UMF Târgu Mureș, Clinica ATI 1

ANESTHESIA AND INTENSIVE CARE COURSES FOR MEDICAL STUDENTS

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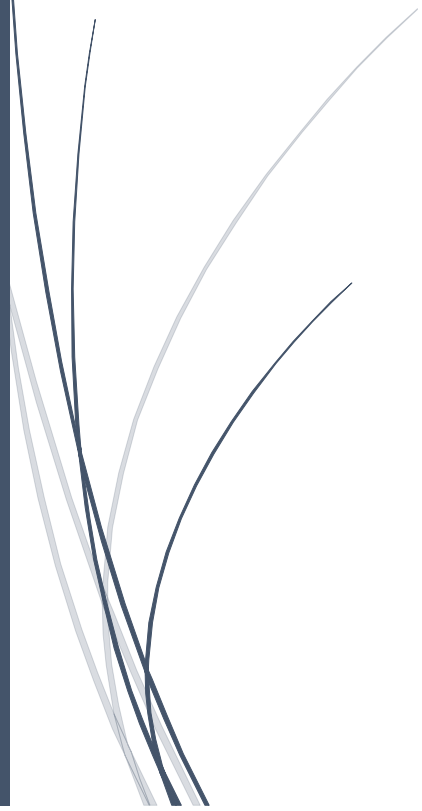

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FOREWORD

Prof. Dr. Copotoiu Sanda-Maria

Anesthesia was born out of an important, acute an intense necessity. The need anesthesia addresses primarily is pain. Pain is a complex sensation, unequally perceived, still unsatisfactorily studied and known, but generally hard to bear. It might limit surgery and invasive investigations if not managed appropriately.

Anesthesia opposes pain but delivers also other benefits, such as muscle relaxation allowing the surgeons to operate on and the anesthetists to intubate, to protect the airways and to ventilate the patients. It induces and maintains hypnosis, a relaxed sleep, reaches and maintains hemodynamic stability, blunts the vegetative responses to noxious stimuli and diminishes the incidence of posttraumatic stress disorder. The mechanisms attributable to the anesthetic effects are far from being elucidated, but technologic progress, the development of pharmaceutical industry implied in the discovery and the promotion of new molecules allowed for the implementation of rescue therapies.

Translation of echography in the operating theatre contributed to the dissemination of regional anesthesia techniques associated with significantly higher success rates and lower complications or accidents compared to the anatomical previous techniques. The development of monitoring increased the patient safety. Applied physics and technology fathered the new generation cardiovascular monitors, promoting novel parameters and allowing for a profound understanding of previously speculated issues. The European and other national and international societies of anesthesia and intensive care issued guidelines and protocols in an attempt to grant a uniform approach of the patients to their best outcome. Clinical trials were either completed or ongoing to test novel hypothesis. We know now more about the critically ill patient but have to work in a very busy climate where the material incentive is an issue. The society resources are scarce or limited while we as doctors have to marry professional efficiency with ethical and moral demands. Because of our commitment to the patients, we ended up in fabricating survivors with a doubtful quality of life, long time deceased if born 20 years ago. Thus, our ethics are on a constant challenge, mainly when they collide with personal values. This is why the approach of the critically ill is protocolized, in order to prevent omissions and to avoid denial of due treatment. Every patient has its' individuality and characteristics that have to be known and understood by the attending anesthetist. In our country, the anesthesia and intensive care are united in just one profession, acknowledging that anesthesia is in fact intraoperative intensive care.

As a result, the anesthetist has to be skilful, to be well documented, and to be able to recall the best approach rapidly, to use his aptitudes, skills and competence. As beginners, we tend to be analytical and to swallow the news indiscriminately. It is

later that we learn to see the whole picture and to assess the real options. It is a process of continuous formation and maturation. The result is the capacity of prioritization of the best decisions for survival and restoration of health, the ultimate aim.

The lectures are addressed to the students of the preterminal year with the aim of triggering awareness as to a specialty afferent to the instinct of survival. The students upon assessment will have to be able to understand, execute and practice the lifesaving maneuvers and attitudes no matter their further orientation. In order to do this, you will have to arouse the dormant knowledge provided in advance and derived from physics, biochemistry, physiology, basic anatomy and pathology. Thus, you will be able to understand our approach.

Do not forget to be fit, awake and ready to perform under supervision while in the wards attending our patients.

Teaching goals

At the end of every lecture, the student must

1. understand the causes, mechanisms, clinical signs and monitoring issues of the defined organ failure
2. understand the approach and the management of the organ failure in cause
3. be able to answer to previously blurred issues
4. acknowledge the existing and feasible opportunities of management of the issues taught
5. take home the important medical messages
6. be able to organize the knowledge he had and the newly acquired
7. understand the skills he must learn or use in order to cope with the critically ill or with the patient attending for surgery

RESPIRATORY FAILURE

Asist. Univ. Dr. Solomon Raluca

Prof. Univ. Dr. Copotoiu Sanda-Maria

DEFINITION

Acute respiratory failure occurs when the pulmonary system is no longer able to meet the metabolic demands of the body

Function of the lungs:

- Get O2 in
- Remove CO2 out
- Regulate acid-base status (pH)
- Other
    - Heat dissipation
    - Metabolize some substance e.g. Angiotensin I to II

Respiratory muscles

Inspiratory muscles:

- Diaphragm – very powerful
- External intercostal muscle – pull the ribs up and forwards
- Accessory inspiratory muscles – scalene muscles and sternomastoids
- Muscles of neck and head (seen in small babies in respiratory distress)

Expiratory muscles:

- Expiration is usually passive and relies on the elastic recoil of the lungs and the chest wall. Under extreme exercise expiration may become active due to the activation of abdominal muscles. Muscles have their use in forced expiration
- Abdominal wall muscles
- Internal intercostal muscles

Patients using their accessory muscles may indicate increased work of breathing.

CLASSIFICATION OF RESPIRATORY FAILURE

According to:

- pathophysiology
- duration of respiratory failure
- etiology

1. Pathophysiology

Ventilation is a mechanical process whereby the ambient gas is taken into the alveoli. Gas exchange takes place between alveoli and the capillary blood. Based on this, respiratory failure can be categorized into two groups depending on the cause, those due to ventilatory defects and those due to impaired gas exchange.

Hypoxemic respiratory failure (type I) is characterized by:

- arterial oxygen tension (PaO_2) ≤ 60 mm Hg
- a normal or low arterial carbon dioxide tension ($PaCO_2$).

This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units.

Hypercapnic respiratory failure (type II) is characterized by a

- $PaCO_2$ ≥ 50 mm Hg.
- Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air.

Hypercapnia results from either increased CO2 production secondary to increased metabolism (sepsis, fever, burns, overfeeding), or decreased CO2 exhaling.

2. Duration of respiratory failure

Respiratory failure may be further classified as either ***acute or chronic*** depending on the duration of respiratory failure and the nature of the compensation. Acute respiratory failure may occur in a person without underlying pulmonary disease or may be superimposed on chronic respiratory failure.

While acute respiratory failure is characterized by life-threatening derangements in arterial blood gases and acid-base status, the clinical signs of chronic respiratory failure are less dramatic and may not be as readily apparent.

Acute hypercapnic respiratory failure develops over minutes to hours; therefore, pH is less than 7.3. Chronic respiratory failure develops over several days or longer, allowing time for renal compensation and an increase in bicarbonate concentration. Therefore, the pH usually is only slightly decreased. The clinical markers of chronic hypoxemia, such as polycythemia or cor pulmonale, suggest a long-standing disorder.

Pulmonary hypertension is frequently present in chronic respiratory failure. Alveolar hypoxemia potentiated by hypercapnia causes pulmonary arteriolar constriction. The increased pulmonary vascular resistance increases afterload of the right ventricle, which may induce right ventricular failure. This, in turn, causes enlargement of the liver and peripheral edema. The entire sequence is known as *cor pulmonale.*

3. Etiology

It can result from primary pulmonary pathologies or can be initiated by extra-pulmonary pathology. Causes are often multifactorial. Acute respiratory failure can be caused by abnormalities in:

- CNS (drugs, metabolic encephalopathy, CNS infections, increased ICP, OSA, Central alveolar hypoventilation)
- spinal cord (trauma, transverse myelitis)
- neuromuscular system (polio, tetanus, Miastenia.Gravis, Guillain-Barre, critical care or steroid myopathy)
- chest wall (Kyphoscoliosis, obesity)
- upper airways (obstruction from tissue enlargement, infection, vocal cord paralysis, tracheomalacia)
- lower airways (bronchospasm, infection)
- lung parenchyma (infection, interstitial lung disease)
- cardiovascular system

BASIC RESPIRATORY PHYSIOLOGY

The act of respiration engages 3 processes:

- Transfer of oxygen across the alveolus
- Transport of oxygen to the tissues
- Removal of carbon dioxide from blood into the alveolus and then into the environment

Respiratory failure may occur from malfunctioning of any of these processes.

Lung volumes

- Tidal volume (TV) is the volume of air moved in and out of the respiratory tract (breathed) during each ventilatory cycle: 8-10ml/kg
- Inspiratory reserve volume (IRV) is the additional volume of air that can be forcibly inhaled following a normal inspiration. It can be accessed simply by inspiring maximally, to the maximal inspiratory level
- Expiratory reserve volume (ERV) is the additional volume of air that can be forcibly exhaled following a normal expiration. It can be accessed simply by expiring maximally to the maximal expiratory level
- Vital capacity (VC) is the maximal volume of air that can be forcibly exhaled after a maximal inspiration. VC = TV + IRV + ERV
- Residual volume (RV) is that volume of air remaining in the lungs after a maximal expiration. It cannot be expired no matter how vigorous or long the effort. RV = FRC - ERV
- Functional residual capacity (FRC) is the volume of air remaining in the lungs at the end of a normal expiration. FRC = RV + ERV
- Total lung capacity (TLC) is the volume of air in the lungs at the end of a maximal inspiration. TLC = FRC + TV + IRV = VC + RV

Spirometry is typically reported in both absolute values and as a predicted percentage of normal. Normal values vary, depending on gender, race, age and height.

Ventilatory capacity is the maximal spontaneous ventilation that can be maintained without development of respiratory muscle fatigue. **Ventilatory demand** is the spontaneous minute ventilation that results in a stable $PaCO_2$.

Normally, ventilatory capacity greatly exceeds ventilatory demand. Respiratory failure may result from either a reduction in ventilatory capacity or an increase in ventilatory demand (or both). A disease process involving any of the functional components of the respiratory system and its controller can decrease ventilatory capacity. Ventilatory demand is augmented by an increase in minute ventilation and/or an increase in the work of breathing.

GETTING OXYGEN IN

The alveolar partial pressure of oxygen (P_AO_2) is dependent on the total alveolar pressure and the partial pressures of the other gases in the alveoli. The sum of the partial pressures of all the gases is equal to the total alveolar pressure

Alveolar pressure = PA O2+PA CO2+PA H2O+PA N2

Partial pressure of each gas in a mixture of gases is directly related to the proportions in which they are present. Therefore, partial pressure of oxygen can be increased by:

- increasing alveolar pressure or
- increasing the proportion of oxygen in the mixture

The alveolar gas equation explains the partial pressure of oxygen in the alveoli. It is **PA O2 = FI O2 × (PB – PH2 O) – PA CO2/R**

- where PA O2 is alveolar PO2, FI O2 is fractional concentration of oxygen in inspired gas, PB is barometric pressure, PH2 O is water vapor pressure at 37° C, PA CO2 is alveolar PCO2 (assumed to be equal to Pa CO2), and R is respiratory exchange ratio. R depends on oxygen consumption and carbon dioxide production. At rest, the ratio of VCO2 to oxygen ventilation (VO2) is approximately 0.8.

It simply means that the oxygen tension in the alveoli is predominantly determined by the concentration of inspired oxygen, the barometric pressure and the carbon dioxide tension in the alveoli.

The alveolar partial pressure of water vapor remains largely constant and therefore does not contribute to changes in PAO2. The proportion of carbon dioxide in alveolar gas does change and therefore factors which affect PACO2 also affect PAO2

As carbon dioxide passes into the alveolus and oxygen passes into the blood the PACO2 rises and the PAO2 falls. Ventilation is required to replenish the alveolar gas with fresh gas.

Thus the factors that result in changes in PAO2 are:

- PACO2
- alveolar pressure
- inspired oxygen concentration
- ventilation

Oxygen supplementation will increase alveolar oxygen content and hence the partial pressure. The oxygen tension in the alveoli will be low in higher altitudes like mountains and will be high in hyperbaric chambers. Conditions with increased carbon dioxide level in blood and hence in alveoli, as in hypoventilation, chronic obstructive airway diseases (COAD) etc. are associated with decreased oxygen tension in the alveoli.

Oxygen cascade

The partial pressure of oxygen that is inhaled from our natural environment through normal inhalation is not maintained at the same figure by the time it reaches the alveoli and then the mitochondria. The process by which this decrease in partial pressure occurs is called **the oxygen cascade.**

The air surrounding us contains 21% of 100KPa oxygen, therefore, 21 KPa or 160mmg. As gas is inspired, it is diluted by water vapors, which reduces the partial pressure of oxygen. When the gas reaches the alveoli, the partial pressure of oxygen will again decrease as some oxygen is absorbed and CO2 is excreted. The partial pressure at this point in the oxygen cascade can be determined by using the alveolar gas equation (106mmHg).

Again, when the gas reaches the arterial blood a further small drop in partial pressure will have occurred as blood known as venous admixture with a lower oxygen content mixes with the oxygenated alveolar blood. Venous admixture is made up of blood that has passed through poorly ventilated regions of lung and thus has a lower O2 partial pressure, blood from the bronchial veins draining the lung parenchyma and the thebesian veins draining the cardiac muscle

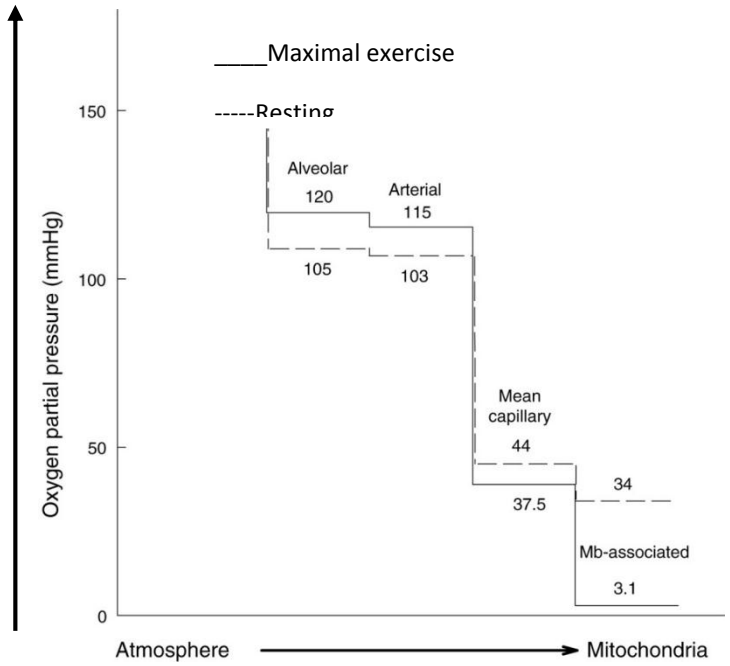
An estimate for PaO2 at sea level (in healthy subjects breathing air) is given as:

PaO2 = 102 – age (years)/3

Extraction of oxygen from this blood further drops the end capillary oxygen partial pressure to 6-7KPa (40 -50mmHg). In the mitochondria, the PO2 varies hugely from 1 to 5KPa (7.5-40mmHg).

- Inspired oxygen ~ 160 mmHg
- Alveolar oxygen ~ 120 mmHg
- Oxygen in the blood ~ 100 mmHg
- Oxygen at tissue level ~ 4-20 mmHg

Oxygen cascade



Picture 1

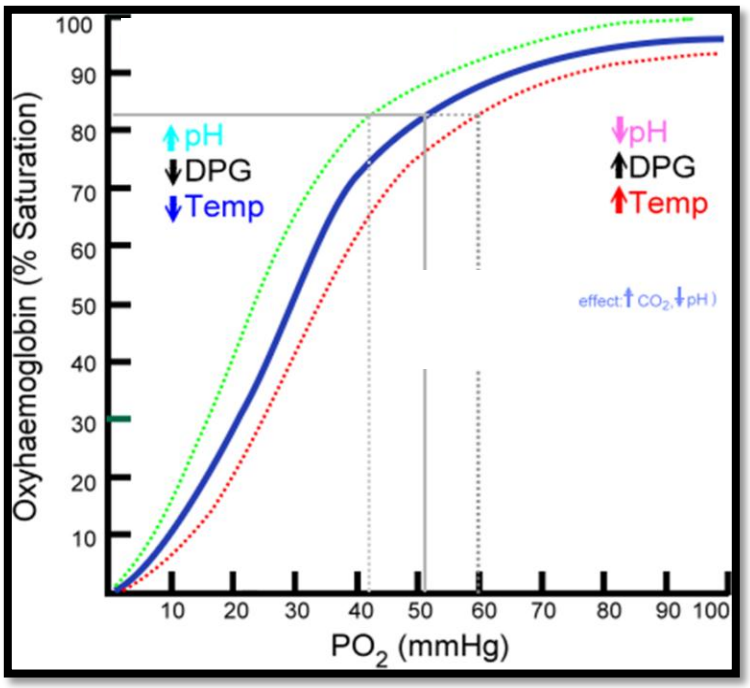
Oxygen transport

Oxygen is carried in two forms in the blood:

- *Oxygen combined to haemoglobin (97%).* Each haemoglobin molecule can bind 4 oxygen molecules (20ml oxygen per 100ml blood) or 15ml oxygen per 100ml in venous blood
- *Oxygen dissolved in the blood* – this accounts for a minimal amount (0.3ml per dl)

The amount dissolved is proportional to the partial pressure 0.023ml per KPa per 100ml blood. The quantity of oxygen combined with hemoglobin depends on the level of blood Pa O2. This relationship, expressed as the **oxygen hemoglobin dissociation curve**, is not linear but has a sigmoid-shaped curve with a steep slope between a Pa O2 of 10 and 50 mm Hg and a flat portion above a Pa O2 of 70 mm Hg.

Oxygen dissociation curve



Picture 2

It describes the relationship of saturation of haemoglobin with oxygen at varying partial pressures. P50 is the point at which Hb is 50% saturated.

- Decreasing pH, increasing temperature, 2,3-DPG and CO2 tension will cause a right shift of the curve
- Increased pH, and CO2 decrease, temperature and 2,3-DPG produce a left shift of the curve

If 2,3-DPG binds to deoxygenated Hb, it reduces the affinity of hemoglobin for oxygen and therefore ensures offloading of oxygen to the tissues.

If a right shift occurs, the Hb molecule is more likely to offload oxygen to the tissues.

In a left shifted situation, the Hb is less likely to release oxygen to the tissues.

Oxygen content of blood

The theoretical maximum oxygen carrying capacity is 1.39 ml O2/g Hb, but direct measurement gives a capacity of 1.34 ml O2/g Hb. 1.34

The oxygen content of blood is the volume of oxygen carried in each 100 ml blood. It is calculated by:

(O2 carried by Hb) + (O2 in solution) = (1.34 x Hb x SpO2 x 0.01) + (0.003 x PaO2)

Where:

SO2 = percentage saturation of Hb with oxygen

Hb = haemoglobin concentration in grams pre 100 ml blood

PO2 = partial pressure of oxygen (0.0225 = ml of O2 dissolved per 100 ml plasma per kPa, or 0.003 ml per mmHg)

GETTING CARBON DIOXIDE OUT

CO2 excretion is inversely proportional to alveolar ventilation (VA). CO2 crosses the alveolar membrane very readily, about twenty times faster compared to O2, and so that diffusion abnormalities and shunting have little effect on CO2 elimination. VA is decreased if total minute ventilation is decreased - secondary to either a decreased respiratory rate or a decrease in tidal volume (Vt), or if the dead space fraction of the tidal volume is increased (Vd/ Vt).

Alveolar ventilation = Respiratory rate x (tidal volume-dead space)

Dead space is that portion of the tidal volume that does not take part in gas exchange.

Therefore, changes in PACO2 are dependent on:

- respiratory rate
- tidal volume
- ventilation-perfusion matching

Carbon dioxide is carried in the blood in 3 ways:

- As bicarbonate – 90%
- As dissolved CO2 – 5%
- As carbamino compounds – 5%

Carbamino compounds are formed by the reaction of the CO2 with terminal amino groups of proteins and side chains of arginine and lysine. Hemoglobin is essential for this process to occur since it has four amino groups per molecule. Albumin also provides amino groups but only one per molecule.

These three forms of CO2 are in equilibrium with one another, and it is the dissolved fraction in plasma that exerts the partial pressure measured as PaCO2.

Gas content in blood:

- Oxygen delivery (DO2) is the amount of oxygen delivered to the peripheral tissue, and is obtained by multiplying the arterial oxygen content (CaO2) by the cardiac output (Q). For CaO2 = 20.1 ml/100 ml and Q = 5 l/min:

Oxygen delivery (DO2) = 1005 ml/min

- The product of the mixed venous oxygen content (CvO2) and the cardiac output give the oxygen returned. For CvO2 = 15.2 ml/100 ml and Q = 5.0 l/min:

  Oxygen return = 760 ml/min

- Oxygen uptake (VO2) is the amount of oxygen taken up by the tissues: 250ml/min. Can be calculated from the difference between oxygen delivery and the oxygen returned to the lungs in the mixed venous blood. Thus: Oxygen uptake (VO2) = (oxygen delivery) – (oxygen return) = 1005 – 760 = 245 ml/min
- The extraction ratio - is the ratio of VO2 to DO2 expressed as a percentage. Normally the extraction ratio is about 25% but can double to 50% if tissue demand increases
- Total amount of oxygen in the body= 1,5l out of which less than half is readily available for metabolic use
- Carbone dioxide production (VCO2)= 200ml/min
- Total amount of carbon dioxide in the body=120l
- Steady state $VCO_2 = CO_2$ elimination

Blood Gas content

GAS	Form	Arterial blood	Venous blood
Oxygen	HbO2	18-20ml%	15ml%
Oxygen	Dissolved	0,3ml%	0,11-0,18ml%
Carbon dioxide	$HbCO_2$	5% of CO2	4-8ml%, 30% of CO2
Carbon dioxide	Dissolved	5% of CO2	2,7ml%, 10% of CO2
Bicarbonate		90% of CO2	50ml, 60% of CO2

Table 1

GAS EXCHANGE

Respiration primarily occurs at the alveolar capillary units of the lungs, where exchange of oxygen and carbon dioxide between alveolar gas and blood takes place. Impaired gas exchange may occur due to a defect in *diffusion* or due to *ventilation and perfusion mismatch*.

Diffusion abnormality is less common. It may be due to an abnormality of the alveolar membrane or to a reduction in the number of alveoli resulting in a decrease of the alveolar surface area**.** Causes include:

- acute respiratory distress syndrome
- fibrotic lung disease.

Ventilation perfusion relationships

During ideal gas exchange, blood flow and ventilation would perfectly match each other, resulting in no alveolar-arterial oxygen tension (PO_2) gradient.

V/Q ratio:

- Normal V (ventilation - alveolar ventilation) is 4 L of air per minute.
- Normal Q (perfusion - cardiac output) is 5L of blood per minute.
    - So normal V/Q ratio is 4/5 or 0.8.

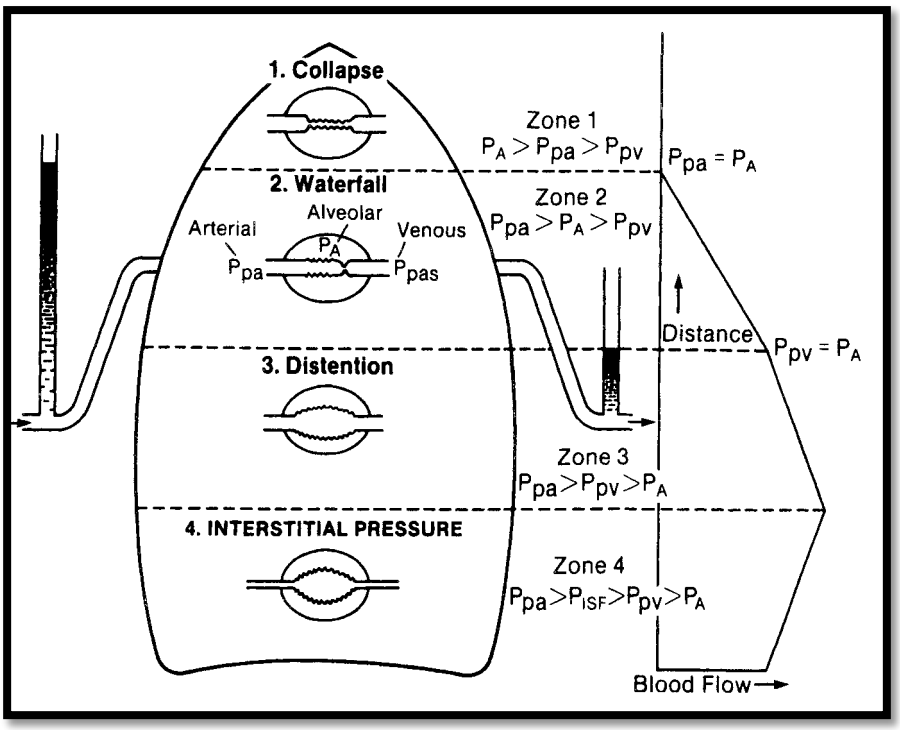
- When the V/Q is higher than 0.8, it means ventilation exceeds perfusion.
- When the V/Q is < 0.8, there is a VQ mismatch caused by poor ventilation.

Even in normal lungs, not all alveoli are ventilated and perfused evenly. For a given perfusion, some alveoli are underventilated, while others are overventilated. Similarly, for known alveolar ventilation, some units are underperfused, while others are overperfused.

Gravity plays a large part in directing blood flow by setting up a hydrostatic pressure gradient, which is higher at the base of the lungs than at the top. Blood is preferentially directed to the lung's bases. As well as the effect of gravity on perfusion and ventilation, the differing pressures within the alveoli, arteries and venous systems heavily influence the outcome. The relationship between these factors describes the *West zones.*

West zones within the lung are four vertically split zones (in the upright subject) which explain how alveoli, arterial and venous pressures differ in each zone and thus affect perfusion and ventilation throughout the lung.

West zones



Picture 3

In zone 1, the alveolar pressure may exceed that of the arterial and venous pressure and thus little perfusion will occur as the vessels collapse, this then leading to dead space.

In zone 2, the arterial pressure will exceed that of the alveoli pressure, but not the venous pressure.

In zone 3, both the arterial and venous pressures exceed the alveoli pressure.

Zone 4 arises in areas of lung where low lung volume reduces the size of extra alveolar vessels, increasing their resistance and reducing blood flow. This happens at the lung bases at low lung volumes.

If flow of blood to the lung units is to match that of ventilation to the same unit, then the ratio of ventilation to perfusion should be 1:1

If the lung is being underventilated but perfused as normal, then we say that the V/Q ratio is <1

If the lung is under perfused then the V/Q is >1

Differences between the apices and bases of the lungs

At the apices there is less ventilation than the bases as alveoli are already very stretched however there is proportionally less perfusion therefore the overall V/Q ratio is higher compared to the base of the lung.

Blood flow is directly affected by gravity and naturally has a tendency to flow to the bases of the lungs thus V/Q ratios towards the lower segments of the lung are usually greater than 1.

The vertical change in V/Q ratios in the lung is because although both ventilation and perfusion increase from top to bottom of the lung, perfusion increases much quicker than ventilation. Thus, the V/Q ratio at the top of the lung is 3.3 whereas at the bases it is around 0.6.

Shunting

Represents a form of ventilation-perfusion mismatch in which alveoli which are not or are poorly ventilated (due to collapse or either pus or edema fluid) while are still perfused. As a result, blood traversing these alveoli is not oxygenated. *This is the most common pathophysiological cause of hypoxemic respiratory failure.*

True shunt refers to a VQ = 0. That means that blood has passed through areas of the lung where no ventilation is occurring. If blood passes through areas of the lung which are poorly ventilated, than VQ<1.

