ACID-BASE DISORDERS Sharon Anderson, MD July 2016

GENERAL ACID-BASE RELATIONSHIPS: Henderson-Hasselbach equation:	pH	[H], nmol/L
$pH = pK + \log HCO_3^-/pCO_2$	7.60	26
$H^+ = 24 \times pCO_2/HCO_3^-$	7.50	32
	7.40	40
0.1 pH unit = $\cong$ 10 nmol/L H^+	7.30	50
	7.20	63
	7.10	80

APPROACH TO ACID-BASE DISORDERS	
Question	Evaluation
1. What is the clinical situation?	Anticipate the disorder!
2. Is the patient acidemic or alkalemic?	Blood pH (< or > 7.40)
3. Is the primary process metabolic or respiratory?	Directional change in pCO_2 and HCO_3^-
4. If metabolic acidosis: Gap or non-gap?	Measure anion gap [Na - (Cl + HCO_3^-)]
5. Is compensation appropriate?	Use formulas to assess
6. Is there more than one disorder present?	Use formulas, and Δ / Δ

SIMPLE ACID-BASE DISORDERS				
Disorder	pH	Primary Disorder	Compensatory Response	**Definition**: By convention, a primary disorder with appropriate compensation is considered to be a single, pure acid-base disorder -- NOT a mixed disorder.
Metabolic acidosis	↓	↓ HCO_3^-	↓ pCO_2	
Metabolic alkalosis	↑	↑ HCO_3^-	↑ pCO_2	
Respiratory acidosis	↓	↑ pCO_2	↑ HCO_3^-	
Respiratory alkalosis	↑	↓ pCO_2	↓ HCO_3^-	

EXPECTED COMPENSATORY RESPONSE		
Disorder	Compensation	Limits
Metabolic Acidosis	Expected pCO_2 = (1.5 x HCO_3^-) + 8 $\pm$ 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

METABOLIC ACIDOSIS

Etiology: Inability of the kidney to excrete dietary H^+ load, or increase in the generation of H^+ (due to addition of H^+ or loss of HCO_3)

METABOLIC ACIDOSIS: ELEVATED ANION GAP

$AG = Na^+ - (Cl^- + HCO_3^-) = 12 \pm 2$ mEq

Note: Diagnostic utility of elevated anion gap is greatest when the AG > 25 mEq/L

"Normal Anion Gap" in Hypoalbuminemia

• The true anion gap is underestimated in hypoalbuminemia (albumin is an unmeasured anion), so for adjusted AG:

- **For every 1.0 ↓ in albumin↑ AG by 2.5**

CATMUDPILERS	GOLDMARK
C- cyanide, CO2, CPK	G – glycols (ethylene, propylene)
A – alcoholic ketoacidosis	O - oxoproline
T – toluene	L – L-lactic acidosis
M – methanol	D – D-lactic acidosis
U – uremia	M - methanol
D – DKA	A - aspirin
P – paraldehyde, phenformin	R – renal failure
I – isoniazid, iron	K - ketoacidosis
L – lactic acidosis	
E – ethylene glycol	Mehta, Lancet 272:892, 2008
R – rhabdo, renal failure	
S - salicylate	

CAUSES OF LOW ANION GAP

1. Fall in unmeasured anions (esp. albumin)
2. Increase in unmeasured cations: Hyperkalemia; lithium intoxication; hypercalcemia; hypermagnesemia; multiple myeloma (cationic IgG paraprotein)

3. Artefactual: Hyponatremia (spurious low Na^+)
   Bromide ingestion (bromide measured as Cl-)
   Hyperlipidemia (overestimation of Cl-)

THE DELTA/DELTA: Δ AG/ Δ HCO_3^-

Rationale: For each unit INCREASE in AG (above normal), HCO_3^- should DECREASE one unit below normal

"Normal" values: Normal AG = 12, normal HCO_3^- = 24

EXAMPLES

AG	HCO_3^-	Diagnosis
18	18	Appropriate compensation; pure AG acidosis
18	22	HCO_3^- has fallen less than predicted; thus HCO_3^- is too high Diagnosis = mixed AG metabolic acidosis AND metabolic alkalosis
18	12	HCO_3^- has fallen more than predicted; thus HCO_3^- is too low Diagnosis = mixed AG metabolic acidosis AND non-gap metabolic acidosis

