.8	23.4	43.5	67.5
Cardiac arrest	7.36	7.01	6.9	8.1	27.5	76.5

Adrogue HJ et al. N Engl J Med 1989, 320 : 1312-1316
Treger R et al. Clin J Am Soc Nephrol 2010, 5: 390-394.

Assessment of the anion gap in plasma



$AG = Na^+ - (Cl^- + HCO_3^-)$

Significance of the anion gap

the past, “normal” anion gap was

12 +/- 4 meq/L

- **At present, changes in the technique for chloride have lowered the anion gap to**

  8 to 10 +/- 4 meq/L

- **Anion gaps less than 20 mEq/L rarely indicate significant acidosis and are most secondary to changes in proteins, phosphate, or charge equivalents**

- **Anion gaps of more than 30 mEq/L are usually caused by easily identifiable acidoses**

The “real” anion gap

Unmeasured cations mEq/L		Unmeasured anions mEq/L	
K	4.5	Proteins	15
Ca	5	PO_4	2
Mg	1.5	SO_4	1
		Organic acids	5
Total	11	total	23

Δ : + 12

Alterations in anion gap by non-acid-base disorders

- **Hypoalbuminemia and hyperphosphatemia**

Correction by following formula

"normal" AG = 2 (albumin g/dl) + 0.5 (phosphate mg/dl)

or

"normal" AG = 0.2 (albumin g/L) + 1.5 (phosphate mmol/L

- Practically: **The approximate correction is a reduction in the normal anion gap of 2.5 meq/l for every 1g/dl decline in the plasma albumin concentration (normal value = 4 g/dl)**
- **Hypercalcemia**
- **Lithium carbonate therapy**
- **Antibiotic administration (e.g. carbenicillin)**
- **Spurious laboratory results (e.g.hyperlipidemia)**

The use of the Delta AG / Delta HCO_3 ratio - Advantages

- **Delta AG / Delta HCO_3 ratio should be equal to 1 in pure high AG acidosis**

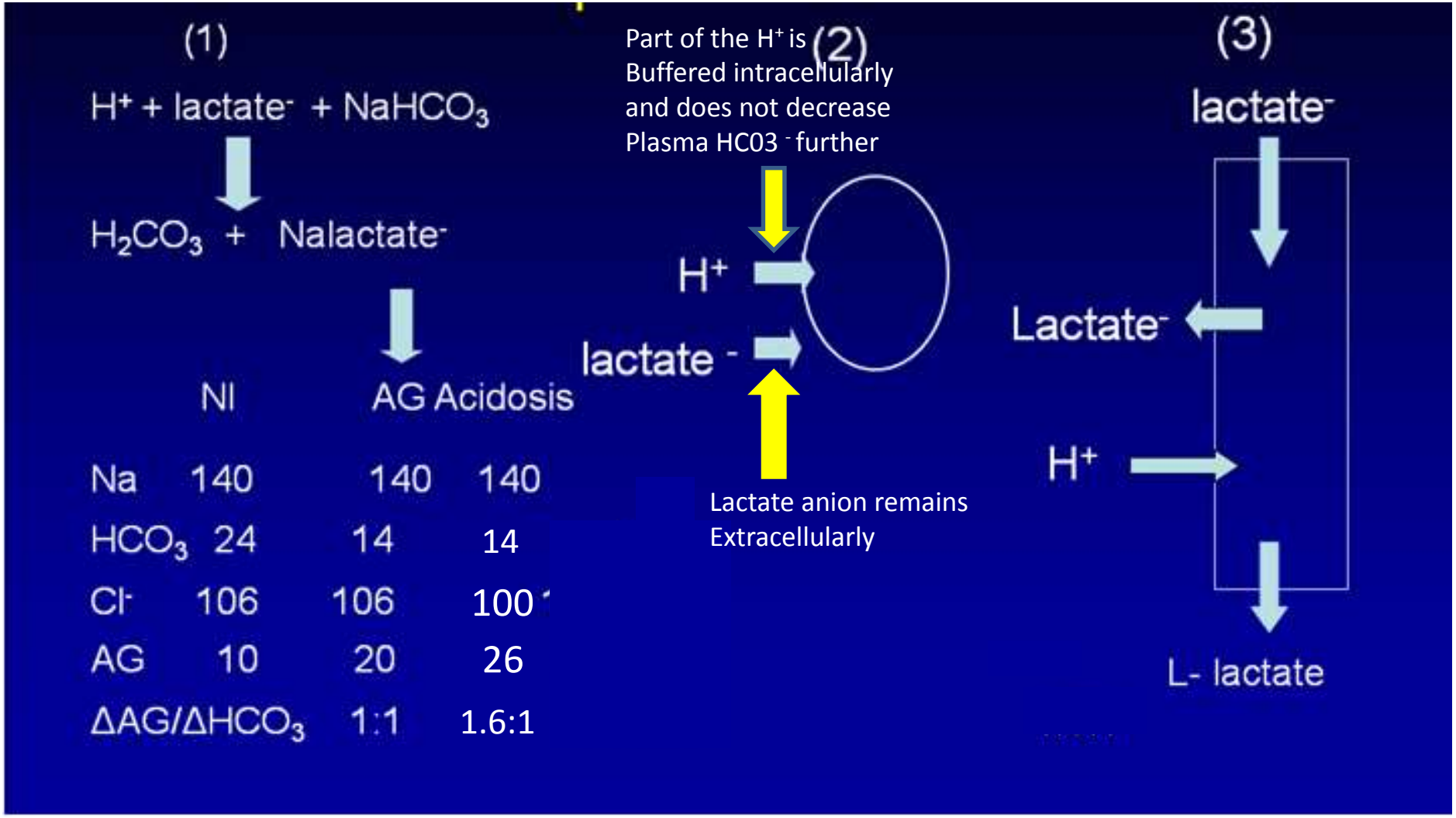
  A value > 1, where the increase in AG is higher than the decrease in HCO_3 could be due to concomitant alkalosis or compensation for respiratory acidosis.

  A value < 1 with a relative decrease of HCO_3 can be due to an concomitant hyperchloremic metabolic acidosis or compensation for a respiratory alkalosis.

Use of the Delta/Delta: Examples

AG	HCO3	Diagnosis
18 (↑ 6)	18 (↓ 6)	Appropriate; pure AG acidosis
18 (↑ 6)	22 (↓ 2)	HCO_3 has ↓ less than predicted, so HCO_3 is too high; mixed AG acidosis AND met alk
18 (↑ 6)	12 (↓ 12)	HCO3 has ↓ more than predicted, so HCO_3 is too low; mixed AG AND non-AG acidosis

Evolution of the serum anion gap
In high anion gap metabolic acidosis



Urinary anion excretion determines $\Delta AG/\Delta HCO_3$ in overproduction acidosis

Disorder	DKA (n = 8)	L-Lactic acidosis (n = 8)	Toluene intoxication (n = 3)
Plasma HCO_3^- (mEq/L)	11.0 ± 1.3	14.9 ± 2.4	11.3 ± 1.5
$\Delta AG/\Delta HCO_3$	1.0 ± 0.1	1.5 ± 0.1	0.3 ± 0.1
Fe anion %	45.8 ± 3.1	4.7 ± 0.3	> 100

Kim et al Clin Nephrol 55: 448, 2001

Anion gap acidosis mnemonic: GOLD MARK:

- Glycols (ethylene and propylene),
- Oxoproline,
- L-lactate, D-lactate,
- Methanol,
- Aspirin,
- Renal failure, and
- Ketoacidosis.

Mehta et al. Lancet 2008;372:892

** Anion gap corrected for albumin is an excellent surrogate for strong inion gap (SIG).*

American Journal of Emergency Medicine (2012) 30, 391

PLoSONE, vol. 8, no.2,2013.

Major pathways of pyruvate and lactate metabolism

Lactic acid production:

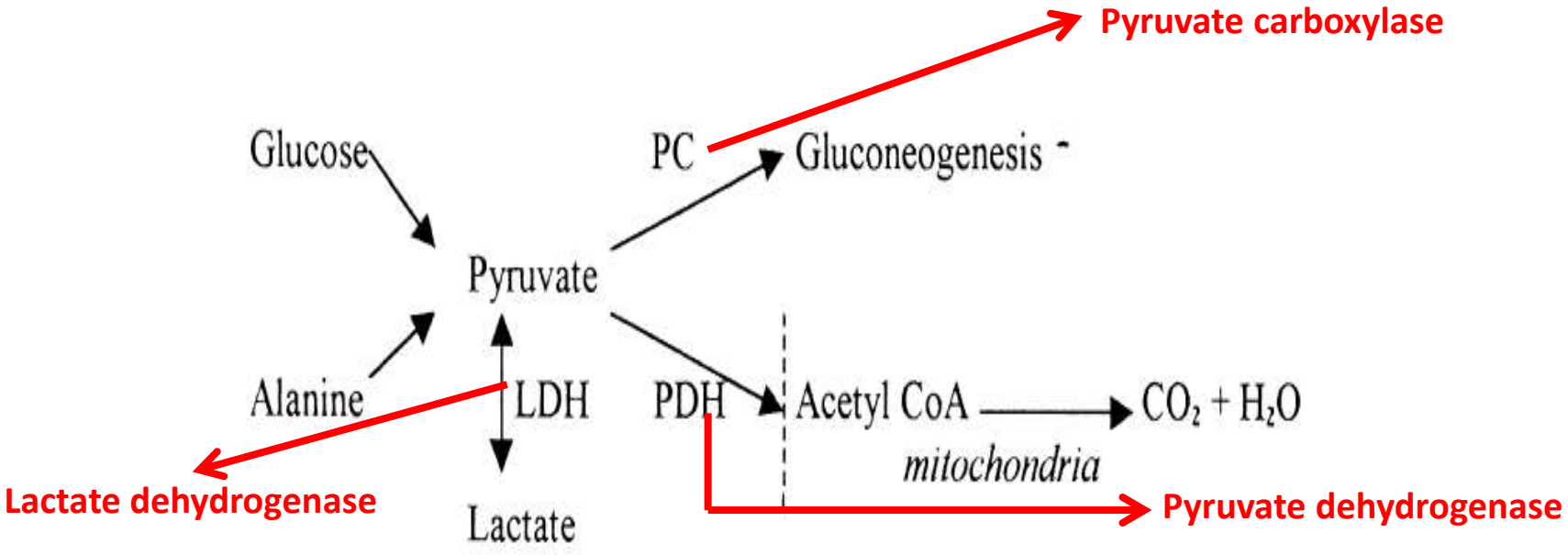
Skin
Erytrocytes
Brain
Muscle

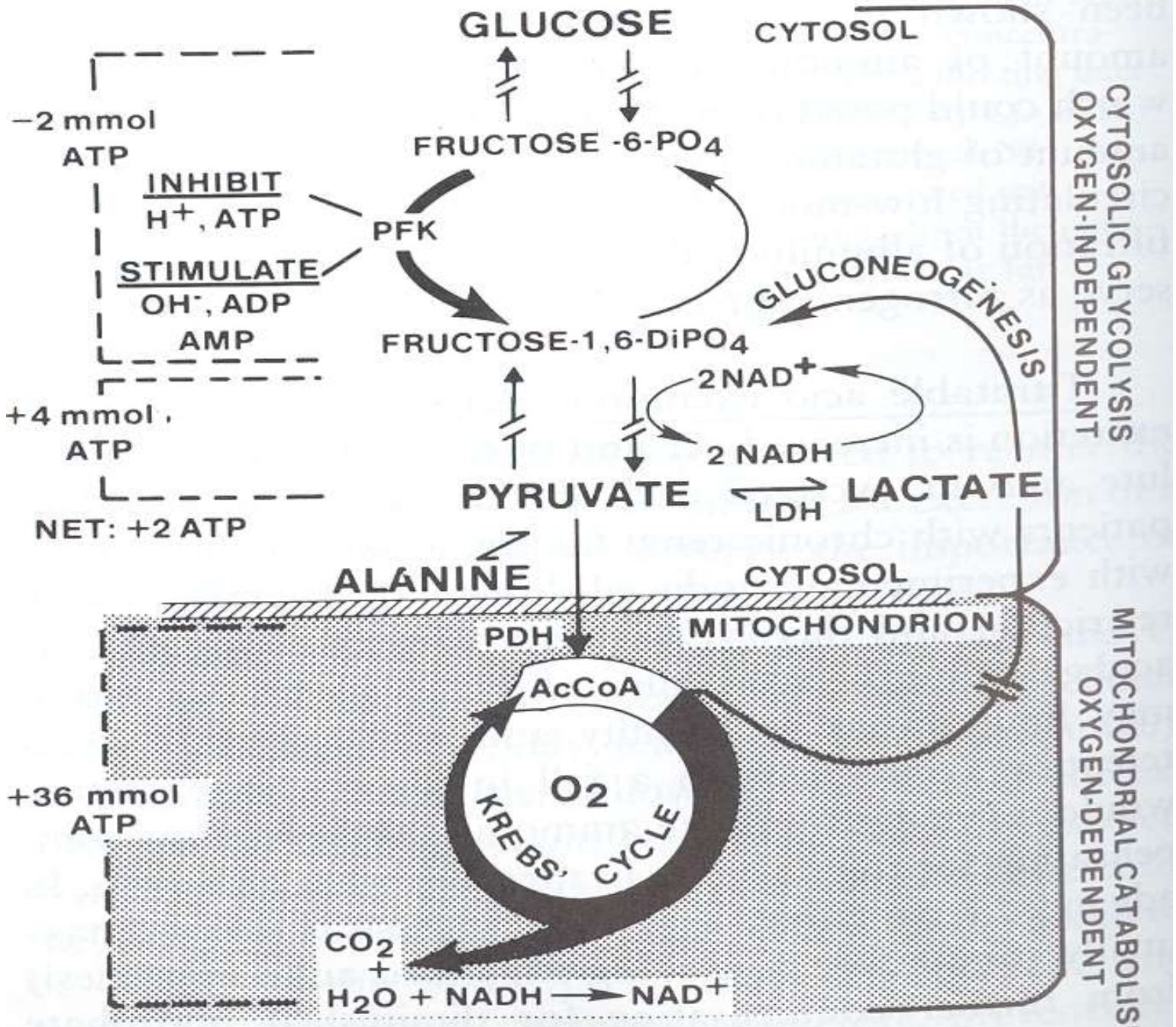
Lactic acid utilisation:

90% by Liver
1. oxydation of pyruvic acid (80%)
2. gluconeogenesis (20%)

10% by Kidney
1. oxydation of pyruvic acid
2. gluconeogenesis
3. excretion

Basal lactate production
Is 0.8 mmol/kg/hr (1300 mmol/day)




GLUCOSE
CYTOSOL
−2 mmol ATP
FRUCTOSE -6-PO4
INHIBIT
H+, ATP
PFK
STIMULATE
OH-, ADP
AMP
GLUCONEOGENESIS
FRUCTOSE-1,6-DiPO4
2NAD+
+4 mmol ATP
2 NADH
PYRUVATE
LDH
LACTATE
NET: +2 ATP
ALANINE
CYTOSOL
MITOCHONDRION
PDH
AcCoA
+36 mmol ATP
O2
KREBS' CYCLE
CO2 + H2O + NADH → NAD+
CYTOSOLIC GLYCOLYSIS
OXYGEN-INDEPENDENT
MITOCHONDRIAL CATABOLISM
OXYGEN-DEPENDENT

Conditions favouring the conversion of pyruvate to lactate

Systemic hypoperfusion necessitating anaerobic metabolism

Regional hypoperfusion and microcirculatory dysfunction

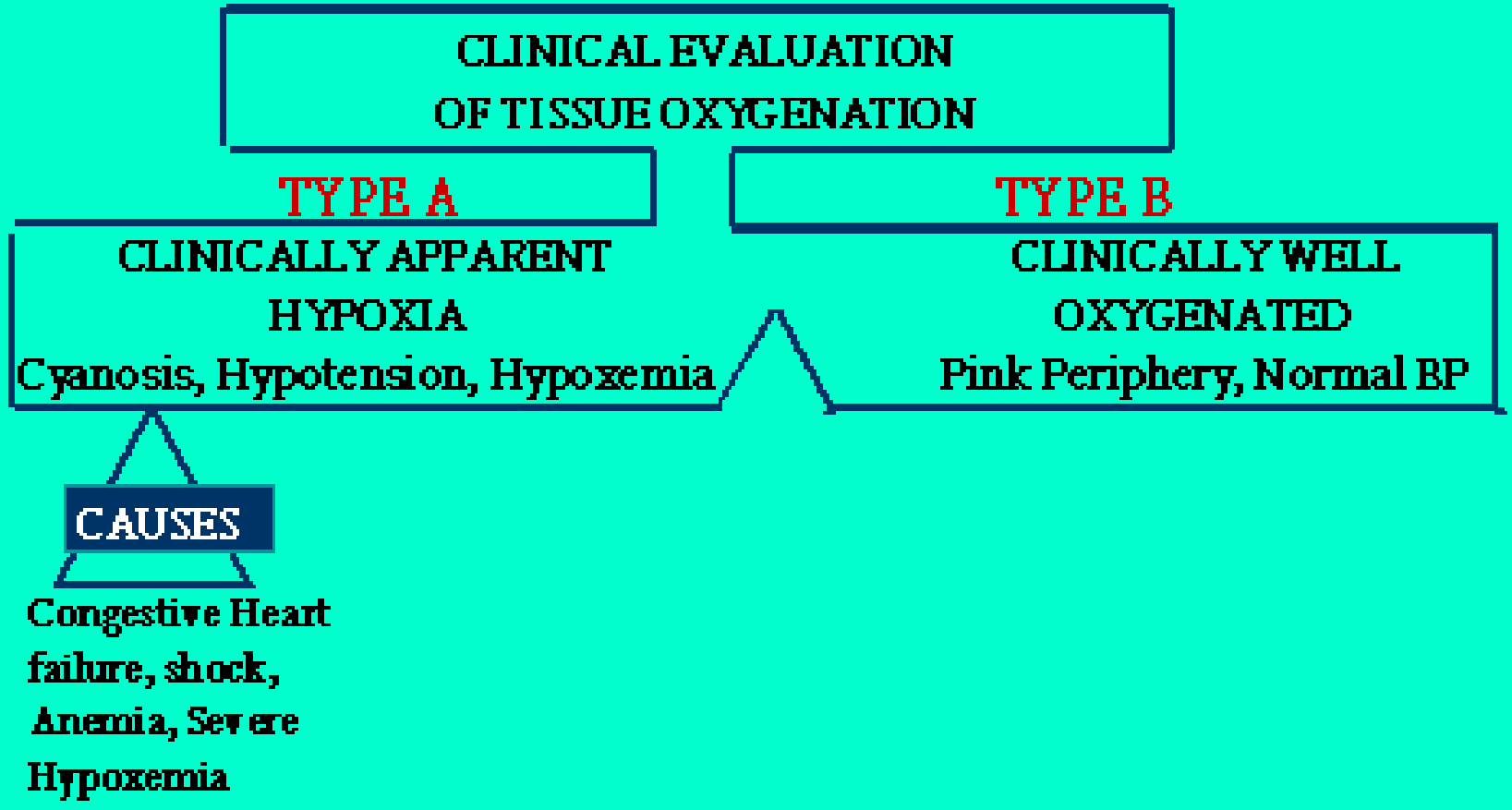
Increased aerobic glycolysis, with pyruvate production exceeding pyruvate dehydrogenase capacity. This condition may be seen in response to cytokine release, increased circulating catecholamine levels, or the accumulation of leukocytes at the site of inflammation/infection

Mitochondrial dysfunction shunting pyruvate away from the tricarboxylic acid cycle, which may be seen in sepsis and drug toxicity (f.e.metformin)

Impaired activity of pyruvate dehydrogenase, which is essential for the conversion of pyruvate into acetyl coenzyme A, a necessary step in aerobic metabolism. This condition may be seen in excessive alcohol use and cofactor deficiency states (beriberi)

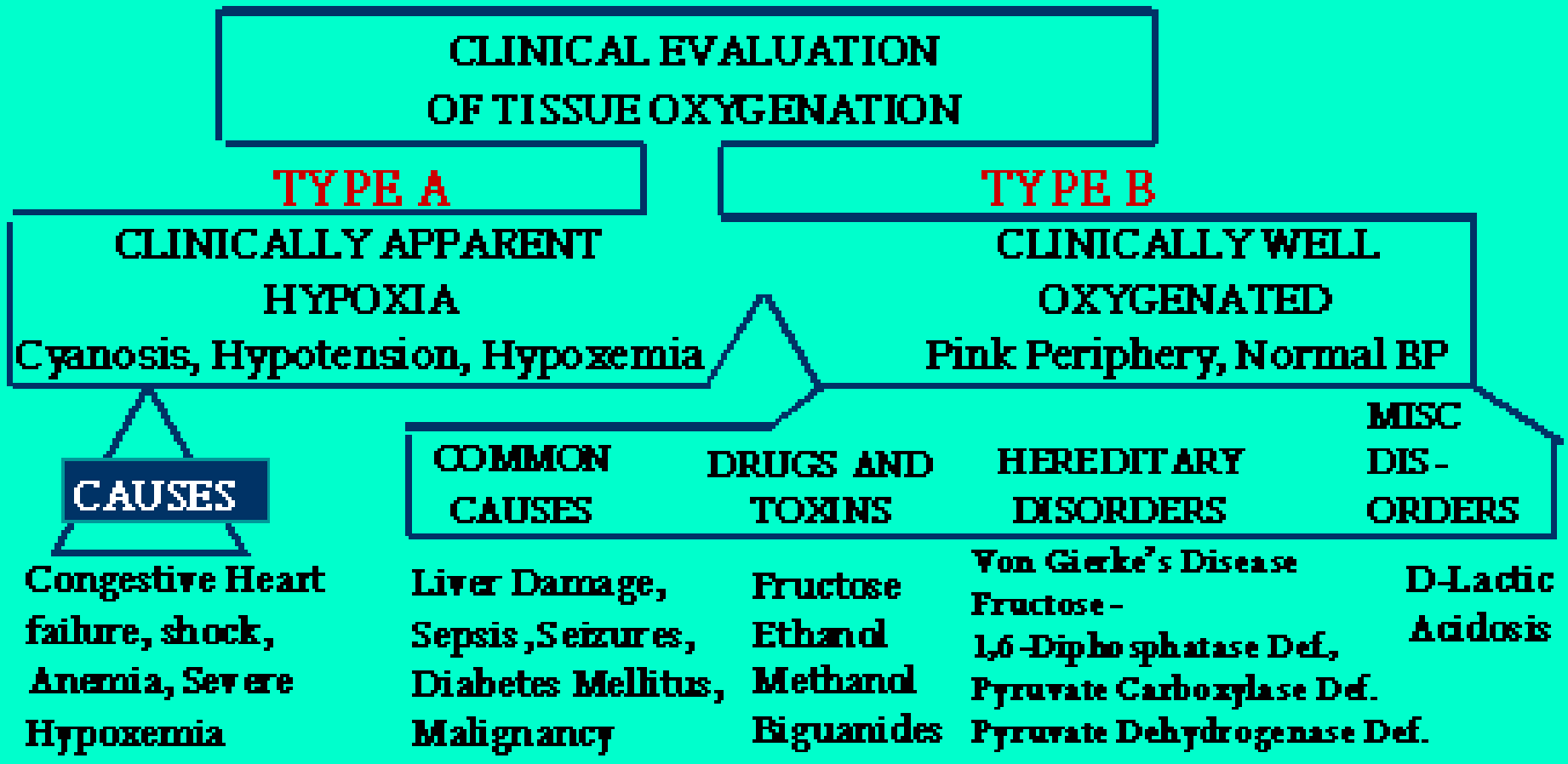
Diagnosis of lactic acidosis (1)

