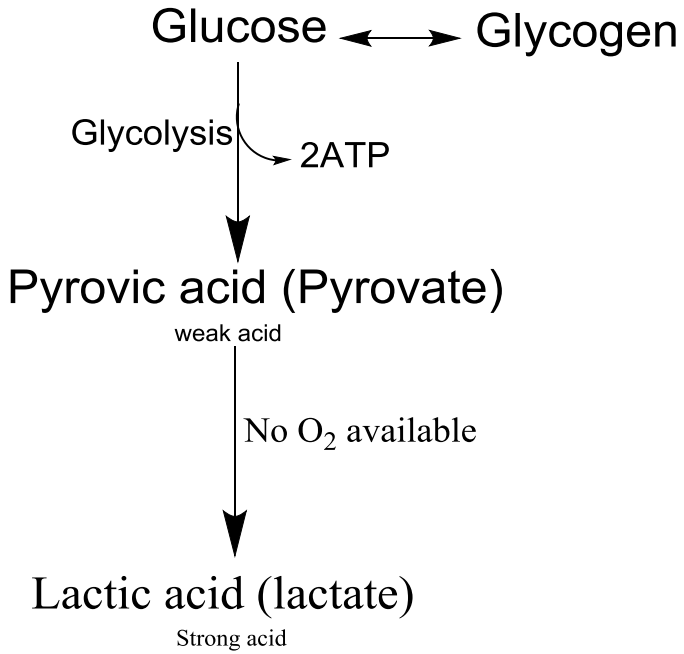
Acid base balance

The normal processes of metabolism result in the net formation of 40-80 mmol of hydrogen ions per 24h. This burden of hydrogen ions is excreted by the kidneys, in the urine.

There is a considerable endogenous turnover of hydrogen ions as a result of normal metabolic processes.

Incomplete oxidation of energy substrates generates acid (e.g. lactic acid by glycolysis, ketoacids from triacylglycerols).



While further metabolism of these intermediates consumes it (e.g. gluconeogenesis from lactate, oxidation of ketones).

Temporary imbalances between the rates of production and consumption may arise in health (e.g. the accumulation of lactic acid during anaerobic exercise), but in general they are in balance and so make no contribution to net hydrogen ion excretion.

Potentially far more acid is generated as carbon dioxide during energy-yielding oxidative metabolism. In excess of 15,000 mmol per 24 h of carbon dioxide is produced in this way, and is normally excreted by the lungs.

Although carbon dioxide itself is not an acid, in the presence of water it can undergo hydration to form a weak acid, carbonic acid (Equation 3.1).

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \qquad (1)$$

Carbonic acid

Temporary imbalances can be absorbed by buffering and, as a result, the hydrogen ion concentration of the body is maintained within narrow limits [35-45 nmol/L (pH 7.35-7.46) in extracellular fluid (ECF)].

Intracellular hydrogen ion concentration is slightly higher but is also rigorously controlled.

however, imbalances between the rates of acid formation and excretion can occur and persist, resulting in acidosis or alkalosis.

Buffering of hydrogen ions

As hydrogen ions are generated they are buffered, thus limiting the rise in hydrogen ion concentration that would otherwise occur.

A buffer system consists of a weak acid, is incompletely dissociated, to give its conjugate base. If hydrogen ions are added to a buffer, some will combine with the conjugate base and convert it to the undissociated acid.

The addition of hydrogen ions to the bicarbonate-carbonic acid system (Equation 2) drives the reaction to the right, increasing the amount of carbonic acid and consuming bicarbonate ions.

$$H^+ + HCO^-_3 \rightleftharpoons H_2CO_3 \qquad (2)$$

Conversely, if the hydrogen ion concentration falls, carbonic acid dissociates, thereby generating hydrogen ions.

The bicarbonate buffer system is the most important in the ECF, yet at normal ECF hydrogen ion concentrations the concentration of carbonic acid is about 1.2 mmol/L, while that of bicarbonate is 20 times greater.