OSMOLAR GAP

Measured serum osmolality > calculated serum osmolality by > 10 mOsm

Calculated: $2\,(Na) + \frac{BUN\ (mg/dl)}{2.8} + \frac{glucose\ (mg/dl)}{18}$

CAUSES OF HIGH OSMOLAR GAP

Isotonic hyponatremia: Hyperlipidemia, hyperproteinemia, glycine or mannitol infusion
Ingestions: Ethanol (divide by 4.6 to get osm), isopropranolol; ethylene glycol; methanol
Contrast media

Relationship between AG and osmolar gap

	AG	Osm gap	Comments
Ethylene glycol	+	+	* Double gap
Methanol	+	+	* Double gap
Renal failure	+	+	* Double gap
Isopropyl alcohol	-	+	Ketosis without acidosis
Ethanol	-	+	Can see AG in severe alcoholic ketoacidosis
Lipids, proteins	-	+	

CAUSES OF NORMAL AG (HYPERCHLOREMIC) METABOLIC ACIDOSIS

High K^+	Low K^+
NH_4Cl	GI losses (diarrhea, pancreas, bili)
Arg HCl	Carbonic anhydrase inhibitors
Oral $CaCl_2$	Renal tubular acidosis
Adrenal insufficiency	Sulfur toxicity
Interstitial nephritis	Ureteral diversions
	Repair phase of DKA

Causes of Normal AG (Hyperchloremic) Metabolic Acidosis

- "HARDUPS"
  - Hyperalimentation
  - Acetazolamide
  - RTA
  - Diarrhea; overcorrected or early DKA
  - Ureterosigmoidostomy
  - Pancreatic fistula, posthypocapnia
  - Spironolactone

USE OF THE URINARY AG IN NORMAL AG ACIDOSIS

Batlle, et al. NEJM 318:594, 1988

Urine AG = (Na + K) - Cl

Negative urine AG = Normal, or GI loss of HCO_3^-

Positive urine AG = altered distal renal acidification (impaired ability to excrete NH_4)

Rationale: In patients with nongap acidosis, there is an increase in NH4 excretion (unmeasured cation), as attempt to excrete the excess acid. Increase in NH4 excretion leads to increase in Cl excretion, so UAG is negative. Patients with RTA are unable to excrete NH4 normally, so UAG will be positive.

Caveats: Less accurate in patients with volume depletion (low urinary Na); and in patients with ↑ in excretion of unmeasured anions (e.g., ß-hydroxybutyrate and acetoacetate in ketoacidosis, hippurate after toluene ingestion); ↑ in urinary Na, K to maintain electroneutrality will cause false positive urine AG)

USE OF THE URINARY AG IN NORMAL AG ACIDOSIS			
Plasma K	**Urine Anion Gap**	**Urine pH**	**Diagnosis**
Normal	Negative	< 5.5	Normal
Elevated	Positive	< 5.5	Aldo deficiency
Elevated	Positive	> 5.5	Distal RTA
Normal or low	Positive	> 5.5	Classic RTA
Normal or low	Negative	> 5.5	GI HCO_3 loss

USE OF THE URINE OSMOLAR GAP IN NORMAL AG ACIDOSIS

Rationale: When UAG is positive, and it is unclear whether increased cation excretion is responsible, urine NH_4 concentration can be estimated from urine osmolal gap

Calc Uosm = (2 x [Na+K]) + urea nitrogen/2.8 + glu/18

- The gap between calculated and measured Uosm = mostly ammonium (caution: not accurate in ketoacidosis)
- In patients with metabolic acidosis, urine ammonium should be > 20 mEq/L. Lower value = impaired acidification