Physiological shunt refers to the amount of venous admixture, which is directly added to main circulatory blood without having passed through the oxygenating mechanism of the lung. Blood from the bronchial veins draining the lung parenchyma and the thebesian veins draining the cardiac muscle represent the physiological shunt (around 5% of cardiac output.).

The fraction of the cardiac output that represents intrapulmonary shunt is known as the *shunt fraction*. In normal subjects, intrapulmonary shunt flow (Qs) represents less than 10% of the total cardiac output (Qt), so the shunt fraction (Qs/Qt) is less than 10%.

Hypoxic pulmonary vasoconstriction diminishes the blood flow to non-ventilated alveoli and reduces the severity of the hypoxemia.

This form of respiratory failure is relatively resistant to oxygen therapy. Increasing the inspired oxygen concentration has little effect because it cannot reach alveoli where shunting is occurring and blood leaving normal alveoli is already 100% saturated.

Causes of shunting:

- intracardiac
    - any cause of a right to left shunt (Fallot's tetralogy, Eisenmenger's syndrome)
- pulmonary
    - pneumonia
    - pulmonary oedema
    - atelectasis
    - collapse
    - pulmonary haemorrhage
    - pulmonary contusion

The gradient between the partial pressure of oxygen in the alveolus (PAO2) and the arterial blood (PaO2) is called *the alveolar-arterial (A-a) gradient.* It is used to determine whether a shunt or diffusion abnormality is present. It is calculated as PAO2 – PaO2. The PAO2 is calculated using the alveolar gas equation. A typical normal value would be around 0.5-1 KPa (5mmHg) though values up to around 15mmHg may be accepted. An increase in the alveolar-arterial PO2 gradient above 15-20 mm Hg indicates pulmonary disease as the cause of hypoxemia.

Dead Space Ventilation

This is the opposite extreme of ventilation-perfusion mismatch. Gas passes in and out of the alveoli but no gas exchange occurs because the alveoli are not perfused. Dead space ventilation is that part of minute ventilation that does not take part in gas exchange. Dead space ventilation (VD) includes:

- air that enters only conducting airways (referred to as anatomic dead space)
- air that reaches alveoli but does not exchange carbon dioxide or oxygen with the capillary blood.

The combined volume of these two areas is often referred to as physiologic dead space (2ml/kgc). Anatomical dead space is constant but physiological dead space depends on the relationship between ventilation and perfusion. In normal subjects, dead space ventilation (VD) accounts for 20 to 30% of the total ventilation (VT), so VD/VT = 0.2 to 0.3

Causes include:

- low cardiac output
- high intra-alveolar pressure leading to compression or stretching of alveolar capillary (mechanically ventilated patients)

Alveolar hypoventilation

At steady state, the rate of carbon dioxide production by the tissues is constant and equals the rate of carbon dioxide elimination by the lung. Failure of the normal ability to exchange gas in the lungs with atmospheric gas will lead to an increase in blood and alveolar CO2 concentrations and a decrease in blood and alveolar O2 concentrations as oxygen that is used is not replaced. Respiratory failure from hypoventilation will therefore be complicated by hypercapnia as well as hypoxia. Hypoventilation is marked by a rise in PaCO2 and a fall in PaO2

Causes of hypoventilation

- Brainstem
    - brainstem injury due to trauma, haemorrhage, infarction, hypoxia, infection etc
    - metabolic encephalopathy
    - depressant drugs
- Spinal cord

- trauma, tumour, transverse myelitis

- Nerve root injury
- Nerve
  - trauma
  - neuropathy (Guillain Barre)
  - motor neuron disease
- Neuromuscular junction
  - myasthenia gravis
  - neuromuscular blockers
- Respiratory muscles fatigue
  - disuse atrophy
  - myopathy
  - malnutrition
- Respiratory system
  - airway obstruction (upper or lower)
  - decreased lung, pleural or chest wall compliance

Lung compliance:

Compliance is the measure of the ease of inflation, the ease of distensibility, or the ease with which the lungs can stretch.

Compliance is defined as the volume change per unit pressure change and is usually expressed in ml/cmH2O

Compliance = ΔV/ΔP

It is classified into chest wall, lung or total lung compliance (distensibility). Normal value of compliance of:

- intact lung = 200ml/cmH2O
- chest wall = 100ml/cmH2O

Lower compliance implies more effort of breathing.

At lower lung volumes, the compliance of the lung is poor and greater pressure change is required to cause a change in volume. This occurs if the lungs become collapsed for a period.

At FRC, compliance is optimal since the elastic recoil of the lung towards collapse is balanced by the tendency of the chest wall to spring outwards. At higher lung volumes, the compliance of the lung again becomes less as the lung becomes stiffer.

Compliance increases in old age and emphysema as elastic lung tissue is destroyed. It is decreased in pulmonary fibrosis, pulmonary edema, and atelectasis.

Dead space ventilation + ↑ intrapulmonary shunt + ↓ lung compliance → ↑ respiratory rate, ↑ work of breathing → ↑ O2 cost of breathing up to 40-50% of O2 delivery (DO2).

The normal oxygen cost of breathing is 2-3% of oxygen delivery.

Hypoxia – is a condition consistent with low oxygen tissue content, or inadequate oxygen delivery to the body tissues and cells.

Hypoxemia is a condition in which there is an inadequate amount of oxygen in arterial blood ($PaO_2 \leq 60$ mmHg, the arterial oxygen saturation-$SaO_2 \leq 90\%$ when breathing room air or decreased hemoglobin content). Hypoxia (low O2 content, low cardiac output, or low oxygen uptake at the tissue level) occurs whether hypoxemia is present or not. Disease processes can severely limit the O2 supply anywhere between the atmosphere and the body's cells.

Causes of hypoxia can be divided into four main categories:

- hypoxic
- stagnant
- histotoxic
- anemic.

Hypoxic hypoxia - inadequate oxygenation of the arterial blood, caused by breathing gas with a low O2 tension or by pathology

1. At high elevations, *low barometric pressure* is the cause of a low PAO2 and PaO2. The concentration of oxygen remains the same at high altitudes (21%), but due to a decrease in the number of O2 molecules, there is less actual O2 available. Those who live in higher elevations adapt to a lower number of molecules by

increasing their amount of hemoglobin. Their PaO2 and PAO2 are lower, but their O2 content is normal. This is the hypoxia that is a hazard to aviators.

2. Hypoventilation - reduces alveolar and arterial O2 tensions, increases the alveolar and arterial CO2 tensions

3. Diffusion limitation - decreased diffusion of oxygen across the alveolar-capillary membrane will lead to a decrease in arterial oxygen concentration and therefore hypoxia.

4. Physiologic shunts (V/Q ratio imbalances) is by far the most common cause of hypoxia

Stagnant hypoxia - Reduced blood flow may – Circulatory failure

Anemic hypoxia - Insufficient amount of functional Hb.

May be caused by deficiency of nutrients (iron, B12) or due to blood loss or large amounts of methemoglobin or carboxyhemoglobin

Histotoxic hypoxia - Tissues unable to use O2 because of inactivation of certain metabolic enzymes (cytochromes) and by chemical poisons (cyanide).

The symptoms of hypoxia vary, depending upon the severity and rapidity of the decrease of arterial Po2 and the efficiency of the compensatory mechanisms.

Three main forms:

1. FULMINANT hypoxia - PaO2<20mmHg

   - Aircraft loses cabin pressure above 30,000 m and no supplemental O2 available
   - Occurs in seconds
   - Unconsciousness in 15-20 sec
   - Brain death in 4-5 min

2. ACUTE hypoxia - 25mmHg< PaO2<40mmHg

   - Altitudes of 18,000-25,000 m
   - Symptoms similar to those of ethyl alcohol: lack of coordination, slowed reflexes, overconfidence
   - Unconsciousness

- Coma and death (in minutes to hours) if the regulatory mechanisms of the body are inadequate

3. CHRONIC hypoxia - 40mmHg< PaO2<60mmHg

   - at altitudes of 10,000-18,000 m for extended periods of time
   - Symptoms similar to those of severe fatigue: dyspnea, shortness of breath, respiratory arrhythmias

Signs of hypoxia:

- Cyanosis (bluish color of tissue) caused by more than 5g of deoxyhemoglobin/dl in capillary blood. Not reliable sign of hypoxia: anemic patients never develop cyanosis but are extremely hypoxic; patients with polycythemia may be cyanotic but they are perfectly oxygenated
- Tachycardia - peripheral chemoreceptor reflex response to Po2
- Tachypnea

Hyperoxia

The use of high concentrations of oxygen (>60%) in the treatment of hypoxemia may be detrimental for some patients and may lead to an irreversible condition known as oxygen toxicity.

The clinical settings in which oxygen toxicity occurs are broadly divided into two groups:

- patient is exposed to very high concentrations of oxygen for short duration, like in hyperbaric oxygen therapy
- lower concentrations of the gas are used but for longer duration.

These two can result in the so-called ‘acute’ and ‘chronic’ oxygen toxictiy, respectively. The acute toxicity has predominant CNS effects, while chronic toxicity has predominant pulmonary effects.

Oxygen toxicity consequences are from exposure of the lung tissues to free radicals that react with and damage the cell mitochondria of lung tissue.

Hypercapnia

Hypercapnia is defined as an arterial PCO2 above 45 mm Hg that does not represent compensation for a metabolic alkalosis. The cause of hypercapnia is often independent of hypoxemia. Hypercapnia results from either:

- increased CO2 production secondary to increased metabolism (sepsis, fever, burns, overfeeding), or
- decreased CO2 excretion. CO2 excretion is inversely proportional to alveolar ventilation (VA). VA is decreased if total minute ventilation is decreased - secondary to either a decreased respiratory rate or a decrease in tidal volume; or if the deadspace fraction of the tidal volume is increased (Vd/ Vt).

Effects of hypercapnia

- Stimulation of ventilation via both central and peripheral chemoreceptors
- Cerebral vasodilation increasing cerebral blood flow and intracranial pressure
- Stimulation of the sympathetic nervous system resulting in tachycardia, peripheral vasoconstriction and sweating
- Peripheral vasodilation by direct effect on vessels
- Central depression at very high levels of pCO2

The treatment of hypercapnia primarily is directed at correcting the underlying disorder. Treatment of hypoventilation also is aimed at assisting ventilation. Use caution when correcting chronic hypercapnia. Rapid correction of the hypercapnia can alkalinize the cerebrospinal fluid, which may cause seizures, and can induce a metabolic alkalosis, placing the patient at risk for cardiac dysrhythmias. Infusion of sodium bicarbonate (NaHCO3) is not indicated for chronic hypoventilation syndromes.

Permissive hypercapnia - satisfactory oxygenation with low tidal volume and inspiratory pressure can be achieved at the cost of increase PaCO2. Beneficial effects of increased PaCO2: increased cardiac output due to increased sympathetic activity, increased splanchnic and renal blood flow. pH monitoring is needed to avoid figures < 7.2/ 7.3.

Hypocapnia is defined as a deficiency of carbon dioxide in the arterial blood (PaCO2 ≤ 35 mm Hg) in the arterial blood.

It is caused by chronic hyperventilation (or an automatic deep breathing pattern) leading to arterial CO2 deficiency.

Hypocapnia causes cerebral vasoconstriction, leading to cerebral hypoxia and this can cause transient dizziness, visual disturbances, and anxiety. A low partial pressure of carbon dioxide in the blood also causes alkalosis, leading to lowered plasma calcium ions and increased nerve and muscle excitability.

Since hypocapnia is based on overbreathing, successful treatment of hypocarbia is based on addressing the cause: chronic hyperventilation. Therefore, treatment of hypocapnia is the same as treatment of hyperventilation.

RESPIRATORY MONITORING

Clinical

The signs of respiratory failure are signs of respiratory compensation, increased sympathetic tone, end-organ hypoxia, hemoglobin desaturation.

- Signs of respiratory compensation
    - Increased work of breathing – tachypnea, use of accessory respiratory muscles, nasal flaring, intercostal/suprasternal/supraclavicular retraction, or a paradoxical or dyskinetic (see-saw) breathing. The most sensitive indicator of increasing respiratory difficulty is a rising respiratory rate. Tidal volume is a less sensitive indicator. Minute ventilation rises initially in acute respiratory failure and then falls precipitously only at a late stage, when the patient is exhausted.
- Increased sympathetic tone
    - Tachycardia, hypertension, sweating
- End-organ hypoxia
    - altered mental status
    - bradycardia and hypotension (late signs)
- Haemoglobin desaturation
    - Cyanosis

Auscultation provides information about the symmetry and quality of air movement. Evaluate the patient for stridor, wheezing, crackles, and decreased breath sounds (alveolar consolidation, pleural effusion).

Pulse oximetry

Estimates arterial saturation not PaO2 using absorption of two different wavelengths of infrared light. The relationship between saturation and PaO2 is described by the oxyhaemoglobin dissociation curve. A pulse oximetry saturation (SpO2) ~90% is a critical threshold. Below this level a small fall in PaO2 produces a sharp fall in SpO2

Sources of error:

- poor peripheral perfusion. This will often lead to a discrepancy between the heart rate displayed by the pulse oximeter and the heart rate measured by other means (ECG).
- false nails or nail varnish
- bright ambient light
- poorly adherent probe
- excessive motion
- carboxyhaemoglobin ($SpO_2 > SaO_2$)

Capnography

Carbon dioxide is only produced in the lungs and, therefore, the presence of carbon dioxide in expired gas confirms that the tip of the endotracheal tube is in the airway. In patients with relatively normal lungs and cardiac output, the end-tidal carbon dioxide tension gives an estimate of $PaCO_2$.

Arterial blood gases

Arterial blood gas analysis should be performed to confirm the diagnosis and to assist in the distinction between acute and chronic forms. This helps to assess the severity of respiratory failure and also helps management guiding. The blood gas should be considered in conjunction with the patient's clinical condition.

Imaging Studies:

Chest X - is essential because it frequently reveals the cause of respiratory failure: pneumonia, pulmonary edema, pulmonary hemorrhage and contusion, atelectasis, pleural effusion. However, distinguishing between cardiogenic and noncardiogenic pulmonary edema often is difficult.

Other investigations should be ordered on the basis of the history and clinical findings. If advanced radiological imaging is indicated consideration should be given to ultrasound scanning because of the low risk of adverse effects and because it may obviate the need to transport the patient to the radiology department.

Patients with acute respiratory failure generally are unable to perform pulmonary function tests. These tests are useful in the evaluation of chronic respiratory failure.

MANAGEMENT

Management of acute respiratory failure begins with a determination of the underlying etiology. While supporting the respiratory system and ensuring adequate oxygen delivery to the tissues, initiate an intervention specifically defined to correct the underlying condition.

Hypoxaemia is damaging to tissues and if uncorrected, fatal. Rapid reversal of hypoxaemia is obviously critical.

Oxygen Supplementation

There are several different devices that can be used to deliver oxygen. Methods that supply a relatively constant oxygen concentration to the lungs are called fixed performance devices. Variable performance devices provide variable concentrations depending on the patient's respiratory rate and inspiratory flow pattern.

They differ in terms of whether they are open or closed systems, whether they deliver low or high oxygen concentrations, and whether they are low or high flow systems.

Their effectiveness depends upon whether they can deliver enough oxygen at a sufficient flow rate to meet the patient's demands.

Patients spontaneously breathing through an open system will "entrain" some room air from their environment with each breath. Thus the ultimate oxygen concentration delivered to them will depend upon how much was delivered by the oxygen device and how much was entrained room air. The lower the flow delivered by the oxygen device, and the higher the patient's own inspiratory flow is, the more room that will be entrained resulting in a lower oxygen concentration.

- High-flow (>15 L/min) oxygen delivery systems include a Venturi-type device that places an adjustable aperture lateral to the stream of oxygen. Oxygen is mixed with entrained room air, and the amount of air is adjusted by varying the aperture size. The oxygen hoods and tents also supply high gas flows.

- Low-flow (<6 L/min) oxygen delivery systems include the nasal cannula and simple face mask. The maximal tracheal FiO2 is not likely to exceed 0.4.

- Resuscitation Bag-Mask-Valve Unit. High oxygen, high flow device. The oxygen flow should be kept high (15 L/min) when this device is used. When the mask is held firmly over the face with a good facemask seal, entrainment of room air is minimized.

- Noninvasive mechanical ventilation refers to assisted ventilation provided with nasal prongs or a face mask instead of an endotracheal or tracheostomy tube. It

can be used in order to avoid or prevent intubation in carefully selected patients. This therapy can be administered to decrease the work of breathing and to provide adequate gas exchange.

MECHANICAL VENTILATION

Conventional mechanical ventilation

If a patient progressed to the point where he was unable to sustain adequate oxygenation and ventilation on his own, then endotracheal intubation and positive pressure ventilation with a mechanical ventilator became necessary. Mechanical ventilation increases minute ventilation and decreases dead space. This approach is the mainstay of treatment for acute hypercapnia and severe hypoxemia.

Abbreviations:

- VT: Tidal volume (mls) = 8-12 ml / kg (IBW)
- RR: Respiratory Rate (bpm) = 10-12 bpm (average)
- MV: Minute Volume = VT X RR (lpm)) (6-10 lpm)
- FiO2: Fraction of inspired Oxygen
- PEEP: Positive end expiratory pressure (cmH20)
- (I:E) Ratio: Ratio of inspiratory to expiratory time.
- Ti: Inspiratory time

There are two main modes of ventilation:

- Volume ventilation: pre-set tidal volume will be delivered to the patient.
- Pressure Ventilation: Pre-set Inspiratory pressure will be delivered to the patient.

Mandatory breaths means breaths that the ventilator delivers to the patient at a set frequency, volume and flow while spontaneous breaths means that the patient is supposed to initiate breathing.

In spontaneous breathing, the sensitivity of the ventilator to the patient's respiratory effort triggers the inspiration. Either flow or pressure setting allows for the ventilator to detect the patient's inspiratory effort. This allows the ventilator to synchronize with the patient's spontaneous respiratory efforts. Patient comfort thus improves during mechanical ventilation.

Modes of Ventilation (most commonly used):

- A/C : Assist-Control
- SIMV : Synchronized Intermittent Mandatory Ventilation
- PSV: Pressure Support Ventilation.
- PCV: Pressure Control Ventilation.
- CPAP: Continuous positive airway pressure.
- BIPAP: Bi-level positive airway pressure.

A/C - Assist-Control Ventilation

The ventilator provides full tidal volume at a minimum preset rate and additional full tidal volumes given if the patient initiates extra breaths. .It assumes most/all of the work of breathing. This mode of ventilation provides near complete resting of ventilatory muscles and can be effectively used in awake, sedated, or paralyzed patients

SIMV

Ventilator provides set tidal volumes at a preset rate. When a ventilator breath is programmed to occur, the ventilator waits for a predetermined trigger period; any patient-initiated breath during this trigger period results in a programmed ventilator delivered breath. The patient can take additional breaths but tidal volume of these extra breaths is dependent on the patient's inspiratory effort

PSV

PSV it is a spontaneous mode of ventilation that can be used alone or in combination with mandatory modes. It is usually used to wean patients from the ventilator. The pressure support is set at the pressure required to generate VT of 8-10 ml/kg. Tidal volume and minute ventilation are dependent on the patient.

PCV

The breath is pressure limited but there is no guaranteed tidal volume and thus there is no guaranteed minute ventilation.

CPAP

In this mode a constant pressure is applied during both inspiration and expiration. The effect of this constant pressure is to splint open alveoli and thereby reduce shunting. CPAP is applied to increase lung volume and may redistribute pulmonary edema fluid from the alveoli to the interstitium. Patient inspiration is initiated from that baseline pressure and airway pressure returns to that level at the end of expiration. The patient controls the rate and tidal volume. In other words, CPAP allows spontaneous breathing at an elevated baseline pressure.

PEEP

PEEP is very similar to CPAP, except the constant pressure is only applied during expiration via a mechanical ventilator to an intubated patient. It opens closed alveolar units thus improving lung compliance and oxygenation but may cause hypotension, reduced cardiac output and increased intracranial pressure.

Nonconventional modes of ventilation

High-frequency oscillatory ventilation (HFOV) - combines small tidal volumes (smaller than the calculated airway dead space) with frequencies of more than 1 Hz to minimize the effects of elevated peak and mean airway pressures. HFOV has proven benefit in improving the occurrence and treatment of air-leak syndromes associated with neonatal and pediatric acute lung injury.

Weaning from mechanical ventilation

Factors to consider:

- Awake, and off sedation.
- Adequate nutrition, fluid status.
- Hemodynamically stable (preferably off pressors, angina controlled, no active bleeding)
- Normal acid-base status
- Bronchospasm controlled
- Normal electrolyte balance
- Oxygenation (O2 requirements <0.5 and PEEP <5 cmH20)

Ventilation-related complications:

- Disconnection, malfunction

- Hemodynamic effects: decreased cardiac output due to impaired venous return to the right heart and increased pulmonary venous resistance due to positive pressure alveolar distension
- Barotrauma or atelectasis
- Oxygen toxicity
- Respiratory alkalosis

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Acute respiratory distress syndrome (ARDS) is the type of acute lung injury associated with recognized risk factors, characterized by diffuse injury of the alveolo-capillar wall, and alveolar and interstitial edema consecutive to increased pulmonary vascular permeability.

ARDS typically occurs in people who are already critically ill or who have significant injuries. Severe shortness of breath — the main symptom of ARDS — usually develops within a few hours to a few days after the original disease or trauma.

The hallmarks of clinical syndrome are: hypoxemia and bilateral radiographic opacities on standard chest X-ray or CT scan.

Physiological derangements include: increased pulmonary venous admixture, increased physiological dead space, decreased pulmonary compliance

Morphological hallmarks are: lung edema, inflammation, hyaline membrane and alveolar hemorrhage.

There is a heterogeneous group of conditions, both direct or indirect insults which predispose to ARDS. Common risk factors for ARDS are characterized by inflammation:

- Direct
    - Pneumonia
    - Aspiration of gastric contents
    - Inhalational injury
    - Near drowning
- Indirect

- Non pulmonary sepsis
- Major trauma
- Multiple transfusions
- Severe burns
- Non cardiogenic shock

Definition

In 1994 the American – European Consensus Conference (AECC) defined ARDS as an acute condition characterized by bilateral pulmonary infiltrates and severe hypoxemia in the absence of evidence for cardiogenic pulmonary edema.

According to the AECC criteria, the severity of hypoxemia was defined by the ratio of the partial pressure of oxygen in the patient's arterial blood (PaO2) to the fraction of oxygen in the inspired air (FIO2):

- ARDS: PaO_2/FIO_2 ratio (P/F) < 200
- ALI (Acute Lung Injury): P/F < 300

In addition, cardiogenic pulmonary edema was excluded either by clinical criteria or by a pulmonary capillary wedge pressure (PCWP) lower than 18 mm Hg in patients with a pulmonary artery (Swan-Ganz) catheter in place.

But this AECC definition was subject to many criticisms:

- Chest Rx - Inter observer reliability is only moderate even when applied by experts
- Hypoxia - Pao2 /Fio2 ratio is not constant across a range of Fio2 and may vary in response to ventilator setting, particularly PEEP.
- Wedge pressure - Patients with ARDS may have an elevated PAWP often because of transmitted airway pressure and/or vigorous fluid resuscitation.

Using a consensus process, a panel of experts convened in 2011 developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance. A draft definition proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia:

- mild (200 mm Hg ≥ PaO2/FIO2 ≤ 300 mm Hg)
- moderate (100 mm Hg≥ PaO2/FIO2 ≤ 200 mm Hg)

- severe (PaO2/FIO2 ≤ 100 mm Hg)

There were also 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤40 mL/cm H2O), positive end-expiratory pressure (≥10 cm H2O), and corrected expired volume per minute (≥10 L/min).

The draft Berlin Definition was empirically evaluated, but the 4 ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition. Using the Berlin Definition, stages of mild, moderate, and severe ARDS were associated with increased mortality and increased median duration of mechanical ventilation in survivors. The term ALI (acute lung injury) is no longer used.

Berlin definition

Timing	**Within 1 week of a known clinical insult or new or worsering respiratory symptoms**		
Chest imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collage, or noduls		
Origin of edema	Respiratory failure not fully explained by cardiac failure of fluid overload Need objective assessment (echocardiography) to exclude hybrostatic edema if no risk factor present		
	Mild	Moderate	Severe
Oxygenation	200< PaO2/FiO2 ≤ 300 with PEEP or CPAP ≥5 cmH2Oc	100< PaO2/FiO2 ≤ 200 with PEEP or CPAP ≥5 cmH2O	PaO2/FiO2 <100 with PEEP or CPAP ≥ 5 cmH2O

Table 2

This updated and revised Berlin Definition for ARDS addresses a number of the limitations of the AECC definition. Compared with the AECC definition, the final Berlin Definition had better predictive validity for mortality

Pathophysiology

The pathogenic basis of ARDS and factors governing susceptibility are incompletely understood but the severity of ARDS depends significantly on the balance between alveolar epithelial and/or vascular endothelial injuries and their repair mechanisms.

ARDS is associated with diffuse alveolar damage (DAD) and lung capillary endothelial injury. The early phase is described as being *exudative,* whereas the later phase is *fibroproliferative* in character.

Initially, a direct pulmonary or indirect extrapulmonary insult is believed to cause a proliferation of inflammatory mediators that promote neutrophil accumulation in the microcirculation of the lung. These neutrophils activate and migrate in large numbers across the vascular endothelial and alveolar epithelial surfaces, releasing proteases, cytokines, and reactive oxygen species. This leads to the pulmonary edema, hyaline membrane formation, and loss of surfactant that decrease pulmonary compliance and make air exchange difficult. ARDS expresses itself as an inhomogeneous process.

The development of ARDS may be promoted by the positive airway pressure delivered to the lung by mechanical ventilation. This is termed ventilator-associated lung injury (VALI).

Treatment

Despite its high incidence and devastating outcomes (mortality rates 30-40%) ARDS has no specific treatment, with effective therapy currently limited to minimizing potentially harmful ventilation and avoiding a positive fluid balance.

Therapy directed at each underlying cause is high priority. Supportive treatment includes: mechanical ventilation, prophylaxis for stress ulcers and venous thromboembolism and nutritional support.

In adults with ARDS, a strategy to provide low tidal volume (6 mL/kg) with optimized positive end-expiratory pressure (PEEP) offers a substantial survival benefit compared with a strategy for high tidal volume (12 mL/kg).

Many pharmacological therapies have been investigated with limited success to date.

Patients who survive acute respiratory distress syndrome are at risk of diminished functional capacity, mental illness, and decreased quality of life.

TAKE HOME MESSAGES

- Conditions with increased carbon dioxide level in blood and hence in alveoli, as in hypoventilation, chronic obstructive airway diseases are associated with decreased oxygen tension in the alveoli.
- The vertical change in V/Q ratios in the lung is attributed to the fact that ventilation and perfusion increase from top to bottom of the lung but perfusion increases much quicker than ventilation.
- Hypoxic pulmonary vasoconstriction diminishes the blood flow to non-ventilated alveoli and reduces the severity of the hypoxemia.
- Shunting is the most common pathophysiological cause of hypoxemic respiratory failure.
- Increasing the inspired oxygen concentration in cases of shunting has little effect because it cannot reach alveoli where shunting is occurring and blood leaving normal alveoli is already 100% saturated.
- Lower compliance means more effort of breathing.
- Those who live at higher altitudes adapt to a lower number of molecules by increasing their amount of hemoglobin. Their PaO2 and PAO2 are lower, but their O2 content is normal.
- The hallmarks of ARDS are: hypoxemia and bilateral radiographic opacities on standard chest X-ray or CT scan.

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HEMODYNAMIC FAILURE OF THE CRITICALLY ILL

Sef. lucr. Dr. Copotoiu Ruxandra

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ACUTE HEART FAILURE

Heart failure occurs when the heart is unable to either receive adequate venous return from, or pump blood into the arterial system (deliver oxygen) at a sufficient rate to meet the metabolic demands of the body (imbalance between offer and demand). Acute heart failure (AHF) is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. It is often life-threatening and requires urgent treatment. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities of cardiac rhythm or to preload and afterload mismatch.

CLINICALLY RELEVANT PHYSIOPATHOLOGY

Cardiac output: the amount of blood ejected from the ventricle (primarily the left ventricle) in a minute (l/min). It reflects the pumping effectiveness.