However, the capacity of the bicarbonate system in the body is greatly enhanced by the fact that carbonic acid can readily be formed from carbon dioxide or disposed of by conversion into carbon dioxide and water (Equation 1).

$$CO_2 + H_2O \rightleftharpoons \underset{\text{Carbonic acid}}{H_2CO_3} \qquad (1)$$

To maintain the capacity of the buffer system, the bicarbonate must be regenerated

Bicarbonate formation can only continue if these hydrogen ions are removed. This process occurs in the cells of the renal tubules, where hydrogen ions are secreted into the urine, while bicarbonate is generated and retained in the body.

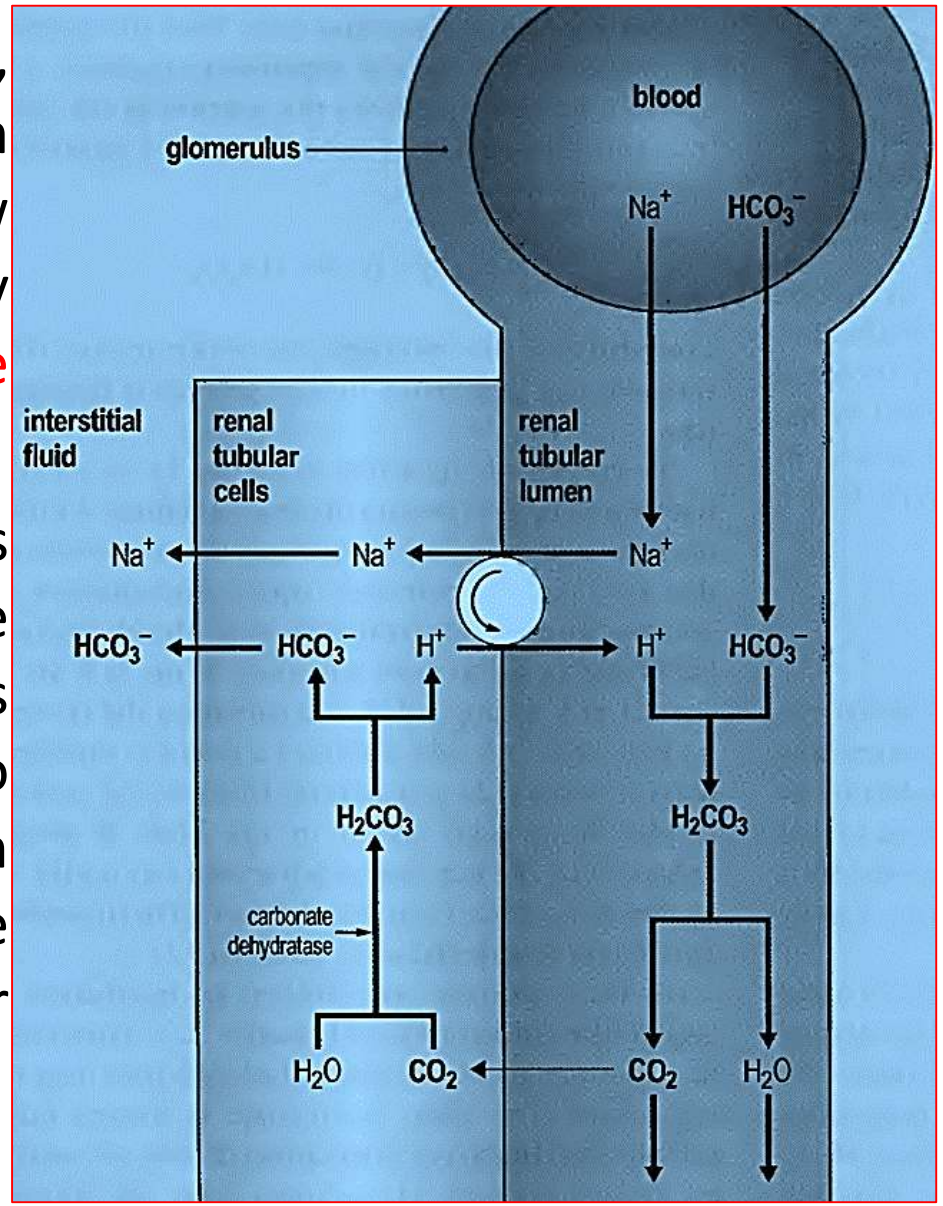
Reabsorption of bicarbonate and excretion of hydrogen ion

