

## OVERVIEW OF GLOMERULAR INJURY May 5, 2014

Etiology	Injury	Manifestation
minimal change disease, DM, SLE, toxins, meds, HIV	podocytes	proteinuria
SLE, IgA nephropathy, DM, amyloid	mesangial expansion	hematuria, some proteinuria, V GFR
Inflammatory disorders: autoimmune disorders, various infections	Bowman's space infiltration with mononuclear cells, epithelial cells, and their fibrous products	hematuria, RBC casts, proteinuria.

Prproteinuria on spot urine protein/creatinine: > 200 mg/ gram, versus albumin 30 mg/gram.

In myeloma, the urine dipstick will be negative for protein, but when urine is tested with sulfasalicylic acid, it will be positive. The dipstick detects only the negatively charged albumin whereas other proteins are positively charged.

**Polyarteritis Nodosa** has hypertension and/or renal insufficiency in 60%, arthritis, arthralgias or myalgias in 64%, perhiperal neuropathy in 51%, abdominal pain, GI bleed, or ischemia or infarctions of bowel, liver or pancreas in 44%, rash, purpura, livido reticularis, or Raynaud's in 43%, CHF, MI, or pericarditis in 36%, and CIVA or seizures in 23%.

Hepatitis B and hepatitis C occurs in 25% and 5% of PAN respectively.

**In patients with chronic renal failure**, restrict phosphate, give Ca Acetate to bind phosphate, and give Ca Acetate **with meals**.

**Differentiate the cause of hypochloremic metabolic alkalosis with a urine chloride:** If low (< 30), the cause is vomiting. If hi (> 30), the cause is a diuretic.

There are 5 pulmonary renal syndromes:

- \*C-ANCA associated: Wegener's syndrome and microscopic polyangiitis.
- \*Churg Strauss (myeloperoxidase or perinuclear staining...P-ANCA)
- \*Goodpasture's syndrome.
- \*Lupus
- \*Cryoglobulinemia vasculitis (e.g., with Hepatitis C).

Case: 36 yo Pakistani woman presents with cough, dyspnea, fever to 104 and petechiae. Creatinine is 3.5 with 3+proteinuria. CXR, negative but CT chest shows diffuse bilateral alveolar infiltrates.

Dx: hepatitis C associated vasculitis with cryoglobulinemia. (NEJM

2006;355:2468.) To detect cryoglobulins: 1) Draw blood fasting. 2) Keep at body temperature. 3) Centrifuge at 37degrees. 4) Put in Freezer at 4 degrees for 3 days. 5) Look for precipitants.

Cryoglobulinemia is present in 40% of patients with chronic hepatitis C, but vasculitis is seen in only 2% of these, consisting of palpable purpura (80%, nerve involvement in 50%, and renal involvement (Type I membranoproliferative glomerulonephritis.. 30%). NEJM 2006;355:2468.

NEPHROTIC SYNDROME: DIFFERENTIAL DIAGNOSIS April 8, 2004

The 4 classical entities below, **PLUS amyloidosis, light chain nephropathy of multiple myeloma, diabetic nephropathy (obvious), and Acute Glomerulonephritis.**

Most patients in these 4 classical entities of nephrotic syndrome in this table present with edema, hypalbuminemia, hyperlipidemia, proteinuria & lipiduria. Hematuria occurs in most patients. with the exception of Minimal Change Disease. A minority in each instant present with hypertension.

	Setting & additional CMs	Causes & associated conditions	Light microscopy	Imm. Fluores	EM	RX	Re-curs
minimal change disease	Rapid onset and proteinuria >9gm/24hrs. Peaks in children & at age 65. ^ ESR !(4) HLA B8 & B12.	Idiopathic; circulating permeability factor; 1) Drugs: NSAIDS, ampicillin, rifampin, lithium. 2) Lymphoproliferative tumors: NHL, leukemia (atopic persons)	Normal	Negative	foot process fusion or loss	1. Prednisone. Hi response but hi relapse. 2. Cycloph or chlorambucil 3. Salt restriction & diuretics	Y in 2/3s
focal segmental glomerular sclerosis	Young & middle age. African Americans (most frequent cause of NS). Hematuria (60%) Malignant HPT Less rapid onset.	circulating permeability factor. HIV(1), heroin, reflux nephropathy (Q33, MKSAP14) and stimulants of renal hyperperfusion: e.g., morbid obesity, SS dis, ureteral reflux, cyanotic heart dis, or loss of a kidney	Focal (% of glomeruli)  Segmental (part of glomerulus).  Collapsing glomerulus.	IgM C3	foot process fusion	Controversial. ACEI, ARB, prednisone (30% response) cyclosporine, mycophelate mofetil. 2. Weight loss in obese. 3. HAART in HIV. Prognosis worse with hi proteinuria at onset.	Y
membranous nephropathy	Mediate age 60. Whites (most frequent cause of idiopathic NS in adults). Most frequent NS-cause of (2) DVT. There is a predilection for the renal vein. Hematuria (60%) HLA-DRW 3 (RR=12+) Less rapid onset.	<u>Idiopathic</u> Inf<n: Hep C, Hep B, Syph, Enterococcal endocarditis, malaria Autoimmune: SLE, RA, Sarcoid, Crohn<s, Hashimoto<s, Grave<s, MCTD, Primary BC, Ank S, Derm H, BullousP, Myasth Gravis Ca: breast, lung, colon, stom, esoph, melanoma, renal cell, neuroblastoma Drugs: NSAIDS, captopril (hi dose) probenecid, chlorthemiazol, gold, penicillamine	Thickened GBM  (Non-proliferative)	Fine granular IgG, C3	Sub-epithelial deposits	Controversial. 1. ACEI and ARB pushed to side effects or proteinuria no longer decreases. 2. Steroids + (cycloph or chlorambucil) 3. Cyclosporine 4. Mycophenolate mofetil 30% progress to ESRD	1/3 resolve  1/3 renal insufficiency.  1/3 renal failure
membrano-proliferative nephrotic syndrome, types I & II	Young & Middle age Hematuria (80%) Type I: VC1,C4. Type II: V C 3. Cryoglobulins, Occ arteritis, skin vasculitis	Hep C (usual cause in type I) (3); Hep B  SLE and other Autoimmune  Chronic infections:SBE, abscesses, fungi, parasites  Multiple Myeloma	Type I: Thick GBM. Proliferation of mesangial cells.  Type II: Lobulation	Granular IgG,C3  C3 only	Mesangial & subepithelial deposits  Dense deposits	1. Interferon alpha + ribavarin. 2. Steroids contraindicated except when cryoglobulinemic vasculitis before plasmapheresis.	

(1) HIV nephropathy is characterized by large echogenic kidneys on ultrasound.

(2) hyper coagulable state of NS is due to loss of anti-thrombin III, protein C, and protein S, and impaired fibrinolysis. Patients can develop venous thrombi, PE, or arterial thrombi (??? anticoagulate)

(3) This can have a prominent nephritic component and begin as acute membranoproliferative GN; see GN table.

(4) Decreased serum albumin causes an increase in the ESR !!!

Disease	pathology	Cms	Rx
Amyloid	Light Microscopy: mesangial expansion & thickening of the glomerular capillary wall. Some Crescent formation. Hyaline Deposits. Congo Red shows apple-green birefringence. <b>AL (more common than AA):</b> monoclonal gammopathy, either idiopathic or MM with lambda light chains (the latter won't show Congo Red stain.) <b>AA:</b> chronic inflammatory conditions (e.g., skin popping) Deposits are in the mesangium.	proteinuria, + or - hematuria + or - orthostatic hypotension. OR HPT. V GFR. DI. RTA Bx: kidney, fat pads, gingiva, rectum. TB	Controversial: Melfalan + prednisone. Other cytotoxic drugs. Colchicine in Familial mediterranean fever. Treat underlying disorder.
Diabetic nephropathy	Mesangial expansion, hyalin deposits in periphery, thickening of GBM, foot process effacement, tubulointerstitial fibrosis. Non-proliferative.	<u>Microalbuminuria (30-300 mg/day)</u> after DM for 5-10 years +	Hgb A1c at 7% or lower. ACEIs, ARBs. BP < 125/75.

**ACUTE GLOMERULONEPHRITIS= ORIGINATING OUTSIDE OF GLOMERULI**

Atheroemboli			
HUS	Microthromboses of glomerular capillaries  On EM: widening of glomerular capillary wall.	E Coli O 157 H7 HIV Pregnancy APL syndrome Drugs: quinine, mitomycin C, cyclosporine, tacrolimus, OCP, ticlopidine, clopidogrel	

Renal-Dermal syndromes: SLE, HSP (palpable purpura), cryoglobulinemia (digital necrosis & ulcers), ANCA associated vasculitis (palpable purpura), leukocytoclastic vasculitis (palpable purpura, bruises, livido reticularis, urticaria, ulcers). (The latter also has abdominal pain and GI mucosal ulcerations, and mono-neuritis multiplex).