RENAL TUBULAR ACIDOSIS			
	Distal (Type 1)	Proximal (Type 2)	Type 4
Basic defect	Decreased distal acidification	Decreased proximal HCO_3- reabsorption	Decreased aldosterone secretion or effect
Serum HCO3 range	Variable, may be < 10	Usually 12-20	> 17
Urine pH	> 5.3	Variable (> 5.3 if above HCO3 reabsorptive threshold)	Usually < 5.3
Plasma K	Usually low	Low	High
Some associated conditions (partial listing)	Nephrocalcinosis, autoimmune disorders, amphotericin	Fanconi syndrome, rickets, myeloma	Renal failure, interstitial nephritis, diabetes, sodium channel blockers
Response to HCO_3 Rx	Good	Poor	Fair

Calculation of the Bicarbonate Deficit

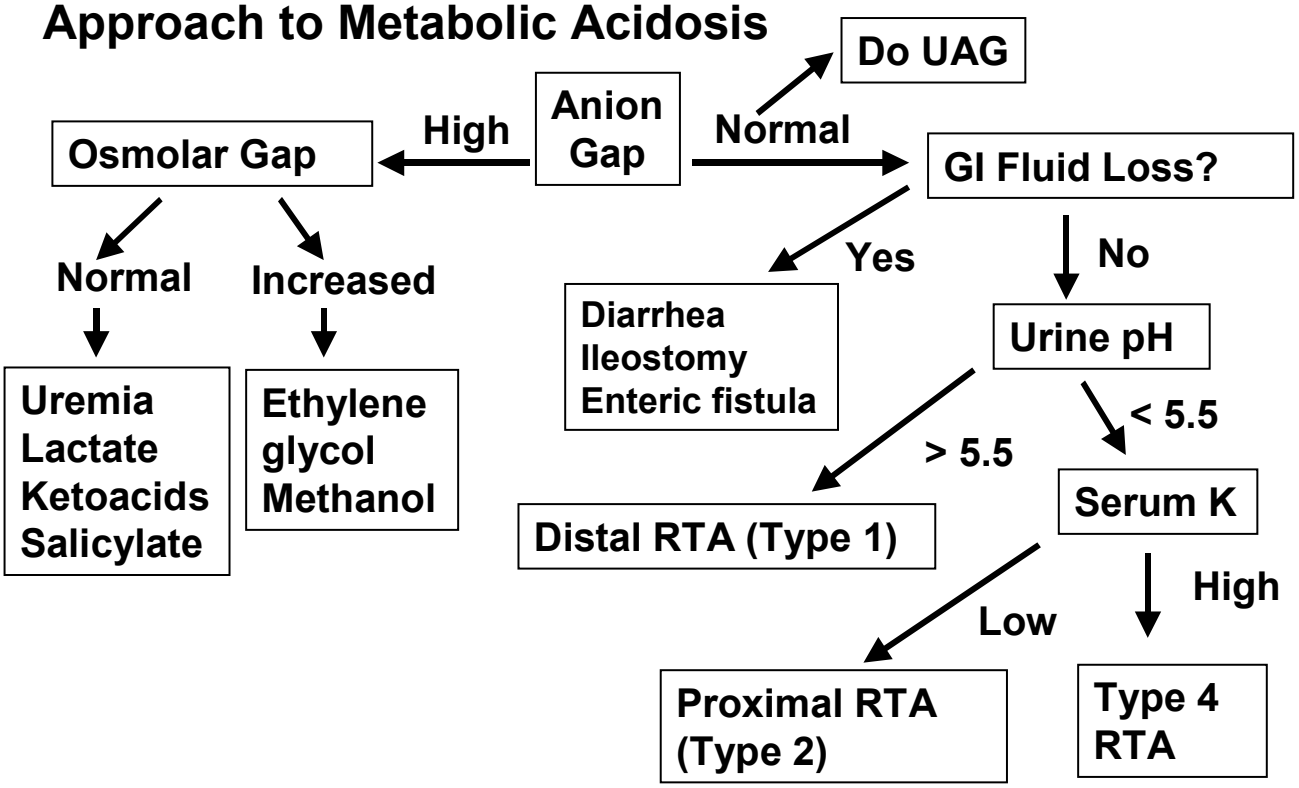
HCO_3- deficit = HCO_3- space x HCO_3- deficit per liter