The cons. of bicarbonate in glomerular filtrate is the same cons. in the plasma. In the health case, Approximately 4300 mmol/L of bicarbonate are filtered by renal glomeruli. If this bicarbonate were not reabsorbed, copious amounts would be excreted in the urine, depleting the capacity of the bodies buffering and causing an acidosis.

The luminal surface of renal tubular cells is impermeable to bicarbonate and, therefore, direct reabsorption cannot occur.

Within the renal tubular cells, carbonic acid is formed from carbon dioxide and water This slow reaction is catalyzed in the kidney by the enzyme carbonate dehydratase (carbonic anhydrase).

The carbonic acid dissociates into hydrogen and bicarbonate ions. The bicarbonate ions pass across the borders of the cells into the interstitial fluid. The hydrogen ions are secreted across the luminal membrane in exchange for sodium ions.



In the tubular fluid, hydrogen ions combine with bicarbonate to form carbonic acid, most of which dissociates into carbon dioxide and water. Some of the carbon dioxide diffuses back into the renal tubular cells while the remainder is excreted in the urine.

Net acid excretion depends upon the same reactions occurring in the renal tubular cells but, in addition, requires the presence of a suitable buffer system in the urine.

This is because the minimum urinary pH that can be generated, 4.6, is equivalent to a hydrogen ion concentration of approximately 25 µmol/L. Given a normal urine volume of 1.5 L/24 h.

The principal urinary buffer is phosphate. This is present in the glomerular filtrate, approximately 80% being in the form of the divalent anion, HPO_4^{2-}. This combines with hydrogen ions and is converted to H_2PO_4.

$$HPO_4^{2-} + H^+ \rightleftharpoons H_2PO_4$$

At the minimum urinary pH, virtually all the phosphate is in the H_2PO_4 form. About 30-40 mmol of hydrogen ions are normally excreted in this way every 24 h.

Ammonia, produced by the deamination of glutamine in renal tubular cells, is also an important urinary buffer. The enzyme that catalyzes this reaction, glutaminase, is induced in states of chronic acidosis, allowing increased ammonia production and hence increased hydrogen ion excretion via ammonium ions.

$$NH_3 + H^+ \rightleftharpoons NH_4^+$$

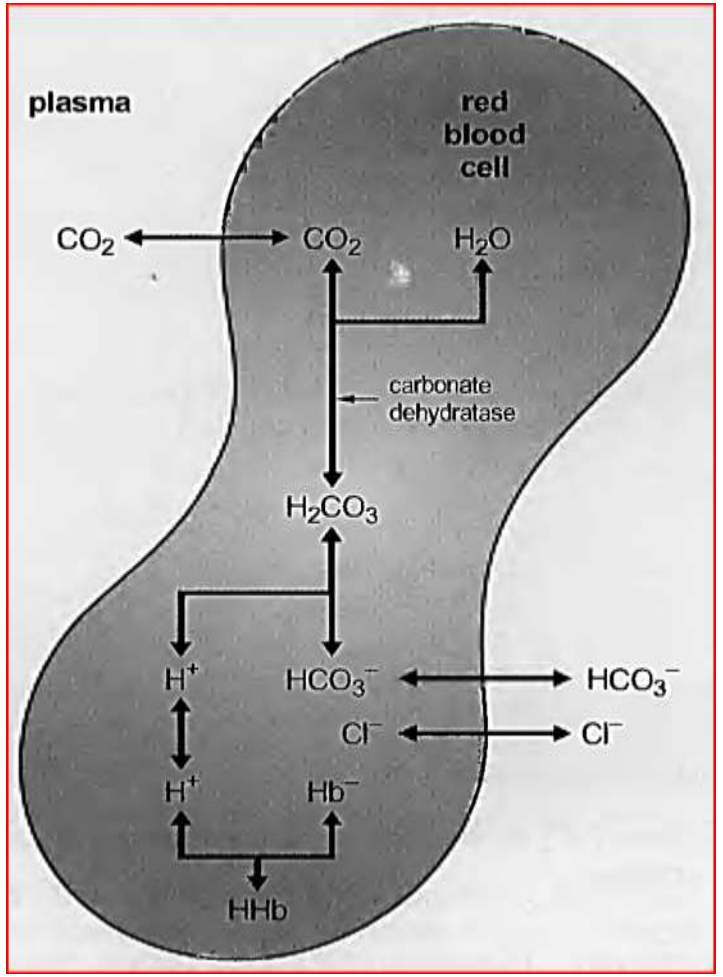
Ammonia can readily diffuse across cell membranes, but ammonium ions cannot therefore, there is no reabsorption of ammonium ions.