- (HCO_3), Pco_2, pH: all low
- Anion Gap: Increased > 12 mM
- Ketotest neg; BUN < 40 mg/dl;
- no intoxication
- serum (lactate) increased > 2 mM

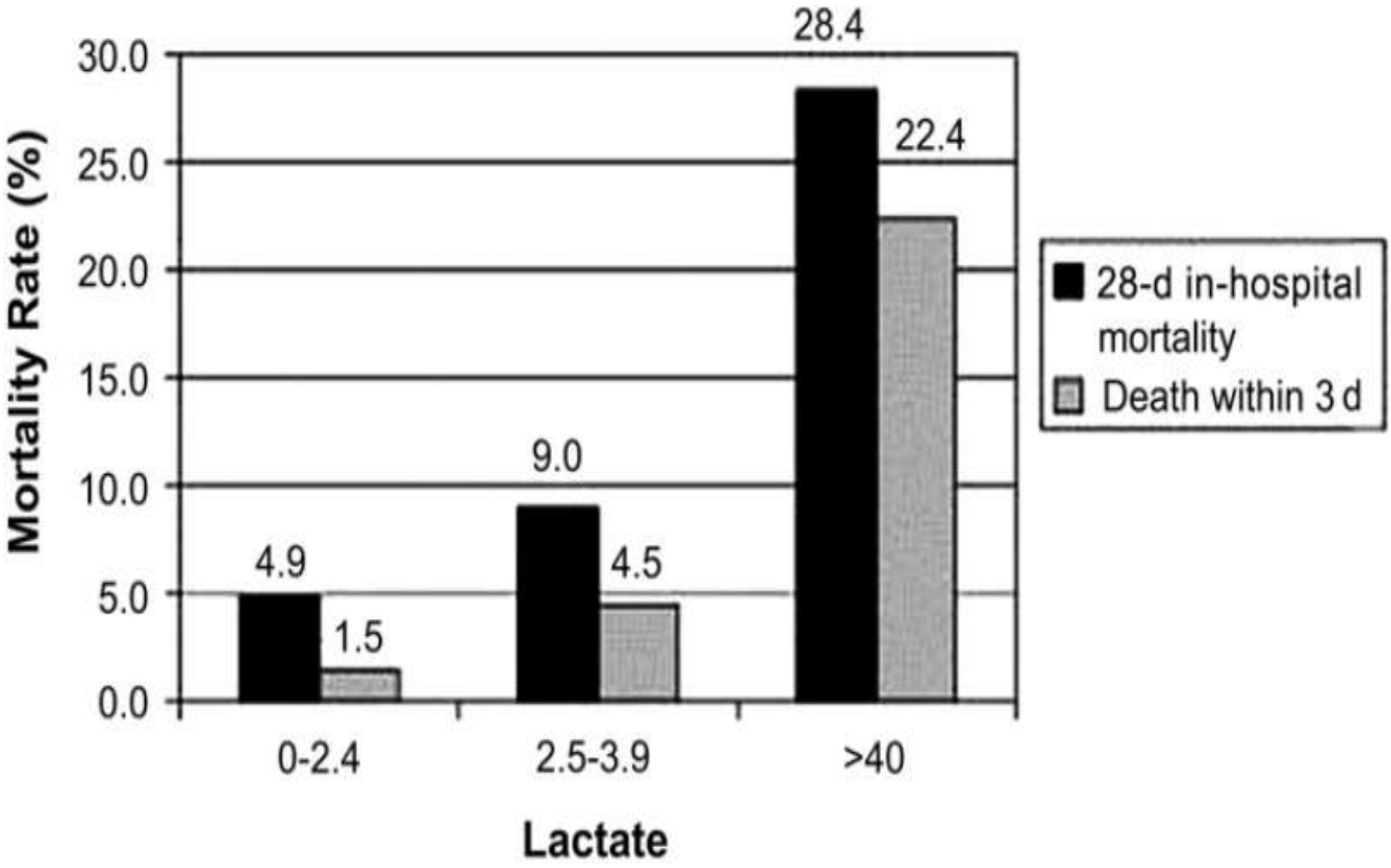


Diagnosis of lactic acidosis (2)

- (HCO_3), Pco_2, pH: all low
- Anion Gap: Increased > 12 mM
- Ketotest neg; BUN < 40 mg/dl;
- no intoxication
- serum (lactate) increased > 2 mM

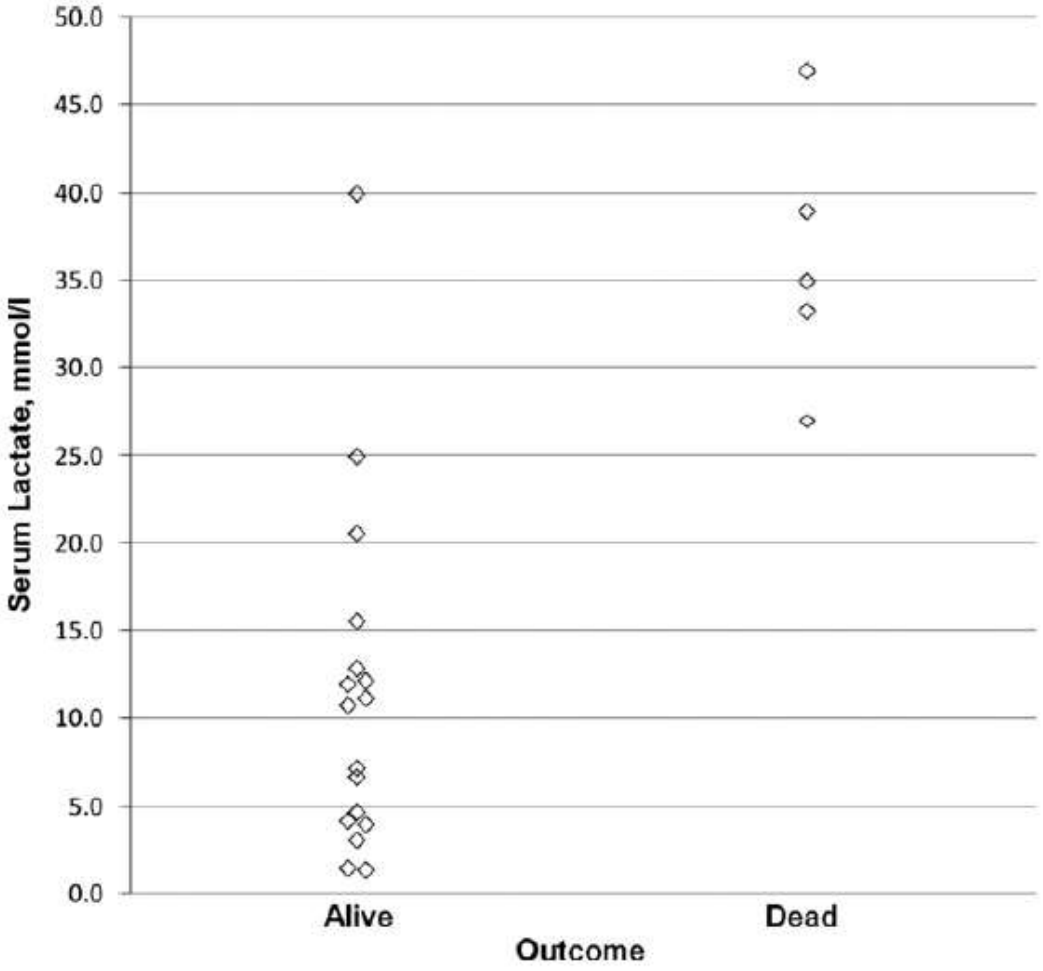


Lactate as a predictor of mortality



Shapiro et al Ann Emerg Med 2005;45(5):524–528;

Metformin overdose- lactate levels



Peak serum lactate concentration and mortality.

Dell'Aglio et al, Ann Emerg Med. 2009;54:818-823

Modification of metformin doses with respect to renal function

CKD stage	eGFR ml/min/1.73 m^2	Dose	% max.
0–1	≥90	2,500 mg daily	100
2	≥60	1,000 mg b.i.d.	80
3	≥45	500 mg b.i.d.	40
3	≥30	500 mg daily	20
4–5	<30	0	0

David Klachko, Adam Whaley-Connell, Cardiorenal Medicine, Vol 1, 2011

Updated US Food and Drug Administration guidelines for the use of metformin in CKD

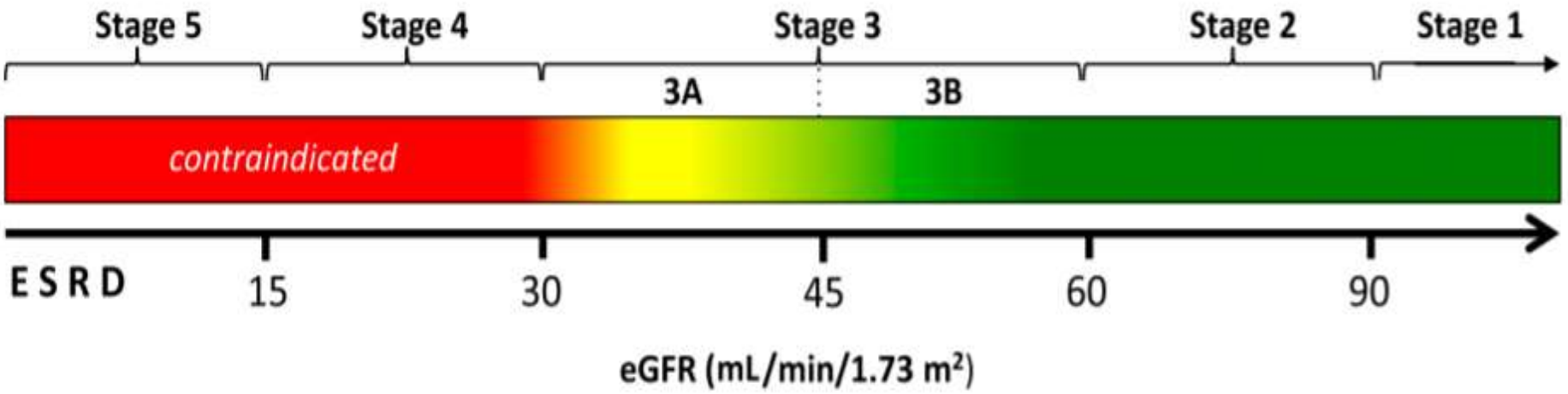


Figure 2—Recently updated U.S. Food and Drug Administration guidelines for the use of metformin in CKD. Metformin may now be used in patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 but is contraindicated in those with an eGFR <30 mL/min/1.73 m^2. If eGFR falls <45 mL/min/1.73 m^2, the benefits and risks of continuing treatment should be assessed. Starting metformin in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended. ESRD, end-stage renal disease.