Cardiac Output = Heart Rate x Stroke Volume

Frank-Starling law: describes the relationship between myocardial muscle length and the force of contraction. The more you stretch the muscle fiber in diastole (the more volume in the ventricle) the stronger the next contraction will be in systole. This phenomenon will occur until a physiological limit has been reached. Once that limit has been reached, the force of contraction will begin to decline, regardless of the increase in amount of fiber stretch.

Preload: the amount of myocardial fiber stretch at the end of diastole (volume in the ventricle).

Compliance: the ratio of a change in volume divided by a change in pressure. Ventricular compliance is determined by the physical properties of the tissues making up the ventricular wall and the state of ventricular relaxation (lusitropy). In a non-compliant ventricle, a greater pressure is generated with very little increase in volume.

- Decreased: Ischemia, ↑afterload, hypertension, inotropes, restrictive cardiomyopathies, ↑intrathoracic pressure, ↑pericardial pressure, ↑abdominal pressure
- Increased: dilated cardiomyopathies, ↓afterload, vasodilators

Afterload: the resistance, impedance, or pressure that the ventricle must overcome to eject its blood volume. It represents the tension developed by the myocardial muscle fibers during ventricular systolic ejection. In the clinical setting, the most sensitive measure of afterload is systemic vascular resistance (SVR) for the left ventricle and pulmonary vascular resistance (PVR) for the right ventricle. In reality, the resistance of the vascular system is derived from the measurements of cardiac output (CO) and mean arterial pressure (MAP). The formulas for calculating afterload look at the gradient difference between the beginning (inflow) of the circuit and the end (outflow) of the circuit.

- SVP = {(MAP-RAP)x80/CO}

MAP – mean arterial pressure

RAP – right atrial pressure

NV: 800-1200 dynes/sec/cm^5

- PVR = {(MPP-PAW)x80/CO}

MPP – mean pulmonary pressure

PAW – pulmonary artery wedge pressure

NV: < 250 dynes/sec/cm^5

Contractility (inotropism): Inherent property of the myocardial muscle fibers to shorten independent of preload and/or afterload. It cannot be directly measured.

Normal pressures at heart levels

Location	Abreviation	Mean value (mmHg)	Limits
Central vein	**CVP**	**6**	**1-10**
Right atrium	RAP	4	-1,+8
Right ventricle systole	RVSP	24	15-28
Right ventricle end diastole	RVEDP	4	0-8
Pulmonary artery systole	PAS	24	15-28
Pulmonary artery diastole	PAD	10	5-16
Pulmonary artery mean	**PAP**	**16**	**10-22**
Pulmonary capillary	**PCWP**	**9**	**5-16**
Left atrium	LAP	7	4-12
Left ventricle systole	**LVSP**	**130**	**90-140**
Left ventricle diastole	LVEDP	7	4-12
Brachial artery systile	**sBP**	**130**	**90-140**
Brachial artery diastole	dBP	70	60-90

Table 3

HEMODYNAMIC MONITORING

Clinical assessement

Mottling – begins usually at the knees

Basic monitoring and assessement of global perfusion

1. ECG: HR important determinant of CO
2. BP: interpreted in the context of patient's usual BP
    a. Indications for invasive monitoring
        - Unstable blood pressure or anticipation of unstable blood pressure
        - Severe hypotension
        - Use of rapidly acting vasoactive drugs; vasodilators, vasopressors, inotropes
        - Frequent sampling of arterial blood.
    b. Contraindications for invasive monitoring
        - Anticipation of thrombolytic therapy
        - Severe peripheral vascular disease preventing catheter insertion
        - Vascular anomalies – AV fistula, local aneurysm, local hematoma, Raynaud's disease
        - Lack of collateral blood flow distally
3. SpO2 monitoring: target > 92%
4. Lactate level: ? poor tissue perfusion

PRELOAD AND FLUID RESPONSIVENESS

Preload is estimated by a single/static measurement

1. Pressure CVP, PAOP
2. Volume: Global end diastolic volume (GEDV), left ventricular end diastolic volume (LVEDV)

Fluid responsiveness (dynamic parameter)

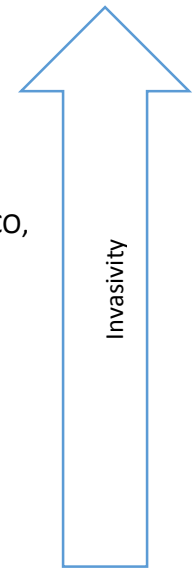
1. Bed side
    a. "fluid challenge": give 500 ml crystalloids (250 ml colloids)over 10-15 min and observe effects on BP, CVP, SV (≥15% rise in baseline CO)
    b. passive leg rise maneuver: the patient is transferred from 45°semi recumbent position to the PLR position (supine, with legs elevated at 45°)
2. Pulse pressure variation (PPV): the difference between the maximum (PPmax) and minimum (PPmin) pulse pressure over a single mechanical breath ≥ 13% (no spontaneous breaths, Vt ≥ 8 ml/kg).
3. Systolic pressure variation (SPV) less specific
4. Stroke volume variation (SSV): ≥ 10%

Volumetric parameter

1. Extravascular lung water (EVLW): estimation of pulmonary edema. It is indexed to the ideal body weight. NV: 3-7 ml/kg

Available monitoring devices

- Pulmonary thermodilution: pulmonary artery catheter
- Transpulmonary thermodilution: PiCCO
- Transpulmonary indicator dilution: LiDCCO
- Arterial pressure wave form derived: PiCCO, LiDCCO, Flotrac/Vigileo
- Esophageal Doppler: CardioQ
- Partial CO2 rebreathing: VICO
- Echocardiography: hemodynamic monitor of choice
- BioimpedanceBioZ, HOTMAN, TEBCO, Lifeguard
- Bioreactance: NICOM



Changes in serial cardiac output determinations within 10% are within the range of measurement errors. A greater variation can be expected in patients with pronounced variability in heart rate (ie, atrial fibrillation).

Assessment of cardiac contractility

Echocardiography is the hemodynamic monitor of choice in diagnosing hypotension of unknown etiology in the critically ill patient (identify/exclude cardiac cause of shock).

1. Ejection fraction

   EF (%) = {(EDV-ESV)/EDV} x 100

   Normal: ≥ 55%

   Mild impairment: 45-54%

   Moderate impairment: 30-44%

   Severe impairment: < 30%

2. Arterial pressure form analysis: maximum speed during ejection phase

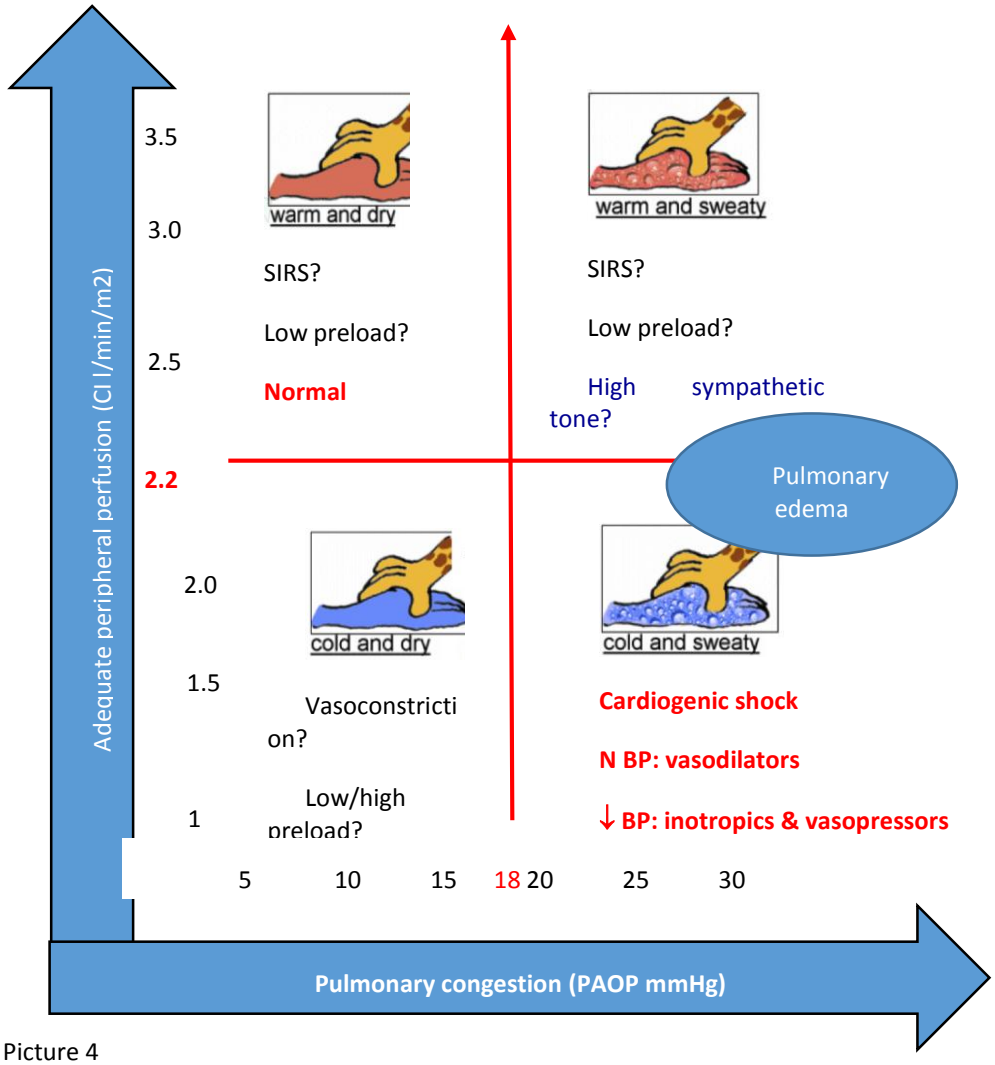
Assessment of tissue perfusion – not available for clinical practice

Low cardiac output syndrome (perfusion – forward flow)

It is a clinical condition with decreased cardiac output associated with evidence of tissue hypoxia in the presence of adequate intravascular volume.

Clinical features: cool peripheries, decreased level of consciousness, confusion, hypotension, low volume carotid pulse, tachycardia or inappropriate bradycardia, low urinary output.

APPROACH



Picture 4

1. Look for noncardiac correctable causes (respiratory, acid-base, electrolyte)
2. Treat ischemia or coronary spasm
3. Optimize preload (PCWP or LA pressure of 18–20 mm Hg)
4. Optimize heart rate at 90–100/min with pacing
5. Control arrhythmias
6. Assess cardiac output and start inotrope if cardiac index is less than 2.0 L/min/m2
    a. Epinephrine unless arrhythmias or tachycardia
    b. Dopamine (if low SVR) or dobutamine (if high SVR)
    c. Inamrinone/milrinone
    d. Insert IABP
    e. Nesiritide if low cardiac index and high filling pressures
7. Calculate SVR and start vasodilator if SVR over 1500
    a. Nitroprusside if high filling pressures, SVR, and blood pressure
    b. Nitroglycerin if high filling pressures or evidence of coronary ischemia or spasm
8. If blood pressure is low with a low SVR:
    a. Norepinephrine if marginal cardiac output
    b. Phenylephrine if satisfactory cardiac output
    c. Vasopressin if refractory to the above
9. Give blood transfusion if hematocrit is less than 26%

CARDIOGENIC PULMONARY EDEMA (CONGESTION - BACKWARD FLOW) (APE)

It is the classic presentation of heart failure.

Clinical features

1. **General**: such patients present with extreme shortness of breath, often unable to speak because of their rapid respiratory rate. Peripheral edema is not always present (especially for the first episode).

2. **Respiratory**: auscultation usually reveals extensive fine crepitations, usually equal bilaterally and greatest at the lung bases. Edema of the bronchial walls generates wheezing (diagnostic confusion). In such patients, the preferred option may be to treat both bronchospasm and pulmonary edema. In the most severely affected and exhausted patients, the chest may be surprisingly silent because of reduced tidal volumes. Cough, especially during semi-recumbency may be the equivalent of orthopnea.

3. **Cardiovascular**: they may present atrial fibrillation. A HR > 70 bpm at presentation has a higher risk for cardiac death. The blood pressure is preserved in approximately 80% of patients, hypotension beeing the single most important factor affecting the treatment

4. **Abdominal**: signs of right heart failure

Investigations:

1. **ECG**: continous monitoring during the acute phase

2. **Cardiac enzymes and other biomarkers**: ideally troponin I or T, assayed at presentation and repeated after 12 hours

3. **Chest Xray**: in diagnostic difficulties

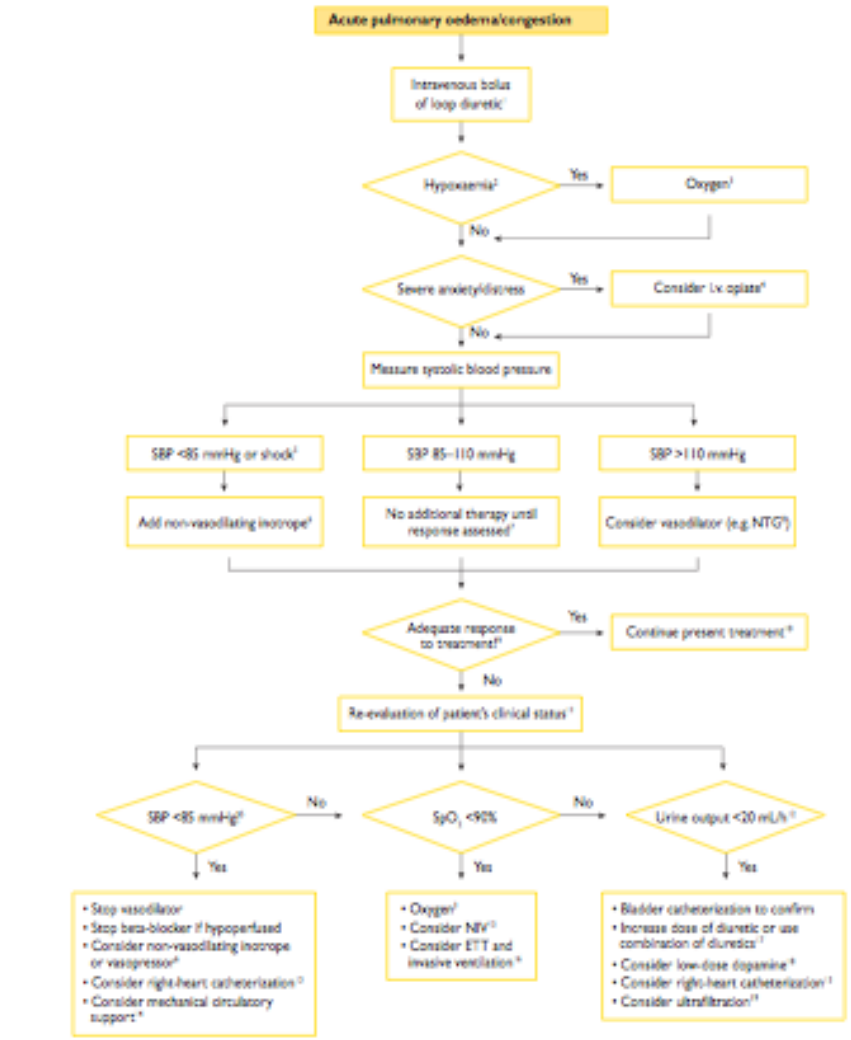
4. **Echocardiography**: carried out rearly, normal or decreades EF having a poor prognostic

5. **BNP**: in the acutely dyspneic patient in whom there is diagnostic dif- ficulty, a high BNP level is very suggestive of underlying cardiac failure. The use of BNP for monitoring progress in heart failure is controversial. Patients with severe heart failure due to cardiogenic shock may exhibit a paradoxically normal or even low BNP level

6. **Central venous catheter**: necessary for inotropres administration. It may give some aides as to righ sided filling pressure.

7. **Swan-Ganz catheter**: in severelly il patients in whom results may influence the treatment vs. echocardiography

Treatment



CPAP = continuous positive airway pressure; ETT = endotracheal tube; i.v. = intravenous; NIPPV = non-invasive positive pressure ventilation; NIV = non-invasive ventilation; NTG = nitroglycerine; PaO_2 = partial pressure of oxygen; SBP = systolic blood pressure; SpO_2 = saturation of peripheral oxygen.

Picture 5

1. **Oxygenation:** may reduce the work of breathing by 40%

Usually start with FiO2 40-60% titrating to SpO2 > 90% or PaO2>60mmHg. Caution is required in patients at risk for CO2 retention.

If the patient fails to respond to oxygen administered via a face-mask, CPAP or non-invasive mask ventilation should be considered. This will reduce the work of breathing and therefore oxygen consumption, minimize pulmonary edema and improve the functional residual capacity. A reduction in ventricular transmural pressure is also thought to reduce myocardial work by reducing left ventricular afterload. Patients in whom poor gas exchange persists may require intubation and invasive mechanical ventilation.

2. **Diuretics:** an i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly. In patients already taking diuretics a dose of 2.5 x the oral one is recommended. Repeat the diuretic as needed. If necessary double the dose (> 250 mg infused over 4 hours).

3. **Opiates**: an i.v. opiate (morphine 4-8mg) along with an antiemetic (metoclopramide 10 mg) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration. Repeat as needed.

4. **Vasodilators**: An i.v. infusion of a nitrate/nitroprusiate should be considered in patients with APE and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. vasodilators

    a. **NTG:** iv infusion at 10 µg/min and doubled every 10 min according to response and tolerability (hypotension)

5. **Inotropes**: are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischemia, and death).

    a. **Dobutamine**: start an i.v. infusion at 2.5 µg/kg/min, doubling dose every 15 min according to response or tolerability (excessive tachycardia, arrhythmias, or ischemia). A dose >20 µg/kg/min is rarely needed. Even dobutamine may have mild vasodilator activity as a result of beta-2 adrenoceptor stimulation.

    b. **Dopamine**: start an i.v. infusion at 2.5 µg/kg/min

c. **Norepinephrine**: restricted to patients with persistent hypoperfusion despite adequate cardiac filling pressures. Start with an infusion rate of 0.2–1.0 μg/kg/min for a target SBP > 90 mmHg.

6. **Thromboembolism prophylaxis**: with LMW is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism (comorbidities, immobilization).

7. **Nesiritide (recombinant human BNP):** for patients with SBP > 90mmHg. It is given by iv bolus (2 μg/kg□□followed by continuous infusion (0.01 μg/kg□min□□as an alternative to NTG. Treatment is usually continued for 24 to 48 hours.

8. **Intraaortic balloon counterpulsation**: improves cardiac parameters, but not outcome

9. **Surgery**:

   a. **Valve replacement**: usually delayed until patient is stable

   b. **Left ventricular assist device:** short (bridge to transplantation) or long term support to the failing left ventricle

   c. **Revascularization:** current evidence certainly does not support aggressive revascularization of all patients with cardiogenic shock, but revascularization may be appropriate in selected patients.

An adequate response includes reduction in dyspnea and adequate diuresis (>100 mL/h urine production in first 2 h), accompanied by an increase in oxygen saturation (if hypoxemic) and, usually, reduction in heart and respiratory rate (which should occur in 1–2 h). Peripheral blood flow may also increase as indicated by a reduction in skin vasoconstriction, an increase in skin temperature, and improvement in skin color. There may also be a decrease in lung crackles.

Therapeutic algorithms

The main goals of acute management of the patient with AHF are to:

1. Resuscitate the patient to stabilize the condition and prevent further deterioration.

2. Assess the severity of the problem so that the patient can be moved to an appropriate setting that can provide optimal monitoring and support.

3. Determine the possible etiology of the acute heart failure. This will enable early intervention when an acute reversible problem exists.

Vasoactive and inotropic drugs

Sympathomimetics

General effects

- α1 and α2 stimulation results in increased SVR and PVR. Cardiac α1 receptors increase contractility and decrease the heart rate.
- β1 stimulation results in increased contractility (inotropy), heart rate (chronotropy), and conduction (dromotropy).
- β2 stimulation results in peripheral vasodilatation and bronchodilatation.

Epinephrine

- potent β1 effects
- dose < 2 μg/min (0.03 μg/kg/min) β2 effects
- dose > 2 μg/min (0.03 μg/kg/min) α effects
- Indications
  - First line in borderline CO in the absence of tachycardia
  - Stimulation of the sinus node
  - Bronchospasm, anaphylaxis
  - Cardiac arrest
- Dose: 1-4 μg/min (0.01-0.05 μg/kg/min)

Norepinephrine

- Strong α and β1 effects
- In marginally ↓CO with ↓BP due to ↓SVR
- Dose: starting dose 1μg/min (0.015 μg/kg/min). > 20 μg/min (0.2 μg/kg/min) causes metabolic acidosis (↓ peripheral & visceral blood flow)

Dopamine

- < 3 μg/kg/min dopaminergic effects
- 3-8 μg/kg/min β1 effects

- > 8 µg/kg/min predominant α effects
- Dose: 2-20 µg/kg/min

Dobutamine

- Strong β1 effects
- Mild α1, β2 effects
- Initial management of patients with acute/chronic systolic HF & ↓CO
- Dose: start with 2-**5** µg/kg/min (without a loading dose) and titrate upward by 1 to 2 µg/kg/min every 15 to 30 minutes until the hemodynamic goal is reached (maximal effects at 10-15 µg/kg/min)

Isoproterenol

- Non selective β agonist with little/no α effect
- Indications:
  - Torsade de pointes refractory to magnesium
  - Inotrope, chronotrop support immediately after cardiac transplant
  - Treatment of PHT secondary to acute pulmonary embolism
  - Bradycardia in the absence of functional pace-maker wires
- Dose: 0.5-5 µg/min (0.01-0.05 µg/kg/min)

Phenylephrine

- Pure α effect
- May cause reflex bradycardia
- Starting dose: 5 µg/min (range 0.05-1.5 µg/kg/min)

Phosphodiesterase inhibitors

Milrinone

- Positive lusitropic effect
- Potent vasodilator (systemic, pulmonary)
- Dose: iv bolus 25-50 μg/kg over 10 min followed by a constant rate infusion of 0.25-0.75 μg/kg/min
- Indications: persistent ↓CO states, RV dysfunction, diastolic dysfunction

Calcium-sensitizing agents

Levosimendan

- Action: increases myofilament sensitivity to calcium. It is a potent vasodilator due to activation of adenosine triphosphate-dependent potassium channels in vascular smooth muscle cells →↓ preload & afterload
- Effects are dose dependent
- T1/2 of active metabolite↑→ effects last 7-9 days after a 24h infusion
- Dose: bolus of 3 to 12 μg/kg followed by infusion of a rate of 0.05 to 0.2 μg/kg/min (some advocate a limit of 0.6). The bolus is skipped in patients with initial blood pressure less than 100 mm Hg.
- There is a short term symptomatic benefit
- It exerts positive lusitropic effects

Hemodynamic effects of commonly used inotropic agents

Agent	SVR	PCWP	CO
Dobutamine	↓	↓	↑
Dopamine (low dose)	↓	↔	↔↑
Dopamine (high dose)	↑↑	↑↑	↑↔↓
Milrinone	↓↓	↓↓	↑↑
Levosimendan	↓↓	↓↓	↑

Table 4

Vasodilators

Nitroprusside

- Rapid onset of action: 1-2 min
- Arterial (systemic and pulmonary) and venous action
- HR unchanged/reduced (reflex sympathetic withdrawal)
- Dose: IV started at a rate of 10 to 20 μg/min (or 0.1 to 0.2 μg/kg/min) and increased by 20 μg/min every 5 to 15 minutes until the goal is achieved (SVR 1000-1200 dynes/sec/cm5, PCWP $\leq$ 16-18mmHg)

Nitroglycerine

- Immediate onset of action
- Venous action (lower infusion rates), arterial action (higher infusion rates)
- No response in significant right-sided failure
- Dose: IV started at a low infusion rate of 20 to 30 μg/min, and increased by 10 to 20 μg/min every 5 to 10 minutes until the desired response is observed or a dose of 400 μg/min is reached

Nesiritide (recombinant human B-type natriuretic peptide)

- Indication: patients with severe acute decompensated heart failure who remain dyspneic despite diuretics, and who are not hypotensive or in cardiogenic shock
- Balanced arterial and venous dilation
- Dose: bolus 2 μg/kg follower by continuous infusion 0.01 μg/kg/min. For patients with BP between 90 and 100 mmHg the rate is reduced by half without a bolus. If needed the dose can be increased by half the starting one (with bolus) every 3-24h up to a maximum of 0.03 μg/kg/min.

Hemodynamic effects of commonly used vasodilators

Agent	SVR	PCWP	CO	HR	MAP
Nitroprusside	↓↓	↓↓	↑	↔↓	
Nitroglycerine	↔↓	↓↓	↑↔↓		
Milrinone	↓↓	↓↓	↑	↑	↓
Neseritide	↓↓	↓↓	↑	↔	↓↓

Table 5

Choice of drugs for patients with ↓CO and ↑ filling pressures

- ↓ SVR: dobutamine, dopamine
- N SVR: nitroprusside, milrinone, dobutamine
- ↑ SVR: nitroprusside, nitroglycerine, neseritide, milrinone

TAKE HOME MESSAGES

- Heart failure occurs when the heart is unable to meet metabolic demands
- Clinically the Frank-Starling law describes the relationship between preload and stoke volume
- There are many methods of hemodynamic monitoring techniques. None of them are perfect or provide 99% accuracy
- Inotropes and vasopressors are administered only if the patient is euvolemic
- Always start with low dose inotropes and/or vasopressors and titrate up
- The Forrester classification is a first step in diagnosing a patient with acute heart failure and also provides valuable information for therapeutic management

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OLIGURIA AND ACUTE RENAL FAILURE

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Acute renal failure (ARF) is frequently encountered in the intensive care unit (ICU) as part of the syndrome of multiple organ failure. It is the most extreme manifestation of acute kidney injury and complicates the course of 5–15% of patients in the intensive care unit depending on the population studied and the criteria used to define. 50% of ARF in the ICU are associated with sepsis. In general, patients who develop ARF have a higher mortality than those who do not, and patients with ARF related to sepsis have a higher mortality that those without sepsis.

Functions of the kidneys:

- Water and electrolyte homeostasis
- Excretion in the urine of waste products of metabolism
- Excretion of chemicals/drugs
- Hormone production: renin, erythropoietin, active form of vitamin D (1,25 dihydroxyvitamin D3)
- Gluconeogenesis – during starvation
- Acid-base balance: HCO3- and H+ excretion

DEFINITION - ACUTE RENAL FAILURE/ ACUTE KIDNEY INJURY

Acute renal failure (ARF) has traditionally been defined as the abrupt loss of kidney function that results in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes.

Today, acute kidney injury (AKI) is considered the correct denomination for the clinical disorder formerly termed ‘acute renal failure’ (ARF). This is a spectrum of disease ranging from those at risk of renal injury (manifested by a slight elevation of creatinine or transient oliguria) through renal injury (greater elevation of creatinine and more prolonged oliguria) to frank renal failure.

In order to stage the severity of AKI, a graded classification, known as the RIFLE criteria **(risk, injury, failure, loss (> 4 weeks), end-stage kidney disease (> 3 months))** was established. The RIFLE criteria incorporate levels of oliguria in addition to incremental serum creatinine elevations. The RIFLE criteria were later modified and referred to as the acute kidney injury network (AKIN) definition:

STAGING OF AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR >0.3 mg/dl (X 26.5mmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for >12 hours
3	3.0 times baseline OR Increase in serum creatinine to>4.0 mg/dl (>353.6mmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in GFR to <35 ml/min per 1.73 m2	<0.3 ml/kg/h for >24 hours OR Anuria for >12 hours

Table 6

It is important to realize that both risk and injury can often be rapidly reversed by treatment but reversal of established renal failure is usually dependent on spontaneous renal recovery. It is, therefore, vital to intervene early in the patient with acute kidney injury.

PATHOPHYSIOLOGY AND FUNCTIONAL CLASSIFICATION

ARF is often categorized as falling into one of three broad pathophysiologic categories:

- reversible '**prerenal'** (PR) ARF due to renal hypoperfusion
- '**intrinsic**' ARF due to nephron injury
- '**post renal'** ARF due to urinary obstruction.

Of course, multiple etiologies may contribute to ARF in a given patient.

It should be noted that under normal circumstances the oxygen extraction of the outer medulla of the kidney is near maximal. As a result this part of the kidney is very susceptible to hypoxia as a result of decreased blood flow.