Transport of carbon dioxide

Carbon dioxide, produced by aerobic metabolism, diffuses out of cells and into the ECF. A small amount combines with water to form carbonic acid, thereby increasing the hydrogen ion concentration of the ECF.

In red blood cells, metabolism is anaerobic and little carbon dioxide is produced. Carbon dioxide thus diffuses into red cells down a concentration gradient and carbonic acid is formed, facilitated by carbonate dehydratase

Haemoglobin buffers the hydrogen ions formed when the carbonic acid dissociates. Haemoglobin is a more powerful buffer when in the deoxygenated state and the proportion in this state increases during the passage of blood through capillary beds, as oxygen is lost to the tissues.



Assessment of ion hydrogen concentration

Hydrogen ion conc. is measured in arterial blood, the difference in $[H^+]$ between artery and vein is small (<2 nmol/L).

The difference is significant for PCO_2 (Approximately 1.1 kPas, 8 mmHg higher in venous blood) and PO_2 approximately 7.5 kPas, 56 mmHg lower in venous blood.

The following equation that is used to calculate $[H^+]$ is derived from the two equations describing the dissociation of carbonic acid.

$$[H^+] = K \frac{PCO_2}{[HCO_3]}$$

An estimation of the relationship between $[H^+]$, bicarbonate conc., and PCO_2 is of fundamental importance to un understanding of the pathophysiology of hydrogen ion homoeostasis then, acid-base balance.

Many conditions are associated with abnormalities of blood hydrogen ion concentration [H^+] and partial pressure of carbon dioxide (PCO_2) and altered partial pressure of oxygen (PO_2) are shown in the following figure.

	Increase		Decrease
PCO_2	peripheral vasodilation		paraesthesiae
	headache		dizziness
	bounding pulse		muscle cramps
	papilloedema	late signs	headache
	flapping tremor	late signs	tetany
	drowsiness, coma	late signs	
PO_2	pulmonary and retinal fibrosis (only with prolonged use of high inspiratory PO_2, particularly in infants)		breathlessness cyanosis drowsiness, confusion and coma pulmonary hypotension (in chronic hypoxaemia)
[H^+]	hyperventilation		hypoventilation
	increased catecholamine release		paraesthesiae
	hyperkalaemia		muscle cramps
	decreased myocardial contractility	severe acidosis only	dizziness
	CNS depression	severe acidosis only	headache
		severe acidosis only	tetany
		severe acidosis only	drowsiness, confusion and coma

Disorders of hydrogen ion homoeostasis

Four components can be identified in the pathophysiology of hydrogen ion disorders (acid-base disorders):

1-Generation

2-Buffering

3-Compensation

4-Correction.

Acid-base disorders are classified as either respiratory or non-respiratory according to whether or not there is primary change in PCO_2. The term acidosis is the $[H^+]$ is above normal. While alkalosis is below normal.

Primary mixed acid-base disorders, that is, disorders of combined respiratory and non-respiratory origin, are common.