Inzucchi SE, Diabetes Care 2017;40:1128–1132 |

Relationship between plasma bicarbonate and GFR in patients with CKD of various causes

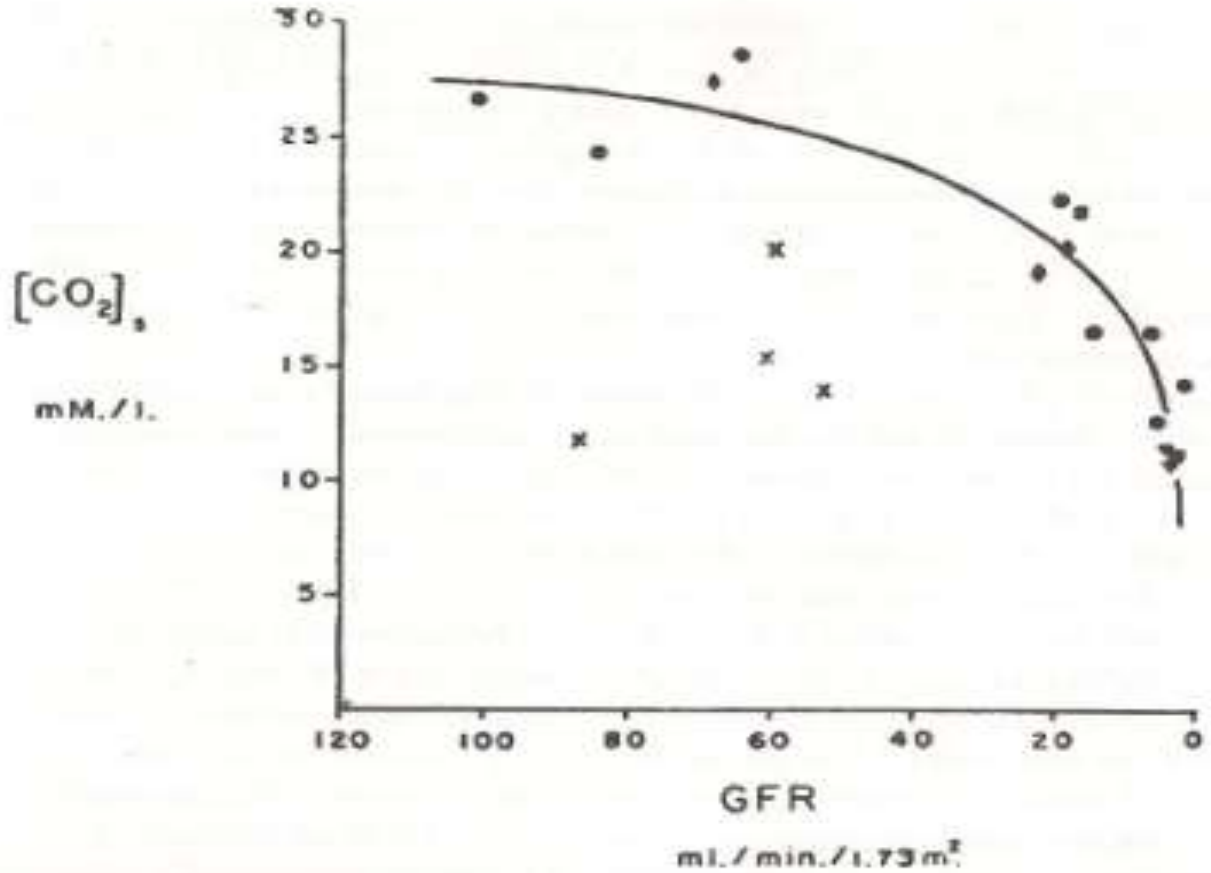
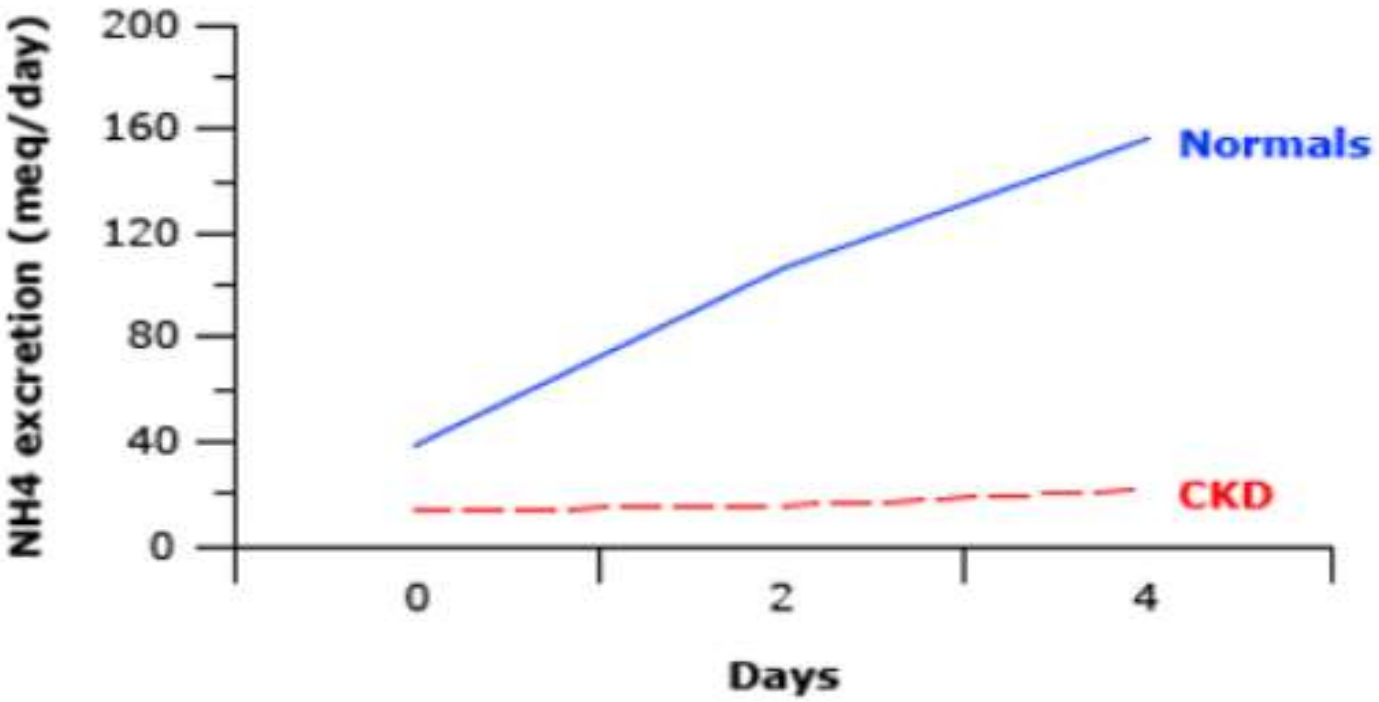


FIG. 1. Relationship between the level of serum total CO_2 concentration and glomerular filtration rate (GFR) in patients with chronic renal disease of various causes, including chronic glomerulonephritis (●), chronic pyelonephritis (■), nephrosclerosis (◆), and polycystic kidney disease (▼). Data from four patients with renal tubular acidosis also are depicted (X). (From ref. 6.)

Elkinton JR Ann Int Med 57:660-684, 1962

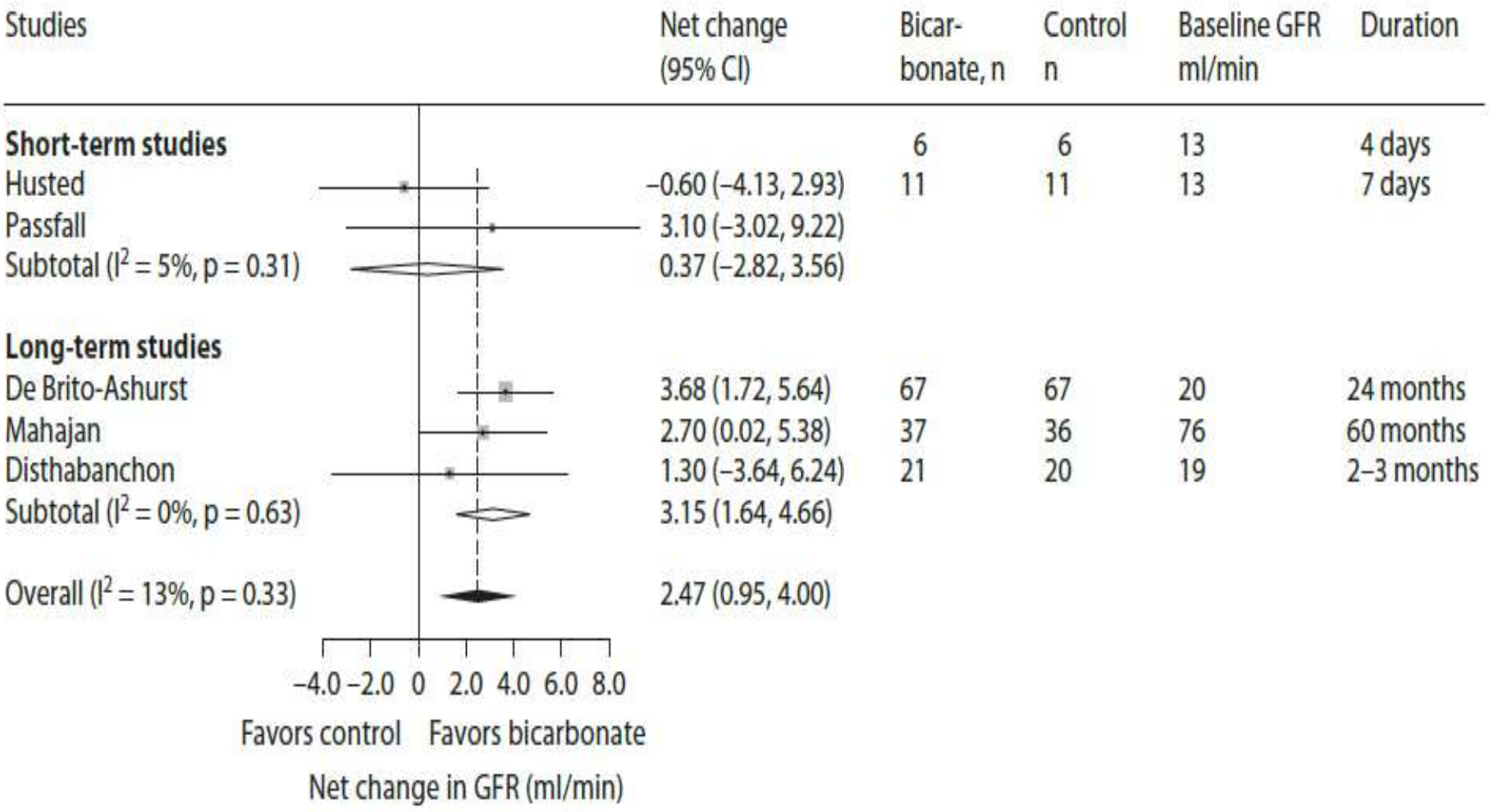
Impaired ammonium excretion in chronic kidney disease-NH4Cl loading in normals and CKD



Urinary excretion of ammonium (NH4) in normals (solid line) and patients with chronic kidney disease (CKD, dashed line) at baseline and after an acid load. The plasma bicarbonate concentration fell from 27 to 22 meq/L in normals and from 22 to 14 meq/L in CKD following the acid load.