**ACUTE KIDNEY INJURY**

Pre-renal: U osm 500+ mosm/Kg; U<sub>Na</sub> <20 meQ/L FE<sub>Na</sub> <1% Bland sediment

Intrinsic renal disease:

Acute glomerulonephritis: Looks like pre-renal except for microscopy.

Acute interstitial nephritis: U osm 300 mosm/Kg; U<sub>Na</sub> 40+ meQ/L FE<sub>Na</sub> 2%+ WBCs, RBCs, WBC casts

Ischemic & toxic ATN: U osm 300 mosm/Kg; U<sub>Na</sub> 40+ meQ/L FE<sub>Na</sub> 2%+ Dark pigmented casts

**CKD with GFR:** 1: 90+, 2: slight decrease in GFR, 3A 45-49 (no complications), 3B 30-44 (complications), 4: 15-29; 5: <15. Rx for 4+: Na bicarb.

Causes: Direct damage: DM, HTN, nephritis, MM, multiple episodes; Iatrogenic (chemo, nsaid, antibiotics); GU abnormalities (stones, ca, obstruction, reflux), Exposures (heavy metals, herbals: aristoloch, chromium, ma huang ephedra), FH: PCKD

Disease	CMs Etc	Lab	Light merscpy	Imm Flr	EM	Rx
Thin basement membrane dis <sup>7</sup>	Hematuria. AD family history	Hematuria, dysmorphic RBCs OTHW nl	nl	nl	thin bm	none
Mesangial proliferative GN: IgA nephropathy ( <u>Berger's Disease</u> )	Age 15-35. <b>Post exercise.</b> <b>△Synpharyngitic</b> <b>△ Latency 3 days.</b> (also cirrhosis, sprue, HLA B27 arthritis, HSP(2)) HPT(40%)	^ Serum IgA in 50% <u>Complement is normal.</u>	Mesangial proliferation  May have segmental sclerosis & crescents.	Mesangial IgA & C3	Mesangial cell proliferation & deposits	Usually none 40% may have ESRD after 20yrs. Worse prognosis if nephrotic HPT, sclerosis or crescents. If heavy proteinuria, use steroids& immunosuppressives. If nephrotic: ACEI, ARBs, Fish oils. Recurs post Trnsp(7)
Post streptococcal GN	Infctn of Pharynx or skin.LP:~15ds HTN in 70%. Transient ^ Cr.	<b>C3 is decreased.</b> C4 is normal ASO Ab. Anti-DNAse Ab	Diffuse proliferation	Granular IgG, C3 on capillary wall.	Subepithelial humps on BM	95% resolve spontaneously. Treat infection if possible. Immunosuppressives if subepithelial mesangial hump.
Immune complex mediated GN (3)	Palpable purpura, HS megaly, lymphadenopathy Alveolar infiltrates	<b>C3 is intermittently low.</b> Mixed cryoglobulin-emia.	Thickening of the GBM and mesangial cell proliferation	subendo, mesangial C3+(IgG or IgM)	double layered membrane	ASA, dipyridamole.  Recurs post transplant.
Lupus nephritis, a special case of immune complex mediated GN Lung-renal S	11 criteria for SLE: 4 skin, 2 serositis, hematologic, renal, CNS, ANA, antibody.	Proteinuria RBC casts (suggests crescents). <b>Low C4 + C3.</b> # + ANA. Anti-DS DNA	I: NL II: Mesangial pro III: Focal pro IV: Diffuse proliferative (60%) V:Membranous	Granular IgG, C3 in mesangium		Prognosis in I & II is good. In DPGN, 25% ESRD in 10 yrs. Non-sclerotic lesions has good response to prednisone & (cyclo-phosphamide or Azoth) Mycophenylate has relapses.
Goodpasture<<s Syndrome, an <b>△anti-GBM disease</b> (4) (not a vasculitis!!) Lung-renal S	Age 20+ & higher Hematuria, cough, hemoptysis, arthralgias. Crackles on Exam. H/O of smoking.	V HCT, ^ Creatinine U/A:acanthotic RBCs, RBC casts,proteinuria. <u>Serum Anti-GBM Ab</u> P-ANCA (30%) CXR: infiltrates <b>Normal Complement</b>	Crescentic GN  <b>(Ab forms to collagen of lung &amp; kidney.)</b>	IgG & C3 along BM	Negative	For hemoptysis give emergency plasmapheresis. Steroids cyclophosphamide. Smoking precipitates relapse. P-ANCA may give better prognosis.
Wegener<<s Granulomatosis, a <b>△pauci immune GN</b> (5) Lung-renal S	<b>^T,vWt,arthralgias</b> mononeuritis, <u>skin vasculitis.</u> Nose, ear & <u>tracheal cartilage.</u> SOB, hemoptysis, hematuria	C3 and C4 Normal U/A: acanthotic RBCs. proteinuria. CXR: <u>nodular densities,</u> transient infiltrates. <b>C-ANCA in 80%</b> <b>Normal Complement</b>	Crescentic GN  <b>(granulomatous vasculitis to medium &amp; small arteries &amp; veins)</b>	None		Plasmapheresis, prednisone & Cyclophosphamide induce remission in 80%.
Primary Rapidly Progressive GN. RPGN = Crescentic GN (6)	Middle age.  All etiologies above except for IgA nephropathy	^ Creatinine. May be acute and/or severe. U/A: Dismorphic RBCs and RBC casts. <b>Normal Complement</b>	Crescentic GN Fibrin,Bowman<<s space: proliferat-ing epithelial cells, macrophgs	No: 50% IgG: 20%. Immune complex in 30%.	Negative	A medical emergency  Recurs post transplant.

Dysmorphic erythrocytes (acanthocytes). 1. FE Na < 3%, similar to pre-renal azotemia, no or minimal proteinuria. Diseases sometimes mimicking these include HUS-TTP, I.S. nephritis, scleroderma crisis, toxemia, atheroembli, & malignant HPT: normal serum C3 and negative or sparse immunofluorescence.

(2)Henoch-Schonlein Purpura: Palpable purpura & IgA in skin (70% in adults), nephritis, and, in children, arthralgias and GI symptoms.

(3) This is a membranoproliferative GN Type I: Rheumatologic: SLE, Sjogrens, RA, MCTD, cryoglobulinemia (has palpable purpura); Infectious: Hep C, Strep, SBE, ventriculo-atrial shunt nephritis, chronic abscess, malaria, syphilis, hep B, HIV, mycoplasma; Lymphoproliferative (leukemia or lymphoma). (Not HSP, which has IgA tissue deposits and normal C3.) MPGN Type II has an autoantibody to C3 nephritic factor.

(4)**△Anti-GBM mediated RPGN** also includes an idiopathic form. Anti-GBM = Anti-Glomerular Basement Membrane Antibody.

(5) Pauci immune GN also includes 2 other pulmonary-renal syndrome, microscopic polyangiitis and Churg-Strauss, and idiopathic crescentic GN. ANCA = **Anti Neutrophil Cytoplasmic Antibody.** C-ANCA: Cytoplasmic pattern. Anti-proteinase 3 antibody; P-ANCA: Perinuclear pattern. Anti-myeloperoxidase antibody. These antibodies make ANCA a less subjective test.

(6) In most AGN, the course is transient increase in creatinine and oliguria followed in days or weeks by diuresis and return to Normal GFR. RPGN is the exception. (7) Maintenance therapy with either axothioprine or mycophenylate mofetil provides lower death rate or renal failure and

lower side effects than with cyclophosphamide. (MKSAP 13 update).

(7) Alport's syndrome (≠hereditary nephritis≠) has an AR (85%), X-linked, or AD pattern with renal failure in childhood to middle age and sensorineural hearing loss and corneal and retinal abnormalities. Carriers may have thin basement membrane disease.

### Evaluation of hyponatremia

<b>Cause</b>	<b>Extracellular Fluid Volume Status</b>			
	<b>Volume depletion</b>		<b>Euvolemia</b>	<b>Volume excess</b>
<b>Clinical</b>	GI fluid loss Sweating Burns Adrenal insuff Renal salt loss (e.g., diuretics)		SIADH <sup>1,4</sup> Hypothyroidism Cortisol deficiency or Panhypopituitarism Psychogenic polydipsia Drugs <sup>2</sup>	CHF Cirrhosis Nephrotic syndrome Acute renal failure
<b>Biochemical</b>	From non-renal Losses	From Renal losses		
Serum sodium meq/L	120 meq/L	120	120	120
Plasma milli-osmoles/kg	250	250	250	250
Urine Na meQ/L	<10	>20	> 40 meQ/L	<10
Fe <sub>Na</sub>	< 1%		> 1%	
Urine mosmoles/kg	>600-800	600-800	inappropriately hi: >100	>300-400
Plasma ADH	hi	hi	hi	hi
BUN	hi	hi	<10	hi <sup>3</sup>
Uric acid (serum)	hi	hi	<4	hi

Volume depletion=poor skin turgor, ortho-stasis, and hypotension.      Volume excess=edema

<sup>1</sup>E.g.: CNS and pulmonary disorders, drugs (anti-psychotics, NSAIDS, opioids, SSRIs, TCAs), HIV, Post op setting, ca (lung, GI, GU, etc).