Non-respiratory (metabolic) acidosis

The primary abnormality in non-respiratory acidosis is either increased production or decreased excretion of hydrogen ions. In some cases, both may contribute. Loss of bicarbonate from the body can also, indirectly, cause an acidosis.

Compensation is effected by hyperventilation, which increases the removal of carbon dioxide and lowers the PCO_2.

$$[H^+] = K \frac{PCO_2}{[HCO_3]}$$

Respiratory compensation can not completely normalize the $[H^+]$?

Causes of non-respiratory acidosis

Increased H^+ formation
ketoacidosis (usually diabetic, also alcoholic)
lactic acidosis
poisoning, e.g. ethanol, methanol, ethylene glycol and salicylate
inherited organic acidoses

Acid ingestion
acid poisoning
excessive parenteral administration of amino acids, e.g. arginine, lysine and histidine

Decreased H^+ excretion
renal tubular acidoses
generalized renal failure
carbonate dehydratase inhibitors

Loss of bicarbonate
diarrhoea
pancreatic, intestinal and biliary fistulae or drainage

The anion gap

When bicarbonate concentration falls in a non- respiratory acidosis, electrochemical neutrality must be maintained by other anions.

In many cases, anions are produced simultaneously and equally with hydrogen ions, for example acetoacetate in diabetic ketoacidosis. When this does not occur, the deficit is met by chloride ions.

The difference between the sums of the concentrations of the principal cations (sodium and potassium) and of the principal anions (chloride and bicarbonate) is known as the anion gap.

$$\text{Anion gap} = ([Na^{+1}] + [K^{+1}]) - ([Cl^{-1}] + [HCO_3^{-1}])$$

In health, the anion gap has a value of 14-18 mmol/L and mainly represents the unmeasured net negative charge on plasma proteins.

In an acidosis in which anions other than chloride are increased, the anion gap is increased. In contrast, in an acidosis due to loss of bicarbonate, for example renal tubular acidosis, the plasma chloride concentration is increased and the anion gap is normal. Therefore, the anion gap may be useful in the analysis of complex acid-base disorders.

The characteristic biochemical changes seen in the blood in non-respiratory acidosis can be summarized as follows:

Non-respiratory acidosis	
$[H^+]$	↑
pH	↓
P_{CO_2}	↓
$[HCO_3^-]$	↓↓

Respiratory acidosis

Some of the many conditions associated with the development of respiratory acidosis are shown in following Figure.

An increase in PCO_2 and bicarbonate ion. The characteristic biochemical changes in arterial blood in acute and chronic respiratory acidosis can be summarized as follows:

Respiratory acidosis

	acute	chronic
$[H^+]$	↑	slight ↑ or high-normal
pH	↓	slight ↓ or low-normal
Pco_2	↑	↑
$[HCO_3^-]$	slight ↑	↑

Causes of respiratory acidosis

Airway obstruction
chronic obstructive airway disease,
e.g. bronchitis, emphysema
bronchospasm, e.g. in asthma
aspiration

Depression of respiratory centre
anaesthetics
sedatives
cerebral trauma
tumours

Neuromuscular disease
poliomyelitis
Guillain–Barré syndrome
motor neuron disease
tetanus, botulism
neurotoxins, curare

Pulmonary disease
pulmonary fibrosis
severe pneumonia
respiratory distress syndrome

Extrapulmonary thoracic disease
flail chest
severe kyphoscoliosis

Non-respiratory (metabolic) alkalosis

Causes of non-respiratory alkalosis are shown in following Fig.

The biochemical features of non-respiratory alkalosis can be summarized as follows:

Non-respiratory alkalosis	
$[H^+]$	↓
pH	↑
Pco_2	↑
$[HCO_3^-]$	↑↑

Causes of non-respiratory alkalosis

Loss of unbuffered hydrogen ion

gastrointestinal:
- gastric aspiration
- vomiting with pyloric stenosis
- congenital chloride-losing diarrhoea

renal:
- mineralocorticoid excess:
  - Cushing's syndrome
  - Conn's syndrome
- drugs with mineralocorticoid activity, e.g. carbenoxolone
- diuretic therapy (not K^+-sparing)
- rapid correction of chronically raised Pco_2
- potassium depletion

Administration of alkali

- inappropriate treatment of acidotic states
- chronic alkali ingestion

Respiratory alkalosis

The main causes of respiratory alkalosis are shown in following Figure.