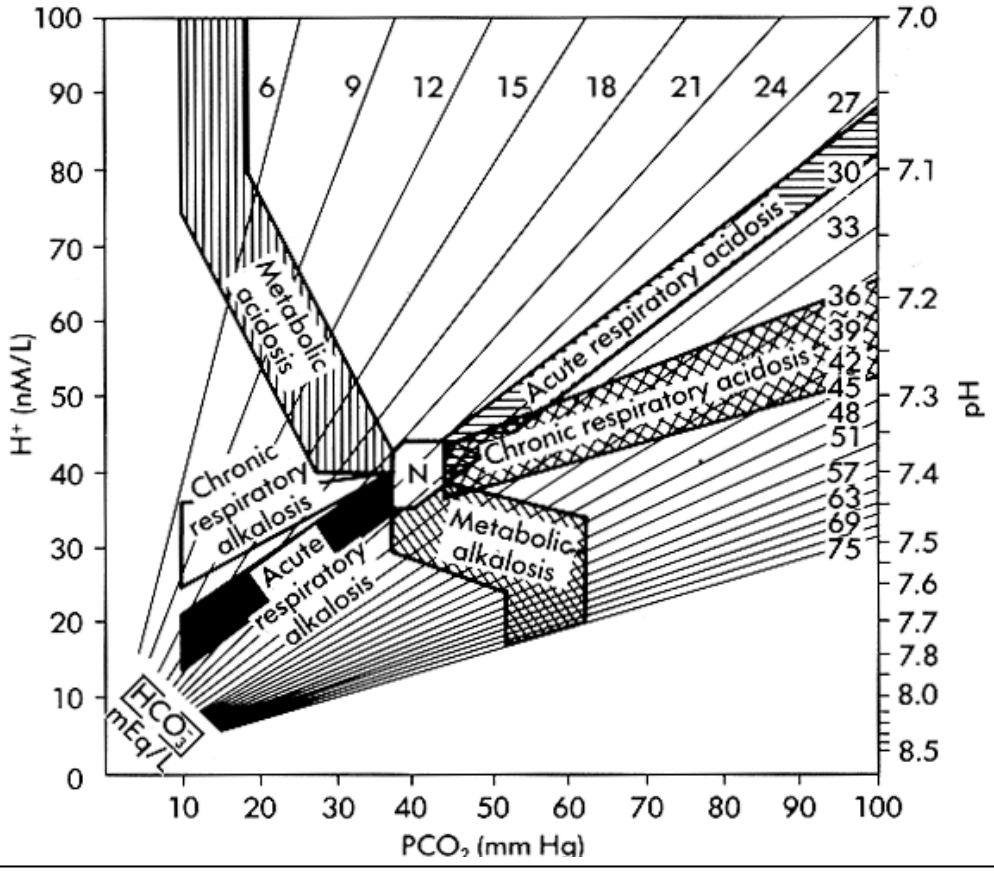
Apparent HCO_3- space = **0.4** x lean body wt (kg)

HCO_3- deficit per liter = [desired HCO_3-] - [measured HCO_3^-]

Example: 70 kg man with serum HCO_3- = 10 mEq/L. HCO_3- deficit = (70) x (0.4) x (24 - 10) = 392 mEq; replace ½ of the deficit over 3-4 hrs, and stop replacement when pH reaches 7.20

Approach to Metabolic Acidosis





METABOLIC ALKALOSIS

Etiology: Requires both *generation* of metabolic alkalosis (loss of H^+ through GI tract or kidneys) **and** *maintenance* of alkalosis (impairment in renal HCO_3 excretion)

Causes of Metabolic Alkalosis

Loss of hydrogen	Retention of bicarbonate	Contraction alkalosis
GI losses Renal losses (diuretics, mineralocorticoid excess) H+ movement into cells (e.g. low K)	Massive blood transfusion Administration of $NaHCO_3$ or sodium acetate Milk-alkali syndrome	Diuretics Gastric losses in achlorhydric patients Sweat losses in cystic fibrosis

Factors causing maintenance of alkalosis (impaired HCO_3 excretion)
- Decreased GFR (decreased volume, renal failure)
- Increased tubular reabsorption (decreased volume, chloride depletion, hypokalemia, hyperaldosteronism)