<sup>2</sup>phenothiazines, cyclophosphamide, vincristine

<sup>3</sup>BUN may not be elevated in cirrhosis.

<sup>4</sup>Treat by fluid restriction

ANION GAP METABOLIC ACIDOSIS

CKD

Alcohol

DKA

Ethylene glycol

Methanol

Type A lactic acidosis (hypoperfusion or hypoxia): Shock (cardiogenic, septic or hemorrhagic)

Type B lactic acidosis (no hypoperfusion or hypoxia):

Medications or toxins: acetaminophen poisoning, ethylene glycol, methanol, metformin, ASA

Systemic disease: liver failure or ca

G6PD deficiency

For methanol or ethylene glycol toxicity: fomepizole.

One can correct hyponatremia by about 5 mEq/L over the 1<sup>st</sup> 24 hours.

### HYPERCHLOREMIC (NON-ANION GAP) ACIDOSES

1. GI loss of HCO<sub>3</sub><sup>-</sup>: Diarrhea, ureterosigmoidostomy. Urine pH < 5.3 and urine anion gap is -50 to -20.

2. HCL ingestion or infusion. (urine pH < 5.3). (Urinary NH<sub>4</sub><sup>+</sup> concentration increases.)

2. Renal Tubular Acidoses:

RTA 1: Distal Tubule, Decreased H<sup>+</sup> secretion, Lo K, hypercalcuria, etc

RTA 2: Proximal Tubule, Decreased HCO<sub>3</sub><sup>-</sup> reabsorption, lo or nl K, Fanconi's syndrome

RTA 4: Distal Tubule, Decreased K<sup>+</sup> secretion, Hi K.

### RENAL TUBULAR ACIDOSES

	RTA 1	RTA 2(Fanconi's syndrome) (1)	RTA 4
Anatomy	Distal tubule	Proximal Tubule	Distal Tubule
Mechanism	^ K <sup>+</sup> excretion. V H <sup>+</sup> excretion.	V HCO <sub>3</sub> <sup>-</sup> reabs<n (1)	V K <sup>+</sup> excretion V NH <sub>4</sub> <sup>+</sup> (ammonium) excretion
Serum K	Low (usually)	Low to Normal	High
Serum HCO <sub>3</sub> <sup>-</sup>	May be < 10 mEq/L	14 - 20 mEq/L	Usually > 15 mEq/L
UA gap(2)	Positive	Negative: Normal (-20 to 0)	Positive
Urine pH	Usually alkaline (>6) (3)	<5.5 VARIABLE (4)	< 5.5: decreased aldosterone >6: Tubular defect (decreased response to aldosterone)
RX	60-100 mEq NaHCO <sub>3</sub> /d K citrate, particularly for Calcium stones	Na restriction. 500- 750 mEq of alkali/d with NaHCO <sub>3</sub> and K citrate. Also replace Phosphate, Vitamin D	Lasix
Causes	C CCCATL <b>HyperCalcuria</b> (renal stones & lo citrate) (+_ hypercalcemia) <b>CTD</b> (Sjogren<s, RA, SLE, chronic active hepatitis) <b>Cirrhosis</b> Amphotericin B Toluene Lithium (5)	M + hyperparathyroidism. <b>Multiple myeloma.</b> Metals: Lead, Copper (Wilson<s disease) AMino Aciduria 6-Mercaptopurine AcetazolaMide Primary Hyperparathyroidism (This last seems as though it would cause Type I RTA with hypercalcuria but see MKSAP 13, Endo, page 72. Possibly relates to PTH as cause of phosphate wasting.)	<u>1. Deficient Renin and Aldosterone:</u> (hyporeninemic hypoaldosteronism) <b>Diabetic nephropathy</b> Drugs: NSAIDS, ACEIs, Cyclosporine. HIV infection_ <u>2. Deficient Aldosterone only:</u> <b>adDison&lt;s disease; ACEIs, ARBs</b> Heparin(x<s aldostn synthesis) <u>3. Deficient response to aldosterone:</u> (Diseased tubules): (5) SS disease, SLE, Interstitial nephritis, obstructive uropathy Drugs: Spironolactone, triamterene, amiloride, Pentamidine, TMP

1. Suspect Type 2 RTA if there is glycosuria with normal serum glucose, low serum uric acid and phosphate.

2.  $Cl^- + UA^- = Na^+ + K^+ + UC^+$  (UA and UC are unmeasured anions and cations.)  $UAGP = UA^- - UC^+ = Na^+ + K^+ - Cl^-$ .

Normally the UAGP is -20 to 0. H<sub>2</sub>P04<sup>-</sup>, SO<sub>4</sub><sup>=</sup>, Mg<sup>++</sup>, and Ca<sup>++</sup> do not change much during acid-base disturbances, but NH<sub>4</sub><sup>+</sup> does change. GI causes of non-anion gap acidosis: UAGP is markedly negative (-20 to -50), because the distal renal tubules generate more NH<sub>3</sub> for the higher serum H<sup>+</sup> to give more NH<sub>4</sub><sup>+</sup> and, to maintain electro-neutrality, Cl<sup>-</sup> in the urine increases. In renal failure, and distal RTAs (Type 1 RTA and Type 4 RTA) the UAGP is positive because the tubules can not generate NH<sub>3</sub>. In proximal RTA the urinary anion gap is negative.

3. For a serum acidosis, a urine pH of less than 5.3 is an appropriate renal response.

4. Initially urine ph is > 5.3, but then it may be < 5.3 !!  $\hat{=}$  Untreated patients ... are in acid-base balance once the plasma bicarbonate concentration has fallen sufficiently so that all of the filtered bicarbonate can be reabsorbed. In this setting, the urine pH may be below 5.3 as the dietary acid load, derived primarily from protein metabolism, is normally excreted.  $\hat{=}$  (UptoDate).

5 SS disease, SLE, and Obstructive Uropathy may have Type 1 RTA mechanism while having hyperkalemia.

Metabolic acidosis	v HCO <sub>3</sub> by 10 >>	v PCO <sub>2</sub> by 12
E.G.	HCO <sub>3</sub> 14*	PCO <sub>2</sub> 28
Metabolic alkalosis	^ HCO <sub>3</sub> by 10 >>	^ PCO <sub>2</sub> by 7
E.G.	HCO <sub>3</sub> 34	PCO <sub>2</sub> 47
Respiratory acidosis, acute	^ HCO <sub>3</sub> by 1	<< ^PCO <sub>2</sub> by 10
E.G.	HCO <sub>3</sub> 25	PCO <sub>2</sub> 50
Respiratory acidosis, chronic	^ HCO <sub>3</sub> by 3.5	<< ^PCO <sub>2</sub> by 10
E.G.	HCO <sub>3</sub> 27.5	PCO <sub>2</sub> 50
Respiratory alkalosis, acute	v HCO <sub>3</sub> by 2	<< v PCO <sub>2</sub> by 10
E.G.	HCO <sub>3</sub> 22	PCO <sub>2</sub> 30
Respiratory alkalosis, chronic	v HCO <sub>3</sub> by 4	<< v PCO <sub>2</sub> by 10
E.G.	HCO <sub>3</sub> 20	PCO <sub>2</sub> 30

\*For metabolic acidosis, you can use the winter formula:  $PCO_2 = 1.5 * Bicarb + 8$ .

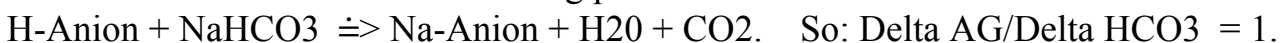
1. Validate the ABG: the calculated HCO<sub>3</sub> of the ABG should equal the measured venous HCO<sub>3</sub>.
2. The PCO<sub>2</sub> = last 2 digits of pH. If it is equivalent, there is no respiratory process.
3. The anion gap = 2.5 - 3\*albumin. So if albumin = 4.5, The anion gap = 2.5 - 13.5 = -11. (If the albumin is lowered due to nephrotic syndrome (e.g.=2), the anion gap would be 2.5-3\*2 = -3.5)

For **anion gap metabolic acidosis**, calculate: Change in Anion Gap/ Change in Bicarb. For a simple anion gap metabolic acidosis, such as with lactic or keto acidosis,  $\frac{\Delta \text{Normal}}{\Delta} = 1$  to 2. THE NORMAL Anion GAP = 12. The normal HCO<sub>3</sub> = 24.