Pre-renal failure (azotaemia) is responsible for about 30 to 40% of cases of oliguria in the ICU and it means a reduction in renal perfusion without cellular injury.

Prerenal indicates that the cause lies outside the kidney, specifically 'before' the kidney and is characterized by a decrease in renovascular flow. The disorders in this category include:

- Decreased blood volume
  - Vomiting
  - Dehydration
  - Hemorrhage
- Reduction in the effective arterial blood flow
  - Congestive heart failure
  - Cirrhosis
- Drugs that impair renal autoregulation
  - NSAID (non-steroidal anti-inflammatory agents)
  - ACE (angiotensin - converting enzyme inhibitors)

The oliguria in these conditions can usually be corrected by fixing the underlying disorder. Prolonged or severe prerenal conditions can lead to renal injury and oliguric renal failure.

Prerenal causes should be excluded in all cases of AKI!

Intrarenal causes of renal failure can be classified according to anatomic location:

- Glomerulus
- Tubule
- Vasculature
- Interstitium

Causes of **acute 'intrinsic' renal failure** usually fall into two categories: acute tubular necrosis (ATN), or acute interstitial nephritis (AIN).

ATN is responsible for over 50% of cases of acute oliguria in the ICU, and is most often caused by inflammatory injury (including sepsis), circulatory shock, and toxic injury from drugs (aminoglycosides), radiocontrast dye, and myoglobinuria. ATN is characterized by (oxidative) injury to the renal tubular epithelial cells with sloughing

of the cells into the lumen of the renal tubules. The sloughed cells create an obstruction that increases the pressure in the proximal tubules. This decreases the net filtration pressure across the glomerular capillaries and reduces the glomerular filtration rate (GFR).

A failure of hemodynamic restoration with a trial of fluid replacement to restore urine output and the exclusion of post-renal pathologies supports the diagnosis.

Acute interstitial nephritis is usually drug related (ATB, NSAIDs). It is characterized by pyuria and white cells casts and the recovery is hastened by short course of steroids: 60-80 mg prednisose for 10 days.

Post-renal failure is due to obstruction of urine flow and accounts for <5% of cases of AKI. Patients with complete bilateral urinary tract obstruction may present with anuria (urine output <50 mL/day).

Causes of urinary tract obstruction:

- Renal
    - Crystal deposition (ethylene glycol ingestion)
    - Uric acid nephropathy (tumor lysis syndrome)
- Extrarenal
    - Prostatic disease (hypertrophy, neoplasia, or infection),
    - Pelvic malignency
    - Retroperitoneal disorders
    - Blood clots, calculi, and urethritis with spasm
    - Neurogenic bladder

Persistent severe oliguria or anuria (lasting several weeks) should prompt suspicion of severe ATN (5% of survivors do not recover renal function) or cortical necrosis. Classically severe, prolonged renal hypoperfusion results in patchy focal tubular damage including necrosis and apoptosis of tubular cells.

RISK FACTORS

Risk factors for developing AKI

- Age > 65 years
- Infection on admission
- Cardiovascular failure
- Cirrhosis
- Respiratory failure
- Chronic heart failure
- Lymphoma or leukemia
- Diabetes mellitus
- Vascular disease, abdominal aortic surgery
- Crush injury

Risk factors for mortality:

- Higher severity index score
- Age > 65 years
- Male gender
- Oliguric acute renal failure
- Sepsis
- Nonrenal organ failure
- Thromcytopenia
- Mechanical ventilation
- Prior compromised health status

CAUSES

The causes of acute renal failure are numerous. The most important are those which are readily reversible such as hypovolaemia, and those for which there are specific supportive treatments (rhabdomyolysis).

Causes of acute renal failure (adapted after [1])

Site of injury	Causes
Circulation	Hypovolaemia Low cardiac output Renal vascular obstruction: occlusion, constriction, emboli, thrombosis, vasculitis, atherosclerosis, abdominal aortic dissection Hepatorenal syndrome
Parenchymal	
Drugs	Antibiotics – aminoglycoside, vancomycin, amphotericin, sulphonamide Radiocontrast agents Angiotensin converting enzyme inhibitors Immunosuppressive therapy – cyclosporine A, tacrolimus Non-steroidal anti-inflammatory drugs Others – diuretics (thiazides, furosemide), phenytoin, allopurinol, cisplatin
Pigment-related	Rhabdomyolysis (myoglobin) Hemolysis (hemoglobin)

Glomerular causes	Immune complexes: systemic lupus erythematous, subacute bacterial endocarditis, post infectious glomerulonephritis Antibodies: Goodpasture's, Wegener's granulomatosis, polyarteritis nodosa Hyperviscosiy syndrome: Multiple myeloma, polycythemia Others: hemolytic uremic syndrome, thrombotic thrombocytopaenic purpura, malignant hypertension, scleroderma, toxemia of pregnancy
Post renal obstruction	Bladder neck obstruction from prostatic hypertrophy, ureteric obstruction from pelvic tumors or retroperitoneal fibrosis, papillary necrosis or large calculi.
Multifactorial	Sepsis Abdominal compartment syndrome

Table 7

INVESTIGATIONS

The initial evaluation of the oliguric patient should be aimed at identifying prerenal or reversible causes of oliguria. Prompt evaluation is necessary because prolonged or severe prerenal conditions can lead to oliguric renal failure, which is not immediately reversible.

Urine flow (urine output) is a vital sign in acute medicine; oliguria is defined as a urine output that is less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h for six consecutive hours in children and adults. In critically ill patients, oliguria is often a sign of acute kidney injury that precedes serum creatinine increases and requires immediate attention. To confirm and monitor oliguria, a urinary catheter should be placed if not already in situ. If oliguria is suspected, urinary output should be monitored hourly. In patients with urinary catheters in situ, an initial assessment of the urinary catheter's position and patency should be performed. Once the clinician has established there is no mechanical reason for the oliguria, further evaluation and diagnosis of oliguria should proceed. A full clinical history and physical examination can frequently identify events and/or disease processes that underlie AKI and suggest an underlying diagnosis.

Urine Microscopy - Microscopic examination of the urine sediment is the easiest diagnostic procedure. The presence of abundant tubular epithelial cells with epithelial cell casts is virtually pathognomonic of ATN. In addition, the presence of white cell casts identifies an interstitial nephritis, and the presence of pigmented casts identifies myoglobinuria. If urine microscopy is unrevealing, measuring the sodium concentration in a spot urine sample can be useful.

Spot Urine Sodium - When renal perfusion is diminished, sodium reabsorption increases and urinary sodium excretion decreases. On the other hand, intrinsic renal disease is usually accompanied by a decrease in sodium reabsorption and an increase in sodium excretion in the urine. Therefore, in the setting of oliguria, **a urine sodium below 20 mEq/L usually indicates a prerenal condition**.

However, a urine sodium above 40 mEq/L does not rule out a prerenal condition when it is superimposed on an underlying case of chronic renal insufficiency (where there is obligatory sodium loss in the urine), or when there is ongoing diuretic therapy. Elderly patients can also have an obligatory loss of sodium in the urine. Therefore, a urine sodium above 40 mEq/L must be interpreted according to the clinical setting.

The fractional excretion of sodium (FENa) measures the percent of filtered sodium that is excreted in the urine. This is equivalent to the sodium clearance divided by the creatinine clearance; this calculation is widely used to help differentiate prerenal disease (decreased renal perfusion) from acute tubular necrosis as the cause of acute kidney injury Fractional Excretion of

$FENa = (P_{Cr} \times U_{Na}) / (P_{Na} \times U_{Cr})$ %

The FENa is normally less than 1%: less than 1% of the filtered sodium is excreted in the urine.

	Prerenal	Intrinsic Renal	Postrenal
U_{Na} (mmol/L)	<20	>40	>40
FE_{Na}	<1%	>1%	>4%

Table 8

There are some exceptions to these criteria: the FENa can be less than 1% in ATN due to myoglobinuria. Despite the occasional exception, the FENa is one of the most reliable urinary parameters for distinguishing prerenal from renal causes of oliguria.

Urea and creatinine are insensitive markers of glomerular filtration rate as they become abnormal only when there has been a huge (>50%) drop. They are affected by nutrition, muscle injury, steroids or gastrointestinal bleeding, conditions that commonly occur in the critically ill patients.

The glomerular filtration rate (GFR) is traditionally considered the best overall index of renal function in health and disease. It is defined as being the volume of plasma completely cleared of the substance by the kidneys per unit of time. Because GFR is difficult to measure in clinical practice, most clinicians estimate the GFR from the serum creatinine concentration. However, the accuracy of this estimate is limited because the serum creatinine concentration is affected by factors other than creatinine filtration.

Several formulas have been developed to estimate **creatinine clearance** from serum creatinine concentration, age, sex, and body size. The most widely used formula to predict creatinine clearance is that proposed by Cockcroft and Gault. This formula is used to detect the onset of renal insufficiency, to adjust the dose of drugs excreted by the kidney, and to evaluate the effectiveness of therapy for progressive renal disease. Estimating Creatinine Clearance (ml/min) - Cockcroft and Gault equation:

CrCl = (140 - age) x IBW / (Scr x 72) (x 0.85 for females)

Creatinine clearance:

- Men (younger than 40 years): 107-139milliliters per minute (mL/min) or 1.8-2.3 milliliters per second (mL/sec)
- Women (younger than 40 years): 87-107 mL/min or 1.5-1.8 mL/sec

Creatinine clearance values normally go down as you get older (normal values go down by 6.5 mL/min for every 10 years past the age of 20).

Routine urgent investigations in patients with acute renal failure should include serum urea, creatinine, sodium, potassium, calcium and creatine kinase, arterial blood gases and urine dipstick testing for hematuria (this is also positive in the presence of myoglobinuria).

Hyperkalaemia is a biochemical indicator of acutely deteriorating renal excretory capacity. Hyperkalaemia may be life threatening, or subject to a hyperacute rise (rhabdomyolysis) and is one of the recognized indications for urgent dialysis in acute renal impairment. Concurrent acidosis can aggravate hyperkalaemia.

Severe hyperkalaemia MUST be treated urgently!!

Renal ultrasound should be carried out in all patients with unexplained acute renal failure. Ultrasonography is a bedside, non-invasive investigation which avoids the need for administration of potentially nephrotoxic contrast media. The main purpose of the investigation is to diagnose or rule out an obstructive cause of oliguria. It also provides information on kidney size, enlarged kidneys being typical for AKI but small kidney(s) for chronic kidney disease.

Renal biopsy is of limited value in the ICU unless vasculitis or glomerulonephritis are suspected.

It is particularly important not to miss those patients with a cause of acute renal failure that requires specific treatment (e.g. urinary obstruction, vasculities, hypercalcaemia).

MANAGEMENT OF ARF IN EMERGENCY

The principal task in the early management of the oliguric patient is to identify and correct volume deficits and discontinue any drugs that could be a source of oliguric renal failure.

Some of the principles of supportive management of ARF include

1) Hemodynamic resuscitation

2) Prevention

3) Aggressive treatment of sepsis

4) Exclusion of obstruction

5) Treatment of hyperkalemia and acid-base disturbance

6) Diuretics

7) Renal replacement therapy.

It is, of course, essential to treat the underlying cause.

Haemodynamic resuscitation

This involves prompt and adequate resuscitation with rapid and carefully monitored restoration of intravascular filling, cardiac output and blood pressure. The ‘fluid challenge’ attempts to identify and treat pre-renal failure that can progress to ATN if not treated promptly. Fluids should be given early and targeted to hemodynamic end points, such as increases in mean arterial pressure, pulse pressure variation, cardiac output, central venous pressure (CVP), central venous oxygen saturation, pulmonary artery occlusion pressure (PAOP), urine output and

improvements in lactic acidosis and skin perfusion Norepinephrine might be used to increase the renal perfusion pressure once adequate preload has been achieved. Using low-dose dopamine to prevent or treat AKI is not recommended.

A common adverse consequence of fluid resuscitation is 'fluid overload' and pulmonary edema with significant reductions in lung function and oxygenation. A threshold may exist beyond which the perceived benefit of additional fluid therapy after resuscitation may be detrimental.

Prevention

Prevention can be divided into primary (before a known renal insult occurs) or secondary (after a renal insult).

- maintain renal perfusion: volume resuscitation, vasopressors
- avoid nephrotoxic antibiotics, angiotensin-converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory agents in volume depleted or otherwise susceptible patients
- use of nonionic contrast agents or avoidance of a contrast study with non-contrast imaging modalities such as ultrasonography
- radiocontrast nephropathy - intravenous saline hydration

Diuretics

Diuretics have not been shown to prevent or ameliorate AKI. Loop diuretics may increase urine output (without an increase in creatinine clearance) facilitating management of fluid and electrolyte balance but their use should not delay commencing renal replacement therapy when deemed clinically necessary. No reduction in the need for renal replacement therapy or mortality has been proved. Diuretics are not a treatment for oliguria. They may be important in the management of volume overload or hyperkalemia.

Renal replacement therapy in the ICU

Methods of Renal Replacement Therapy (RRT):

- IHD – intermittent hemodialysis
- SLED – slow low-efficiency dialysis
- CRRT – continuous RRT
- PD – peritoneal dialysis

The two main modes of renal replacement therapy in ICU are continuous renal replacement therapy (venovenous hemofiltration) and intermittent hemodialysis.

CRRT vs. IHD in critically ill patients:

- Better hemodynamic stability
- Less hypotensive episodes
- Volume control continuous, not episodic
- Superior control of metabolic acidosis
- Rapid phosphate removal
- No restriction for TPN
- Septic-shock associated renal dysfunction
- Removal of soluble inflammatory mediators
- Removal of severe extravascular lung water
- Severe unrelenting hyperthermia

Early initiation is beneficial.

Indications for starting renal replacement therapy

- Nonobstructive oliguria (urine output <200 mL/12 h) or anuria
- Severe acidemia
- Azotemia (blood urea nitrogen >80 mg/dL)
- Hyperkalemia (K+ >6.5 mmol/L) IHD
- Uremia (encephalopathy, pericarditis, neuropathy, myopathy)
- Severe dysnatremia (Na+ >160 or <115 mmol/L)
- Hyperthermia (temperature >39.5°C)
- Clinically significant organ edema (especially lung)
- Drug overdose with dialyzable toxin

- Coagulopathy requiring large amounts of blood products in a patient at risk for adult respiratory distress syndrome

Any one of these indications is sufficient to consider initiating renal replacement therapy. Two of these indications make renal replacement therapy desirable.

Prognosis

If the cause of ARF is removed, recovery may start to occur within 4-5 days but may take weeks. However, a number of patients especially those with pre-existing chronic renal failure may progress to requiring long term renal replacement therapy.

TAKE HOME MESSAGES

- Both risk and injury can often be rapidly reversed by treatment but reversal of established renal failure is usually dependent on spontaneous renal recovery. It is, therefore, vital to intervene early in the patient with acute kidney injury.
- If oliguria is suspected, urinary output should be monitored hourly.
- The FENa is one of the most reliable urinary parameters for distinguishing prerenal from renal causes of oliguria
- Diuretics have not been shown to prevent or ameliorate AKI
- Early initiation of continuous renal replacement therapy in critical patients is beneficial.

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ACUTE HEPATIC FAILURE

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Acute Hepatic Failure (AHF) will include both acute liver failure (ALF) and acute on chronic liver failure (ACLF).

DEFINITION

- ALF is a rapidly progressive, life-threatening condition, which occurs when there is massive liver injury, with necrosis of the liver parenchyma.
- ALF is defined as the presence of encephalopathy (regardless of grade) and coagulopathy (international normalized ratio [INR] ≥1.5) within 26 weeks of the appearance of symptoms in patients with no previous history of underlying liver disease.

The condition is characterized by coagulopathy and encephalopathy that occurs within days or weeks, usually preceded by a prodromal illness of nausea and vomiting.

It is often complicated by multi-organ failure. Liver necrosis triggers an inflammatory cascade, which drives vasoplegic cardiovascular collapse, renal failure and, to some extent, cerebral edema. Aggressive resuscitation of the circulation ameliorates hepatic parenchymal ischemic injury and promotes regeneration. Hypoglycemia must be actively sought, monitored and treated.

The key to a successful outcome rests in timely recognition, resuscitation and referral to a specialist center for consideration of transplantation.

Patients with ALF may initially appear relatively well, but can rapidly progress to develop multi-organ failure. The diagnosis of the cause of these patients' ALF must go hand in hand with basic resuscitative maneuvers.

Chronic liver disease is more common than ALF.

The classification is important as the incidence of cerebral edema and prognosis after transplantation is different:

Trey and Davidson: development of HE within 8 weeks of onset of symptoms

British Classification: (includes only patients with encephalopathy) Subclassification depending on the interval between jaundice and HE:

- Hyperacute liver failure: 0 to 7 days
- Acute liver failure: 8 to 28 days
- Subacute liver failure: 29 to 72 days
- Late-onset acute liver failure: 56 to 182 days

French Classification: a rapidly developing impairment of liver function

Severe acute hepatic failure: prothrombin time or factor V concentration below 50% of normal with or without HE

Subclassification:

- Fulminant hepatic failure: HE within 2 weeks of onset of jaundice
- Subfulminant hepatic failure: HE between 3 and 12 weeks of onset of jaundice

International Association for the Study of Acute Liver Failure (occurrence of HE within 4 weeks after onset of symptoms)

Subclassification:

- Acute liver failure—hyperacute: within 10 days
- Acute liver failure—fulminant: 10 to 30 days
- Acute liver failure—not otherwise specified

Subacute liver failure (development of ascites and/or HE from 5 to 24 weeks after onset of symptoms)

ETIOLOGY

1. Drug injury – developed nations
    a. **Acetaminophen**
    b. Antituberculous drugs
    c. Recreational drugs (ecstasy, cocaine)
    d. Idiosyncratic reactions – anticonvulsants, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs)
    e. Aspirin in children may lead to Reye (or Reye's) syndrome
    f. Amiodarone

g. Carbamazepine

h. Ketoconazole

i. Interferon alpha

j. Oral contraceptives

2. Hepatitis – the most common precipitant in the developing world-

   a. Human hepatitis A, **B**, C, D, E, G (mostly coinfection)

   b. Herpes virus

   c. Cytomegalovirus,

   d. Chickenpox

   e. Epstein Barr virus

   f. Adenovirus

   usually limited to immunocompromised hosts associated mortality ~75%

3. Toxins

   a. CCl4

   b. Amanita phalloides

   c. Yellow phosphorus

   d. Herbal products

   e. Alcohol

4. Vascular

   a. Ischemic

   b. Veno-occlusive disease

   c. Budd-Chiari syndrome

   d. Malignant infiltrations

5. Miscellaneous

   a. Wilson disease

   b. Autoimmune hepatitis

c. Acute fatty liver of pregnancy

d. Lymphoma

e. Trauma

ACLF – decompensations are usually precipitated by an acute event (infection or bleeding)

1. Sepsis – classical definition not applicable in chronic liver disease - characterized only by exacerbation of circulatory changes already present at baseline.

   a. The main sites of infection in cirrhosis are the peritoneal space (ascites), urinary tract, lungs and blood. The commonest organisms are *E. coli,* followed by *Staph. aureus, E. faecalis, Strep. pneumoniae, Pseudomonas* and *Staph. epidermidis.* MRSA, VRE and ESBL-producing enterobacteria are becoming increasingly common and 1st and 2nd generation cephalosporins therefore fail in a substantial proportion of patients.

   b. Infection may predispose to variceal bleeding because of an elevation in sinusoidal pressure – and hence portal pressure and a worsening of coagulopathy. It is recommended that patients with bleeding complications also be treated with antibiotics. Choice of antibiotic therapy is informed by local prescribing policy and drug resistances, but should include broad Gram-negative cover.

2. Spontaneous bacterial peritonitis (SBP)

   a. It represents the infection of cirrhosis-related ascites. It may cause a florid sepsis syndrome with shock and renal failure, or have an onset that is insidious and only detected at paracentesis. Pyrexia, changes in mental state and abdominal tenderness are common. It is extremely important to differentiate SBP from secondary peritonitis.

3. Multiple organ failure

   a. Pneumonia

   b. Circulatory failure

   c. Relative adrenal insufficiency

Clinical features - nonspecific

- Encephalopathy (EP)– grade 1-4

- when liver failure develops quickely, EP may precede the development of jaundice and the prodromal illness is absent

Stages of encephalopathy

Grade	Mental status	Tremor	EEG
I	Euphoria, occasionally depression; fluctuating mild confusion; slowness of mentation and affect; slurred speech; disorder in sleep rhythm	slight	normal
II	Drowsiness; inappropriate behavior.	present	generalized slowing
III	Sleeps most of the time but is arousable, confused; incoherent speech.	present	abnormal
IV	Unarousable, may respond to painful stimuli	absent	abnormal

Table 9

- Jaundice
- Hepatomegaly – shrinking liver = poor prognostic sign in acute and subacute liver failure
- Ascites
- Vascular
- Vital signs: ↓BP (hyperdynamic and low vascular peripheral resistance), hyperventilation, metabolic derangements (! hypoglycemia)

SEVERITY SCALES

(mortality 50-80%)

The most important risk factor for in-hospital mortality was determined to be the severity of non- hematologic organ failure, best assessed after three days from admission.

Child Pugh score – sensibility and specificity 80%

	1	2	3
Encephalopathy	None	Minimal (I /II)	Advanced (coma)
Ascites	Absent	Controlled	Refractory
Bilirubin (µmol/l)	<34	34-51	>51
(mg/dl)	<2	2-3	>3
Albumine (g/l)	>35	28-35	<28
Prothrombin (sec)	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

Table 10

In primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/l (4 mg/dl) and the upper limit for 2 points is 170 µmol/l (10 mg/dl).

Grade A: 5-6

Grade B: 7-9

Grade C: >9

King's College prognostic criteria used for liver transplantation

Acetaminophen overdose	Non-acetominophen liver injury
Arterial pH < 7.3 (irrespective of grade of encephalopathy) *OR*	PT > 100 sec (INR > 6.5) (irrespective of grade of encephalopathy) ***OR any three of the following***
PT > 100 sec (INR > 6.5)	Age < 10 or > 40 years
Serum creatinine > 3.4 mg/dL (>300 µmol/L)	Non-A, non-B, halothane hepatitis, idiosyncratic drug reactions
Grade III and IV hepatic encephalopathy	Jaundice > 7 days before onset of encephalopathy
	Serum bilirubin > 17.4 mg/dL (>300 µmol/L)
	PT > 50 sec

Table 11

MELD (Model of End Stage Liver Disease) score >32

MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

UNOS has made the following modifications to the score:

- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)

Range 6-40

Various prognostic criteria

1. Clichy Criteria
   a. Factor V < 20% in person < 30 years or both of the following:
      I. Factor V < 30% in patients > 30 years
      II. Grade III or IV encephalopathy
2. Serum Gc globulin: decreasing levels due to dying hepatocytes

3. Serum α-fetoprotein: Serial increase from day 1 to day 3 has shown correlation with survival

4. Liver biopsy: 70% necrosis is discriminant of 90% mortality

5. Blood lactate levels:

   a. >3.5 mmol/l at four hours after transfer or admission despite volume therapy

   b. >3 mmol/l at 12 hours or following volume therapy

COMPLICATIONS

- Neurological – encephalopathy, cerebral edema
- Cardiovascular and hemodynamic
- Respiratory
- Coagulation: excessive thrombosis, DIC
- Renal
- Acid-base derangements: lactic acidosis, alkalosis
- Metabolic derangements: hypoglycemia, hyponatremia, hypokalemia, hypophosphatemia
- Bacterial & fungal infections

EVALUATION AND INTERPRETATION OF THE LABORATORY DATA

1. ALT (GPT) is more specific for the liver.

2. In acute toxic injury and ischaemic hepatitis, the serum concentration of aminotransferase enzymes may be increased to several thousand IU/l, whereas in CLD, levels may be modestly increased or even normal.

3. In alcohol-related liver disease AST activity is frequently twice that of ALT.

4. Falling plasma aminotransferase concentrations in a patient with ALF do not necessarily imply that liver function is improving (it rather suggests a massive necrosis, in the setting of worsening clinical features).

5. Elevated ALP is seen most frequently in patients with biliary disease.

6. Elevated GGT may be seen in patients with enzyme induction as well as in biliary obstruction.

7. If the international normalised ratio (INR) remains prolonged after intravenous vitamin K repletion it is likely that there is significant liver dysfunction, assuming there is not disseminated intravascular coagulation, although the two may co-exist.

8. Eosinophilia may be present in liver disease caused by drugs, but its absence should not preclude this diagnosis.

MANAGEMENT

Staff protection – universal precautions.

1. Assessement of severity and prognosis
2. Monitoring key variables and trends in organ dysfunction
    a. ICP
    b. Standard invasive hemodynamic variables
    c. Urine output
    d. Oxygen saturation, arterial blood gases
3. Laboratory variables
    a. Full blood count
    b. Liver and renal biochemistry, ammonia levels
    c. Coagulation profiles
    d. Biological fluids should be cultered – if suspicion of infection (>250 PMN/mm^3 ascitic fluid)
    e. Specific tests to determine the etiology
4. Imaging
    a. Chest Xray
    b. Liver ultrasound
5. Minimizing complications

Liver transplantation is the only proven and definitive treatment option. Liver transplantation is offered to those who fulfill poor prognostic criteria (predicted

mortality > 90%). One year survival post transplantation is 75-80%, the most of mortality beeing seen in the first three months post transplantation.

Cerebral edema

General measures

- Head of bed elevation to 30° angle, pts neck in neutral position
- ETT for grade III or IV EP
- Minimaze tactite and tracheal stimulation
- Avoid hypovolemia & hypervolemia
- Avoid hypertension
- Avoid hypercapnia & hypoxemia
- Monitor & maintain ICP < 15 mmHg
- Maintain CPP > 50 mmHg

Management of intracranial hypertension

- Manitol boluses: 0.5-1.0 g/kg
- Hyperventilation: $PaCO_2$ 28-30 mmHg
- Induced moderate hypothermia: 32-33°C
- Na levels: 145-155 mEq/L
- Induced coma with propofol/pentobarbital
- CVVH for oliguria and hyperosmolarity (>310 mOsm/L)

Management of encephalopathy associated with CLD may involve:

- Resuscitative measures e.g. control of airway, support of circulation.
- Diagnosis and treatment of the precipitant.
- Treat infection and biochemical abnormalities.
- Protein intake of 1–1.5 g protein/kg/day depending on level ofencephalopathy (can be reduced to 0.5 g/kg/day transiently). Vegetable protein is preferable to animal protein.

- Lactulose/lactilol. The cathartic effect removes endogenous and exogenous ammonia-generating compounds from the bowel and maintains an acidic environment that retains ammonia within the bowel lumen.
- Neomycin may have an additive benefit but is not often used because of the risk of oto-and nephrotoxicity.
- Zinc supplementation is recommended as zinc is a necessary substrate in the metabolism of ammonia to urea and many patients are zinc deficient.
- There is no evidence to support the use of benzodiazepine antagonists.
- Recent studies suggest benefit with rifaxamin in preventing encephalopathy in an outpatient setting.
- Use of ammonia lowering agents such as L-ornithine and L-arginine have some role in chronic liver disease but had no beneficial effect when studied in the context of ALF.

Coagulopathy

There is no evidence that support of coagulation with transfusion of fresh frozen plasma (FFP), platelets or cryoprecipitate has anybeneficial impact on outcome, and should not be undertaken without clear clinical indication. In patients who have variceal haemorrhage it is conventional practice to maintain the INR below 1.5 and the platelet count above 70 x 10^9/l (70 x 10^3/mm^3).

Artificial liver support

As bridge to transplantation.

