RESPIRATORY SYSTEM
Excretion of volatile acid (CO₂)

LIVER
Net producer of H⁺ or Net consumer of H⁺

RENAL SYSTEM
Bicarbonate reabsorption of HCO₃⁻ Excretion of fixed acids (H⁺)

LIVER
Producer of weak acids Main determinant Aᵢ

RENAL SYSTEM
Excretion of CI⁻ and other strong ions Main determinant SID

ACID BASE PHYSIOLOGY
Terminology
Acids have been defined in a number of ways (initially in a latin sour). Arrhenius theory describes an acid as a substance which dissociates in water to produce hydrogen ions. Bronsted-Lowry defined an acid as a substance which donates a proton and the substance which accepts the proton is the conjugate base. This is the most commonly used definition in biological sciences. Note that CO₂ is not a B-L acid but represents the potential to be an acid via combination with H₂O to form carbonic acid, and is often therefore called an acid regardless of this. Three main approaches to interpreting acid base physiology. The conventional approach and the physico-chemical approach first described by Stewart.

Conventional approach Analysis based on the interactions of hydrogen ions, bicarbonate and carbon dioxide. Underpinned by the Henderson-Hasselbach equation which is based on the law of mass action. The overall daily production and consumption of hydrogen ions is very large, for example, less than 0.1 mmol as ATP turnover and mitochondrial activity (>500 mmolars). The net production requiring either excretion from the lungs (volatile -12 mmoles) or from the kidney (fixed - 0.1 mole) is much smaller but of significant physiological importance. In the conventional approach it is the interaction of the hydrogen ions which determine the pH, the bicarbonate which is the most important buffer in the system and is regulated by the kidney and the pCO₂ which is regulated by the respiratory system which determine the physiological acid-base state. The benefits of this system is that it can be applied clinically to assess patient acid base status based on their history, the severity of the disorder and identify mixed disorders.

Stewart Approach Developed using the physicochemical laws including the law of mass action, law of electroneutrality, and the conservation of mass. Stewart characterised 2 independent variables. The total ionised acid (A⁺), which is sum of all ionised acids (by definition are incommensurably dissociated), is often simplified when considering the IV compartment to albumin which predominates. The amount of albumin is determined by the liver (therefore independent). The second independent variable is the pCO₂, which is controlled by the resp system. The final variable is the strong ion difference (SID) which is the difference between the completely dissociated cations (Na⁺, K⁺, Ca⁺², Mg⁺²) and anions (Cl⁻ and other anions). It is often simplified to Na⁺ - Cl⁻ and is usually around 40-45. It is determined by the kidneys and to a lesser extent GIT system. Using the three independent variables it is possible to determine the dependent variables which include [H⁺], [Hₐ⁺], [A⁺], [OH⁻], [HCO₃⁻], using a 4th order polynomial equation to solve for the six physicochemical laws (which include the henderson-hasselbach).

Importance of pH. There are two main reasons why pH is so important. The first is the Davis hypothesis and relates primarily to small molecules. This states that many biologically significant compounds are completely ionised near neutral pH and therefore are trapped within the cell and its organelles. The second reason relates to larger proteins which maintain optimal performance at a specific pH intra cellularly and extracellularly. We usually require to infer the ICF pH from ECF measurements when attempting to maintain a neutral pH. This becomes somewhat feasible when taking into account the setting of changing temperatures because as the temperature drops the CO₂ becomes less soluble in water (CO₂ decreases as the temperature decreases). Some teaching supports correcting the plasma pH to a neutral pH (7.4) by adjusting the system (adding more CO₂) this is the pH stat approach. While this is often used experimentally however is that imidazole groups intracellularly buffer pH regardless of temperature, therefore pH remains near neutrality (6.8) despite temp changes. This approach advocates accepting that plasma pH will vary with temp (usually by 0.015 pH units per degree) but this will not affect the ICF pH. Alpha stat is more accepted.

Buffering a buffer is a substance with the capacity to bind or release H⁺ and thus minimise changes in pH. Buffers consist of a mixture of a weak acid and its conjugate base. A buffer is most effective at its pKa, at which it is 50% ionised. Most of the buffering capacity in the body occurs in a narrow range of pH. The effectiveness of a buffer in a physiological system is also dependent on if it is open like the bicarbonate system where CO₂ may be removed via the lungs or closed (chemical). Buffering may occur for a target pH of 7.4 which is the pH of the ECF or 6.8 which is the pH of the ICF. RBCs are usually considered in the ECF category due to its importance as a buffer in its compartment. The major buffer system in the ECF is the CO₂-bicarbonate buffer system. This is responsible for about 80% of extracellular buffering. It is the most important ECF buffer for metabolic acids but it cannot buffer respiratory acid-base disorders. The components are easily measured and are related to each other by the Henderson-Hasselbach equation. pH = pKa + log10 ([HCO₃⁻] / 0.03 x pCO₂) The pKa valve is dependent on the temperature, (H⁺) and the ion concentration of the system. It has a value of 6.099 at a temperature of 37°C and a plasma pH of 7.4. On chemical grounds, a substance with a pKa of 6.1 should not be a good buffer at a pH of 7.4 if it were a simple buffer. The system is more complex as it is ‘open at both ends’ (meaning both [HCO₃⁻] and pCO₂ can be adjusted) and this greatly increases the buffering effectiveness of this system. The excretion of CO₂ via the lungs is particularly important because of the rapidity of the response. The adjustment of pCO₂ by change in alveolar ventilation has been referred to as physiological buffering. Protein buffers in blood include haemoglobin (150g/l) and plasma proteins (70g/l). Buffering is by the imidazole group of the histidine residues which has a pKa of about 6.8. This is suitable for buffering respiratory acid-base disorders because it has about 6 times more ionisation than the plasma proteins as it is present in about twice the concentration and contains about the same number of histidine residues per molecule. The phosphate system HPO₄⁻² and H₂PO₄⁻ has a pKa of 6.8 and so has a theoretical advantage over bicarbonate. It only exists in very small concentration in the ECF however and is a closed system so makes minimal contribution. It is however a significant buffer in the ICF.