However, If there is also a metabolic alkalosis, the bicarb will not be as suppressed because some bicarb is generated, so the Ratio will be greater than 2.

If there is an additional non-anion gap metabolic acidosis, the ratio will be less than 1, because even more bicarb will be consumed and the change in bicarb will be greater.

Why is the normal D/D not equal to 1? Here is basic explanation (see UpToDate): We would expect the D/D, the Change in Anion Gap/ Change in Bicarb to equal 1 because for ever 1 mole of H-Anion generated by the metabolic acidosis, one mole of plasma NaHCO<sub>3</sub> is consumed in the buffering process. I.E:



However, there are multiple other variables:

Factors that raise the D/D:

\*More than 50% of buffering is done intracellularly, sparing the serum Bicarb.

In particular, for lactic acidosis, the D/D averages 1.6.

\*The more severe the acidosis, the more the buffering is done intracellularly.

\*Increases occur in unmeasured anions

- >when there is hemo concentration which increases the concentration of protein, or
- >when acidosis releases phosphates from cells and causes hyperphosphatemia.

#### Factors that lower the D/D:

\*Excretion of anions in the urine occurs, when renal function is normal. This excretion typically occurs with keto acidosis. This will reduce the elevated AG. In ketoacidosis, the D/D averages 1. (In the usual lactic acidosis, L-lactate is re-absorbed by kidneys.)

\*In D-Lactic acidosis (rare), in Jejuno-ileal bypass or in short bowel syndrome with bacterial overgrowth, patients given glucose and starch make D-Lactic acid, which is not re-absorbed by the kidney and hence is excreted in the urine.

\*In toluene exposure (glue sniffing), hippuric acid is formed and hippurate is rapidly excreted, so this can look like Type I RTA with a normal anion gap acidosis.

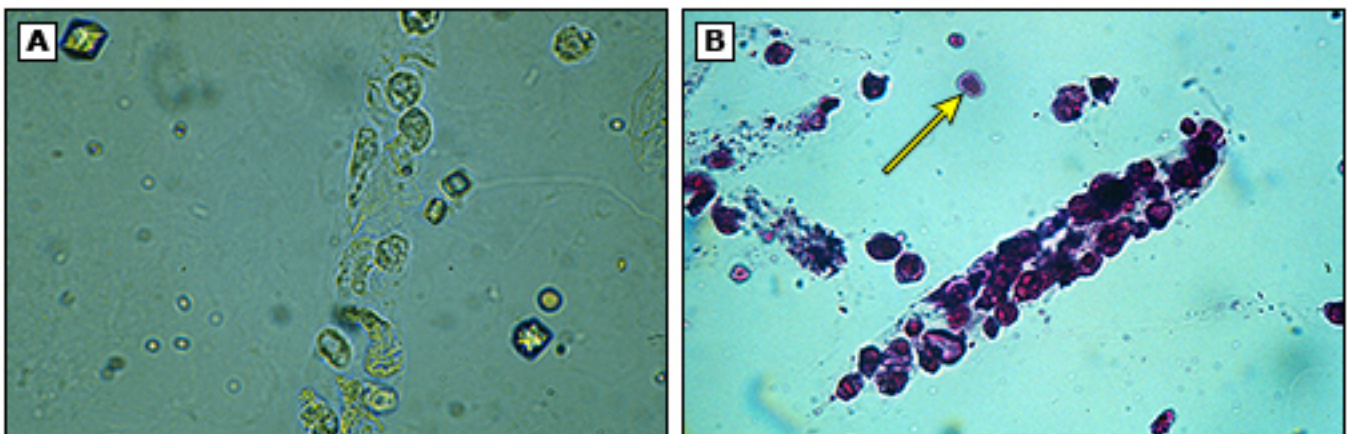
\*Newer auto-analyzers measure more chloride. So, rather than a normal AG = 10, the normal AG may be = 7.

Summary:  $\hat{=}$ Strict recommendations that apply to all patients cannot easily be made. ...the Delta/Delta in an uncomplicated high AG metabolic acidosis should be between 1 and 2.  $\hat{=}$  (Change in anion/Change in HCO<sub>3</sub>; The introduction of one mole of an anion consumes less than one mole of serum bicarbonate because of cellular buffering). A lower value reflects urinary ketone losses (e.g., DKA), some cases of chronic renal failure, or a combined process of high AG acidosis and a normal AG acidosis. A D/D above 2 usually reflects a concurrent metabolic alkalosis, as with vomiting. UpToDate gives multiple original clinical research references.

E.G.: 62 y.o. man with hypothermia, hypotension, alcoholism, stupor.

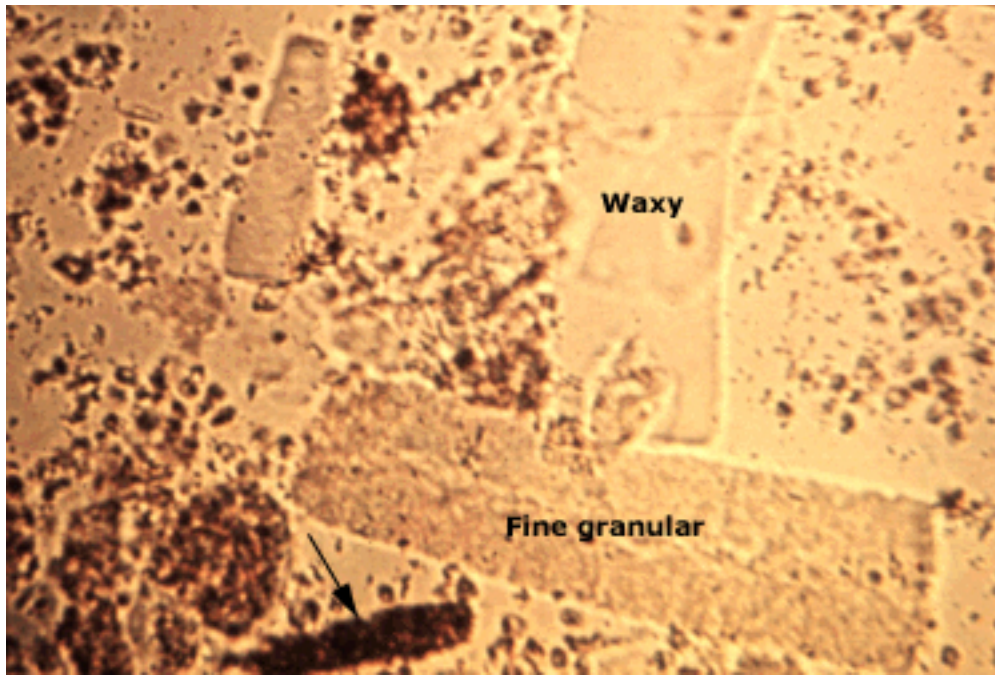
Na=153, K=4.2, Cl=102, HCO<sub>3</sub>=6. TP=7.5, Albumen=4.4, Anion Gap = 45. Lactic acid level = 6.

D/D = 33/19 = 1.7.



Tubular Epithelial casts in ATN. The arrow shows an epithelial cell with a large nucleus.





These are granular casts. The Arrow shows the muddy brown cast of ATN.

### METABOLIC ALKALOSIS (RX: acetazolamide)

1. BP tends to be low: CHF, cirrhosis, nephrotic syndrome
2. BP normal
  - a. Urine chloride  $< 15$  meQ/L (saline responsive). Usually vomiting or remote diuretic use
  - b. Urine chloride  $15+$ : Diuretic use, Bartter S, Gitelman S
3. BP High (Urine chloride will be high)
  - a. Hi renin & aldo: renovascular HTN, coarc, renin secreting tumor
  - b. Low renin and high aldo: hyperaldosteronism, glucocorticoid remedial hyperaldosteronism
  - c. Low renin and low aldosterone:
    - i. Plasma deoxycorticosterone increased; Deoxycorticosterone tumor
    - ii. Plasma deoxycorticosterone normal:
      1. Urinary cortisol/cortisone increased but less than 5: licorice
      2. Urine cortisol/cortisone ratio  $\gg 5$  and decreased urine cortisone: Familial syndrome of apparent mineralcorticoid excess (11 B hydroxysteroid dehydrogenase deficiency... like licorice)
      3. Urine ratio increased and both are elevated: ectopic ACTH syndrome
      4. Increased urine cortisol and cortisone: Cushings syndrome, CAH (1 B hydroxylase def)
      5. Urine cortisol and cortisone both normal: Liddle syndrome (gain of function mutation of ENaC in the DCT)

---

The mechanism for increased BUN in pre-renal insufficiency is that more urea is re-absorbed due to volume-mediated stimulation of ADH and renin-angiotensin-aldosterone (see MKSAP 12, page 98, Q 48).