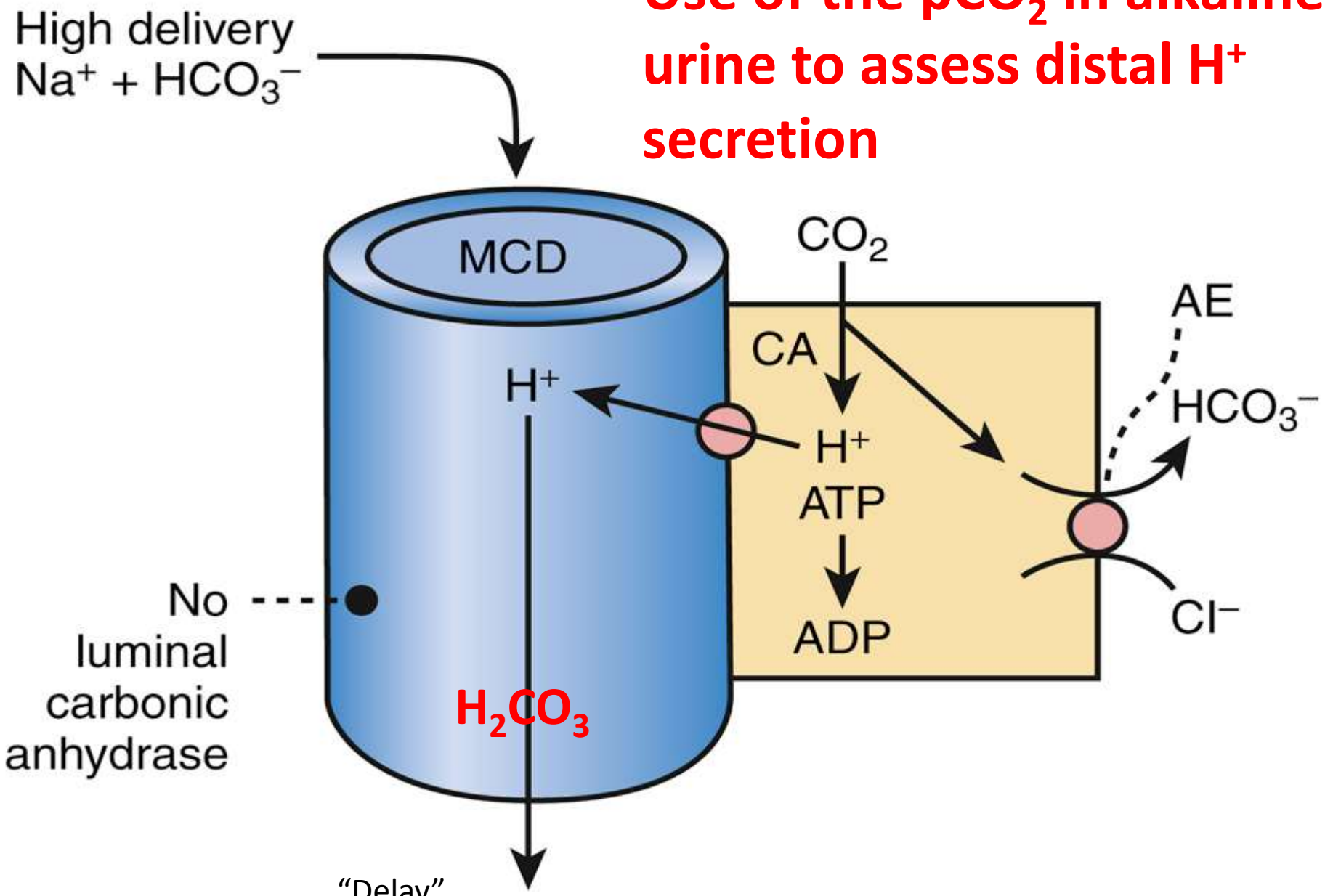
Welbourne et al, J Clin Invest 1972, 51: 1852

Beneficial effects on GFR decline of bicarbonate treatment of acidosis in CKD

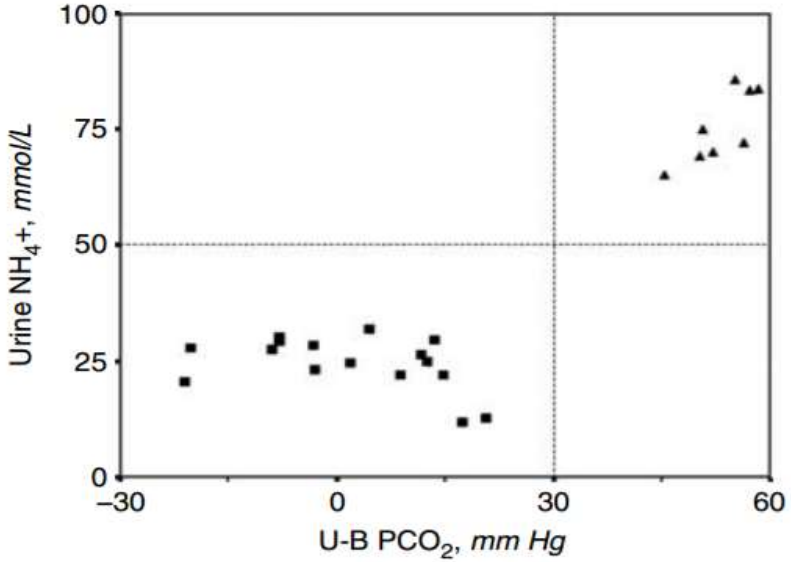


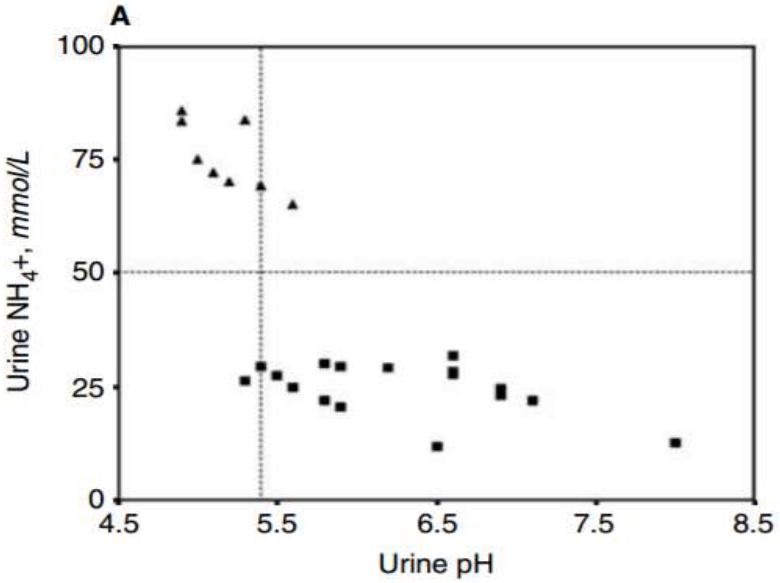
Susantitaphong et al, Am J Nephrol 2012;35:540–547