Regulation of the Acid-Base There are two major systems which regulate acid base physiology and several lesser contributors. The first is the respiratory system. Important characteristions are; the only acid excreted by the lungs, this excretion is very rapid and the system is high capacity compared to the kidneys (15 mols vs 0.1 mols). The control of the system is based on central chemoreceptors which rely on CO₂ crossing the BBB and increasing local (H⁺) which is relayed to the respiratory centre in the medulla to alter ventilation and therefore the pCO₂. This is augmented by the peripheral chemoreceptors in the aortic arch and carotid bodies. These sense changes in pCO₂, pCO₂ and pH, and therefore are very important in a metabolic acidosis providing the stimulus for respiratory compensation (H⁺ does not cross the BBB therefore the central chemoreceptors do not play a role). The other main system is the renal system which is involved in the excretion of fixed acids is the distal tubule and the reabsorption of bicarbonate in the proximal tubule. It is the balance of these two processes which determines the kidneys response to changes in pH (in alkalosis less HCO₃⁻ is reabsorbed and H⁺ is excreted, in acidosis the opposite). The renal response is influenced by the pCO₂, the pH, the bicarbonate level, ECF volume, angiotension, aldosterone and hypokalaemia. Minor regulation takes place by the bones (in persistent metabolic acidosis as a source of CaCO₃ for buffering) and the liver as a net producer or consumer of hydrogen ions through metabolic processes.

Analysis of blood gas. A deranged pH is responded to by the body in three ways, buffering, compensation and correction. The most important aspect to assessment is a clinical history, especially regarding the chronicity (and therefore opportunity for appropriate compensation).

Respiratory Acidosis
Definition: is a primary acid base disorder in which arterial pCO₂ rises to a higher level than expected. Excretion of CO₂ to decreased alveolar ventilation. Others are increased inspired CO₂ or CO₂ production increases (increased CO₂), increased ventilation, central hypoxia, hyperventilation, decreased intracelualar metabolism and central depression at high levels of CO₂.
Acute buffering: Intracellular buffering with Hb leads to increased HCO₃⁻. Expected HCO₃⁻ = 24-26 x (pH/7.4) (outside mixed = disorder correction)
Correction: Increase ventilation

Respiratory Alkalosis
Definition: is a primary acid base disorder in which arterial pCO₂ decreases to a level less than expected. Causes due to increased alveolar ventilation Effects: (decreased CO₂), cerebral vasoconstriction and vasoconstriction of short term IC drop, arrhythmia, decreased myocardial contractility, increased neuro muscular irritability, decreased respiratory drive, H₂O₂ curve left.
Acute buffering: Intracellular and plasma proteins, leads to decreased HCO₃⁻. Expected HCO₃⁻ = 24-26 x (pH/7.4) (outside mixed = disorder correction)
Corrections: Renal loss of H₂CO₃ which is slower →H⁺ and leads to a more pronounced correction, pCO₂. Expected pCO₂ = 24 x (pH/7.4) (outside mixed = disorder correction)

Metabolic Acidosis
Definition: is a primary acid base disorder leading to an increase in fixed acids in the blood. Causes: loss of H⁺ (ET in Starvation) from the kidney (diabetes) or gut (vomiting, NG tube -90% total) or increased H⁺, decreases bicarbonate (metabolic acidosis), reduced bicarbonate (metabolic alkalosis), increased acetonemia, increased ammonium excretion, decreased pH (ET in Starvation), increased pH (ET in Starvation), added bicarbonate by Na⁺, increased urinary acidosis.
Effects: Decreased myocardial contractility, decreased cerebral blood flow, confusion, decreased neuro muscular excitability, H₂O₂ shift left.
Hypokalaemia can be life threatening
Acute compensation: decreased respiratory rate
Expected pCO₂ = 0.7(actual [HCO₃⁻]) +20 (+/- 5) Correction: Treat precipitant and the maintaining process (without which the kidney usually corrects the system quickly by excreting bicarbonate). Give oxygen! Replace chloride and potassium.

Metabolic Alkalosis
Definition: is a primary acid base disorder leading to an overall increase in bicarbonate in the blood. Causes: loss of H⁺ (ET in Starvation) from the kidney (diabetes) or gut (vomiting, NG tube -90% total) or increased H⁺, increases bicarbonate (metabolic alkalosis), reduced bicarbonate (metabolic acidosis), increased acetonemia, increased ammonium excretion, decreased pH (ET in Starvation), increased pH (ET in Starvation), added bicarbonate by Na⁺, increased urinary acidosis.
Effects: Increased myocardial contractility, increased cerebral blood flow, confusion, increased neuro muscular excitability, H₂O₂ shift left.
Hypokalaemia can be life threatening
Acute compensation: increased respiratory rate
Expected pCO₂ = 0.7(actual [HCO₃⁻]) +20 (+/- 5) Correction: Treat precipitant and the maintaining process (without which the kidney usually corrects the system quickly by excreting bicarbonate). Give oxygen! Replace chloride and potassium.