Use of the Urinary Chloride in Metabolic Alkalosis	*Newer machines: < 25 mEq/L vs. > 40 mEq/L*
Chloride-responsive (U_{Cl} < 15 mEq/L)	Chloride-resistant (U_{Cl} > 20 mEq/L)
GI loss (emesis, NG suction, villous adenoma, CF) Renal loss (diuretics, posthypercapnea) Low chloride intake Exogenous alkali ($NaHCO_3$, transfusions, antacids) Refeeding	With urinary potassium < 15 mEq/L Laxative abuse Severe K depletion With urinary potassium > 20 mEq/L Hypotensive: Bartter's syndrome Hypertensive/low PRA: Primary hyperaldo Hypertensive/high PRA Endogenous: Cushing's, hyperreninism, CAH, Liddle's syndrome) Exogenous (licorice, chewing tobacco)

CLEVER PD
- Contraction alkalosis
- Licorice
- Endo: Conn's, Cushing's, Bartter's
- Vomiting
- Excess Alkali
- Refeeding alkalosis
- Post-hypercapnia
- Diuretics

Use of Spot Urine Cl and K

Urine Chloride

→ Virtually absent (< 10 mEq/L): Vomiting, NG suction; Postdiuretic, posthypercapneic; Villous adenoma, congenital choridorrhea, post-alkali

↓ > 20 mEq/L

Urine Potassium

→ Low (< 20 mEq/L): Laxative abuse; Other causes of profound K depletion

↓ > 30 mEq/L

Diuretic phase of diuretic Rx
Bartter's, Gitelman's syndromes
Primary aldo; Cushings; Liddle's;
Secondary aldosteronism

Therapy of Metabolic Alkalosis

1. Remove the offending culprits (diuretics, NG suction, alkali therapy) if possible.
2. Chloride (saline) responsive alkalosis: Replete volume with NaCl.
3. Chloride non-responsive (saline resistant) alkalosis:
   Acetazolamide (carbonic anhydrase inhibitor) increases renal $NaHCO_3$ excretion
   Hydrochloric acid infusion; need to calculate bicarbonate excess to establish dosing
   HCl, concentration 0.1 or 0.2 M (100-200 mEq/L) into a central vein
   Amount: 0.2 x predicted reduction in HCO_3 needed to lower pH; follow ABGs closely
   Correct hypokalemia (mineralocorticoid excess, hypokalemic states)

Calculation of Bicarbonate Excess (*Note that bicarb space differs in metabolic alkalosis*)

HCO_3- excess = HCO_3- space x HCO_3- excess per liter

Apparent HCO_3- space = **0.5** x body wt (kg)

HCO_3- excess per liter = [measured HCO_3-] - [desired HCO_3^-]

Example: 60 kg man with serum HCO_3- = 40 mEq/L. HCO_3- excess = (60) x (0.5) x (40-24) = 480 mEq; replace ½ of the deficit over 12 hrs, then the remainder over the next 24 hrs

RESPIRATORY ACIDOSIS

Etiology: Reduction in alveolar ventilation, or imbalance between ventilation and perfusion, with CO_2 retention

Causes of Respiratory Acidosis

Inhibition of the medullary respiratory center
- Acute: drugs, oxygen (in CO_2 retainers), cardiac arrest, central sleep apnea
- Chronic: extreme obesity (Pickwickian), CNS lesions

Disorders of the respiratory muscles and chest wall
- Acute: Muscle weakness (myasthenia gravis, Guillain-Barré syndrome, hypokalemia, hypophosphatemia)
- Chronic: Muscle weakness (spinal cord injury, polio, ALS, multiple sclerosis, myxedema); kyphoscoliosis, extreme obesity)

Upper airway obstruction
- Acute: foreign body or vomitus aspiration, obstructive sleep apnea, laryngospasm

Disorders affecting gas exchange across the pulmonary capillary
- Acute: COPD exacerbation, ARDS, pulmonary edema, severe asthma or pneumonia, hemo- or pneumothorax
- Chronic: COPD, extreme obesity

Mechanical ventilation

Treatment of Respiratory Acidosis

1. Specific treatment of causative disorder.
2. Weight loss and carbohydrate restriction in obese patients.
3. Ventilation.