1. Detoxifying systems
   a. Charcoal
   b. Albumine (MARS) – survival benefit at 3 months, but not at 6
2. Biortificial system – no definitive role

Hepatorenal syndrome (HRS)

HRS = renal vasoconstriction in the setting of systemic and splanchnic arterial vasodilation in patients with advanced cirrhosis

Incidence:

- 18% within 1 year of diagnosis of advanced cirrhosis
- 40% at 5 years

Classification

HRS type 1	HRS type 2
• ***Rapid*** deterioration in kidney function • Scr increasing by ***more than 100% from baseline*** to ***greater than 2.5 mg/dL*** within a ***2 week period*** • Untreated – median survival 2 weeks	• Patients with ***refractary ascites*** • ***Steady but moderate*** degree of functional renal failure (***< 1.5 mg/dL***) **or** • Deterioration in kidney failure that ***does not fulfill the criteria for HRS type 1*** • Untreated – median survival 4-6 months

Table 12

Major diagnostic criteria (International Ascites Club)

- Cirrhosis with ascites
- Creatinine > 1.5 mg/dL
- No improvement of serum creatinine after at least 2 days of diuretic withdrawal and volume expansion with albumine (1g/kg of body weight per day, max of 100g/day)
- Absence of shock
- No current or recent treatment with nephrotic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria (> 500 mg/day), microhematuria (> 50 RBC/high power field) and/or abnormal renal ultrasonography

Evaluation of renal function

- Serum creatinine measurements should be used to evaluate renal function until more reliable methods of measuring become generally available

- GFR derived equations should be used cautiously since they tend to overestimate GFR
- Classify AKI according to RIFLE criteria
- Acute on CKD
  - ↑ Scr ≥ 0.3 mg/dL inless than 48h ***or***
  - ↑ Scr ≥ 50% from baseline ***or***
  - Baseline GFR < 60 ml/min (MDRD) for > 3 months

Management

Treat the underlying etiology with

- Liver transplantation
- Combined liver-kidney transplantation

3 years survival 60%

<u>Hemodynamic monitoring for fluid management</u>

- Prevent relative renal hypoperfusion
- Maintain an effective circulating volume
- Renal perfusion pressure

<u>HRS type 1</u> – allow survival to transplantation

- **evaluation after 4 days**
  - no options in nonresponders (no decrease Scr < 1.5 mg/dL)
- Albumine
  - 1g/kg for 2 days (max 100mg/day)
  - 20-40g/day + vasoconstrictor
- Vasoconstrictor
  - CI
- Ischemic heart disease

- Peripheral vascular disease
- Cerebrovascular disease

Treatment

Drug	Dose	Goal	Duration
Terlipressin	0.5-2.0 mg IV every 4-6 h with stepwise dose increment every few days up to 12 mg/day	Scr decrease to < 1.5 mg/dL in two measurements	Min 3-5 d Max 14 d
Vasopressin	0.01-0.8 U/min	MAP ↑ 10 mmHg from baseline **or** MAP > 70 mmHg	
Noradrenaline	0.5-3 mg/h	MAP ↑ 10 mmHg	
Midodrine+ **Octreotide**	7.5-12.5 mg PO TID 100-200 µg sc TID **or** Bolus 25 µg + 25 µg/h	MAP ↑ 15 mmHg	outpatient

Table 13

- TIPS (Transjugular Intrahepatic Portosystemic Shunt)
  - CI
    - Severe liver failure
      - » Bilirubin > 5 mg/dL
      - » INR > 2
      - » Child-Pugh score > 11
      - » EP
    - Severe cardiopulmonary disease

HRS type 2

- Vasoconstrictor
  - Midodrine + octreotide
- TIPS – refractary ascites which require large-volume paracentesis

RRT for transplant candidates

Artificial liver support for research protocols.

SBP prevention

- Albumin (1.5 g/kg IV at infection diagnosis and 1 g/kg 48 h later) + cefotaxim
- Oral prophylaxy with norfloxacin
- Pentoxifylline 400 mg TID to pts with severe acute alcoholic hepatitis

Hepatopulmonary syndrome (HPS)

Definition: HPS is caractherized by the triad of liver disease, pulmonary gas exchange abnormalities leading to arterial deoxygenation and evidence of intrapulmonary vascular dilatations.

Incidence: 4-47% (different cut-off points for defining arterial hypoxemia)

Clinical features:

- Dyspnea
- Platypnea – dyspnea exacerbated by sitting up and relieved when lying down
- Orthodeoxia – hypoxia worse in the standing position (corrected with supplemental oxygen)
- Spider nevi may well represent a cutaneous marker for intrapulmonary vascular dilatations.

Natural history

- median survival time 10.6 months
- 2.5 years mortality rate 63%
- long time survival worse for baseline $PaO_2 < 50$ mmHg

Diagnosis

- HPS should be diagnosed if patients present liver disease associated with the presence of IPVD and arterial gas exchange abnormalities (PA-a,$O_2 \geq 15$ mmHg or $PaO_2 < 80$ mmHg).

- IPVD

    - contrast echocardiography using intravenous injections of agitated saline or indocyanine green to produced bubbles of at least 15 microns in diameter

    - the bubbles are seen in the left heart after the third heart beat, usually between the third and sixth heart beat

Management

Liver transplantation is the only effective therapy.

TAKE HOME MESSAGES

- The mortality of fulminant liver failure is higher than 50%
- Acute intoxication with acetaminophen and mushrooms are the usual causes of fulminant hepatic failure
- Hepatopulmonary syndrome consists of liver disease, abnormal pulmonary gas exchange, and intrapulmonary vascular dilatation
- Diagnosis of hepatorenal syndrome follows the criteria of the International Ascites Club
- Liver transplantation is the treatment of choice for patients with hepatorenal syndrome
- Type 1 hepatorenal syndrome is reversible after treatment with intravenous albumin and vasoconstrictors

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WATER AND ELECTROLYTE DISTURBANCES

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TOTAL BODY WATER

Total body water represents about 60% of body weight for men and 50% for women. In a 70-kg man, total body water is about 600 mL/kg (42L).

Total body water can be divided into two basic components:

- Intracellular
- extracellular

Extracellular compartment

It is divided into plasma and interstitial fluid. The extracellular compartment represents 40% of total body water.

Intracellular compartment

It is defined as all the body water within cells. It represents about 60% of total body water.

The transcellular compartment

The fluid in this compartment is a part of the extracellular fluid volume. It may vary from 1L to as much as 10L, with larger volumes occurring in disease states (bowel obstruction)

Body fluid compartments		**Water content**	***Table11***
	age	M (%)	F (%)
Plasma volume	10-15	60	57
Blood volume	15-40	60	50
Interstitial volume	40-60	55	47
Extracellular	>60	50	45
Intracellular	350		
Total body fluid	600		

Table 14

TONICITY

Water is regulated by arginine vasopressin (AVP or ADH) and is influenced by water intake and output. AVP is produced in the supraoptic and paraventricular hypothalamic nuclei and stored in the posterior pituitary.

Antidiuretic hormone (ADH) secretion is tightly regulated by

- changes in serum osmolality (as little as 1%-2%) that are detected by osmoreceptors in the anterior hypothalamus
- changes in mean arterial pressure and/or blood volume detected by baroreceptors in the aortic arch and carotid bodies.

ADH controls the water permeability of the kidney by directing the insertion of aquaporin-2 channels on the luminal surfaces of the distal tubules and collecting duct.

ADH induces an increase in AQP-2 channels and acts to stimulate free water reabsorption and antidiuresis.

Osmolality is a measure of the number of osmoles per Kg water and osmolarity is a measure of the number of osmoles per L water. The osmolality of the extracellular compartment is due to sodium. The osmolality of the body fluids is 290-295 mosm/kg.

Calculated osmolality=2x[Na]+[Glucose]/18+[BUN]/2.8

Osmolal gap=calculated osmolality-determined osmolality (normal values <10 mosm/L). Substances that increase the osmolar gap are ethanol**,** ethylene glycol, methanol, acetone, and propylene glycol**.**

HYPONATREMIA

Hyponatremia is defined as a serum sodium concentration less than 135 mmol/L.

The presence of hyponatremia indicates an excess in body water relative to body sodium content.

Clinical Presentation

Symptoms attributable to hyponatremia reflect neurological dysfunction induced by cerebral edema.

A reduction in serum sodium creates an osmotic gradient that favors water movement into the brain. This increase in brain intracellular volume contributes to

cerebral edema and raised intracranial pressure and leads to the appearance of neurological manifestations.

Mild hyponatremia (serum Na^+ 130-135 mmol/L) can often be asymptomatic. Nonspecific symptoms, such as fatigue, malaise, nausea and unsteadiness, may occur with a serum sodium value in the range of 125 to 130 mmol/L. Rapid declines to a serum sodium value less than 115 to 120 mmol/L can provoke headache, restlessness, lethargy, and obtundation that may progress to seizures, coma, brainstem herniation, respiratory arrest, and death.

Hyponatremia can broadly be classified based on serum osmolality into hypo-osmolar, iso-osmolar, and hyper-osmolar.

Causes of Hyponatremia	
Hyponatremia associated with elevated arginine vasopressin	Hypovolemia Congestive heart failure Cirrhosis Diuretic therapy Syndrome of inappropriate antidiuretic hormone secretion Adrenal insufficiency Hypothyroidism Pregnancy
Hyponatremia in which AVP may be appropriately suppressed	Advanced renal failure Primary polydipsia (associated with psychiatric illness or use of ecstasy) Malnutrition Beer-drinker's potomania

Hyponatremia with normal or elevated plasma osmolality	Hyperglycemia Mannitol Maltose (intravenous immune globulin) pseudohyponatremia due to hyperlipidemia or hyperproteinemia Transurethral prostate resection Hysterectomy

Table 15

Hypo-osmolar hyponatremia

Hypo-osmolar hyponatremia is most commonly encountered in critically ill patients, can generally be classified, according to an assessment of ECV, as hypovolemic, isovolemic, or hypervolemic.

The simultaneous loss of solute and water from the extracellular space results in a reduced ECV and triggers the nonosmotic release of ADH in an attempt to restore vascular volume.

Subsequent intake of hypotonic fluids or free water by ingestion or infusion leads to hyponatremia.

Cerebral salt-wasting syndrome is a disorder of the hypothalamic-renal axis characterized by natriuresis and volume depletion followed by ADH-induced water retention. The resulting hyponatremia is caracterized by an inappropriately high urine osmolality, a high urine sodium.

Isovolemic hypo-osmolar hyponatremia

Causes of isovolemic hypo-osmolar hyponatremia:

- SIADH
- adrenal insufficiency
- pregnancy

SIADH is characterized by an inappropriate or persistent release of ADH that results in a decreased capacity for free water excretion.

This syndrome is the most common cause of acquired hyponatremia in hospitalized patients.

The major criteria for the diagnosis of SIADH are:

- serum hypo-osmolality (<275 mOsm/kg)
- urine osmolality greater than 100 mOsm/kg.

In addition, patients are euvolemic, have normal acid-base and potassium balances, and have urine sodium concentrations higher than 40 mmol/L.

SIADH can be broadly categorized into

- disorders of the central nervous system
- pulmonary disorders
- disorders associated with medications or tumors

Adrenal insufficiency generally leads to hyponatremia because of an increased release of ADH and diminished water excretion.

Cortisol deficiency may contribute to reductions in cardiac output and blood pressure, thus stimulating a nonosmotic release of ADH.

During pregnancy, increased serum levels of human chorionic gonadotropin released from the placenta are associated with a downward-reset osmostat (≥5 mmol/L), leading to mild asymptomatic hyponatremia.

Hypervolemic hypo-osmolar hyponatremia

Several conditions can predispose to hypo-osmolar hyponatremia in the context of an excess of total body water and sodium:

- congestive heart failure
- cirrhosis
- chronic kidney disease

Congestive heart failure is associated with extracellular fluid overload, but the reductions in cardiac output (and blood pressure) cause a relative reduction in ECV. These hemodynamic changes activate carotid baroreceptors that stimulate the nonosmotic release of ADH. Additionally, the impaired cardiac output leads to reduced renal perfusion, which in turn activates the renin-angiotensin-aldosterone and sympathetic nervous systems.

Cirrhosis is characterized by significant splanchnic and systemic vasodilatation. This leads to relative reductions in ECV, nonosmotic release of ADH, and diminished capacity for free water excretion, leading to serum sodium values less than 125 to 130 mmol/L.

The increase in ADH secretion and, thus, the level of hyponatremia, is often proportional to the underlying progression and severity of cirrhosis.

In advanced chronic kidney disease, the reduction in nephron mass and glomerular filtration are associated with progressive impairments in capacity for maximal urine dilution and free water excretion such that water retention commonly predisposes to hyponatremia.

Hyperosmolar Hyponatremia

The accumulation of osmotically active particles in the plasma induces an osmotic efflux of water from the intracellular space to the extracellular space, resulting in both hyponatremia and hyperosmolality. This condition is encountered in:

- marked hyperglycemia (diabetic ketoacidosis, hyperosmolar nonketotic hyperglycemia)
- mannitol, glycerol,ethanol or sorbitol administration

Hyperosmolar hyponatremia has also been described with the use of intravenous immune globulin suspended in 10% maltose solution.

Iso-Osmolar Hyponatremia

Iso-osmolar hyponatremia can occur with:

- accumulation of isotonic non-sodium-containing fluid in the extracellular space
- elevations in serum proteins and lipids.

HYPERNATREMIA

Hypernatremia is defined as a serum sodium concentration higher than 145 mmol/L.

Large shifts in brain water content can decrease brain volume and predispose to vascular damage and intracerebral and/or subarachnoid hemorrhage, and can lead to irreversible neurological injury.

A late complication after rapid correction of hyponatremia is osmotic myelinolysis.

Initial symptoms may nonspecific and include lethargy, muscle weakness, and nausea, hyperreflexia, seizures, and coma.

Diabetes Insipidus

Central diabetes insipidus refers to polyuria and a urine concentration defect as a consequence of a deficiency of ADH secretion from the hypothalamic-pituitary axis.

The etiology includes:

- injury to the hypothalamus after pituitary surgery
- traumatic brain injury
- aneurysmal subarachnoid hemorrhage
- brain death
- autoimmune disease

Nephrogenic diabetes includes

- polyuria
- a defect in urine concentration due to renal resistance to the antidiuretic effects of ADH

Osmotic diuresis is caused by:

- an excess of urinary solute, nonreabsorbable, which induces polyuria and hypotonic fluid loss. Osmotic diuresis can result from hyperglycemia (diabetic ketoacidosis), use of mannitol, increased serum urea, or administration of other hypertonic medication.

Acute and severe hypernatremia can be induced by administration of hypertonic sodium-containing solutions or by a massive ingestion of salt.

In critically ill patients, the administration of sodium bicarbonate metabolic acidosis, tricyclic antidepressant overdose, and rhabdomyolysis, can potentially lead to hypervolemic hypernatremia. Similarly, hypernatremia can occur with use of hypertonic saline for intracranial hypertension in traumatic brain injury.

Disorders of Potassium Balance

Potassium is the most abundant cation in the intracellular fluid and has several important functions cell's physiology.

More than 98% of body potassium is intracellular (≈3000 mEq), whereas less than 2% is contained in the extracellular fluid (≈60 mEq).

The intracellular potassium concentration is approximately 140 to 150 mmol/L, whereas the normal serum potassium concentration is 3.5-4.5 mmol/L. In order to maintain an intracellular concentration of 140 mmol/L and an extracellular

concentration of 4 mmol/L, the Na^+, K^+-ATPase pumps sodium out of the cells and potassium into the cells. The entry of potassium in the cell is an active transport via the Na^+, K^+-ATPase, whereas exit from the cell occurs by passive diffusion.

Stimulants of the activity of Na^+, K^+-ATPase:

- Insulin
- Aldosterone
- Catecholamines
- alkalosis

Stimulation of b_2-adrenergic receptors by epinephrine and other b_2 agonists enhances the Na^+, K^+-ATPase pump.

Insulin promotes potassium uptake by muscle and liver cells, this effect being independent of the hypoglycemic activity of insulin.

Aldosterone is essential for potassium excretion by the kidney. Mineralocorticoid stimulation can enhance cellular uptake of potassium and increase potassium secretion in the colon.

In metabolic acidosis, potassium shifts from the intracellular compartment to the extracellular compartment as the hydrogen ion enters the cells to be buffered.

In metabolic alkalosis, the process is reversed. Respiratory acidosis and alkalosis have little impact on potassium distribution.

HYPOKALEMIA

Hypokalemia is defined as a serum concentration below 3.5 mmol/L.

The three different mechanisms that may be responsible for the development of hypokalemia are:

- reduction in potassium intake
- increase in renal or digestive losses
- redistribution of potassium from the extracellular to the intracellular compartment

The Na^+,K^+-ATPase pump maintains potassium distribution. An increase in the activity of the pump can cause transient hypokalemia without a decrease in total body potassium. In diabetic ketoacidosis and a nonketoacidosis hyperosmolar state, plasma potassium concentration rapidly falls after the administration of insulin.

Since β_2-adrenergic receptor stimulation increases Na^+, K^+-ATPase pump activity, stressful situations, such as coronary ischemia, alcohol withdrawal, and acute illness, associated with an increase in endogenous catecholamines may induce a drop in serum potassium level.

During alkalosis, there is an efflux of hydrogen ion out of the cell to buffer the extracellular pH. As hydrogen leaves a cell, potassium moves into the cell to maintain its electroneutrality.

In diarrhea, the potassium concentration in stool decreases as water content increases, but the enlarged volume explains the ensuing hypokalemia.

Hypokalemia during vomiting or tube drainage is subsequent to increased renal losses.

Clinical Manifestations

- Muscular weakness,
- general malaise,
- restless leg syndrome, cramps, and myalgias

HYPERKALEMIA

Hyperkalemia is defined as a serum concentration more than 5.5 mmol/L.

Hyperkalemia may result from the following mechanisms:

- increased potassium intake
- reduction in renal excretion of potassium
- redistribution of potassium from the intracellular to the extracellular compartment

Increased potassium intake is normally not a cause of hyperkalemia unless it is an acute phenomenon or the patient has impaired renal excretion (renal failure).

In metabolic acidosis, excess hydrogen ion buffering in the cell and potassium efflux into the extracellular fluid to maintain electroneutrality induce an increase in extracellular potassium concentration.

Metabolic acidosis causes a greater shift of potassium than respiratory acidosis.

Insulin promotes potassium uptake by the cell, insulin deficiency and insulin antagonists (such as somatostatin and diazoxide) promote hyperkalemia.

Hyperosmolality induced by hyperglycemia, mannitol, or hypernatremia may also cause hyperkalemia; the osmotic force drives a water movement out of the cell, and some potassium is carried along with water by solvent drag.

Direct cell destruction, as in tumor lysis syndrome, hematoma reabsorption, hemolysis, rhabdomyolysis, burns, or crush syndrome, result in the release of potassium.

Chronic hyperkalemia is due to a defect in potassium secretion at the distal nephron. All conditions inducing hypoaldosteronism can cause hyperkalemia.

Unfractionated heparin and low-molecular-weight heparins may induce a reversible reduction in the number of adrenal angiotensin II receptors in the zona glomerulosa and cause an increase in potassium levels.

Potassium-sparing diuretics are frequently associated with the development of hyperkalemia. Spironolactone and eplerenone decrease aldosterone binding to its receptor.

Hyperkalemia shortens the refractory period (and hence speeds the repolarization) and induces a reduction in conduction velocity. The former is the first abnormality to appear and can be seen with a serum potassium level of 5.5 to 6.0 mmol/L.

Electrocardiographic changes include

- increased T wave amplitude with ST segment shortening
- P wave flattening
- QRS complex widening

Treatment

1. Glucose-Insulin

Insulin enhances the entry of extracellular potassium into the cells by increasing the activity of the Na^+,K^+-ATPase pump. Generally 10 to 20 units of fast-acting insulin are given intravenously with 50 to 100 g of glucose.

2. β_2 Agonists

β_2-Adrenergic receptor agonists decrease serum potassium concentrations by inducing a transcellular shift. Intravenous, subcutaneous, nebulized, or inhaled forms are effective.

3. Sodium Bicarbonate

Sodium bicarbonate promotes potassium shift into cells.

Hypernatremia, sodium retention, carbon dioxide retention, and hypocalcemia are adverse effects associated with administration of excessive sodium bicarbonate.

4. Digestive Elimination

Potassium excretion from the gastrointestinal tract can be forced by digestive elimination. Their effect usually occurs after a few hours (>2 hrs). Sodium polystyrene sulfonate can be given orally (20-30 g with sorbitol) or by enema (50-100 g diluted in 200 mL of water).

5. Renal Elimination

Restoring diuresis is helpful for potassium elimination and the use of diuretics of the loop of Henle enhance renal potassium excretion

6. Extracorporeal Elimination

When all the above interventions fail, continuous renal replacement therapies can be employed.

CALCIUM

Calcium is essential for normal cellular functions and for extracellular processes. Extracellular calcium ion concentration is kept within a relatively narrow range (total calcium, 8.4-10.4 mg/dL or 2.1-2.6 mmol/L; ionized calcium, 1.1-1.3 mmol/L). Extracellular calcium levels are controlled by the combined activity of parathyroid and C thyroid cells, bone cells, and renal tubules. Intracellular calcium concentration is about 10,000 times lower than the extracellular calcium concentration and even more tightly controlled.

HYPOCALCEMIA

Hypocalcemia is defined by total calcium lower than 7-7.5 mg/dL and i-Ca lower than 0.7-0.9 mmol/L.

Hypocalcemia has been more commonly found in patients affected by sepsis, pancreatitis, severe burns, and major trauma.

Clinical manifestations	
Neuromuscular symptoms	Muscle weakness
	Myalgia
	Paresthesia
	Cramps
	Tetany
	Dysphagia
	Laryngospasm
	Bronchospasm
	Biliary colics
	Intestinal colics
	Focal and general seizures
	Papilledema
Behavioral symptoms	Anxiety
	Irritability
	Psychosis
	Dementia
	Confusion
Cardiovascular symptoms	Impaired myocardial contractility
	Bradycardia
	Hypotension
	Ventricular dysrhythmias
	Prolongation of QT interval and ST segment on electrocardiography

Table 16

HYPERCALCEMIA

Hypercalcemia can be defined as total corrected serum calcium level from more than 2.6 to 3.0 mmol/L (10.5 to 12 mg/dL), and severe hypercalcemia as serum calcium greater than 3.0 mmol/L (>12 mg/dL).

When i-Ca is taken into account, hypercalcemia can be defined as i-Ca level higher than 1.33 mmol/L. Hypercalcemia occurs when calcium influx into blood from bone and/or the intestine exceeds the efflux to bone, intestine, and/or kidney.

The most common causes of increased calcium levels are

- malignancies
- acute endocrine disturbances
- prolonged immobilization

Any type of tumor can produce hypercalcemia, although breast and lung carcinoma and multiple myeloma are the most common causes. Neoplastic diseases can induce hypercalcemia through either direct bone destruction or secretion of calcemic factors by malignant cells.

Hyperthyroidism secondary to subacute thyroiditis can occasionally cause hypercalcemia in critically ill patients. The increased calcium levels are due to osteoclast stimulation by thyroid hormones.

Another endocrine disease that can cause hypercalcemia in critically ill patients is acute Addison's disease. Hypercalcemia in this disorder is due to a combination of increased calcium release from bone and reduced calcium removal by the kidney.

Symptoms of hypercalcemia correlate with the value and the rapidity in the rise of calcium; mild hypercalcemia is generally asymptomatic. Severe hypercalcemia is associated with neurological, cardiac, gastrointestinal, and renal symptoms.

Symptoms	
Neurological symptoms	Depression
	Mental confusion
	Psychosis
	Weakness
	Drowsiness
	Lethargy to coma
Cardiac symptoms	Prolonged PR interval
	Shortened QT interval
	Bradycardia or atrioventricular block
	Increased sensitivity to digitalis
	Severe arrhythmias through cardiac arrest
Gastrointestinal symptoms	Anorexia
	Nausea
	Vomiting
	Constipation
	Peptic ulcer disease
	Acute pancreatitis
Renal symptoms	Marked polyuria
	Dehydration
	Nephrolithiasis
	Nephrocalcinosis

Table 17

DISORDERS OF MAGNESIUM BALANCE

Magnesium (Mg^{++}) is the second most abundant intracellular cation and the fourth most prevalent cation in the body.

Magnesium is a cofactor in a wide spectrum of enzymatic reactions required for DNA and RNA synthesis and nucleic acid polymerization. Various phosphokinases and phosphatases involved in energy metabolism also need magnesium.

Magnesium is essential for the activation of adenosine triphosphatases (ATPases) involved in maintaining adequate intracellular electrolyte content and in many other ATPases distributed in all cell compartments.

The generation of cyclic adenosine monophosphate (cAMP), the intracellular second messenger, comes from the conversion of Mg^{++}-ATP in the presence of adenylate cyclase.

Mg^{++} competes with calcium (Ca^{++}) for membrane-binding sites and affects Ca^{++} binding with and release from the sarcoplasmic reticulum. Magnesium is a physiological antagonist of calcium, acting as a calcium channel blocker and a modulator of calcium channel activity.

Hypomagnesemia

A serum total magnesium concentration less than 0.75 mmol/L is usually considered abnormal.

Central neuronal excitability and neuromuscular transmission are increased in situations of magnesium depletion. Clinical manifestations include tremor, myoclonic jerks, seizures, Chvostek's and Trousseau's signs, spontaneous carpopedal spasm, ataxia, nystagmus, and dysphagia.

In severe hypomagnesemia, PR and QT intervals are prolonged, predisposing to ventricular arrhythmias, tachycardia, and abnormal T wave.

Causes of Magnesium Deficiency	
Gastrointestinal	Diarrhea Malabsorption syndromes Prolonged nasogastric suction Inadequate intake Malnutrition Refeeding syndrome Intestinal and biliary fistulas
Renal	Osmotic diuresis Diuretic (loop or thiazides) Volume expansion Hypercalcemia and hypercalciuria Post-transplantation Polyuric phase (after acute tubular necrosis or obstruction) Drugs (cyclosporine, amphotericin B, cisplatin, foscarnet, pentamidine, aminoglycosides) Hypophosphatemia
Redistribution	Acute pancreatitis Hungry bone disease Correction of chronic systemic acidosis Severe burns Massive blood transfusion

Table 18

Treatment

In the patient with seizures or cardiac arrhythmias, 8 to 12 mmol of magnesium should be rapidly given in 5 to 10 minutes, followed by a perfusion over several hours. Because renal magnesium reabsorption is slow and inversely proportional to

serum magnesium concentration, rapid magnesium infusion will result in excretion of up to 50% of the dose given.

Hypermagnesemia

Hypermagnesemia corresponds to a serum concentration in excess of 0.95 mmol/L .

Hypermagnesemia is one of the metabolic complications of tumor lysis syndrome, massive tissue damage from seizure, and ischemia.

Symptoms of hypermagnesemia are uncommon when serum magnesium levels are less than 2 mmol/L. The first symptoms to appear are nausea, vomiting, and flushing with reduced tendon reflexes. Neurological manifestations include flaccid paralysis, lethargy, coma, and respiratory depression.

Cardiovascular effects of hypermagnesemia occur with serum magnesium concentrations above 2 to 2.5 mmol/L. Calcium antagonist properties of magnesium induce bradycardia and hypotension. Prolongation of PR interval, QRS complex, and QT interval may be seen at higher concentrations, between 2.5 and 5 mmol/L.

Treatment

Discontinuation of magnesium intake (supplementation, medication, parenteral nutrition) is the first step in management of hypermagnesemia. In patients with normal kidney function, discontinuing magnesium intake allows hypermagnesemia to correct itself; in patients with renal failure or with severe symptomatic hypermagnesemia, renal replacement therapy may be necessary. Hemodialysis is preferable to hemofiltration because the decline in magnesium serum concentration occurs faster with the former. When severe symptoms are present, calcium may be given as a magnesium antagonist to reverse cardiac arrhythmias, hypotension, and respiratory depression. The usual dose is 50 to 100 mg elemental calcium over 5 to 10 minutes.

TAKE HOME MESSAGES

- Electrolyte disturbances are very common in the intensive care department
- Rapid correction of hypo/hypernatremia can lead to significant neurologic complications (pontine demyelization, cerebral edema, subdural hemorrhage)
- Hyperkalemia can lead to cardiac arrest specially with a fast rise in serum potassium
- When medical management of hyperkalemia fails, renal replacement therapy should be started
- Hypokalemia can be very resistant to potassium supplementation

- Potassium should be administered through a central vein at a rate of no more than 20-30 mEq per hour
- Calcium chloride contains more calcium then calcium gluconate
- Calcium salts should be administered slowly

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ACID-BASE DISORDERS

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ACID–BASE HOMEOSTASIS

Acid–base homeostasis is the part of human homeostasis concerning the proper balance between acids and bases. Maintenance of stable pH in body fluids is necessary for normal enzyme activity, ion distribution and protein structure.