Urine: Normal specific gravity is  $1.009 \pm 0.01$ .

Urine: pH is less than 5.3 for an appropriate response to acidosis.

Na is decreased by 1.6 mEq/L for every 100 gm/dL glucose increase above 100 gm/dL.

Calcium is increased by 0.8 mg/dL for every one gm/dL of albumin less than 4.

Formula for Correcting Hyponatremia:

Q: How much Na is required, what is the solution, and how fast is it given?

A:  $\text{mEq Na} = 0.6 \text{ (or } 0.5 \text{ in women)} * \text{Body Weight} * \text{Desired increase in plasma Na/L}$

E.G.: A woman weighing 60 Kg, with a Na = 120 mEq/L:

$\text{Na required} = 0.5 * 60\text{L} * (140\text{mEq/L} - 120\text{mEq/L}) = 600 \text{ mEq Na}$ . Each liter of 3% NS has 513 mEq/L so give  $600\text{mEq}/513\text{mEq/L} = 1.2\text{L}$

(Each liter of 3% saline has 513mEq)

Correct this no faster than 0.5 mEq/L/Hour or 12 mEq/Day. So the total days would be  $20\text{mEq}/12\text{mEq/D} = 1.7 \text{ days}$ . So  $1.2 \text{ L}/1.7\text{days} = 0.7 \text{ Liters/day} = 700\text{cc}/24\text{hrs} = 29\text{cc/hr}$ .

Alternatively, you can use NS, which is 154mEq/L.

So give  $600\text{mEq}(\text{the required Na})/154\text{mEq/L} = 3.9\text{L}$

The 20 mEq/L has to occur at 12 mEq/L/24hours, so this would require  $20\text{mEq/L}/12\text{mEq/L}/24\text{hours} = 1.7\text{days}$ .

So give the  $3.9\text{L}/1.7\text{days} = 2.3\text{L/day} = 2300\text{cc}/24\text{hrs} = 95\text{cc/hour}$

FORMULA FOR CORRECTING HYPERNATREMIA:

Q: How much fluid is required?

$\text{Volume of Fluid} = 0.5 \text{ (0.4 in women)} * \text{Body Weight in kg} * (\text{Naser} - 140)/140$

So for Na = 168 in a 60 kg woman:

$= 0.4 * 60 * (168 - 140)/140 = .4.8\text{L}$

Again, do not correct more than 0.5 mEq/L/hr.

So correct the 28 mEq at 12mEq/day or over  $28/12 = 2.3 \text{ days}$ . So give the 4.8 liters of  $\text{D5W}/2.3 \text{ days} = 4800\text{cc}/(2.3\text{days} * 24\text{hrs/day}) = 2400\text{cc}/41\text{hrs} = 87\text{cc/hr}$

(Note that the patient will need fluids for an obligatory sensible loss of about 40 cc/hr so this should probably be added to the 87 cc/hr to give 127cc/hr. The point is to check the Na every 4 hours during this period.)

Risk factors for Hyperkalemia (NEJM 2004;351:585):

Chronic kidney disease

DM

CHF

Volume depletion

Advanced age

Drugs: ACEIs or ARBs

NSAIDS

Beta Blockers

Cyclosporine, tacrolimus (calcineurin inhibitors)

Heparin (blocks aldosterone synthesis (Q32, MKSAP14))

Ketoconazole

Spirolactone, tramterine, amiloride

TMP/SMX

Pentamidine

Potassium supplements including salt substitutes and certain herbs

NOTES FROM Q & A OF HARRISON'S AND CECIL

### UTI.

\*Although the diagnosis of UTI should be confirmed by urinalysis, there is evidence that history alone can be very accurate. If a woman complains of dysuria and increased frequency without vaginal discharge, the likelihood ratio of UTI is about 25, and UTI can be predicted with greater than 90% probability.

\*UTI can then be diagnosed simply with WBC > 10 / HPF in a midstream urine, so long as there are few squamous epithelial cells (which would reflect contamination). The 2+ leukocyte esterase and 10 RBCs/ hpf are additional support for the Dx.

\*Indications for culture are: Recurrent UTI, suggestion of pyelonephritis, pregnant, diabetic, immunocompromised, or in a child.

\*RX is with: Nitrofurantoin, TMP/SMX, or Cipro. If there is an allergy to these, try cephalexin, amoxicillin-clavulanate, or doxycycline.

\*Give phenazopyridine HCL (pyridium) to reduce bladder discomfort.

### **PYLEONEPHRITIS:**

\*Risk factors for pyelonephritis include: advanced age, hi frequency of sexual intercourse, diabetes, recent antibiotic use, indwelling catheter, neurogenic bladder, or immunosuppression.

\*RX of pyelonephritis, uncomplicated, with mild-moderate symptoms, can be done as an outpatient with oral levofloxacin 500 QD for 7 days. Cephalexin and amoxicillin-clavulanate are alternatives.

### **CHRONIC PYELONEPHRITIS AND REFLUX NEPHROPATHY:**

CM<<s:

Occurrence: In children and young men. Diabetics with neurogenic bladder.

In children, there is dribbling and incomplete voiding.

In adults, it can present as incontinence, incomplete voiding, and can lead to chronic pyelonephritis, with bacteruria, pyuria, etc.

PATHOGENESIS: A vesicoureteral junction defect transmits high intravesical pressure to the ureter and kidney. With severe vesicoureteral reflux, urine may actually reflux into the kidney, so-called intrarenal reflux. When the urine becomes infected, the intrarenal reflux of infected urine results in cortical scarring of the kidney.

LAB::

All patients with urinary tract infection within the first 5 years of life are to be evaluated for vesicoureteral reflux.

large residual volume on ultrasound or radio nuclide cystogram; bacteruria, pyuria.

Renal scarring is demonstrated by 99-technicium DMSA (dimercaptosuccinic acid).

Renal ultrasound is much less sensitive  $\hat{=}$  with sensitivity that may be only 50%.

Proteinuria and nephrotic syndrome may develop.

RX: It is very important to consider surgery as the primary modality, rather than repeated rx with antibiotics.

### **In urinary tract obstruction:**

Polyuria may occur.

There may be no hydronephrosis on ultrasound (although there usually is), particularly if patient is dehydrated.

RTA IV can occur.

Infection is a frequent complication.

### **Hematuria** can be caused by

\*Hemoglobinuria

\*cystitis (e.g., from cyclophosphamide)

\*papillary necrosis (e.g, from ss disease, or analgesic nephropathy).

\*GN: IgA nephropathy, HSP, etc.

**Acute GN** typically has no hypoalbuminemia and hypercholesterolemia, but these can develop later with nephrotic syndrome.

\*Proteinuria may be none or slight, initially.

\*There is low urinary sodium and fractional excretion of sodium, as in a pre-renal condition.

### **INTERSTITIAL NEPHRITIS:**

\*I.S. can develop at any time from 1 day to months after beginning a drug.

\*CMs: Fever (15%), rash (27%), mild eosinophilia (23%). U/A shows WBC casts (classically), eosinophils with + Haneszel stain (sensitivity=67%, specificity = 83%), WBCs, RBCs, no or occult proteinuria. The classic trio of fever, rash and eosinophilia occurs in only 10%. Other symptoms are n, v, malaise, or no symptoms.

\*Causes are

>drugs (71% of cases) : NSAIDs, penicillins (notably methicillin) and cephalosporins, rifampin, TMP/SMX, ciprofloxacin, allopurinol, PPIs, sulfasalazine, gold, penicillamine and many others.

>autoimmune disorders: sarcoid. Sjogren syndrome. Uveitis.

>legionella, strep infections, CMV, & leptospirosis

Rx:

\*With drug withdrawal, renal function improves within 4 - 7 days in 60% of patients.

\*If there is no improvement or creatinine is very high, give steroids, and possibly cyclophosphamide and plasmapheresis.

\*Renal biopsy is usually not indicated unless more aggressive therapy is used.

**In diabetic nephropathy from DM I**, virtually all patients have hypertension and retinal vascular disease, and most have nephrotic-range proteinuria. So the absence of retinal vascular disease usually excludes diabetic nephropathy. The absence of these concomitant features should draw the diagnosis

of diabetic nephropathy into question. Even with overt diabetic nephropathy, ACE inhibitors are efficacious by slowing loss of renal function.

**In renal calculi, hexagon shaped crystals** indicate **cystinuria**, a common aminoaciduria effecting 1 in 7,000 individuals. Cystine is the least soluble of aminoacids, and hence the tendency to form stones. Rx is with alkalinization of the urine.