The biochemical features of respiratory alkalosis can be summarized as follows:

Respiratory alkalosis		
	acute	chronic
$[H^+]$	↓	slight ↓ or low-normal
pH	↑	slight ↑ or high-normal
P_{CO_2}	↓	↓
$[HCO_3^-]$	slight ↓	↓

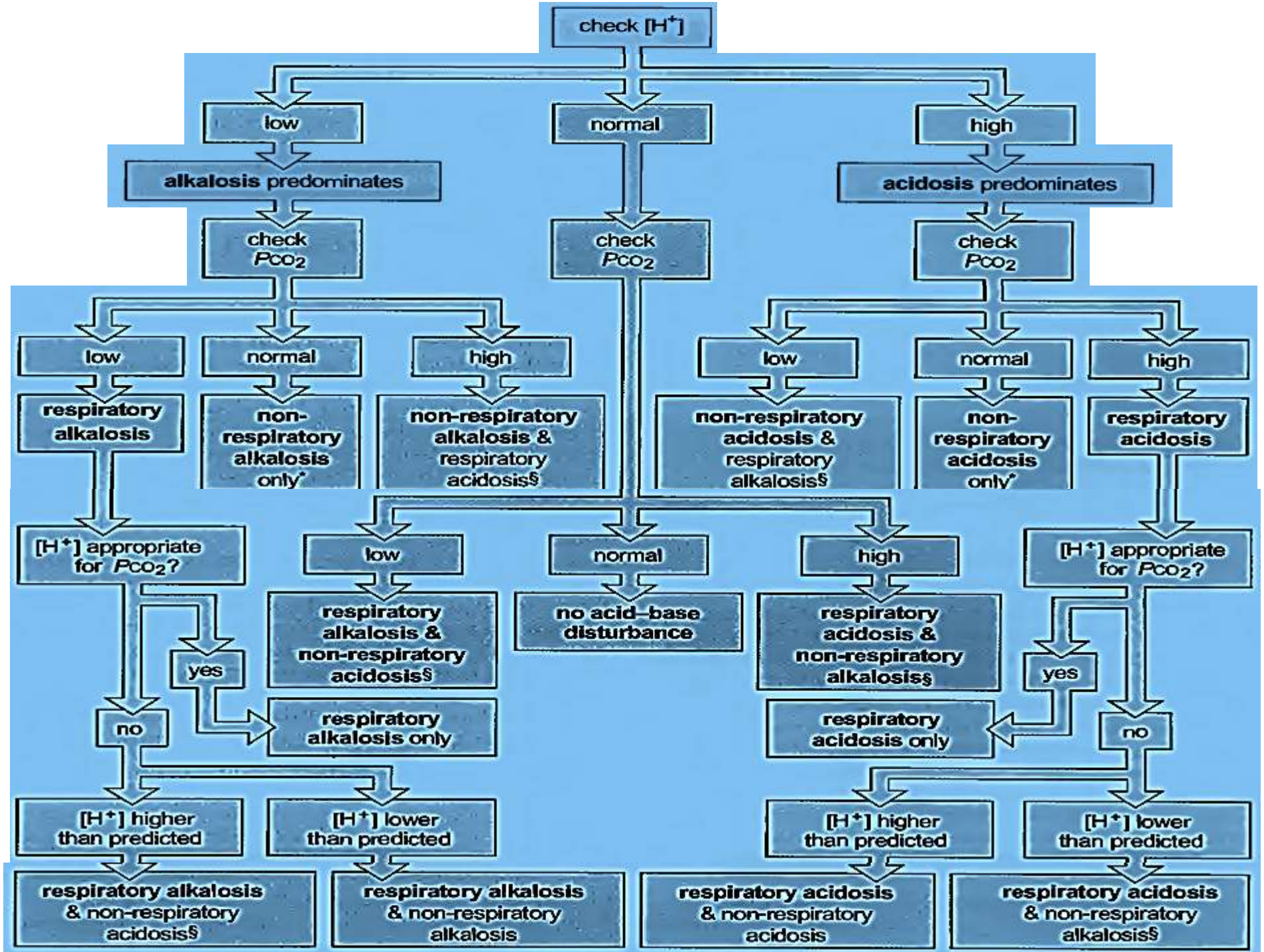
Causes of respiratory alkalosis

Hypoxia
high altitude
severe anaemia
pulmonary disease

Increased respiratory drive
respiratory stimulants, e.g. salicylates
cerebral disturbances, e.g. trauma, infection and tumours
hepatic failure
Gram-negative septicaemia
primary hyperventilation syndrome
voluntary hyperventilation

Pulmonary disease
pulmonary oedema
pulmonary embolism

Mechanical overventilation


check [H+]
low
normal
high
alkalosis predominates
acidosis predominates
check Pco2
check Pco2
check Pco2
low
normal
high
low
normal
high
respiratory alkalosis
non-respiratory alkalosis only*
non-respiratory alkalosis & respiratory acidosis§
non-respiratory acidosis & respiratory alkalosis§
non-respiratory acidosis only*
respiratory acidosis
[H+] appropriate for Pco2?
low
normal
high
[H+] appropriate for Pco2?
respiratory alkalosis & non-respiratory acidosis§
no acid–base disturbance
respiratory acidosis & non-respiratory alkalosis§
yes
yes
respiratory alkalosis only
respiratory acidosis only
no
no
[H+] higher than predicted
[H+] lower than predicted
[H+] higher than predicted
[H+] lower than predicted
respiratory alkalosis & non-respiratory acidosis§
respiratory alkalosis & non-respiratory alkalosis
respiratory acidosis & non-respiratory acidosis
respiratory acidosis & non-respiratory alkalosis§