Use of the pCO_2 in alkaline urine to assess distal H^+ secretion

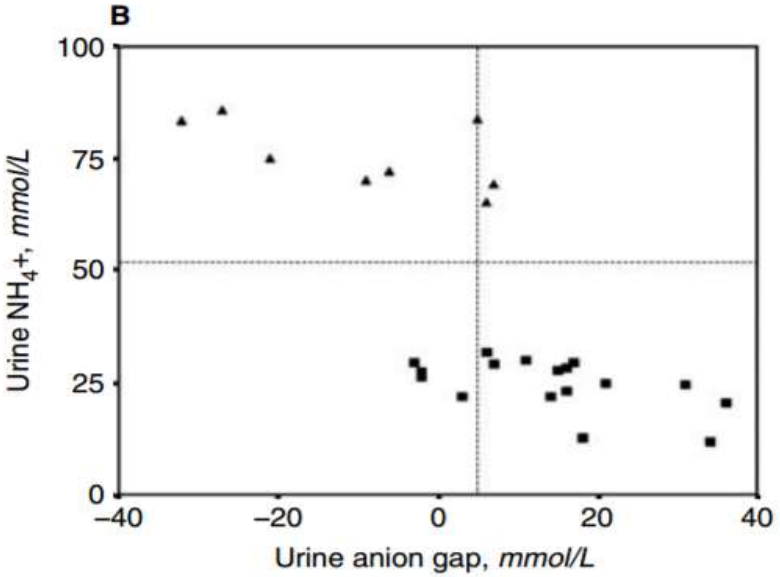


The U-B pCO_2 after bicarbonate loading in dRTA vs controls



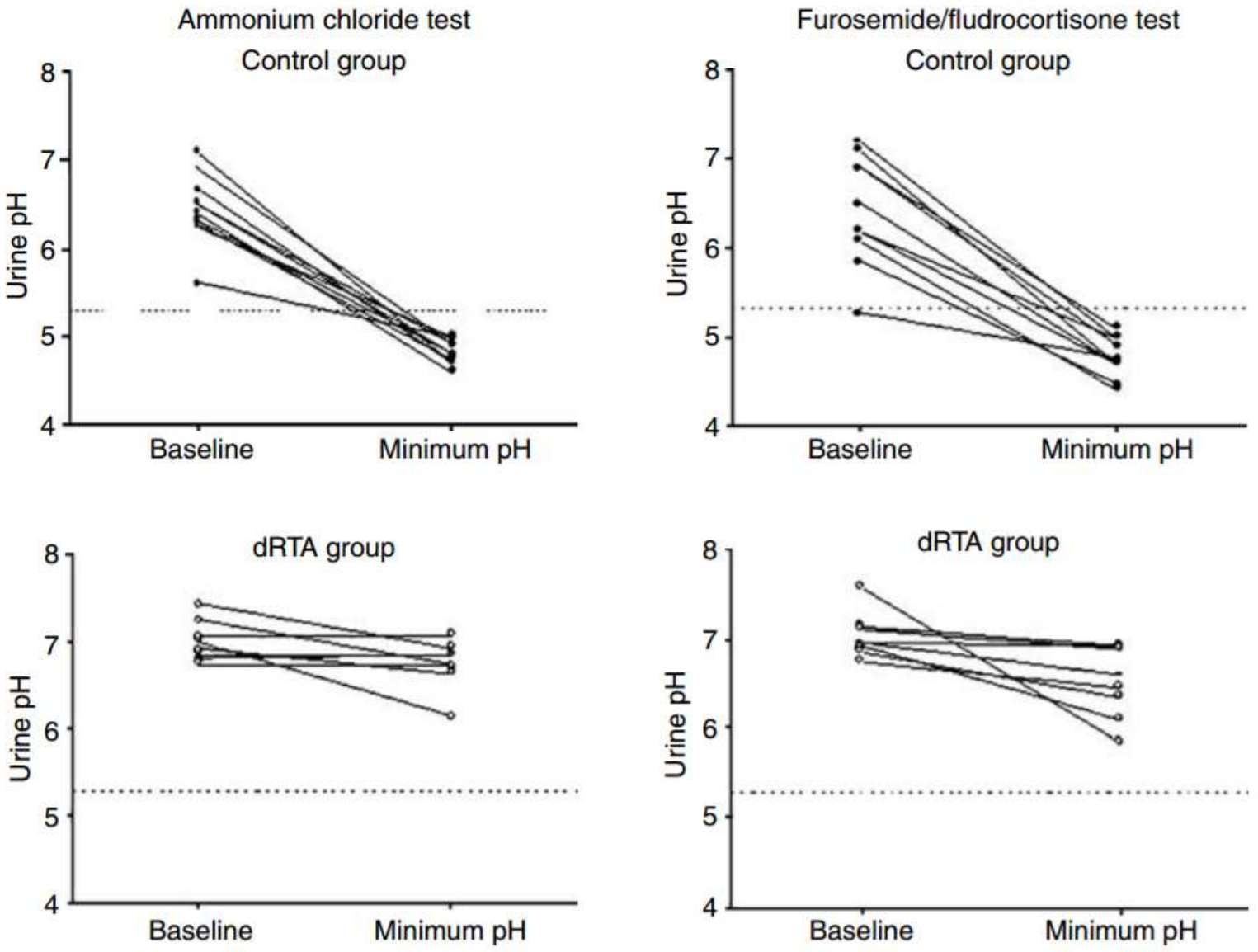


Infusion of 2.75% NaHCO3 solution (4ml/kg/hr. Urine and blood samples at 2hr intervals until the plasma bicarbonate concentration reached 26 mmol/L. Urine and blood PCO2 were measured using a blood gas analyzer (Nova, Waltham, MA, USA), and the U-B PCO2 was calculated when the urine pH was raised to 7.5.



Kim et al, Kidney Int 66 (2004), 761–767

The furosemide-hydrocortison test for acidification



Walsh et al, Kidney International (2007) 71, 1310–1316

The different types of renal tubular acidosis

	Proximal RTA (type II)	Distal RTA (type I)			Type IV RTA
	Bicarbonate wasting	Classic Ia (secretory)	Hyperkalaemic Ib (voltage-dependent)	Rate-limited	Hyperkalaemic (hypoaldosteronism)
During acidosis					
Urine anionic gap	Negative	Positive	Positive	Positive	Positive
Urine pH	<5.5	>5.5	>5.5	<5.5	<5.5
Plasma K	↔ ↓	↓	↑	↔	↑
After bicarbonate loading					
$FeHCO_3$	>15%	<5%	<5%	<5%	<10%

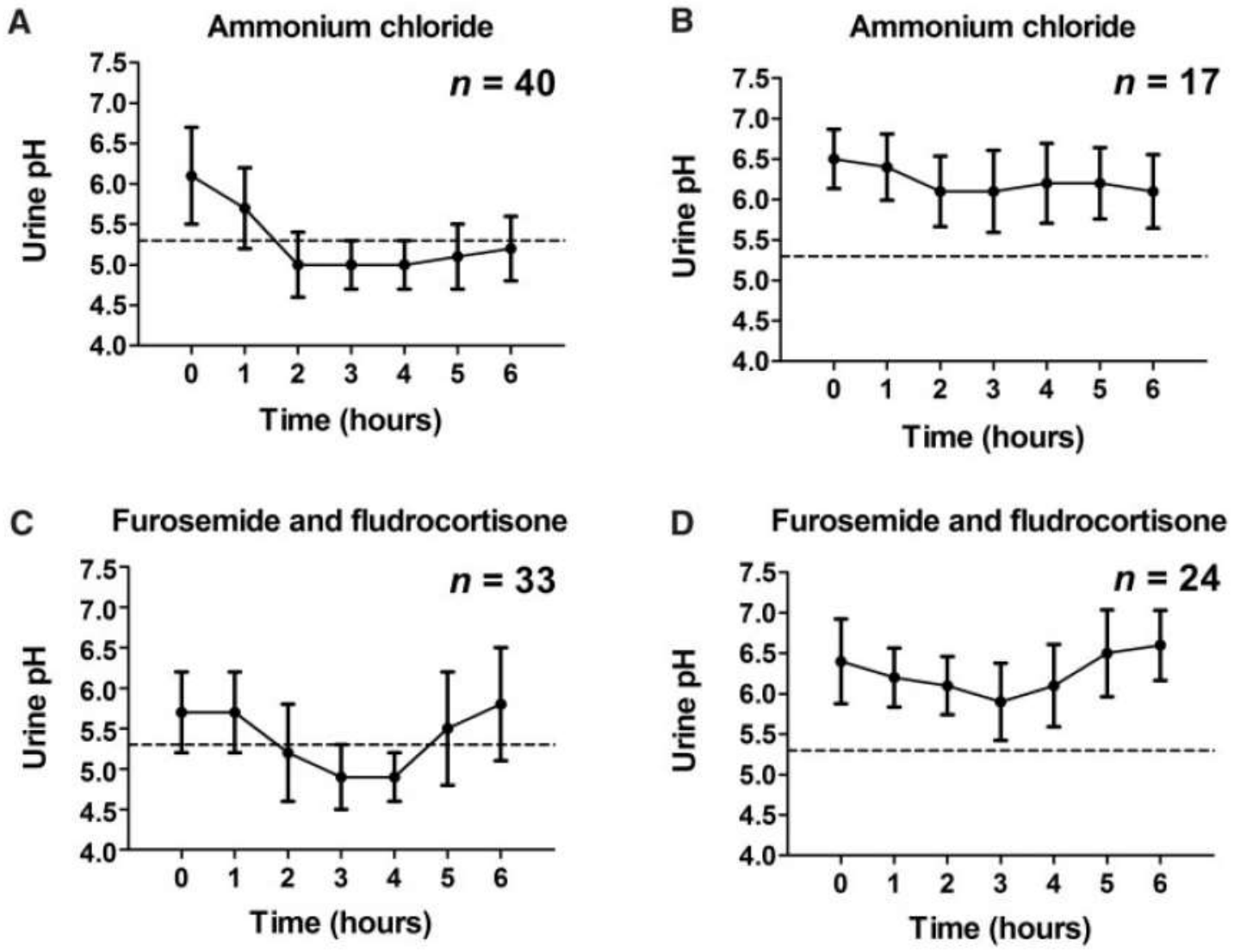
Schwarz et al Nephrol Dial Transplant (2006) 21: 2615–2620

Classification of distal renal tubular acidosis

Voltage Defect	H+ Secretory Defect	H+ Gradient Defect	Defect in Ammonium Secretion
Inherited forms			
Mutation in ENaC subunits	Mutations in H+ATPase (vacuolar)	None	None
Mutations in mineralocorticoid receptor	Mutations in AE1		
	Mutations in CAII		
	Medullary sponge kidney		
Acquired forms			
Hypoaldosteronism	Autoimmune disease	Medication	Associated with hyperkalemia
Any cause	Sjögren syndrome	Amphotericin	
Medications	Lupus		
NSAIDs	Thyroid disease		
Amiloride	Medications		
Cyclosporine	Topiramate		
Lithium	Acetazolamide		
RAAS inhibitors			
Heparin			
Potassium levels			
Normal or elevated	Usually low	Usually low	Elevated
Renal insufficiency			
May be present	Usually absent	Variable	Often present

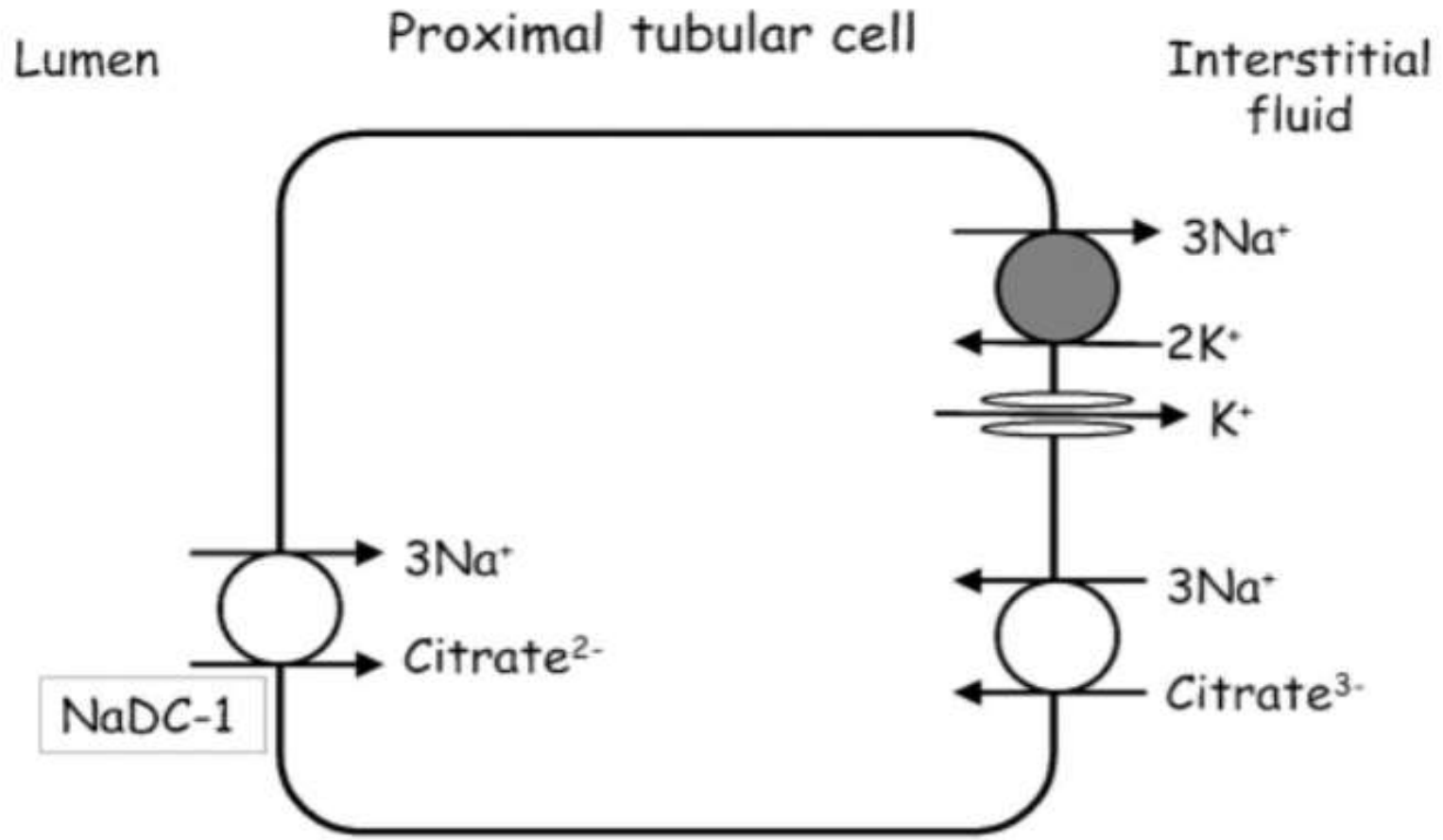
Rosner et al , Clin J Am Soc Nephrol 10: 530–539, 2015