An acid is a proton or hydrogen ion (H+) donor, and a base is a proton or hydrogen ion acceptor. A large number of potential hydrogen ions exist in the body, most of which are buffered and therefore not in free form.

Ph is the negative logarithm of the hydrogen ion concentration (H+). A complete definition requires that the logarithm is defined as being to the base ten and the concentration be measured as activity in moles per liter.

Ph= - Log (Base 10) of [H+] in Mol/L

Any changes in pH are inversely related in changes in H+, a decrease in pH is associated with an increase in H+ (in acidity).

Normally, blood pH is maintained at 7.35-7.45. This corresponds to a hydrogen ion (H+) concentration of 35-45 nmol/l.. Range of [H+] compatible with life is about 20 to 160 nmol/L (pH 6.8 to 7.7).

- Plasma contains ~ 40 nmol H+/l (pH 7.4)
- Intracellular fluid contains ~ 100 nmolH+/l (pH 7.0)

Intracellular pH changes with extracellular pH.

H+ is constantly being added to the body because of metabolic activities (very little is in food). The major source is carbonic acid ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$). Other sources are inorganic acids (sulfuric acid and phosphoric acid) produced as by-products of protein metabolism. Also, intermediary metabolism results in the production of organic acids such as fatty acids and lactic acid.

The pH of the body is controlled by three systems:

- Buffers in tissues and blood, which minimise the increase in H+ concentration.
- The respiratory center which regulates the removal of volatile CO_2 as a gas in the expired air from the plasma and therefore also regulates bicarbonate (HCO_3)

from the body fluids via the pulmonary circulation. This response occurs in minutes. The lungs excrete about 15-20 000 mmol H+ per day.

- The kidneys which can excrete either acid or alkaline urine, thereby adjusting the pH of the blood. This response takes place over hours or even days, but represent a more powerful regulatory system. The kidneys excrete appoximately 60-80mmol.

BUFFERING AGENTS

A buffering agent is a solution of a weak acid and a base used to maintain the acidity (pH) of a solution near a chosen value after the addition of another acid or base. Acids in aqueous solution provide hydronium (H3O+) ions, while alkalis provide hydroxide (OH-) ions. The pH of the solution is a measure of the relative concentrations of these ions. A solution containing a buffering agent can, up to a point, absorb the additional hydronium or hydroxide ions that are introduced when an acid or base is added without any alteration to the H3O+/OH- ratio, and thus no change in pH.

The buffer system can be activated within seconds and thus is considered the first line of defense against changes in pH.

The Major Body Buffer Systems

Site	Buffer System
Interstitial fluid	Bicarbonate, Phosphate, Protein
Blood	Bicarbonate, Haemoglobin, Plasma protein, Phosphate
Intracelular fluid	Proteins, Phosphates
Urine	Phosphate, Ammonia
Bone	Ca carbonate

Table 19

The buffering systems of the organism are extracellular and intracellular. The ratio between extracellular and intarcellular buffers is 1:1.

- The most important extracellular buffers include: bicarbonate and carbonic acide
- Proteins and phosphate act as intracellular buffers

The Bicarbonate Buffer System

The major buffer system in the ECF is the CO2-bicarbonate buffer system. This is responsible for around 80% of extracellular buffering. It is the most important ECF buffer for metabolic acids but it cannot buffer respiratory acid-base disorders (this buffer system is dependent on a functioning respiratory system to excrete the carbon dioxide).

Bicarbonate ions can absorb H+ ions to form carbonic acid which can be transported to the lungs where the reaction is reversed. The protons are converted to water molecules and CO2 is excreted.

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

Carbonic anhydrase is an enzyme found in erythrocytes and renal tubular epithelial cells which catalyzes the reversible reaction in which carbon dioxide and water combine to form carbonic acid; it is an enzyme with great catalytic efficiency so it can be present in very low concentrations and still be effective.

Volatile acid - referring to carbonic acid or the bicarbonate ion which can be excreted by the lungs into the atmosphere.

Fixed acid - referring to any acid other than carbonic acid or the bicarbonate ion, acids which are found in and contributes to the pH of body fluids and to physiological acid-base balance. These physiological or metabolic acids, usually organic acids, cannot be excreted by the lungs into the atmosphere and are, instead, excreted into the urine (lactate, phosphate, sulphate, acetoacetate and beta-hydroxybutyrate).

The hydrogen ion concentration in extracellular fluid is determinated by the balance between the partial pressure of carbone dioxide (PCO2) and the concentration of bicarbonate (HCO3) in the fluid.

[H+]=24*(PCO2/HCO3)

pH = 6.1 + log [HCO3-]/ 0.03 PCO2

The CO2/HCO3- buffer system is considered very effective because of the vast quantity of bicarbonate in the body and the ability to excrete the CO2 formed via ventilation.

Protein buffer system

Proteins can both give up and take up H+. This is the most important buffering system in the ICF, and is of minor importance in the ECF.

Hemoglobin buffer system

Hemoglobin takes up the H+ generated from CO2 during its transport in the blood.

Phosphate buffer system

This system is important in buffering the urine and the ICF: NaH2PO4 + Na+ Na2HPO4+ H+

Bones

Represents an important site of buffering acid load. An acid load is associated with the uptake of excess H+ ions by bones in exchange for surface Na+ and K+. The dissolution of bone mineral results in the release of buffer compounds, such as NaHCO3, CaHCO3, and CaHPO4.

After the acute changes in buffering pH with chemical acid-base buffering systems, the **lungs** represent the second line of regulation of pH.

Increased pCO2 will lead to a decrease in pH. The lungs ability to release CO2 from the blood allows it to regulate pH, as increased ventilation will vent CO2, increase pH by adjusting the hydrogen ion concentration.

CO2 is constantly formed in the cells as the by-product of metabolic processes. Therefore there is a permanent need to get rid of it. If the metabolic formation of CO2 increases, the pCO2 increases, and the ventilation rate must increase to accommodate this change as an attempt to balance the extracellular fluid.

Thus hyper- and hypoventilation cause alkalosis and acidosis respectively. Similarly, hyper- or hypoventilation may compensate for non-respiratory acidosis or alkalosis respectively, by returning pH towards normal.

The respiratory buffering system is a buffering system with limited gain: It can't completely compensate for changes in pH (only 50-75% compensation), but the relative speed at which it can make significant changes in pH makes it efficient, and helps buffer pH changes until the renal excretion of acids and bases comes into play.

RENAL CONTROL OF ACID-BASE BALANCE

The kidneys control acid-base balance by excreting either an acidic or basic urine.

The kidneys filter large volumes of bicarbonate and the extent to which they are either excreted or reabsorbed determines the removal of “base” from the blood.

The kidneys secrete large amount of H+ into the tubule lumen, thus removing H+ from the blood.

The “gain” of the adjustment of pH by the kidney and the acid base balance it regulates is nearly infinite, which means that while it works relatively slowly, it can COMPLETELY correct for abnormalities in pH. The “metabolic” or renal regulation of the balance of H+ or HCO3- excreted will determine if there is a net loss of H+ or HCO3-, and will determine the pH of the urine. The kidneys regulate extracellular fluid pH by secreting H+, reabsorbing HCO3-, and producing new HCO3-

During alkalosis, excess HCO3- is not bound by H+, and is excreted, effectively increasing H+ in the circulation and reversing the alkalosis.

In acidosis, the kidneys reabsorb all the bicarbonate and produce additional bicarbonate which is all added back to the circulation to reverse the acidosis.

H+ is secreted and HCO3- reabsorbed in all segments of the kidney except for the thin limbs of the loop of Henle. However, HCO3 is not readily permeable through the luminal membrane.

Acidosis and alkalosis

The different types of acid-base disorders can be defined using the normal ranges for pH, pCO2 and HCO3 concentration in extracellular fluid. The normal ranges are:

- pH: 7,35-7,44,
- PCO2: 36-44 mmHg,
- HCO3: 22-26mEq/l

An excess of acid in the blood is called **acidemia** and an excess of base is called **alkalemia**.

The process that causes the imbalance is classified based on the etiology of the disturbance (respiratory or metabolic) and the direction of change in pH (acidosis or alkalosis). There are four basic processes: metabolic acidosis, respiratory acidosis, metabolic alkalosis, and respiratory alkalosis. One or a combination may occur at any

given time. A change in PCO2 or HCO3 must be accompanied by proportional change in the other determinant to keep the ph and PCO2/HCO3 ratio constant.

- pH < 7,35 – acidosis
- pH > 7,44 – alkalosis
- pCO2 > 44mmHg - respiratory acidosis
- pCO2 < 36mmHg - respiratory alkalosis

COMPENSATORY RESPONSES

Acid Base disoders are associated with defense mechanisms referred to as *compensatory responses* that function to reduce the effects of the particular disorder on the pH. **They do not restore the pH back to a normal value**. This can only be done with correction of the underlying cause.

In each of these disorders, compensatory renal or respiratory responses act to minimize the change in H+ concentration by minimizing the alteration in the pCO2 /[HCO3-] ratio. The basis of compensatory responses is to maintain the pCO2/[HCO3-] ratio.

The primary defect (metabolic or respiratory) will go in the same direction as the pH. That is towards an acidosis if the pH is low or towards an alkalosis if the pH is high. The compensatory effect (respiratory or metabolic) will go in the opposite direction. The compensation will tend to bring the pH back towards normal. Therefore, the direction of the compensatory response is always the same as that of the initial change.

For example: if there seems to be a metabolic acidosis and a respiratory alkalosis, the pH tells you which one is primary and which one is compensatory. If the pH is low, the primary defect is metabolic acidosis with respiratory compensation. If the pH is high, the primary defect is respiratory alkalosis with metabolic compensation.

Compensatory response to respiratory disorders is two-fold; a fast response due to cell buffering and a significantly slower response due to renal adaptation. Compensatory response to metabolic disorders involves only an alteration in alveolar ventilation. The period for chronic compensation is hours to days only. Thus, evidence of chronic compensation does not necessarily imply that the patient has a long-standing disorder.

Primary disorder	Primary change	Compensatory change
Respiratory acidosis	PCO2↑	HCO3↑
Respiratory alkalosis	PCO2↓	HCO3↓
Metabolic acidosis	HCO3↓	PCO2↓
Metabolic alkalosis	HCO3↑	PCO2↑

Table 20

Expected compensatory changes resulting from acid base disorders

Abnormality	**Expected range**
Metabolic acidosis (↓ HCO3)	PCO2 ↓ 1.25 mmHg for each mmol/l ↓ in HCO3
Metabolic alkalosis (↑ HCO3)	PCO2 ↑ 0.75 mmHg for each mmol/L ↑ in HCO3 up to max of ~60 mmHg
Acute respiratory acidosis (↑ PaCO2)	HCO3 ↑ ~1 mmol/L for each 10 mmHg ↑ in PaCO2 (up to 30 mmol/l)
Chronic respiratory acidosis (↑ PaCO2)	HCO3 ↑ 4 mmol/L for each 10 mmHg ↑ in PaCO2 (up to 36 mmol/l)
Acute respiratory alkalosis (↓ PaCO2)	HCO3 ↓ 2 mmol/L for each 10 mmHg ↓ in PaCO2 (down to 18 mmol/l)
Chronic respiratory alkalosis (↓ PaCO2)	HCO3 ↓ 4 mmol/L for each 10mmHg ↓ in PaCO2 (down to 18 mmol/l)

Table 21

If there is a mixed acid base disturbance the "compensatory" change may lie outside the range expected as a result of compensation.

ANION GAP

The term anion gap (AG) represents the concentration of all the unmeasured anions in the plasma. The anion gap is defined as the quantity of anions not balanced by cations. Na + Unmeasured cations = Cl^- + $HCO3^-$ + Unmeasured anions

- The major unmeasured cations are calcium, magnesium, gamma globulins and potassium.
- The major unmeasured anions are negatively charged plasma proteins (albumin), sulphate, phosphates, lactate and other organic anions.

The anion gap is estimated by subtracting the sum of Cl- and HCO3- concentrations from the plasma Na concentration.

Anion gap = [Na] – ([Cl-] + [HCO3-])

This is usually equal to 12 ± 4 mEq/L and is usually due to the **negatively charged plasma proteins** as the charges of the other unmeasured cations and anions tend to balance out. A 50% reduction in albumin concentration reduces the anion gap by approximately 6 mmol/L.

The anion gap helps in differentiating between causes of a metabolic acidosis: high anion gap versus normal anion gap metabolic acidosis.

Metabolic acidosis with high anion gap: ketoacidosis, uremia, lactic acidosis, toxins (ethylene glycol, methanol, paraldehyde, salicylate).

Metabolic acidosis with normal anion gap: diarrhea, early renal insuficiency, infusion of isotonic saline, renal tubular acidosis, acetazolamide, leakages between the ureters an gastro intestinal tract.

RESPIRATORY ACIDOSIS

Respiratory acidosis is a clinical disorder characterized by a low arterial pH (< 7.36), an elevation in the pCO2 (hypercapnia) and a compensatory increase in the plasma [HCO3-].

This occurs when there is inadequate ventilation and CO2 production is greater than CO2 elimination. Any increase in PCO2 due to increased CO2 production is rapidly handled by increased alveolar ventilation. Because of the lung's excellent capacity to excrete excess CO2, increases in PCO2 are always due to hypoventilation and never to increased CO2 production. Hypoventilation can occur with any

interference in the respiratory process. Common etiologies are neuromuscular disorders, CNS depression, disorders of the chest wall, chronic obstructive lung disease and acute airway obstruction.

Symptoms are caused by acute respiratory acidosis and not by chronic respiratory acidosis and usually include neurologic abnormalities. Initial symptoms include headache, blurry vision, restlessness, and anxiety, which can progress to tremors, asterixis, delirium, and lerthargy or coma (CO_2 narcosis). Severe hypercapnia increases cerebral blood flow and cerebrospinal fluid pressure. Signs of increased intracranial pressure such as papilledema may be seen.

The key to management of respiratory acidosis is correction of its primary cause. For some patients this will require endotracheal intubation and mechanical ventilation be it noninvasive positive-pressure ventilation.

RESPIRATORY ALKALOSIS

Respiratory alkalosis is an acid base disturbance characterized by elevated arterial pH, hyperventilation resulting in a low pCO_2 and a usually compensatory decrease in plasma HCO_3^- concentration.

This occurs with hyperventilation. The hyperventilation may be in response to hypoxaemia and hypoxic respiratory drive. The lungs are more efficient at eliminating CO_2 than at absorbing O_2 so patients with diseased lungs frequently have hypoxaemia with a normal or low CO_2. An acute reduction in CO_2 release hydrogen ion from the tissue buffers and minimizes the alkalaemia by reducing plasma bicarbonate.

Causes of respiratory alkalosis:

- acute hipoxia- pneumonia, pulmonary oedema
- chronic hypoxia- fibrosis, cyanotic heart disease, hight altitude, anemia
- non hypoxic respiratory centre stimulation - anxiety, fever, sepsis, salicylate intoxication, cerebral disease (tumor, encephalitis), hepatic cirrhosis, pregnancy, excessive mechanical ventilation
- mechanical ventilation with a large minute volume

Clinical manifestations - vary according to duration and severity and depend on the underlying disease process. In acute respiratory alkalosis, acute onset of hypocapnia can cause cerebral vasoconstriction. Therefore, an acute decrease in PCO_2 reduces cerebral blood flow and can cause neurologic symptoms, including dizziness, mental confusion, syncope, seizures, paresthesias, numbness around the mouth.

Treatment is aimed at the condition that causes respiratory alkalosis. Breathing into a paper bag - or using a mask that causes you to re-breathe carbon dioxide -- sometimes helps reduce symptoms.

METABOLIC ACIDOSIS

A primary metabolic acidosis is characterized by low arterial pH (< 7.35), reduced plasma HCO3- concentration, and compensatory alveolar hyperventilation resulting in decreased PCO2.

Multiple etiologies:

- Loss of bicarbonate due to GIT losses or chronic renal disease **(normal anion gap)**
- Addition of inorganic acids such as diabetic ketoacidosis, lactic acidosis associated with tissue hypoxia, salicylate, ethylene glycol and other toxins, decreased acid excretion in renal failure **(increased anion gap)**

Metabolic acidosis with hight anion gap:

- Lactic acidosis - Lactic acid is produced under normal aerobic states in cells of the brain, retina, and erythrocytes. Under normal circumstances, lactate is circulated to the liver, and to a lesser degree to the kidneys, where it is converted into glucose or CO2 and H2O. Lactate accumulation and lactic acidosis result in states of low tissue perfusion such as shock, or in states of mitochondrion dysfunction. There are primarily two types of lactic acidosis:
    - Type A – Due to tissue hypoperfusion and hypoxia: shock, severe hypoxemia, anemia, post convulsion, severe sepsis
    - Type B – Not due to tissue hypoperfusion and hypoxia: drugs and toxins: ethanol, methanol, ethylene glycol, salicylates, metformin, hereditary (glucose-6-phosphate deficiency), pancreatitis, liver diseases, renal failure, malignancies (leukemia, lymphoma)
- Ketoacidosis- is a common form of elevated anion gap metabolic acidosis seen in patients with insulin requiring diabetes mellitus, alcoholics and patients undergoing fasting or starvation and is due to the overproduction of ketone bodies (ketosis) leading to accumulation of ketones in plasma (ketonemia) and urine (ketonuria).
- Uremia
- Intoxication: methanol, ethanol, salicyllates

Metabolic acidosis with normal anion gap: this condition can appear in diarrhea, pancreatic or biliary drainage, urinary diversion, renal tubular acidosis.

Most symptoms are caused by the underlying disease or condition that is causing the metabolic acidosis. Metabolic acidosis itself usually causes rapid breathing. Confusion or lethargy may also occur. Severe metabolic acidosis can lead to shock or death. In some situations, metabolic acidosis can be a mild, chronic (ongoing) condition.

Treatment is aimed at the underlying condition. In certain circumstances, sodium bicarbonate may be given to improve the acidity of the blood.

METABOLIC ALKALOSIS

Primary metabolic alkalosis is characterized by an elevation in the arterial pH, an increase in the plasma HCO3- concentration, and a compensatory hypoventilation, resulting in a rise in the pCO2.

Metabolic alkalosis can be induced by a loss of hydrogen ions, transcellular H+ shift, exogenous alkali administration or by contraction alkalosis. These factors are known as initiator factors because they are said to initiate the alkalosis. Under normal circumstances, alkalosis should never develop because the kidney is excellent at excreting excess bicarbonate. However in conditions where kidney function might be impaired, excretion of bicarbonate may become compromised. Metabolic alkalosis is always associated with an initiating factor and and an impairment in kidney function referred to as the maintenance factor, that is thought to maintain the alkalosis.

The initiating cause in most cases is:

- loss of gastric acid (vomiting, pyloric stenosis),
- diuretic therapy
- mineralocorticoid excess

Another factor that maintains alkalosis is hypokalemia.

To differentiate between these conditions, it is usually helpful to measure the urinary chloride concentration. In causes of metabolic alkalosis associated with a reduction in the extracellular volume, there will be a stimulus for avid Na and Cl reabsorption to replenish extracellular volume. In these setting urinary Cl should be expected to be very low, less than 25 mEq/L. In such a hypovolemic state, the administration of NaCl and water to replenish the extracellular volume should stop the stimulus for aldosterone production and in turn should lead to appropriate excretion of excess HCO3- and improvement of hypokalemia. Thus, leading to

correction of the metabolic alkalosis. Such causes of metabolic alkalosis are said to be **saline responsive.**

In contrast, states of mineralocorticoid excess are associated with an expanded volume and sometimes hypertension. The urinary Cl will be high (> 40 meq/L). In these patients, administration of saline would further expand the extracellular volume and worsen hypertension. It would not correct the alkalosis which is primarily due to hypokalemia. Such causes of metabolic alkalosis are said to be **saline resistant.**

Metabolic alkalosis has a profound effect on the CNS and is frequently associated with metabolic encephalopathy. This is the result of the alkalosis itself and of compensatory hypoventilation that leads to changes in blood flow and oxygenation. Significant cerebral tissue hypoxia is a result of cerebral vasoconstriction and increased hemoglobin affinity for oxygen.

Symptoms include confusion, obtundation, delirium, and coma. The seizure threshold is lowered, and tetany, paresthesias, muscular cramping, and other symptoms reflecting low free calcium levels are observed.

Treatment

Saline - Responsive metabolic alkalosis

- Re-expand volume with Normal Saline
- Treat hypokalemia (alkalosis associated with severe hypokalemia will be resistant to volume resuscitation until K is repleted)
- H+ blockers or proton pump inhibitors if vomiting to prevent further losses in H+ ions
- Discontinue diuretics
- HCl or NH4Cl in emergency. (HCl can cause hemolysis, NH4Cl should not be used in liver disease)
- Hemodialysis in patients with marked renal failure

Saline – Unresponsive metabolic alkalosis (Mineraldocorticoid excess)

- Surgical removal of mineralocorticoid producing tumor
- Aldosterone inhibitor
- ACE inhibitor

- Discontinue steroids
- Potassium repletion (only intervention needed to treat the alkalosis)

MIXED ACID BASE DISORDERS

Mixed acid base disorders occur when there is more than one primary acid base disturbance present simultaneously. They are frequently seen in hospitalized patients, particularly in the critically ill (septic shock, multiple organ dysfunction, cardiac arrest).

Mixed acid base disorders are quite common and can be detected by non parallel change in HCO3 and the anion gap, chloride and pCO2. The pH is normal but there is an abnormal pCO2 and/or bicarbonate. Changes in pCO2 and bicarbonate occur in opposing directions. Change in pH is opposite to that predicted from the pCO2 and HCO3. Compensation exceeds upper or lower limits.

TAKE HOME MESSAGES

- The pH of the body is controlled by three systems: buffers in tissues and blood, the respiratory center which regulates the removal of volatile CO2 as a gas in the expired air and the kidneys which can excrete either acid or alkaline urine.
- The primary defect (metabolic or respiratory) will go in the same direction as the pH, while the compensatory effect (respiratory or metabolic) will go in the opposite direction.
- The anion gap helps in differentiating between causes of a metabolic acidosis

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NUTRITION OF THE CRITICALLY ILL

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MALNUTRITION

Malnutrition is a state in which a deficiency of nutrients such as energy, protein, vitamins and minerals causes measurable adverse effects on body composition, function or clinical outcome. Malnutrition is both a cause and a consequence of ill health and places stressed patients at a greatly increased risk for morbidity and mortality.

Malnutrition has two forms: protein malnutrition (kwashiorkor or hypoalbuminemic malnutrition) and protein-calorie (marasmus or protein-energy) malnutrition.

- Protein malnutrition is a type of malnutrition classically considered to be caused by dietary deficiency (particularly of protein) that develops over several weeks or months. In acute care hospitals in the developed world, a syndrome with important similarities follows the stress response. It can be persistent and severe if feeding is not commenced within 7 to 10 days. Protein malnutrition results in:
    - Marked hypoalbuminemia.
    - Anemia.
    - Edema.
    - Muscle atrophy.
    - Delayed wound healing.
    - Impaired immunocompetence
- Protein-caloric malnutrition is caused by dietary deficiency of protein and calories that develops over months. It is characterized by weight loss, reduced basal metabolism, depletion of subcutaneous fat and tissue turgor, bradycardia, and hypothermia. This type of malnutrition usually results from a mild injury response caused by a chronic disease.

Nutritional assessment is the first step in the treatment of malnutrition. The initial assessment of nutritional status requires a careful history, a physical examination, and laboratory tests.

Evaluation of the patient's overall appearance and thorough physical examination of the skin, eyes, mouth, hair, and nails may provide a clue to the presence of malnutrition.

Weight loss is often the first clue to an underlying cause of malnutrition. Recent unintentional loss of 10% to 20% of the patient's usual weight indicates moderate protein-caloric malnutrition, and loss of more than 20% indicates severe protein-calorie malnutrition. The major variable that limits the usefulness of weight and height as indicators of nutritional assessment is water retention, which can occur in many disease states.

Anthropometric measurements, such as triceps skinfold thickness (TSF) and mid-arm muscle circumference (MAMC), are used to estimate subcutaneous fat and skeletal muscle stores objectively by the means of comparing:

- measured values with standardized controls.
- serial measurements over time in the same patient

Malnutrition may be classified as **mild, moderate, or severe** on the basis of anthropometric measurements: body mass index, arm muscle circumference, and skin fold thickness. Thus patients with a history of unintentional weight loss and Body Mass Index below 18 and 16 with corresponding reduction of mid-arm circumference may be regarded as moderately and severely malnourished respectively. BMI: is derived from the weight (Kg) / height(m)2

Labs

Serum proteins used in conjunction with other assessment parameters to determine the patient's overall nutritional status include:

- Albumin
- Transferrin
- Prealbumin

Albumin is a complex, high-molecular-weight protein produced by the liver. Decreased albumin levels have been shown to correlate with increased morbidity and mortality in hospitalized patients. For this reason it is often used as a prognostic indicator. If exogenous albumin is administered, then the serum albumin level loses its predictive value. In addition, certain states of major albumin loss (severe nephrosis) and impaired synthesis (severe hepatic insufficiency) may limit its usefulness.

Serum transferrin is a beta-globulin that transports iron in the plasma. It has a serum half-life of 7 to 10 days. Serum levels of transferrin are affected by nutritional factors (as are serum levels of albumin during a stress response) and iron metabolism. The shorter half-life of transferrin gives it a theoretical advantage over albumin as a nutritional marker.

Prealbumin functions in thyroxine transport and as a carrier for retinol-binding protein. Its serum half-life is 2 to 3 days. Measurable changes occur in prealbumin levels within 1 week of a change in nutrient intake. Changes occur more rapidly with metabolic stress.

Immune function It is common knowledge that malnutrition leads to a decline in immune function. Total Lymphocyte Count is a clinical measure of immune function.

TLC = [% lymphocytes x WBC] / 100

A TLC less than 900 indicates severe depletion, 900 to 1500 is moderate, and 1500-1800 is mild depletion. TLC is increased with infection and leukemia, and decreased following surgery, and in chronic disease states.

ESTIMATING ENERGY/CALORIC NEEDS

The three organic (carbon-based) fuels used by the human body are carbohydrates, proteins, and lipids. In the process O2 is used and CO2 produced. The energy yield from the combustion of these fuels is measured as heat production in kilocalories (kcal) per gram of substrate: proteins 4,1 kcal/g, glucose 3,7 kcal/g and lipids 9,3 kcal/g. Provision of adequate daily energy requirements by nonprotein calories to spare proteins from being degraded to provide energy is important. No evidence shows one substrate to be better than any other.

Basal Energy Expenditure (BEE) accounts for the largest portion of total daily energy requirements. BEE is determined largely by gender, body size and body composition. The daily energy expenditure of each individual patient can be estimated or measured.

Measurements of energy expenditure are more accurate than predictive equations in patients in the ICU, but the differences are not of great clinical significance.

To best determine the energy expenditure in a critically ill patient, metabolic monitoring systems have been used to calculate caloric requirements by indirect calorimetry. Indirect calorimetry is a technique that provides accurate estimates of energy expenditure from determination of heat production of an oxidation reaction by measuring uptake of oxygen and/or liberation of carbon dioxide and nitrogen excretion and then calculating the amount of heat produced.

The Harris-Benedict equation is a mathematical formula used to calculate BEE, but it frequently overestimates caloric requirements of hospitalized patients.

Adult males: BEE (kcal/day) = 66 + (13.7 x wt in kg) + (5 x ht in cm) - (6.8 x age).

Adult females: BEE (kcal/kcal) = 655 + (9.6 x wt in kg) + (1.7 x ht in cm) - (4.7 x age).

The following simple formula for estimation is acceptable for clinical use in the ICU:

BEE (kcal/day) = 25 x Body weight (kg)

Some adjustments in the BEE can be made to allow for enhanced energy expenditure in hypermetabolic conditions that are commonly found in ICU patients. Total energy expenditure (TEE) (kcal/day) = BEE x stress/activity factor.

- Fever: BEE x 1.1 (for each ºC above the normal body temperature)
- Mild to moderate stress: BEE x 1.2
- Moderate to severe stress: BEE x 1.4

CALORIE SOURCES

Fluid requirements are affected by the patient's functional cardiac, pulmonary, hepatic, and renal status. Fluid requirements increase with fever, diarrhea, hemorrhage, surgical drains, and loss of skin integrity (burns, open wounds), whereas patients with cardiac, pulmonary or renal disease may require less fluid intake. The average adult requires approximately 35-45 ml/kg of water per day.