A 2-day-old neonate becomes lethargic and uninterested in breast feeding. Physical examination reveals tachypnea (rapid breathing) with a normal heartbeat and breath sounds. Initial blood chemistry values include normal glucose, sodium, potassium, chloride, and bicarbonate (HCO_3^-) levels; initial blood gas values reveal a pH of 7.53, partial pressure of oxygen (PO_2) normal at 103 mmHg, and partial pressure of carbon dioxide (PCO_2) decreased at 27 mmHg. Which of the following treatment strategies is indicated?

a. Administer alkali to treat metabolic acidosis

b. Administer alkali to treat respiratory acidosis

c. Decrease the respiratory rate to treat metabolic acidosis

d. Decrease the respiratory rate to treat respiratory alkalosis

e. Administer acid to treat metabolic alkalosis

Tachypnea in term infants may result from brain injuries or metabolic diseases that irritate the respiratory center. The increased respiratory rate removes (blows off) carbon dioxide from the lung alveoli and lowers blood CO_2, forcing a shift in the indicated equilibrium toward the left

$$CO_2 + H_2O \rightleftharpoons H_2CO_2 \rightleftharpoons H^+ + HCO_3^-$$

Carbonic acid (H_2CO_2) can be ignored because negligible amounts are present at physiologic pH, leaving the equilibrium:

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

The leftward shift to replenish exhaled CO_2 decreases the hydrogen ion (H^+) concentration and increases the pH (-log10[H^+]) to produce alkalosis (blood pH above the physiologic norm of 7.4). This respiratory alkalosis **is best treated by diminishing the respiratory rate to elevate the blood [CO_2], force the above equilibrium to the right, elevate the [H^+], and decrease the pH.** The newborn does not have acidosis, defined as a blood pH below 7.4, either from excess blood acids (metabolic acidosis) or from increased [CO_2] (respiratory acidosis). The baby also does not have metabolic alkalosis, caused by loss of hydrogen ion from the kidney (e.g., with defective tubular filtration) or stomach (e.g., with severe vomiting).