Prevalence of DRTA in 57 patients with Sjögren disease



Both et al, Rheumatology 2015;54:933-939

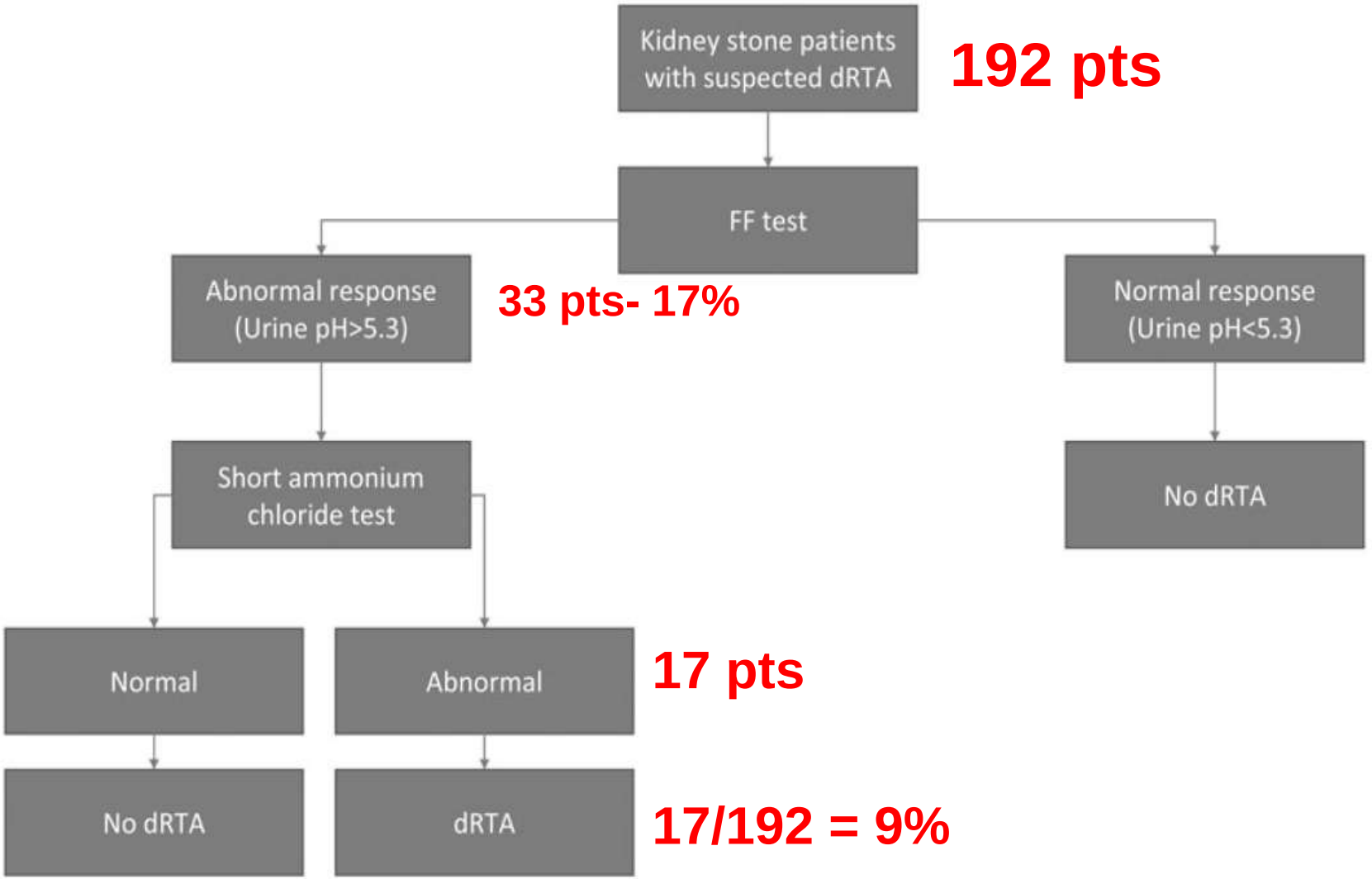
Mechanisms of citrate uptake in the proximal tubule



NaDC-1: Na+-dicarboxylate co transporter

Unwin et al, Nephron Physiol 2004;98:15–20

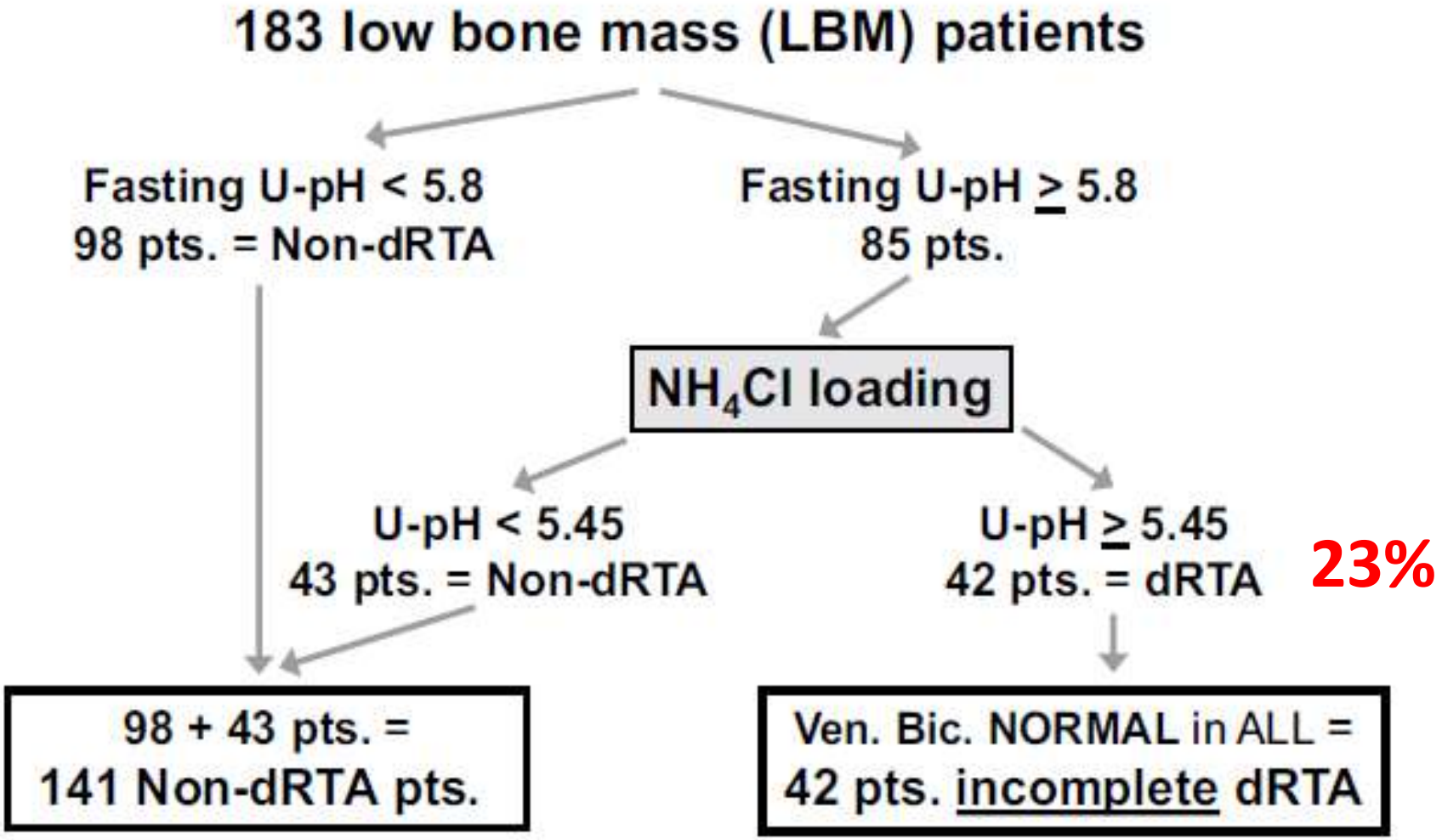
Prevalence of distal tubular acidosis in recurrent kidney stone formers



FF test false positive: 16/33 (49%)

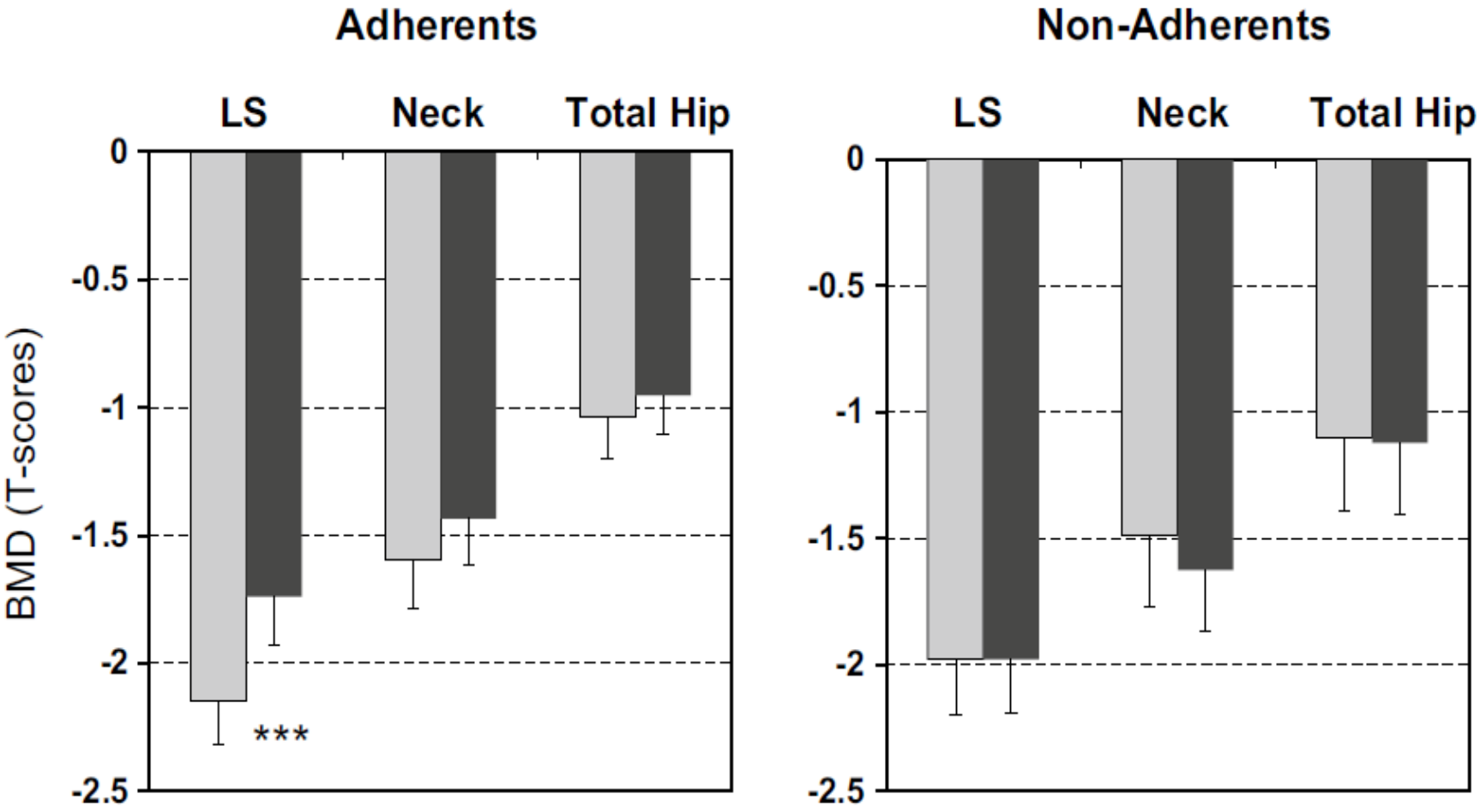
Shavit et al Nephrol Dial Transplant (2016) 0: 1–7