### **NSAIDs can cause:**

- \***renal ischemia** from inhibition of prostaglandin and constriction of afferent arterioles,
- \***allergic interstitial nephritis** with hematuria, pyuria and proteinuria, but usually not eosinophilia, fever and rash of allergic i.s. due to antibiotics.
- \***Hyperkalemia** with Type IV RTA due to inhibition of renin and aldosterone secretion, (Urinary tract obstruction can also cause hyperkalemia with RTA.)
- \***chronic interstitial nephropathy** often with **papillary necrosis**, probably the result of medullary ischemia from decreased medullary blood flow, associated with a long-standing use of greater than 3 kg of combinations of analgesics, small kidneys with hydronephrosis and demonstrated fragments of tissue in the urine, from sloughing of the papillary tip into the ureters bilaterally.

**In acute renal failure**, the indication for protein restriction is advanced azotemia without availability of dialysis; otherwise, because of the hypercatabolism in acute r.f., patients are not protein restricted.

### **SEVERE RENAL INSUFFICIENCY:**

- \*When GFR is below about 20 to 25% of normal, there is an absolute retention of organic and inorganic acid anions, leading to an increased anion gap.
- \*Urine is normally acid.
- \*Giving the patient bicarbonate has no effect, because the kidney<<s do not retain the bicarbonate, but excrete it.
- \*Early in renal insufficiency, the resulting acidosis generates renal production of ammonia which buffers and excretes the acid.
- \*Hyperkalemia worsens acidosis by suppressing ammonia production.
- \*In patients using loop diuretics, hypokalemia impairs the renal excretion of ammonia and leads to hyperammonemia. (SO SHOULD PATIENTS BE HYPO OR HYPER-KALEMIC??)
- \*Advancing peripheral neuropathy should be looked for in progressive renal disease and it is an indication for dialysis.
- \*Low thyroxine due to decreased thyroxin binding globulin.

### **ESRD:**

**Isothenuria** (urine osmolality = plasma osmolality).

**Vitamin D** in serum decreases due to failure of hydroxylation of Vit D to 1,25 dihydroxyvitamin D.

**Hypocalcemia** : is due to decreased Ca absorption from gut from decreased vitamin D.

**Monitor hypocalcemia** with Chevostock<<s sign (tapping malar eminence) and Trousseau<<s sign (inflate bp cuff for 3 minutes and look for carpal spasm.)

**Hyperphosphatemia** is due to impaired renal excretion of phosphate.

**Increased PTH** caused by both **hyperphosphatemia** and **hypocalcemia**.

- \*Lower the serum phosphate, which secondarily lowers the PTH. Via
  - >Dietary phosphate restriction at GFR < 60 ml/min and
  - >Calcium acetate (PhosLo), 1334 mg with each meal, and increase gradually to bring the serum phosphate value <6 mg/dL as long as hypercalcemia does not develop (usual dose: 2001-2868 mg calcium acetate with each meal); do not give additional calcium supplements, or
  - >Sevelamer (Renagel), 800 to 1600 mg, TID.

>Following the lower of phosphorus, give calcitriol to suppress PTH and renal bone disease. (Do NOT give calcitriol first, as this may precipitate calcium.)

>If these measures are ineffective, give Cinacalcet (Sensipar), a calcimimetic agent, which increases sensitivity of parathyroid gland to calcium, lowers serum calcium, but improves secondary hyperparathyroidism, and is approved for this treatment (JAMA; 2005;293:1772). It reduces PTH, Ca, P, and the Ca X P product. Target the Ca X P product as < 55.

Acquired cystic kidney disease associated with ESRD occurs in patients on PD or hemodialysis, gives pain and gross hematuria, is rare in patients w/o renal failure, is associated with renal cell ca (bilateral in 10%!), and has a male predominance.

**Bleeding** in uremic patients is due to platelet dysfunction and is treated with: \*dialysis, \*ddavp, and \*estrogens (?)

**Renal osteodystrophy**, use calcium carbonate (least toxic) or calcium acetate. Eventually, use vitamin D (which, unfortunately, causes increased GI absorption of phosphates, and therefore only give after phosphate levels are being reduced by calcium.) Avoid aluminum and magnesium.

**Protein restriction**: It is unclear whether protein restriction may slow progression of renal disease, but moderate restriction is recommended, particularly in glomerular disease with protein excretion > 1gm/day.

### **POLYCYSTIC KIDNEY DISEASE.**

Usually autosomal dominant.

Rx injections with TMP/SMX or ciprofloxacin which penetrates the cysts.

**Medullary Sponge Kidney**, caused by congenital ectasia and calcification of medullary collecting tubules, has no renal insufficiency, but may cause hematuria, renal stones, UTIs, and decreased renal concentrating ability.

**Renal cell carcinoma (RCC)** can present with anemia, polycythemia, hypertension, pyrexia, hypercalcemia, elevated erythrocyte sedimentation rate, abnormal liver function, myopathy/neuropathy, and weight loss. Percutaneous biopsy of RCC carries the risk of tumor seeding along the needle tract. Both acquired cystic renal disease and von Hippel-Lindau disease impose greater risk for the occurrence of renal cell carcinoma.

HLA compatibility in transplantation: The HLA haplotype in a patient has a 25% chance of matching that of a sibling. Look up in Cecil, chapter 118.2. MHC class 2 antigens are on B lymphocytes and vascular endothelial cells.

### **Complications of PD:**

Peritonitis, usually caused by gram positive organisms (Staph) from the skin.

Hypoalbuminemia

Hyperglycemia. However, this only requires insulin added to the dialysate and does not lead to severe problems in glycemic control.

Hypertriglyceridemia

Right pleural effusion

### **Complications of hemodialysis:**

Hypotension

Anaphylactoid reaction

Infection

Muscle cramps

Dialysis disequilibrium: Headache, confusion and seizures due to excessively rapid metabolic correction.

40 mEq of NaCl is in 1 gram of sodium. So a 2 gm sodium diet has 80 mEq of NaCl. To replace salt, use 6 grams of sodium.

NEPHROLITHIASIS KEY POINTS: Documentation: non-contrast helical CT.

WORK UP:

\*Target Calcium oxalate stones.

\*Short bowel syndrome (^ oxalate absorption), bariatric surgery, primary hyperparathyroidism, sarcoidosis, oxalate in the diet from nuts, spinach, vitamin C; RTA.

\*Collect urine for ca, oxalate, urate, citrate (lo is bad), pH (NI:5.8-6.2; looks for supersaturation for CaP, CaUrate, RTA), urate (gout), phosphate, Na (excess salt is bad), K, Mg.

\*Serum testing: For RTA: HCO3 & K, For hypercalcemic states (^PTH, sarcoid): Ca.

\*Supersaturation (CaOxalate/Ca or CaPhosphate/Ca) is the driving force in stone formation. At a ratio below 1, crystals dissolve, while > 1 crystals form.

RX:

\*For all stones: increase fluids, low sodium diet, low protein diet, and maintain dietary calcium.

\*For calcium oxalate stones: Thiazide diuretic (HCTZ 25 mg BID or chlorthalidone 12.5 mg).

\*For hypocitraturia, K citrate 30 meQ BID

\*Enteric hyperoxaluria: Calcium carbonate 1-2 gm with meals.

\*Uric acid stones: urine pH <6.0: K citrate 40-80 meQ/d.

\*Indications for hospitalization are vomiting or uncontrollable pain.

\*Rx: 1) Fluids, HCTZ, K citrate. 2) Pain management: NSAIDs are as effective as opioids and may decrease ureteral smooth muscle tone. 3) Tamsulosin may be better than nifedipine.

\*Stone passage and size: <1mm 87%/2-4mm 76%/5-7mm 60%/ 7-9mm 48%/ >9mm 25%.

\*Stones < 8 mm, give alpha blockers (tamsulosin), CCBs (nifedipine) and hydrate. For stones that are 8 mm or more in diameter, do lithotripsy. If these does not work and stone is in proximal ureter, do percutaneous nephrolithotomy; if the stone is in the distal ureter, do ureterorenoscopy.

\*Urgent urology consult in urosepsis, ARF, Anuria, unyielding pain, Vomiting, stone >10mm, & failure to pass stone after medical Rx, particularly with stone > 5mm.

\*Options for further Rx are: shock wave lithotripsy, ultrasound endoscopic lithotripsy, laser probes, percutaneous lithotomy (go through renal pelvis and get the stone), and laparoscopic removal. Shock waves don't work for cysteine stones.