Carbohydrate: 30 to 70% of the total calories can be supplied as carbohydrate. This is usually given as glucose. Insulin may be required to maintain blood glucose concentration within normal limits, since insulin resistance is often seen as part of the response to stress. Daily intake of carbohydrates is necessary to ensure proper functioning of the central nervous system, which relies heavily on glucose as its principal fuel source.

Fat: 20 to 50% of the total calories is to be given as fat. Critically ill patients often utilize fat better than carbohydrate as an energy source. An ideal diet utilizes lipid to provide approximately 30% of the daily energy needs. The only dietary fatty acid that is considered essential and must be exogenously provided is linoleic acid, a long chain, polyunsaturated fatty acid (PUFA). Deficiency of this leads to cardiac dysfunction, increased susceptibility to infection, scaly dermopathy.

Protein: The protein intake should match the rate of catabolism. The protein requirement during normal metabolism is 0.8 to1.0 g/kg and in Hyper metabolism is 1.2 to 1.6 g/kg. Subsequent protein needs should be detemined by Nitrogen Balance studies.

Nitrogen balance (g)= (Protein intake (g)/6.25)-(urinary urea nitrogen +4).

One gram of urinary urea represents 6.25 g of degraded protein and factor 4 represent nitrogen loss other than urinary nitrogen. Positive nitrogen balance indicates a good progress. The goal is to maintain a positive balance of 4 to 6 grams by providing enough non protein nitrogen.

Vitamins are an essential component of a patient's daily requirement because they are necessary for normal metabolism and cellular function. Vitamin C and Vitamin E are important antioxidants.

Trace elements are metabolic cofactors essential for the proper functioning of several enzyme system. Seven trace elements are considered essential in humans: Chromium, Copper, Iodine, Iron, Manganese, Selenium, Zinc. Trace element deficiency is rare except in burns patients and those receiving prolonged artificial nutrition (>4 weeks).

ARTIFICIAL NUTRITION SUPPORT

Refers to the administration of nutrient solutions by the enteral or intravenous (parenteral) routes. Enteral feeding includes the use of oral supplements and tube feeding. The method of tube feeding may be by:

- Long-term nutrition:
    - Gastrostomy (surgical or percutaneous – PEG, inserted by gastroenterologist)
    - Jejunostomy
- Short-term nutrition:
    - Nasogastric feeding
    - Nasoduodenal feeding
    - Nasojejunal feeding

Parenteral nutrition may be administered by peripheral or central veins.

In many patients, either the enteral route, the parenteral route, or a combination of both routes (combination feeding) should be used to meet nutritional needs. The method of administration must be individualized to each patient's specific needs.

The functioning and capacity of the GI tract, underlying disease states and patient tolerance must be assessed in order to determine the appropriate administration method. The energy requirements are the same for both methods of feeding. Wherever possible the oral or enteral route should be used for reasons of cost and safety. In previously malnourished patients parenteral nutrition may be initiated early within 24 – 48 hours once patient is hemodynamically stable. Otherwise one may wait for up to 7 days before initiating parenteral nutrition. Even a small amount of enteral nutrition will preserve the entero-hepatic circulation and barrier function of the GI tract.

Nutrition support should be considered in:

- People who are malnourished, as defined by any of the following:
  - a body mass index (BMI) of less than 18.5 kg/m2
  - unintentional weight loss greater than 10% within the last 3–6 months
  - a BMI of less than 20 kg/m2 and unintentional weight loss greater than 5% within the last 3–6 months.
- People at risk of malnutrition, defined as those who have:
  - eaten little or nothing for more than 5 days and/or are likely to eat little or nothing for 5 days or longer
  - a poor absorptive capacity and/or high nutrient losses and/or increased nutritional needs from causes such as catabolism

Nutrition support should be cautiously introduced in seriously ill or injured people requiring enteral tube feeding or parenteral nutrition. It should be started at no more than 50% of the estimated target energy and protein needs. It should be built up to meet full needs over the first 24–48 hours according to metabolic and gastrointestinal tolerance. Full requirements of fluid, electrolytes, vitamins and minerals should be provided from the outset of feeding.

While nutrition may not reverse the catabolic response, it enhances protein synthesis and may retard protein catabolism, and therefore may reduce the total burden of body protein loss if introduced early in the management of the acutely ill patient.

METHODS OF PROVIDING NUTRITION

Enteral Nutrition -"*If the gut works, use it*"

Enteral feeding provides physiologic, metabolic, safety, and cost benefits over parenteral nutrition.

Gut integrity is maintained by enteral nutrients through the prevention of bacterial translocation from the gut, sytemic sepsis, and potential increased risk of multiple organ failure. Lack of GI stimulation may promote bacterial translocation from the gut without concurrent enteral nutrition.

Early feeding results in reduced infections, better wound healing and other indicators of better nutrition. Maximum delay should not exceed 5-7 days. If there is evidence of prior malnutrition, parenteral nutrition should be considered after 1-2 days.

Contraindications for tube feeding are circulatory shock, intestinal ischemia and complete bowel obstruction. In cases of diarrhea, enterocutaneous fistula, partial mechanical obstruction and pancreatitis clinical judgment is mandatory to select the route enteral vs parenteral

Enteral tube feedings are administered either on a continuous or intermittent basis. Continuous feedings are used to prevent GI intolerance and minimize risk of aspiration. Intermittent feedings may be used in medically stable patients who have adequate absorptive capacity to tolerate bolus feedings. An enteral infusion device (feeding pump) may enhance the safety and accuracy of enteral feedings.

General principles of feeding formulas.

Number of feeding formulas and commercial preparations are available. These formulas generally meet the nutritional requirements noted above if given in sufficient quantities. Most of the formulas provide 1 to 1.5 kcal/liter of solution. High energy rich formulas up to 2 kcal/liter are also available. Tube feeding is usually infused at a rate of 1.2 – 1.8 ml/kg/hour to provide adequate calories.

The major share of the calories, 65% to 70%, derive from carbohydrates. Osmolality of 1kcal/lit is around 300mOsm/kg and they are close to isotonic body fluids. If calorific density increases to 2kcal/liter, the osmolality increases up to 1000mOsm may lead to diarrhea.

Protein availability is around 35 to 40 grams/liter. Some formulas have small peptides to facilitate easy absorption. Lipids are represented mostly by long chain triglycerides derived from vegetable oils.

COMMON COMPLICATIONS

Tube occlusion is a common problem which can be overcome by flushing the tube with warm water after every feed. If this is ineffective sodium carbonate solution or pancreatic enzymes have to be used to relieve the occlusion.

Aspiration is a major problem. Regurgitation occurs in 80% of the cases. Elevating the head to 30 to 45 degrees can reduce the risk of reflux, therefore aspiration. This is usually the preferred position used to prevent mechanical ventilation associated pneumonia.

Diarrhoea occurs in 30% of the cases who receive enteral nutrition. In most cases, the feeding formula is not responsible for the diarrhea Clostridium difficile enterocolitis is also a possible cause of diarrhea during enteral feeding and must be excluded.

PARENTERAL NUTRITION

When enteral nutrition is not possible or when enteral feeding cannot match the required nutrient, parental nutrition should be started.

Parenteral nutrition is usually administered using a composite, pre-mixed bag, in which all the necessary constituents (proteins in the form of amino acids, carbohydrates in the form of glucose, fat as a lipid emulsion, electrolytes, vitamins and trace minerals) mixed together in one bag under sterile conditions.

Central PN is a hyperosmolar, concentrated formula and must be delivered into a high flow venous system (central line). Peripheral PN has similar nutrient components as central PN but in a lower concentration, so it may be delivered by peripheral vein. Large fluid volumes must be administered to provide comparable nutrients. Peripheral PN is typically used for short periods (up to two weeks) because of limited tolerance.

Complications

- Immediate and delayed complications of central venous catheter placement
- Infection
- Metabolic complications: hyperglycemia, hypoglycemia, electrolytes disturbances, trace element deficiencies (only important for chronic long term > 4 week TPN) hyperlipidemia, vitamin deficiencies.

Frequent monitoring of the blood chemistry will prevent metabolic complications.

Monitoring

Patients who are receiving parenteral feeding need the most intensive monitoring. This will include measurement of weight, temperature and fluid balance, and biochemical monitoring of electrolytes, particularly sodium, potassium, magnesium and phosphate. Blood glucose should be maintained in the range of 6–10 mmol/L (110- 180mg/dl). Beware of rebound hypoglycaemia if PN is stopped abruptly. Venous catheters must be inspected daily with reference to the exit site and veins.

TAKE HOME MESSAGES

- Malnutrition may result in: marked hypoalbuminemia, anemia, edema, muscle atrophy, delayed wound healing, impaired immunocompetence
- Loss of more than 20% of the patient's usual weight indicates severe protein-calorie malnutrition.
- Nutrition may not reverse the catabolic response, BUT it enhances protein synthesis and may retard protein catabolism, and therefore may reduce the total burden of body protein loss.
- "If the gut works, use it"

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SHOCK

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INTRODUCTION. DEFINITION

Shock occurs when an imbalance between oxygen supply and demand results in tissue hypoxia.

Shock can also be defined as an acute physiological injury resulting from inadequate production of ATP.

CLASSIFICATION

Hinshaw and Cox proposed a classification of circulatory shock involving four categories:

- hypovolemic
- cardiogenic
- distributive
- obstructive shock

The first category is hypodynamic shock (low cardiac output state), which includes the hypovolemic, cardiogenic, and obstructive shock.

The second category, hyperdynamic shock (high cardiac output state), includes distributive shock. Endocrine shock was also proposed as a separate category.

The central features of hypodynamic shock are a low cardiac index and a high systemic vascular resistance. Increased oxygen extraction and lactic acidosis usually parallel the decrease in cardiac output. In hyperdynamic shock, the cardiac index is usually high, reflecting decreased systemic vascular resistance. The lactate increasease as a consequence of impared tisuue oxygen utilization.

Shock types

HYPOVOLEMIC SHOCK

The primary feature of hypovolemic shock is loss of circulating volume. Blood loss (hemorrhage) is the most common cause of hypovolemic shock followed closely by loss of asanguineous fluid loss.

Common causes include trauma, gastrointestinal bleeding, bleeding during and after surgery, rupture of aortic aneurysm, peripartum catastrophes, bowel obstruction, diabetic ketoacidosis, major burns, acute pancreatitis.

CARDIOGENIC SHOCK

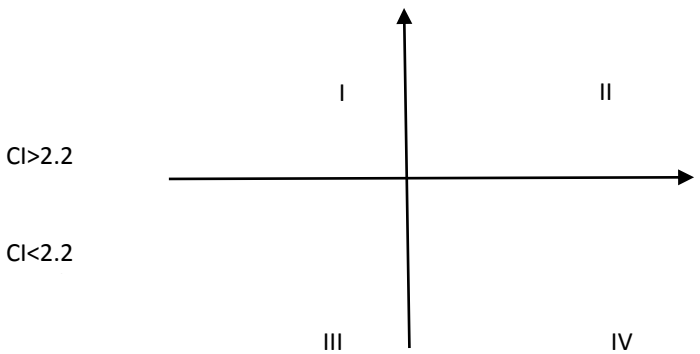
Cardiogenic shock is a hypoperfused state due to acute heart failure, and describes primarily severe myocardial dysfunction.

Diagnostic criteria

- hypotension (systolic blood pressure <90 mmHg or a decrease in mean arterial pressure by more than 30% form baseline)
- hypoperfusion of end organs due to reduced cardiac index (CI<2.2)
- Clinical signs of shock as detailed below

A quick clinical classification of acute cardiac failure was made by Forrester, describing four possible states, based on pulmonary auscultation or measurement of pulmonary capillary wedge pressure("wet", "dry" lungs) and peripheral perfusion ("cold", "hot").

Forrester classification



Picture 6

Forrester Class IV describes cardiogenic shock: increased pulmonary congestion due to high filling pressures and low cardiac index.

Etiology of cardiogenic shock:

- acute myocardial infarction
- valvular heart disease (acute mitral insufficiency due to papillary muscle rupture)
- dysrhythmias
- myocardial contusion
- myocarditis
- endocarditis
- ventricular septal rupture
- acute decompensated chronic heart failure
- decompensation of hypertrophic cariomyopathy

PATHOPHYSIOLOGICAL ASPECTS OF CARDIOGENIC SHOCK

In cardiogenic shock there is loss of contractility of the heart with subsequent fall in stroke volume and cardiac output.

In cardiogenic shock both systolic and diastolic function are failing. Marked reduction in stroke volume causes hypotension and systemic hypoperfusion, compromising the coronary perfusion, causing myocardial ischemia and compensatory vasoconstriction secondary to neuroendocrine activation and fluid retention.

Although the contractility is severely impaired, peripheral systemic vascular resistance in only marginally or moderately elevated, and thus not able to fully compensate the decrease in cardiac output.

This inappropriate vasoconstriction in relation to the severity of myocardial depression, reflects a systemic inflammatory reaction (SIRS) to be present in cardiogenic shock.

SIRS in cardiogenic shock is thought to appear due to reperfusion, with release of vasodilatatory mediators.

The compliance of the left ventricle will be reduced by myocardial ischemia, and subsequently the left ventricular end diastolic pressure will rise putting the patient at risk for developing pulmonary edema.

CLINICAL FEATURES

The crucial aspect in the diagnosis of cardiogenic shock is the identification of hypoperfusion in the setting of myocardial dysfunction.

The following signs are suggestive of hypoperfusion:

- Pallor or cyanotic skin
- Cold peripheries (forearms and/or lower legs), cold skin, moist and clammy
- Altered mental status
- Oliguria (<0.5ml/kg/hour)
- Threaded pulse
- Arterial hypotension
- Pulmonary congestion: rales on auscultation

DIFFERENTIAL DIAGNOSIS OF CARDIOGENIC SHOCK

- Hypovolemic shock
- Dissection of the aorta
- Pulmonary embolism
- Neurogenic shock
- Anaphylactic shock
- Takotsubo syndrome

TREATMENT

- Coronary intervention in acute coronary syndromes
- Emergency surgery
- Fluid administration: in life threatening situations with severe hypotension and tissue hypoperfusion, a fluid challenge is attempted. Fluid administration is not considered to be beneficial in patients with cardiogenic shock due to high filling pressures. Too much fluid will cause more harm by further increasing end diastolic pressure and oxygen consumption, aggravating myocardial ischemia.
- Vasopressor administration: in critical hypotension, noradrenaline is the preferred drug associated with dobutamine and/or levosimendan.
- Intraaortic balloon counter pulsation provides effective haemodynamic support as it increases coronary blood flow. Main IABP effects include reduced afterload,

a rise in diastolic pressure, increase in cardiac output and increased coronary blood flow. The recommendations for intraaortic balloon placement are: medically refractory cardiogenic shock, post cardiac surgery, refractory angina. Absolute contraindications: aortic regurgitation.

- Anticoagulation

- Compensation of acidosis is attempted but not always feasible. Administration of sodium bicarbonate may cause an elevation in lactate by shifting the oxyhemoglobin dissociation curve to the left. This leftward shift causes oxygen to be dissociated harder form the hemoglobin molecule and thus aggravating tissue ischemia.

OBSTRUCTIVE SHOCK

Mechanical obstruction of cardiac output can be caused by impaired ventricular filling due to:

- cardiac tamponade
- tension pneumothorax
- pulmonary embolus
- haemothorax

Cardiac tamponade occurs as a complication of acute myocardial infarction with rupture of the free ventricular wall, after cardiac surgery or trauma.

A relatively small but rapidly expanding accumulation of blood within the pericardium (less than 200ml) impairs ventricular filling. A slowly accumulating fluid can also eventually cause a drop in cardiac output, but much higher amounts of pericardial fluid are necessary.

Typical clinical features of tamponade are tachycardia, jugular venous distension, muffled heart sounds and pulsus paradoxus. Hypotension is relatively resistant to fluid administration. The diagnosis is usually made by echocardiography. Pulsus paradoxus appears whne there is a large fall in systolic pressure during inspiration. The normal fall in systolic pressure should not exceed 5-10 mmHg. Usually the clinician hears the heart sounds but no peripheral pulse during inspiration.

Drainage of accumulated fluid is the definitive treatment.

Tension pneumothorax presents with similar clinical picture but with absent breath sounds and hyperresonance at percussion and suggestive chest x-ray if there is time to performe one. It develops when air entering the pleural space cannot escape due to flap-valve mechanism.

Intrapleural accumulation of air leads to a rise in intrathoracic pressure, collapse of the affected lung and mediastinal shift, with reduced cardiac filling and low cardiac output.

Obstruction of the pulmonary artery by pulmonary emboli may cause a clinical picture similar to that described above. Pulmonary emboli lead to a sudden increase in right ventricular afterload and right ventricular failure.

DISTRIBUTIVE SHOCK: SEPTIC SHOCK

DEFINITION

Sepsis is an abnormal response to infection characterized by systemic inflammation and widespread tissue injury.

Clinical diagnosis requires evidence of infection plus at least two signs of systemic inflammatory response syndrome. Severe sepsis is defined as sepsis with new onset of organ failure. Septic shock is defined as severe sepsis with hypotension despite adequate volume resuscitation.

SIRS diagnostic criteria:

- White blood cell count (>12,000/µL or < 4,000/µL or >10% immature band forms)
- Fever of more than 38°C or less than 36°C
- Heart rate above 90 beats/min
- Respiratory rate higher than 20 per minute or arterial carbon dioxide partial pressure lower than 32 mmHg

At least 2 criteria for diagnosis must be met.

CLINICAL FEATURES

Patients with septic shock have an infection and show signs of systemic inflammation, and will be hypotensive with concomitant symptoms and signs of inadequate tissue perfusion despite adequate fluid ressucitation.

Patients may have fever or be hypothermic. Heart rate and respiratory rates are elevated.

The typical picture is one of high cardiac output and reduced systemic vascular resistance (high output failure).

Systolic blood pressure below 90 mmHg or mean arterial pressures below 70 mmHg are commonly seen. Signs of inadequate tissue hypoperfusion, such as hyperlactatemia and decreased capillary refill time or mottled skin are also present.

Mixed or central venous oxygen saturation are often elevated because of reduced peripheral extraction

Other high output shock states

Neurogenic shock results from spinal cord damage at or above the upper thoracic level after trauma.

The central nervous system injury causes autonomic dysfunction.

Disruption of sympathetic innervation leads to vasodilation and bradycardia. It is characterized by severe hypotension, warm skin, and bradycardia. The relative hypovolemia is treated with fluids. Vasopressors are indicated when hypotension persists despite adequate fluid ressucitation.

Anaphylactic shock occurs when a sensitized patient with preexisting IgE antibodies is exposed to an antigen. The binding of antigen to its corresponding IgE antibody on the surface of mast cells cause type I immune response with mast cell degranulation and release of vasoactive substances such as histamine.

The clinical picture reflects the resulting vasodilatation, increased vascular permeability, bronchospasm.

Treatment consists of:

- stopping the antigen exposure,
- adrenaline
- oxygenation, securing the airway
- fluid resuscitation
- corticosteroids and
- antihistamines

PATHOPHYSIOLOGY OF SHOCK

Circulatory shock represents a final common pathway of cardiovascular failure.

Circulatory shock can be defined as a syndrome in which tissue perfusion is reduced such that blood flow is inadequate to meet cellular metabolic requirements. If the cardiac output decreases, and hence oxygen delivery, the oxygen extraction will increase in order to maintain metabolic needs.

After a critical point the oxygen extraction becomes supply limited and oxygen debt occurs. The greater the oxygen debt the greater the mortalilty.

Determinants of oxygen delivery

A common feature of all shock states (except septic shock) is a decrease in oxygen delivery (DO_2) to tissues such that the transport of oxygen into cells is inadequate to meet metabolic demands.

$DO_{2\ index} = CO \times C_aO_2$

$CO = SV \times HR$

C_aO_2 = Hb bound O_2 + dissolved O_2= (1.39 X Hb X Arterial oxygen saturation) + (0.03 X P_aO_2)

Where DO_2=oxygen delivery, CO= cardiac output, SV=stroke volume, HR=heart rate, C_aO_2=arterial oxygen content

Initially tissues compensate for reduced oxygen delivery through increased oxygen extraction, thus maintaining normal levels of oxygen consumption. This mechanism cannot compensate for oxygen delivery reductions below a certain level, beyond witch oxygen consumption becomes supply limited and oxygen debt develops.

Stroke volume is dependent on preload, afterload and contractility.

The term preload is defined as the myocardial stretch at end diastole and correlates with end-diastolic volume, not pressure. Clinicians usually use end diastolic pressure as a surrogate for end diastolic volume, although in recent years bedside techniques for global end-diastolic volume have been implemented using thermodilution technology.

End-diastolic pressure doesn't correlate well with end diastolic volumes especially in the ischemic myocardium where compliance is low. Diastolic compliance decreases in ischemic conditions and myocardial hypertrophy.

As a consequence the CVP and pulmonary capillary wedge pressure do not reflect cardiac preload.

Intrathoracic pressure also influence preload. Increased intrathoracic pressure decreases venous return, decreasing preload. This is the main mechanism for example in patients with shock due to tension pneumothorax.

COMPENSATORY RESPONSES TO SHOCK

Shock can be divided into three distinct stages.

- The first stage has been called early, reversible, compensated shock. This stage is characterized by compensatory responses.
- The second stage of shock is the beginning of microvscular and cellular injury.
- The third stage of shock is irreversible or decompensated shock.

Oxygen debt occurs when oxygen consumption (VO_2) becomes directly dependent on oxygen delivery (DO_2). It is determined by both the magnitude of drop in VO_2 and the length of time VO_2 is bellow baseline.

Autonomic nervous system

The neural compensation of shock implies a series of physiologic responses.

Activation of baroreceptor reflex via stretch receptors located in the carotid sinus, aortic arch, is extremely sensitive to small decreases in arterial blood pressure. Hypovolemia can also activate stretch receptors. Activation of these receptors increases outflow through the sympathetic nervous system. The compensatory responses mediated by the sympathetic system are:

- Redistribution of blood away from skeletal muscle and splahnic viscera
- Augmentation of myocardial contractility and heart rate
- Increased venous return
- Activation of renin-angiotensin system
- Release of adrenocortical hormones

Renin is released by the juxtaglomerular cells in the nephron when there is a drop in flow.

Renin is also released due to sympathetic stimulation. Angiotensin-converting enzyme converts angiotensin 1 to angiotensin 2. The formation of angiotensin 2 occurs in lungs.

In shock, angiotensin 2 stimulates de release of aldosterone form adrenal cortex and promotes renal retention of sodium and water. It also increases vascular tone primarily in the mesenteric bed.

Arginine vasopressin (ADH) is a nonapeptide secreted by the posterior pituitary gland, also known as antidiuretic hormone. The hormone is released in response to hypovolemia or hyperosmolarity.

ADH increases the permeability of renal collecting tubules to water.

As shock states progress for a period of time without appropriate resuscitation, the syndrome eventually becomes refractory to treatment and multiorgan failure ensues (MODS).

TREATMENT OF SHOCK

Resuscitation starts with the ABCDE's of shock. This includes establishing an Airway, providing and controlling the work of breathing, optimizing circulation, assuring adequate oxygen delivery and achieving end-point of resuscitation.

Mechanical ventilation and sedation to decrease the work of breathing and oxygen consumption.

Circulatory or hemodynamic stabilization begins with intravascular access through large bore peripheral venous lines.

Central venous access will aid in assessing volume status (preload) and monitoring central venous oxygen saturation ($ScvO_2$).

Fluid resuscitation begins with isotonic crystalloid. Most patients in shock have either absolute or relative volume deficit, except patients with cardiogenic shock.

Fluid is given rapidly, in set quantities 500ml or 1000 ml with reassessment of the patient after each amount.

Vasopressor agents are used when there has been an inadequate response to volume resuscitation.

Arterial saturation should be maintained to physiological values and hemoglobin above 10 g/dL. If cardiac output can be assessed, it should be increased using volume infusion and inotropic agents until $ScvO_2$ and lactate normalize. Traditional resuscitation end points have included the normalization of blood pressure, heart rate, and urine output.

A goal directed approach at achieving urine output >0.5ml/kg/hour, CVP 8-12 mmHg, MAP 65-90 mmHg, $ScvO_2$ >70% has been shown to decrease mortality.

VASOACTIVE AND INOTROPIC DRUGS

INDICATIONS

- Inotropic therapy is often considered in patients with cardiogenic shock or advanced heart failure
- Inotropic therapy may also be considered in high-risk surgical patients, even in the absence of reduced myocardial contractility, to achieve supranormal levels of oxygen delivery (DO_2) during the perioperative period to prevent tissue hypoxia and organ dysfunction.
- In cases of septic shock, dobutamine is generally considered the inotropic drug of choice when myocardial contractility is severely depressed

DOPAMINE

Dopamine is the precursor of epinephrine and norepinephrine.

At low doses (1 to 3 µg/kg/min), dopamine directly activates dopaminergic receptors in the kidney and splanchnic arteries, causing vasodilation. The resultant increase in renal blood flow leads to increased urine output and sodium excretion.

At moderate doses (3 to 8 µg/kg/min), dopamine is a weak partial agonist at myocardial β_1-receptors and causes the release of norepinephrine from sympathetic nerve terminals in the myocardium and vasculature.

The direct stimulation of myocardial β-adrenergic receptors exerts positive chronotropic and inotropic effects. The increased release of norepinephrine from nerve terminals also contributes to myocardial stimulation, but in addition may exert a vasoconstrictor effect due to stimulation of vascular α-adrenergic receptors.

At high doses of dopamine (10 to 20 µg/kg/min), the effect of peripheral α-adrenergic stimulation predominates, resulting in vasoconstriction in all vascular beds and leading to increases in mean arterial pressure and systemic vascular resistance.

DOBUTAMINE

Dobutamine is a direct-acting synthetic sympathomimetic amine that stimulates β_1-, β_2-, and α-adrenergic receptors.

Clinically, it is available as a racemic mixture in which the (+) enantiomer is both a β_1- and β_2-adrenergic receptor agonist and an α-adrenergic receptor competitive antagonist, and the (–) enantiomer is a potent β_1-adrenergic receptor agonist and an α-adrenergic receptor partial agonist.

Dobutamine causes a relatively selective stimulation of β_1-adrenergic receptors, and accordingly, dobutamine's primary cardiovascular effect is to increase cardiac output by increasing myocardial contractility. This positive inotropic effect is associated with relatively little increase in heart rate. The drug causes modest decreases in left ventricular filling pressure and systemic vascular resistance due to a combination of direct vascular effects and the withdrawal of sympathetic tone (β_2 effect).

NOREPINEPHRINE

The myocardial and peripheral vascular effects of this endogenous catecholamine are similar to those of epinephrine except that norepinephrine causes little stimulation of vascular β_2-adrenergic receptors and therefore causes more intense vasoconstriction.

Norepinephrine may be used to provide temporary circulatory support in the setting of hemodynamically significant hypotension (e.g., following cardiac surgery or with cardiogenic shock complicating acute myocardial infarction or pulmonary embolism). Norepinephrine is titrated to improve blood pressure at doses of 2 to 10 µg/min. As with epinephrine, the use of norepinephrine in the cardiac intensive care unit may be limited by arrhythmias, myocardial ischemia, renal impairment, or tissue necrosis at the site of local infiltration.

EPINEPHRINE

Epinephrine stimulates β_1- and β_2-adrenergic receptors in the myocardium, thereby causing marked positive chronotropic and inotropic responses. It also has potent agonist effects at vascular α-adrenergic receptors causing increased arterial and venous constriction. Because of this latter effect, epinephrine (like high-dose dopamine and norepinephrine) plays little role in the acute management of heart failure, except when complicated by severe hypotension. Epinephrine may be useful for the treatment of low cardiac output, with or without bradycardia, immediately following cardiopulmonary bypass or cardiac transplantation.

MILRINONE

The breakdown of cAMP is mediated by phosphodiesterase (PDE). In myocardium and vascular smooth muscle, the predominant isoform of this enzyme, termed type III, is inhibited by the type-III selective PDE inhibitors milrinone and inamrinone, leading to an increase in intracellular cAMP concentrations.