RESPIRATORY ALKALOSIS

Etiology: Hyperventilation

Causes of Respiratory Alkalosis:

Hypoxemia (pulmonary disease, CHF, hypotension or severe anemia, high altitude residence)
Pulmonary disease (interstitial lung disease, pneumonia, pulmonary embolism, pulmonary edema)
Direct stimulation of medullary respiratory center
- Psychogenic or voluntary hyperventilation
- Liver failure
- Gram-negative sepsis
- Salicylate intoxication (with concurrent primary metabolic acidosis)
- Pregnancy, luteal phase of menstrual cycle, due to progesterone; megace?
- Postcorrection of metabolic acidosis
- Neurologic disorders (cerebrovascular accidents, pontine tumors)

Mechanical ventilation

Treatment of Respiratory Alkalosis

No specific therapy; treat the underlying disease

MIXED ACID-BASE DISORDERS

MIXED ACID-BASE DISORDERS: CLUES

-- Degree of compensation for primary disorder is inappropriate (too high or too low)

-- Delta AG/delta HCO_3^- < 1.1 or > 2.1

-- Clinical history: ANTICIPATE THE DISORDER!

Use of Venous vs. Arterial pH

Venous (c/w arterial) ↓ pH 0.03 - 0.04 ↑ H+ 5 nEq/L ↑ $pC0_2$ 7-8 mmHg ↑ HCO_3 1 mEq/L

Common Clinical States and Associated Acid-Base Disturbances

Clinical State	Acid-Base Disorder
Pulmonary Embolus	Respiratory Alkalosis
Hypotension	Metabolic Acidosis
Vomiting	Metabolic Alkalosis
Severe Diarrhea	Metabolic Acidosis
Cirrhosis	Respiratory Alkalosis
Renal Failure	Metabolic Acidosis
Sepsis	Respiratory Alkalosis/Metabolic Acidosis
Pregnancy	Respiratory Alkalosis
Diuretic Use	Metabolic Alkalosis
COPD	Respiratory Acidosis

Acid-Base Disorders in GI Disease

Gennari JF, Weise WJ. CJASN 3:1861, 2008

GI Disorder	Acid-Base Disorder	Potassium	ECFV
Vomiting, NG suction	Metabolic alkalosis	Low	Low
Diarrheal states			
Cholera, infections	Metabolic acidosis	Low	Very low
Autoimmune	None	Normal	Normal
Congenital achloridorrhea	Metabolic acidosis	Low	Low
Villous adenoma	Variable	Normal-low	Normal-low
Laxative abuse	None unless severe	Low	Normal-low
Panc/biliary drainage	Metabolic acidosis	Normal-high	Low
Ileostomy drainage	Metabolic acidosis, metabolic alkalosis	High Normal	Low Low
Short bowel	Metabolic acidosis (D-lactic acidosis)	Normal	Normal

Acid-Base Disorders with Antibiotic Therapy

Zietse R, et al. Nat Rev Nephrol 5:193, 2009

Drug	Acid-Base Disorder	Mechanism	Frequency
Penicillin	Anion gap acidosis	Pyroglutamate	Rare
Linezolid	Anion gap acidosis	Mitochondrial toxicity	Rare
Most antibiotics	Anion gap acidosis (D-lactic acidosis)	Bacterial overgrowth	Rare
Tetracyclines, aminoglycosides	Non-gap acidosis	Fanconi syndrome	Rare
Trimethoprim	Non-gap acidosis	Blocks eNAC	Frequent
Ampotericin B	Non-gap acidosis	Proton leak	Frequent
Aminoglycosides	Metabolic alkalosis	Bartter-like	Rare
Capreomycin	Metabolic alkalosis	Bartter-like	Rare

Acid-Base Disorders in Liver Disease

Ahya SNR, et al. Semin Nephrol 26:466, 2006

Acid-Base Disorder	Mechanisms	Frequency
Anion gap metabolic acidosis	Type B lactic (compensated), Type A lactic (not compensated)	10-20% 30-40%
Non-gap metabolic acidosis	Diarrhea (lactulose); distal RTA; Wilson's disease; PBC	Variable
Respiratory alkalosis	Hypoxemia; progesterone	Most common
Metabolic alkalosis	Volume contraction from diuretics	Variable