#### TREATMENTS FOR RENAL STONES

stone type	Ca Oxalate	Ca Urate	
Hydration	+++	+++	
Potassium citrate		+++	
Increase Ca intake	+++		
Salt restriction	+++		
Thiazide diuretic	+++		

#### URINE SEDIMENT BY DISEASE TYPE

glomerulonephritis red cell casts dysmorphic RBCs 1-2+protein

membranous nephrop hyaline casts

interstitial nephritis WBC casts WBCs

ATN: muddy or tubular epithelial cell casts cells: CKD has granular casts. Pre-renal has hyaline casts

Condition	casts	other
glomerulonephritis	RBCs	dysmorphic rbc, 1-2+ Protein
Membranous nephropathy	hyaline	
interstitial nephritis	WBC	WBCs
ATN	Muddy or tubular epithelial	WBCs
CKD	Granular, waxy	
Prerenal	hyaline	
pyelonephritis	WBC	

### DIFFERENTIAL DIAGNOSIS OF HYPOKALEMIA

1. Diuretic use.
2. No hypertension, cellular redistribution: Alkalosis, chloroquine, quetiapine, resperidone, periodic paralysis.
3. No hypertension, no cellular redistribution:
  - a. Urinary K decreased: (spot urine <15 meQK/gm Cr): Diarrhea, vomiting, NG suction
  - b. Urinary K increased
    - i. Acidosis: RTA
    - ii. Alkalosis: diuretics, Bartter's syndrome, Gitelman's syndrome
4. Hypertension: measure renin and aldosterone (R & A)
  - a. R and A both increased: Renovascular HTN, coarc, renin tumor
  - b. R decreased, A increased: Hyperaldosteronism, glucocorticoid remedial aldosteronism
  - c. R and A both decreased: Cushings, 11 B Hydroxysteroid dehydrogenase deficiency (genetic, licorice), CAH (11 B hydroxylase def), Liddle syndrome (gain of function of ENaC in DCT)

HYPERKALEMIA: Therapy: IV Ca to antagonize membrane effects, Shift K into cells (Insulin and glucose, nebulized albuterol), Remove total body K (dialysis, Kaxalate, Loop diuretics)

1. Exclude lab error
2. Intracellular shift: tissue injury (e.g, rhabdo), insulin def, acidosis, beta blockers, periodic paralysis
3. Type 4 distal RTA:
  - a. Hypoaldosteronism
    - i. Low renin: DM nephropathy, NSAIDS, HIV infection.
    - ii. High renin: Adrenal insufficiency, ACEIs, ARBs, Heparin
  - b. Collecting duct defects (deficient response to aldosterone): K sparing diuretics (eplere, spiro, amil, triam), diseased tubules.

Tb nephritis:

Due to granuloma in glomeruli. May persist for decades and then become symptomatic.

Insidious onset. Dysuria, hematuria.

WBCs and RBCs no casts, minimal protein.

Urine does not usually grow TB.

A positive culture for E Coli or other usual urinary pathogens does not exclude urinary TB.

IVP: blunting of calyces and frank papillary necrosis.

Diagnosis is by clinical syndrome of a) dysuria, b) sterile pyuria, c) hematuria, and d) IVP findings.

Confirmation requires demonstration of tubercle bacilli in urine.

3 to 6 cultures first morning void.



False negatives with broad spectrum antibiotics.

(Other conditions associated with g-u TB are: serum amyloid A amyloidosis, rifampin induced nephritis, hyponatremia with SIADH.)

ALPORT'S SYNDROME:

\*X-linked hereditary nephritis: Males only, positive family history, GN picture and hearing loss.

Hartnup disease: reduced gi absorption and renal re-absorption of amino-acids. It is treated with nicotinamide. Symptoms are similar to Pellagra, but patients with Hartnup disease have aminoaciduria with normal excretion of praline.

Classical complement pathway: Low C3, C4, and CH50. Decreased in SLE

Alternative complement pathway: Low C3 and CH50. ANCA associated disease.

C4 is normal in ANCA associated disease.

C4 is decreased in membranoproliferative GN types I and III.

Stimulants of ADH are: SSRIs, pain, nausea, hypoglycemia, pregnancy, eva, hiv infection, drugs, including chlorpropamide, vincristine and cyclophosphamide.

To correct SIADH due to pain, treat the pain !!

DI can be caused by lithium and vinblastine.

Severe hyponatremia can result from anesthesia impair the thirst mechanism.

Steroids act by inhibiting T cell activation thru inhibition of lymphokine production by antigen presenting cells.

Review the correction of hyponatremia. Patient with Na 110. ? correct approach. 3% S at 30 ÷ 40 cc/hr.

Check out Cecil 112.2 To determine whether na is low in a hypernatremic dehydrated patient??!!

(Cecil, Ch. 112.2)

(Patient has both v NA and v K.)

Calculation of water replacement needs is based on total-body water, since water loss occurs from both intracellular and extracellular sites. In this case, a 60-kg woman has a plasma sodium of 160 mmol/L, which one would like to lower to 140 mmol/L. Total-body water is roughly 60% of weight (36 L). To reduce the plasma sodium, this volume must be increased to 160/140 times 36 L, or about 41 L. Thus, a positive water balance of 5 L (41 - 36) is needed. This deficit is best corrected fairly slowly, with the aim being to replace about half the water deficit in the first day. If correction is done in this conservative fashion with close monitoring of electrolytes, progressive central nervous system dysfunction is not likely. If the patient had signs of circulatory collapse indicating an associated sodium deficiency, treatment would begin with normal saline to provide intracellular volume. In certain situations, such as hyperosmolar diabetic coma, the plasma osmolarity is elevated because of hyperglycemia as well as hypernatremia. Therefore, initial treatment should consist of normal saline to ensure circulatory integrity and insulin to lower plasma glucose and partially reduce intracellular osmolarity. Finally, half normal saline could be used to slowly replace the remaining water and salt deficits.

They corrected a dehydrated nursing home resident with sodium of 165 with NS !! See Harrison's CH 41.

Chronic metabolic acidosis induces calcium loss from bone associated with hypercalcuria. See NEJM 2005;353:513 for a case report of Sjogren's syndrome causing RTA Type I causing osteomalacia !

CONDITION-SPECIFIC ANTI-HYPERTENSIVE RECOMMENDATIONS(1)  
MKSAP 13 Update. JAMA 2003; 289: 2560.

Condition	HCTZ	beta blocker	ACEI	ARB	CCB	spirono-lactone
CHF	x	x	x	x		x
Post MI		x	x	x		
CAD risk	x	x	x	x		
DM	(x)(2)	x	x	x	x	
Kidney dis			x	x		
Prevent repeat CVA	x		x	x		

(1) These reflect recommendations for initial therapy. E.G. Patients post MI begin with beta blocker and ACEI. Patients with DM begin with ACEI or an ARB. Patients with CHF begin with HCTZ and ACEI.  
(2) Hypokalemia due to HCTZ can cause increased insulin resistance and diabetes (Messerli, 2003).

New Lupus Nephritis Classification (Weening, 2004)

Minimal mesangial LN.

Mesangial proliferative LN.

Focal LN.

Diffuse LN: S type: Diffuse segmental; G type: Diffuse global.

Membranous LN.

Advanced sclerosing LN

Risk factors for hyperkalemia in patients taking ACEIs or ARBs:

DM

Kidney disease

CHF

Hypovolemia

Advanced Age

Drugs: NSAIDs, heparin, betablockers, TMP/SMX, ketoconazole, pentamidine, cyclosporine.

---

To cope with this, prescribe HCTZ, HCO<sub>3</sub> (but NaHCO<sub>3</sub> is contra-indicated in hypertension and heart disease), inquire about OTC salt substitutes, and stop drugs if K>5.5. (Palmer, 2004).

PREVENTION OF RADIOCONTRAST NEPHROPATHY (RCN):

Iodixanol is the safest radiocontrast agent.

Stop diuretics, NSAIDs, and metformin.

About 3 cc/kg of 154 meq/L of sodium bicarb 1 hour before a radiocontrast study and for 6 hours after appears to be more effective than isotonic saline volume expansion, which takes 12 hours before and 12 hours after. (Merten, JAMA 2004).

NACysteine may be effective.

Statins, ARBs, and ACEIs (best evidence) reduce proteinuria and decrease the decline in kidney function. Combination therapy with an ACEI and an ARB is now used to lower protein and blood pressure to optimal levels: <130 systolic and less than 30 mg/gm Creatinine.

In pregnant patients, there is no evidence that treatment of mild HPT (140/90 to 179/109) in patients with essential hypertension lowers risk to mother or fetus!! (MKSPAP 13 nephrology update, question 8).

NSAIDs provide better pain relief than do opioids for acute renal colic. BMJ 2004;328:1401.

Anti-diuretic hormone causes the kidneys to retain water but not sodium in response to reduced fluid volume via pressure receptors in veins, atria and carotids and in response to increased sodium concentration via osmoreceptors in the hypothalamus. ADH is secreted by the posterior pituitary.

Alcohol and caffeine cause diuresis by suppression of ADH.

Diagnosis of SIAD.

SIAD may be caused by inappropriate secretion of antidiuretic hormone or by reset of the osmostat such that lower concentrations of sodium are detected as normal (further reduction in sodium below the new normal level suppresses ADH.)