Prevalence of abnormal distal renal tubular acidification in patients with low bone mass



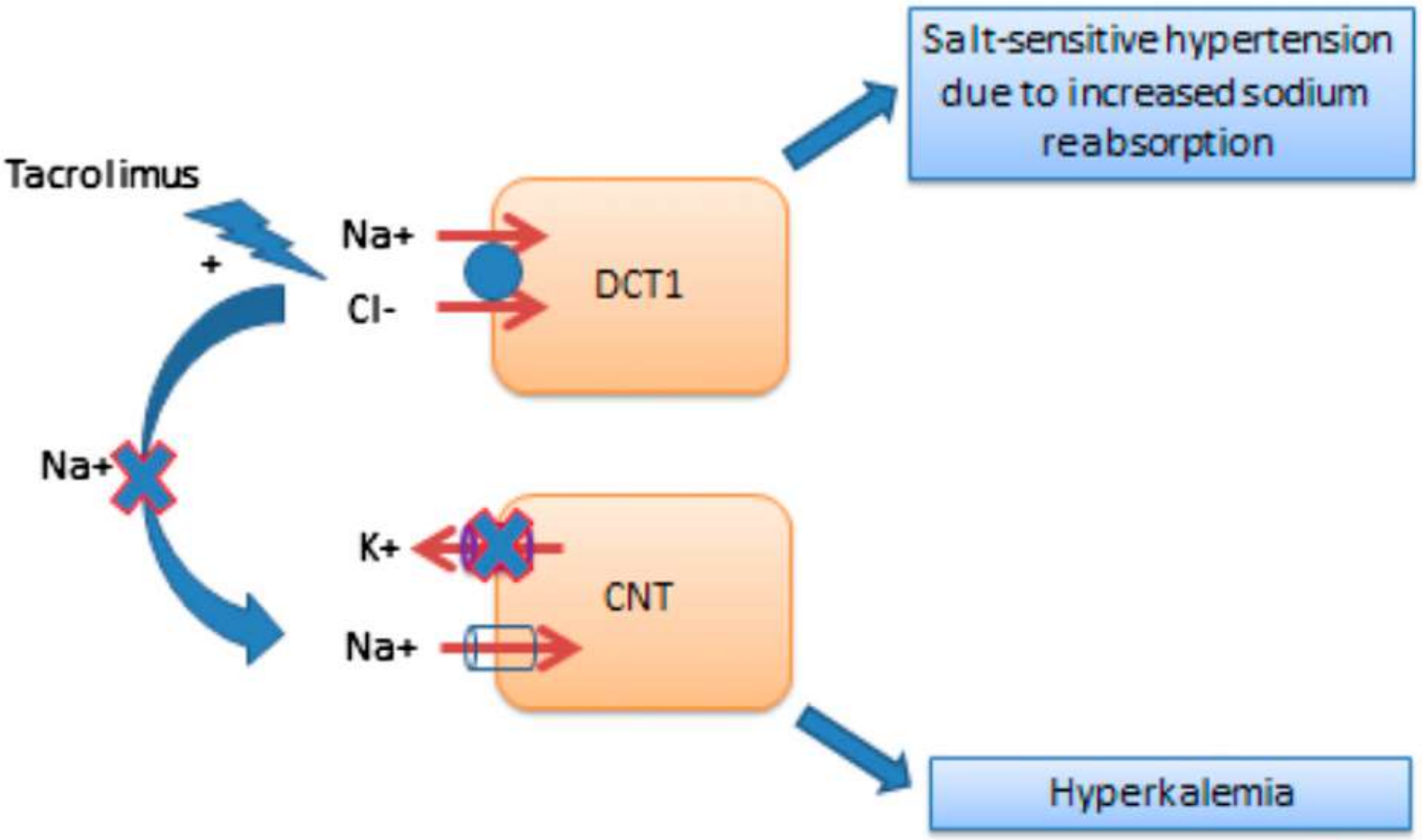
Sromicki,Hess, Urolithiasis, 2016

Effect of chronic alkali treatment on bone density (at start and FU)



Sromicki,Hess, Urolithiasis, 2016

Mechanism of CNI-induced hyperkalemia and renal tubular acidosis



Rosner et al, Clin J Am Soc Nephrol 11: 735–744, 2016

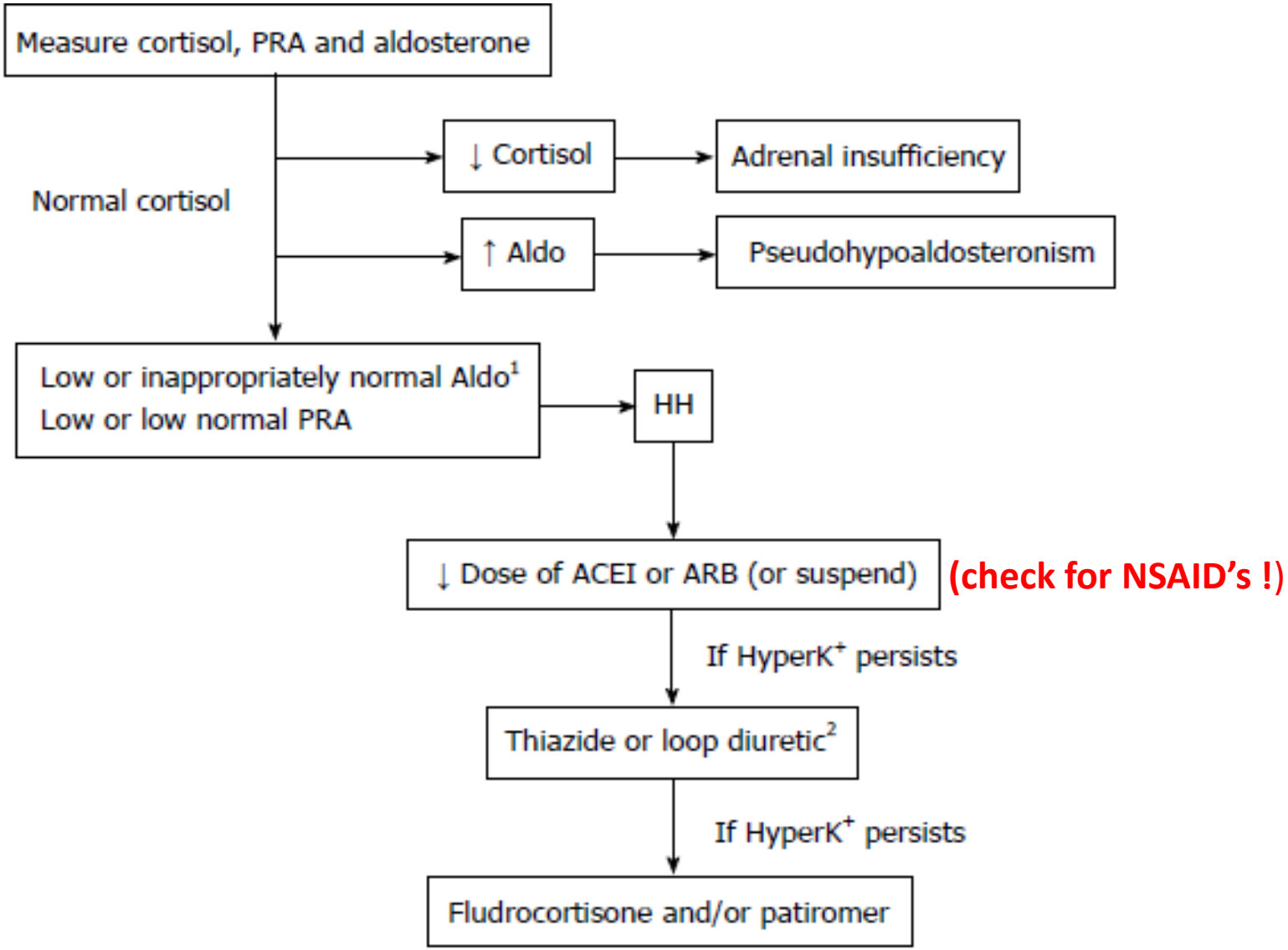
Metabolic acidosis and electrolytes in RTA subtypes at least 1yr post -tx

76/576 pts 13%

	RTA Ia (classic) $n=28$	RTA Ib (hyperkalaemic) $n=11$	Rate-limited RTA $n=16$	RTA IV $n=21$	Normal
Acidosis					
PAG (mmol/l)	12.8±2.6	12.4±1.2	11.8±1.6	11.8±2.0	8–16
UAG (mmol/l)	23±20	28±9.7	22±9.2	22±7.9	–
UpH	6.2±0.38	6.3±0.49	5.2±0.24	5.2±0.21	<5.5 (during acidosis)
HCO_3 (mmol/l)	18.95±0.99	19.58±0.55	19.40±0.89	18.56±0.99	23–27
PCO_2 (mmHg)	41±4	43±5	40±5	40±4	42–50 (venous)
K (mmol/l)	4.48±0.38	5.19±0.16	4.55±0.35	5.45±0.40	3.5–5.0
FeK (%)	13.97±5.27	10.79±2.61	10.31±3.51	11.04±3.83	4–16
PpH	7.32±0.04	7.32±0.03	7.33±0.03	7.31±0.03	7.35–7.43
TRP (%)	74±10	75±7	78±9	71±12	80–90
Ca/24 h (mmol/day)	1.91±1.78	0.87±1.26	1.46±2.21	0.69±1.08	3–7
Bicarbonate loading					
$FeHCO_3$ (%)	1.42±1.17	3.05±2.33	1.06±0.97	1.89±1.77	<5

Schwarz et al Nephrol Dial Transplant (2006) 21: 2615–2620

In a diabetic nephropathy patient with suspected hyporeninemic hypoaldosteronism type 4 RTA



Hyporeninemic hypoaldosteronism: clinical features

Mean age 65 yr
Asymptomatic hyperkalemia (75%)
Weakness (25%)
Arrhythmia (25%)
Hyperchloremic metabolic acidosis (>50%)
Renal insufficiency (70%)
Diabetes mellitus (50%)
Cardiac disorders
Arrhythmia (25%)
Hypertension (75%)
Congestive heart failure (50%)

Brenner & Rector; The Kidney 2016