Diagnosis of SIAD requires 6 essential features:

- \*Clinical euvolemia.
- \*Decreased effective osmolality (measured osmolality minus BUN/2.8).
- \*Increased urine sodium > 40 meQ/liter with normal sodium intake.
- \*Increased urine osmolality >100 mOsm/L during hypotonicity.
- \*Normal thyroid and adrenal function (thyroid hormone and cortisol are both required for free water clearance).
- \*No recent use of diuretics.

Supporting features:

- \*BUN < 10mg/dL
- \*Uric acid <4 mg/dL
- \*Fractional excretion of sodium > 1%.
- \*Correction of hyponatremia thru fluid restriction.

To estimate correction of hyponatremia when symptomatic:

- \*Estimate the amount of sodium required:  $\text{Ideal weight(kg)} * 0.5 * (\text{Na (nl)} - \text{Na(obs)meQ/L})$ .
  - \*Volume of sodium containing fluid required: Normal saline is 0.9% NaCl = 155 meQ of Na.
- If the sodium containing fluid is 3% NaCl, the concentration of this is 515 meQ/L:  
Volume (liters) = Sodium required/515 meQ/L.

- \*The rate of correction should be no more than 12 meQ/24 hours.

Example:

- \*Patient is euvolemic,
- \*Na serum = 120 meQ/L, BUN = 8, effective tonicity = measured osmolality (250) - 8 = 242mosm/L.
- \*Urine osmolality = 180 mosm/L
- \*Urine sodium = 80 meQ/L
- \*TSH is normal and cortisol is 25 mcg/dL (i.e., somewhat elevated due to stress).
- \*patient is not on recent diuretic.

This patient with lung ca is somnolent and confused mental status changes 5 days ago.

(Patient could have other pulmonary disease or CNS lesions or disease. His weight is 70 kg with average BMI.)

Sodium deficit =  $70\text{kg} * 0.5\text{L/kg} * (140\text{ meQ/L} - 120\text{ meQ/L}) = 700\text{ meQ}$ .

Using 3% NaCl, the volume required for correction =  $700\text{ meQ} / 515\text{ meQ/L} = 1.4\text{ liters}$ .

Change the sodium concentration 10 meQ in 24 hours (i.e., give 0.7 liters plus 0.15 liters due to kidney concentration of 80 meQ/L) = 0.85 liters.

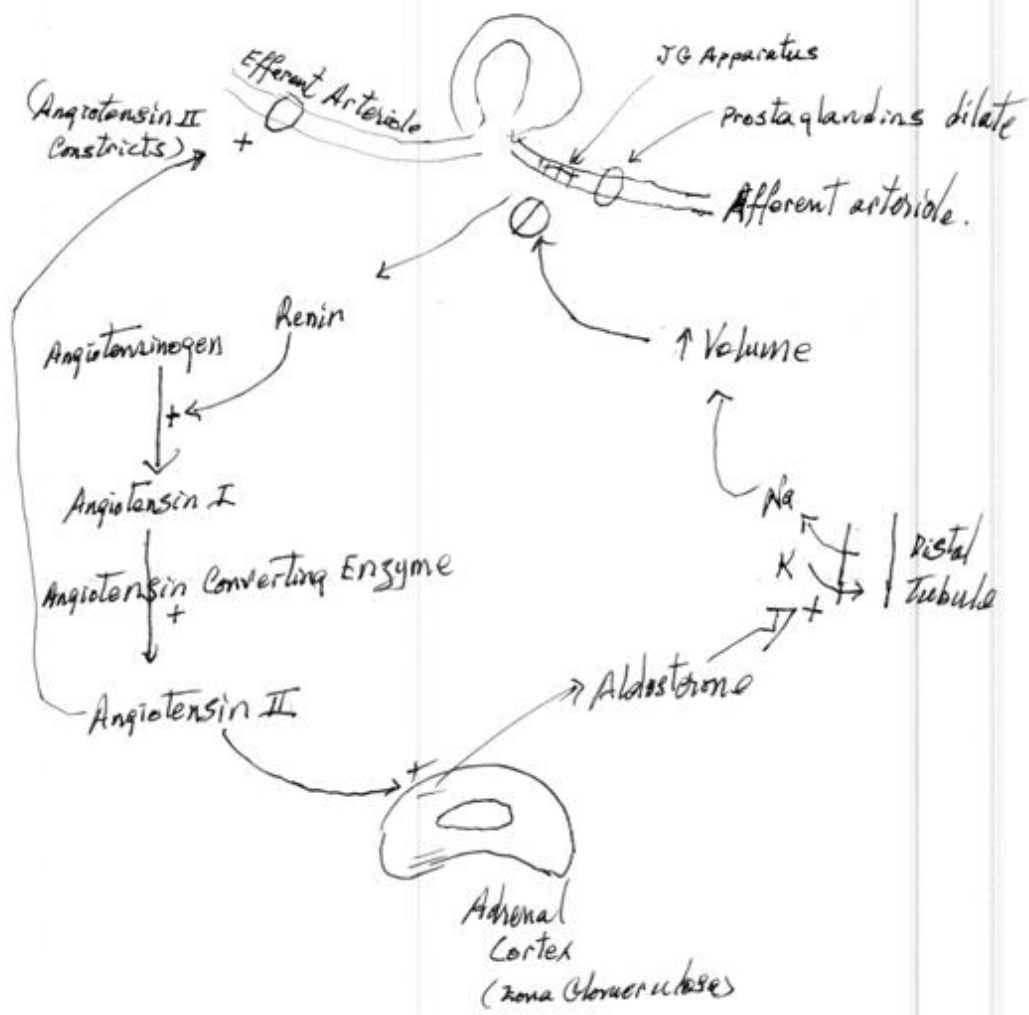
Rate =  $850\text{ cc} / 24\text{ hours} = 35\text{ cc/hr}$ .

Beta hydroxy butyrate is converted into aceto-acetate and acetone. Nitroprusside reacts with aceto-acetate and acetone but not beta hydroxybutyrate. Beta hydroxy butyrate makes up 75% of ketones in DKA, but this

can reach 90% in alcoholic keto-acidosis or concurrent lactic acidosis. Hence keto-acids may not be measured. One way to follow the improvement is to look at the correction of the anion gap. Another way is to add hydrogen peroxide to the urine to convert the Beta hydroxybutyrate to acetoacetate and then measure the aceto-acetate.

Sympathetic tone is increased in obstructive sleep apnea and obesity and hence these cause hypertension.

Beer potomania: A condition of hypo-natremia owing to the decreased solute with relatively high water intake owing to the fact that there is a minimum urine osmolality (which happens to be 60 mosm/liter). For example, if only 240 mosmoles per day is taken in and then excreted, the maximum water output is  $240 \text{ mosm} / 60 \text{ mosm/L} = 4 \text{ Liters}$ . Intake of water above this causes hyponatremia.



IC: K, CL, PO4  
EC: Na, Cl, HCO3

Distinguish Dehydration from Volume Depletion:

Dehydration: loss of free water: E.G.: Fever in a nursing home patient who is unable to obtain free water.

Lab: High Sodium. High BUN/Cr

Rx: Calculate water deficit:

For males, water deficit =  $[(\text{Na-observed} - 140)/140] * 0.6 * \text{Wt (kg)}$

For females, water deficit =  $[(\text{Na-observed} - 140)/140] * 0.5 * \text{Wt (kg)}$

A quick check of volume requirement =  $\Delta \text{Na}/3$ .

Generally, dehydration has 2.5 x more water loss than hypovolemia.

Treatment would be water plus sodium so as not to lower sodium by more than 5 meQ/L/hour. The best solution is normal saline.

VS

Hypovolemia: loss of sodium and water: E.G.: Diarrhea or Excess use of diuretics, third spacing, burns  
Orthostatic changes

Lab: Normal or Low Sodium; high BUN/Cr

Rx: NS. Again, correct by no more than 5 meQ/L/hour in 1<sup>st</sup> 24 hours.

For fever in a nursing home patient there can be

Free water loss >> ^Na (tonicity) >> ^SIADH. >> ^ Water absorption.

v Volume >> ^Aldosterone >> ^Na absorption and v Naturetic peptides.

It is interesting that each uses the opposite salt vs water mechanism.

Renal artery stenosis is best evaluated by **intra-arterial digital subtraction angiography**.

HEPATORENAL SYNDROME CRITERIA:

\*liver disease with ascites

\*Renal disease: creatinine 1.6+ mg/dL

\*Renal function not improved by fluid challenge (including albumin 1 gm/kg x 2 days)

\*No other cause for renal dysfunction (no shock and no renal toxins)

\*No renal parenchymal disease

ASA toxicity with acidosis: Rx = Na HCO3.

Prerenal azotemia may have FENa >1% if diuretics are used.

Acute interstitial nephritis has WBC casts and eos.

Gestational hypertension occurs after 20 weeks of gestation.