In the myocardium, intracellular cAMP increases both contractility and the rate of relaxation (positive lusitropic effect).

PDE III inhibitors are also potent vasodilators in the systemic and pulmonary vasculature

In patients with heart failure, milrinone is administered as a 25 to 50 µg/kg intravenous bolus over 10 minutes followed by a constant infusion at 0.25 to 0.75 µg/kg/min. Lower infusion rates without a bolus may be used in patients with low baseline blood pressure.

LEVOSIMENDAN

Positive inotropic agents, such as dobutamine and milrinone, act by increasing myocyte calcium influx, and therefore may be associated with increased arrhythmias. An alternative approach that may avoid such complications is to enhance myocardial response to a given concentration of calcium with a class of agents referred to as “calcium sensitizers”.

Levosimendan, increases myocardial contractility by increasing myofilament sensitivity to calcium. Levosimendan is also a potent vasodilator due to activation of adenosine triphosphate-dependent potassium channels in vascular smooth muscle cells, leading to decreases in both preload and afterload. In patients with severe heart failure, levosimendan increases cardiac output and reduces pulmonary capillary wedge pressure and systemic vascular resistance.

The effects of levosimendan are dose-dependent at infusion rates ranging from 0.05 to 0.6 µg/kg/min, with higher incidence of side effects (headache, nausea, and hypotension) at rates above 0.2 µg/kg/min.

FLUID REPLACEMENT SOLUTIONS

CRYSTALLOIDS

Crystalloids are solutions that contain both water and electrolytes. They are grouped as isotonic, hypertonic, and hypotonic solutions based on tonicity. Crystalloid solutions distribute freely within the intravascular and interstitial compartments.

Approximately one third of intravenously administered crystalloid remains intravascular and two thirds are distributed extravasculary.

Balanced salt solutions have an electrolyte composition similar to that of extracellular fluid (ECF) (e.g., lactated Ringer's solution, Normal saline). With respect to sodium, they are hypotonic. A buffer is included (e.g., lactate in lactated Ringer's), which is metabolized in vivo to generate bicarbonate.

Normal saline

Normal saline (0.9% NaCl) is slightly hypertonic and contains more chloride than ECF. When used in large volumes, mild hyperchloremic (non-anion gap) metabolic acidosis results. Normal saline contains no buffer or other electrolytes besides sodium and chloride. Normal saline is preferred to lactated Ringer's solution (which contains a hypotonic concentration of sodium) when brain injury, hypochloremic metabolic alkalosis, or hyponatremia occurs.

Hypertonic salt solutions

Hypertonic salt solutions are less commonly used, and their sodium concentrations range from 250 to 1200 mEq/L. The greater the sodium concentration, the lower the total volume required for satisfactory resuscitation. This difference reflects the movement due to osmotic forces of water from the intracellular space into the extracellular space. The reduced volume of water injected may reduce edema formation. This effect could be important in patients predisposed to tissue edema (e.g., prolonged bowel surgery, burns, and brain injuries). However, the intravascular half-life of hypertonic solutions is no longer than that for isotonic solutions of an equivalent sodium load

Five percent dextrose

Five percent dextrose functions as free water, because the dextrose is metabolized. It is iso-osmotic and does not cause the hemolysis that would occur if pure water were injected intravenously. It may be used to correct hypernatremia but is most often used in the prevention of hypoglycemia in diabetic patients who have had insulin administered, or in patients receiving high concentrations of dextrose via total parenteral nutrition immediately prior to surgery.

COLLOIDS

Colloid solutions are composed of large-molecular weight substances that remain in the intravascular space longer than crystalloids.

Five percent albumin or plasma protein fractions have a colloid osmotic pressure of 20 mm Hg.

Dextran

The dextran solutions are water-soluble glucose polymers synthesized from sucrose by bacteria. The mean molecular weight of dextran 40 is about 40,000 daltons (40 kDa), and the mean molecular mass of dextran 70 is about 70,000 daltons (70 kDa).

Dextran 40 is used in vascular surgery to prevent thrombosis but is rarely used as a volume expander. Dextran solutions are ultimately degraded enzymatically to glucose.

Side effects:

- anaphylactic or anaphylactoid reactions
- increased bleeding time caused by decreased platelet adhesiveness
- interference with cross-matching of blood

Hydroxyethyl starch

Hydroxyethyl starches (HES) are synthetic colloid solutions of natural polysaccharides. They are characterized by their concentration and average molecular weight.

The average molecular weight can be:

- low (<70 kDa)
- medium (130 to 270 kDa)
- high (>450 kDa)

Two other characteristics of HES are important:

- the molar substitution
- C_2 to C_6 ratio

The molar substitution refers to the number of hydroxyethyl residues per 10 glucose subunits. HES preparations with 5 hydroxyethyl residues per 10 glucose subunits (a ratio of 0.5) are called pentastarches.

Generally, the higher the molecular weight and molar substitution, the more prolonged the volume effect and more side effects.

The C_2 to C_6 ratio describes the pattern of hydroxyethyl substitution on specific carbon atoms of the HES glucose subunits.

HES preparations with higher C_2 to C_6 ratios are more resistant to breakdown by amylase, and have prolonged duration of action.

Side effects:

- coagulation disturbances (interferes with von Willebrand factor, factor VIII, and platelet function)
- renal toxicity

BLOOD COMPONENTS

PACKED RED BLOOD CELLS

Packed red blood cells have a 70-75% hematorcrit in a 250- to 300-mL volume and used for treatment anemia due to surgical blood loss.

The goal is to increase the oxygen delivery of blood. A single unit of packed red blood cells will increase the hemoglobin concentrations about 1 g/dL. Administration of packed red blood cells is facilitated by reconstituting them in crystalloid solutions, such as 50 to 100 mL of saline.

The use of hypotonic glucose solutions may theoretically cause hemolysis, whereas the calcium present in lactated Ringer's solution may cause clotting if mixed with packed red blood cells.

PLATELETS

Administration of platelets allows treatment of thrombocytopenia. Platelets are derived from donors (cytapheresis and plateletpheresis).

Pooled platelet concentrates are derived from whole blood donation. During surgery, platelet transfusions are probably not required unless the platelet count is less than 50,000 cells/mm.

The life span of platelets is approximately 7 days. It is important to remember that aspirin or other antiaggregants can inactivate even transfused platelets.

FRESH FROZEN PLASMA

Fresh frozen plasma (FFP) is obtained from a single unit of whole blood that is frozen within 6 hours of collection.

All coagulation factors, except platelets, are present in FFP, which explains the use of this component for the treatment of hemorrhage from presumed coagulation factor deficiencies.

FFP transfusions during surgery are not necessary unless the prothrombin time (PT) or partial thromboplastin time (PTT), or both, are 1.5 times longer than normal. FFP and platelets are given in specific ratios with red blood cells in trauma patients (1:1:1). Other indications for FFP are urgent reversal of warfarin and management of heparin resistance (fresh frozen plasma contains antithrombin III).

CRYOPRECIPITATE

Cryoprecipitate is the fraction of plasma that precipitates when FFP is thawed. This component is useful for treating hemophilia A (contains high concentrations of factor VIII in a small volume) that is unresponsive to desmopressin. Cryoprecipitate is also be used to treat hypofibrinogenemia (as induced by packed red blood cells) because it contains more fibrinogen than FFP.

COAGULATION AND FIBRINOLYSIS

The blood-clotting cascade consists of a series of linked reactions. In each reaction, a serine protease, once activated, is capable of activating its downstream substrate.

Common laboratory tests of hemostasis

Bleeding time

Determination of bleeding time:

- a standardized incision 9 mm long and 1 mm deep is made on the anterior surface of the forearm
- pressure maintained by inflating a blood pressure cuff on the upper part of the arm to 40 mm Hg of pressure

The bleeding time is prolonged with platelet counts less than 100,000 cells/µL with poor predictive values for perioperative bleeding.

Prothrombin time

Prothrombin time determination

- citrated plasma is recalcified
- tissue thromboplastin is added to activate factor X in the presence of factor VII
- the time until clot formation is measured in seconds

Prolongation of PT

- Low levels of factors VII, X, V, prothrombin, and fibrinogen
- Factor VII deficiency is the only cause of a prolonged prothrombin time (PT) with a normal partial thromboplastin time (PTT)

The international normalized ratio (INR) standardizes reagent differences between PT results across laboratories and is useful in monitoring oral anticoagulant treatment (normal range 0.8-1.2).

Partial thromboplastin time

Partial thromboplastin time determination:

- Citrated plasma is recalcified, and phospholipids are added to initiate coagulation.
- Plasma activators such as kaolin, celite, ellagic acid, or silica speed the reaction by providing the surface for contact activation of factor XII.
- The time to clot formation is measured in seconds.

Prolongation of PTT:

- Low levels of factors VIII, IX, XI, and XII. Adequate amounts of factor X, factor V, prothrombin, and fibrinogen must also be present.

This test is useful to monitor heparin therapy.

Thrombin time

Thrombin time determination

- Citrated plasma is recalcified, and thrombin is added
- The time until clot formation is measured in seconds.

The thrombin time is prolonged with low levels of fibrinogen (<100 mg/dL), in the presence of abnormal fibrinogen, and in the presence of circulating anticoagulants such as heparin.

Activated clotting time

The activated clotting time (ACT) measures the amount of time in seconds required for whole blood to clot in a test tube.

Finely divided clay (celite or kaolin) shortens the time until clotting and reduces test variability.

The ACT is used to monitor heparin therapy in the operating room.

Fibrinopeptides and fibrin monomer levels

Thrombin releases two peptides (fibrinopeptides A and B) from fibrinogen to generate a fibrin monomer.

Fibrin monomers polymerize and cross-link in the presence of factor XIII.

Elevated levels of fibrinopeptide or fibrin monomer suggest intravascular coagulation.

D-dimer levels

D-dimer fragments are released when plasmin cleaves cross-linked fibrin. Elevated D-dimer levels are present with fibrinolytic states and in more than 90% of patients with thrombotic or thromboembolic disorders.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC is a disorder characterized by uncontrolled intravascular activation of coagulation and fibrinolysis with bleeding and thrombosis.

Generalized intravascular thrombin generation and fibrin deposition in small blood vessels lead to the formation of microvascular thrombi causing tissue hypoxia.

Diagnosis

- decreased platelet count
- decreased fibrinogen
- prolonged PT and PTT
- elevated fibrin degradation products or D-dimers

Both fibrin degradation products and D-dimers are elevated with trauma or surgery.

Treatment

Patients with active bleeding should be transfused with platelet, plasma, cryoprecipitate, and red blood cells as needed. Heparin treatment has little role unless thrombosis is profound.

The Subcommittee on DIC of the International Society on Thrombosis and Haemostasis (ISTH) has developed a scoring card for disseminated intravascular coagulation (DIC) - each for "overt" and "non-overt" DIC. Following is the scoring for "overt" DIC:

1. Platelet count (more than 100 = 0; less than 100 = 1; less than 50 = 2)

2. Elevated fibrin degradation products (no increase = 0; moderate increase= 2; strong increase= 3)

3. PT upper limit of ref. range (less than 3 secs = 0; more than 3 secs = 1; more than 6 sec. = 2)

4. Fibrinogen level (more than 100 mg/dl = 0; less than 100 mg/dl = 1)

Score of 5: compatible with overt DIC

TAKE HOME MESSAGES

- Shock represents an imbalance between oxygen delivery and consumption
- Shock treatment strategies rely on augmenting oxygen delivery and maintaining perfusion pressure
- All inotropic and vasopressors have important side effects and the clinician needs to administer de minimal necessary dose
- Before starting inotropic/vasopressor infusion adequate volume status should be assured
- Fluid administration in cardiogenic shock might be harmful
- Bicarbonate infusion will inactivate inotropes and vasopressors
- Blood component therapy is associated with significant side effects
- Colloid resuscitation of trauma victims offers no advantage over crystalloid resuscitation

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NEUROLOGICAL FAILURE IN THE ICU

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COMA

DEFINITIONS

Consciousness is defined as the state of awareness of the self and the environment. The phenomenon of consciousness requires two intact and interdependent physiologic and anatomic components:

- arousal (or wakefulness) underlying neural substrate, the ascending reticular activating system (ARAS) and diencephalon
- awareness – (awareness of self and environment, i.e. the content of consciousness) is clinically defined as the ability to obey commands. It requires the functioning cerebral cortex of both hemispheres.

Alterations of arousal:

- ***Alert***: normal state
- ***Stupor***: a state of unarousability in which strong external stimuli can transiently restore wakefulness. Stupor implies that at least a limited degree of cognitive activity accompanies the arousal, even if transient.
- ***Coma***: uninterrupted loss of the capacity for arousal. The eyes are closed, sleep/wake cycles disappear, and even vigorous stimulation elicits at best only reflex responses.
- ***Lethargy***: range of behavior between arousal and stupor.

Vegetative state (VS) is characterized by arousal without signs of awareness, a wakeful unconscious state.

- Persistent: VS present one month after initial brain injury, but it does not mean that it is irreversible
- Permanent (irreversible): VS present at three months after a non-traumatic or at 12 months after a traumatic brain injury

ETIOPATHOGENIC TYPES

1. Diffuse or extensive multifocal bilateral dysfunction of the cerebral cortex, and impairment of cortical-subcortical physiologic feedback excitatory loops
2. Direct damage to a paramedian upper brainstem and posterior-inferior diencephalic ascending arousal system
3. Wide- spread disconnection between the cortex and subcortical activating mechanisms
4. Diffuse disorders, usually metabolic in origin

Roughly, there are two types of lesions:

Structural	Non structural
Vascular Vertebrobasilar strokes, bilateral diencephalic infarcts Bilateral cortical or sub-cortical infarcts Occlusion of vessel supplying both hemispheres	**Vascular** Vasculitis*, DIC*, hypertensive encephalopathy*, thrombotic thrombocytopenic purpura (TTP)*
Infective with mass effect Abscess, subdural empyema	**Severe infections** Meningitis*, encephalitis*, cerebral malaria. Infected devices e.g. shunts and encephalopathy due to systemic sepsis.
Neoplastic Primary or metastatic	**Endocrine disorders** Hypoglycemia, non-ketotic hyperosmolar state, diabetic ketoacidosis, myxedema, Addison's crisis
Trauma Hemorrhagic contusions, edema, hematoma	**Electrolyte imbalance** Hypo- or hypernatremia, hypocalcaemia, hypophosphatemia, severe hypomagnesaemia
Increased intracranial pressure Reduces cerebral blood flow	**Toxic reaction**

	Ethanol, drug overdose, carbon monoxide (CO) poisoning, lead intoxication
Mass effect Acute lateral shift of the brain e.g., due to hematoma (subdural, epidural, intraparenchymal) Herniation due to brain-stem compression or mass in one hemisphere causing compression of the other resulting in bilateral hemisphere dysfunction	**Medication side effects** Reye's syndrome, neuroleptic malignant syndrome, central anticholinergic syndrome, serotonin syndrome
	Deficiency states Thiamine deficiency (Wernicke), niacin deficiency (pellagra)
	Organ failure Uremia, hypoxemia, hepatic encephalopathy*, Hypoxic-ischemic encephalopathy (HIE) – post-resuscitation from cardiac arrest, CO2 narcosis
	Epileptic Status epilepticus (incl. non-convulsive status), post-ictal state
	Hypothermia and hyperthermia
	Psychogenic coma

Table 22

APPROACH

1. Initial stabilization – emergency treatment – empirical – ABC algorithm

   1.1. The coma cocktail: urban myth?

   D: dextrose 50 ml 50% (blood glucose before administration)

   O: oxygen

   N: naloxone 0.4-2mg IV

   T: thiamine 100 mg

2. Complete neurological assessment

   2.1. General examination (evidence of head trauma, meningeal irritation, purpura, elevated intracranial pressure or other diagnostic findings).

   2.2. Neurological examination

   2.2.1. Best motor responses

The recommended noxious stimuli are pressure to: the supraorbital ridge, the nail beds of the fingers and the toes, the sternum and the temporomandibular joints. Spontaneous, purposeful or non-purposeful movements, withdrawal or posturing reflexes, including any evidence of lateralization of signs, to noxious stimuli are noted. Eye opening, if not present to voice or spontaneously, in response to the noxious stimulus is also noted.

   2.2.2. Brain stem reflexes

Brain-stem reflexes testing should at least include pupillary responses and ocular motility. Holding eyelids opened to observe eye position and movements could easily test ocular motility. Most comatose patients have only a slight exophoria, so position of both eyes should be conjugate. Disconjugate eye positions suggest the presence of a brain-stem lesion. Vestibulo-ocular responses tested by lateral head movement ('doll's eyes maneuver') may be used to elicit eye movements if they are not present spontaneously, but should be avoided if a fracture or dislocation of the cervical spine is possible. In these cases, cold caloric testing is preferred, provided that the tympanic membrane is intact. Corneal reflex testing is rapid and may have major prognostic value. Tracheal suctioning in mechanically ventilated patients allows testing of the cough reflex.

2.2.3. Respiratory pattern

The pattern of respiration helps to determine both the level of brain damage and the cause of coma (Cheyne–Stokes, bradypnea, apneustic breathing, ataxic breathing). However, the need for stabilizing vital functions and the urgent need for mechanical ventilation may decrease their value.

2.2.4. Reflexes

Examination of deep tendon reflexes and plantar responses can be informative particularly when lateralization of pathology is suggested.

2.3. Standardized assessment

Full Outline of UnResponsiveness Score (FOUR Score)	**Glasgow Coma Scale (GCS)**
Eye response **4** = eyelids open or opened, tracking, or blinking to command **3** = eyelids open but not tracking **2** = eyelids closed but open to loud voice **1** = eyelids closed but open to pain **0** = eyelids remain closed with pain	**Eye response** **4** = eyes open spontaneously **3** = eye opening to verbal command **2** = eye opening to pain **1** – no eye opening
Motor response **4** = thumbs-up, fist, or peace sign **3** = localizing to pain **2** = flexion response to pain **1** = extension response to pain **0** = no response to pain or generalized myoclonus status	**Motor response** **6** = obeys commands **5** = localizing pain **4** = withdrawal from pain **3** = flexion response to pain **2** = extension response to pain **1** = no motor response
Brain-stem reflexes **4** = pupil and corneal reflexes present **3** = one pupil wide and fixed **2** = pupil or corneal reflexes absent **1** = pupil and corneal reflexes absent	**Verbal response** **5** = oriented **4** = confused **3** = inappropriate words **2** = incomprehensible sounds

0 = absent pupil, corneal, and cough reflex	**1** = no verbal response
Respiration **4** = not intubated, regular breathing pattern **3** = not intubated, Cheyne–Stokes breathing pattern **2** = not intubated, irregular breathing **1** = breathes above ventilator rate **0** = breathes at ventilator rate or apnea	

Table 23

3. Laboratory investigations

3.1. Neurodiagnostic imagining

3.2. EEG

3.3. Emergency laboratory test for metabolic coma

3.3.1.Immediate Tests

3.3.1.1. *Venous blood:* glucose, electrolytes (Na, K, Cl, CO2, PO4), urea and creatinine , osmolality

3.3.1.2. *Arterial blood (check color):* pH PO2 PCO2 HCO3 HbCO (if available)

3.3.1.3. *Cerebrospinal fluid:* Gram stain, cell count, glucose

3.3.1.4. Electrocardiogram

3.3.2.Deferred Tests (Initial Sample, Process Later)

3.3.2.1. *Venous blood:* sedative and toxic drugs, liver function tests, coagulation studies, thyroid and adrenal function, blood cultures, viral titers

3.3.2.2. *Urine:* sedative and toxic drugs, culture

3.3.2.3. *Cerebrospinal fluid:* protein, culture, viral and fungal titers

CONVULSIVE DISORDERS

Seizures in ICU have an incidence of 3%.

When a patient in the ICU has altered consciousness, seizure should be ruled out and EEG performed. Subtle myoclonus is highly suggestive (eyelids, fingers). Metabolic disorders, interruption of sedatives, especially of antibiotics (beta-lactams and renal failure), drug withdrawal, are the main causes of seizures in ICU patients.

Status epilepticus

Generalised convulsive status epilepticus (GCSE) is defined as sustained seizure activity lasting for more than 5 minutes or 2 episodes of convulsive seizures with persistent alteration of consciousness.

About 25 per cent of cases occur in patients having known epilepsy. The majority of the patients have no epilepsy and seizures occur as a complication of brain tumours, infections, traumatic brain injury, metabolic disorders, illicit drug intake or cerebrovascular disease. In patients with known epilepsy, the most common precipitating factor is withdrawal from medication or noncompliance with the regimen. Status epilepticus may recur in 26% of patients and has a high (22%) mortality rate. For SE lasting > 1 h mortality is 32%. SE with subsequent anoxia has a mortality of 70%.

Pathophysiology: inbalance between cerebral excitation and inhibition leading to intracellular toxic levels of ca.

Diagnostic

EEG!!!

Treatment

- Treatment initiation – as early as possible
  - 2 h window
  - 30 min – 80% response to 1st line AED
  - Multiple team members
  - **3-5 min from onset**
- Prehospital ?
- Preserve airway & oxygenation

- Secure IV (preferable 2)
- Check vitals
- Glucose level???

1. **First line**: BZP (***lorazepam***) – not a long term therapy to prevent occurrence

   Loading dose: 4-8 mg IV (0.2 mg/kg)

   Onset of action: 3-10 min

   Duration of effect: 12-24 h

   Elimination T1/2: 14 h

2. **Second line**:

	Phenytoin	Fosphenytoin	Valproate
Loading dose	20 mg/kg IV, max infusion rate 50 mg/min	20 mg/kg IV, max infusion rate 150 mg/min	40 mg/kg over 10 min, additional 20 mg/kg over 5 min
Maintenance	5-7 mg/kg/d in 2-3 doses	5-7 mg/kg/d in 2-3 doses	1 g IV q6h 2-8 mg/kg/h
Onset of action	20-25 min	20-25 min	
Contraindications	Heart block; caution liver & renal impairement		Severe liver, thrombocytopenia, active bleeding
Main drug interactions	↑ Free levels other drugs, precipitation		Levels decreased by meropenem
Main side effects	Cardiac - 157 -nopposed- 157 -z, hypoBP, hepatotoxicity, - 157 -nopposed- 157 -ze, phlebitis		Hepatotoxicity, ↓Plt, pancreatitis
Target serum levels	Total 15-25 µg/ml; free level 2-3 µg/ml		Total: 80-140 µg/ml Free: 4-11 µg/ml

Table 24

Refractory SE

- **Definition**: SE that persists despite first & second line AED regardless of the elapsed time
- **Incidence and prevalence**: underestimated
- **Treatment**: continous IV 24-72 h after cesation of EEG seizures

	Midazolam	**Propofol**	**Pentobarbital**
Loading dose	0.2 mg/kg, repeat every 5 min (max 2mg/kg)	1 mg/kg, repeat 1-2 mg/kg every 5 min (max 10 mg/kg)	5 mg/kg repeat until seizures stops
Continuous IV	0.05-0.1 mg/kg	1-15 mg/kg (max 5 mg/kg/h for > 48h) (2)	0.5-10 mg
Dose range	0.05-29 mg/kg/h		
Time to stop SE	Min, less than 1h	< 10 min	
Elimination T1/2	1.5-3.5h		15-60h
Elimination T1/2	1.5-3.5 h		Levels decreased by meropenem

Table 25

Non- convulsive status epilepticus (NCSE) may occur, particularly in comatose neurological or neurosurgical ICU patients. NCSE is - 158 -nopposed- 158 -zed by subtle (e.g. reduced GCS, nystagmus, eye or facial twitching) seizures. Timing of treatment of these conditions is largely unknown, but experts recommend rapid treatment.

NCSE may often follow GCSE, particularly in refractory form of GCSE and may explain about 10% of comatose states of unknown origin.

Outcome:

- SE Mortality
  - Discharge: 9-21%
  - 30 days: 19-27%
  - RSE: 23-61%
- Poor outcome predictors
  - Old age
  - Impairement of consciousness
  - Duration of seizures
  - Presence of medical complications

BRAIN DEATH

Brain death is ***irreversible*** unconsciousness with complete loss of brain function, including the brain stem, although the heartbeat may continue. Death is a continuous process, pin-pointing the exact moment being extremely difficult, although the effects are apparent. Brain death is accepted as the equivalent of cardiac death (the usual statutory cause of death). Cardiac asystole usually follows within days or weeks despite continuation of mechanical ventilation and full supportive therapy

Types:

- Higher brain (neocortical): lack of consciousness
- Brainstem death
- ***Whole brain death***: neocortical and brain stem

Diagnostic

Two certified physician (ICU, neurology) with at least 5 years' experience should carry out the examination. The interval between the two sets of tests is 6 hours.

All of the following conditions must be fulfilled to allow the diagnosis of death following irreversible cessation of brain- stem function to be undertaken.

1. Essential precondition: coma of known aetiology (Clinical or neuroimaging evidence of an acute CNS catastrophe that is compatible with the clinical diagnosis of brain death)

2. Necessary prerequisites

    2.1. Normal MAP

    2.2. No severe hypothermia (> 32°C)

    2.3. Absence of neurodepressor drugs effect (blood levels necessary; if not available wait 5 x T1/2)

    2.4. Abscence of neuromuscular blockers effect (neurostimulation tests)

    2.5. Abscence of anticholinergic drugs effect

    2.6. Abscence of severe metabolic disturbances

The three cardinal findings in brain death are coma or unresponsiveness, absence of brainstem reflexes, and apnea.

1. Coma or unresponsiveness–no cerebral motor response to pain in all extremities (nail- bed pressure and supraorbital pressure)

2. Absence of brainstem reflexes

    2.1. Pupils

        2.1.1. No response to bright light

        2.1.2. Size: midposition (4 mm) to dilated (9 mm)

    2.2. Ocular movement

        2.2.1. No oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent)

        2.2.2. No deviation of the eyes to irrigation in each ear with 50 ml of cold water (allow 1 minute after injection and at least 5 minutes between testing on each side)

    2.3. Facial sensation and facial motor response

        2.3.1. No corneal reflex to touch with a throat swab

        2.3.2. No jaw reflex

2.3.3. No grimacing to deep pressure on nail bed, supraorbital ridge, or temporomandibular joint

2.4. Pharyngeal and tracheal reflexes

2.4.1. No response after stimulation of the posterior pharynx with tongue blade

2.4.2. No cough response to bronchial suctioning

3. Apnea–testing performed as follows:

3.1. Prerequisites

3.1.1. Core temperature $\geq$ 36.5°C

3.1.2. Systolic blood pressure $\geq$ 90 mm Hg

3.1.3. Euvolemia. Option: positive fluid balance in the previous 6 hours

3.1.4. Normal PCO2. Option: arterial PCO2 $\geq$ 40 mm Hg

3.1.5. Normal PO2. Option: preoxygenation to obtain arterial PO2 $\geq$ 200 mm Hg

3.2. Connect a pulse oximeter and disconnect the ventilator.

3.3. Deliver 100% O2, 6 l/min, into the trachea. Option: place a cannula at the level of the carina.

3.4. Look closely for respiratory movements (abdominal or chest excursions that produce adequate tidal volumes).

3.5. Measure arterial PO2, PCO2, and pH after 5 and 10 minutes and reconnect the ventilator.

3.6. If respiratory movements are absent and arterial PCO2 is $\geq$ 60 mm Hg (option: 20 mm Hg increase in PCO2 over a baseline normal PCO2), the apnea test result is positive (ie, it supports the diagnosis of brain death).

3.7. If respiratory movements are observed, the apnea test result is negative (ie, it does not support the clinical diagnosis of brain death), and the test should be repeated.

3.8. Connect the ventilator if, during testing, the systolic blood pressure becomes < 90 mm Hg or the pulse oximeter indicates significant oxygen desaturation and cardiac arrhythmias are present; immediately draw an arterial blood

sample and analyze arterial blood gas. If PCO2 is ≥ 60 mm Hg or PCO2 increase is ≥ 20 mm Hg over baseline normal PCO2, the apnea test result is positive (it supports the clinical diagnosis of brain death); if PCO2 is < 60 mm Hg or PCO2 increase is < 20 mm Hg over baseline normal PCO2, the result is indeterminate, and an additional confirmatory test can be considered.

Confirmatory laboratory tests are mandatory if WBD definition is used. They search for intracranial phenomena, mainly:

1. **Cerebral circulatory arrest**

   1.1. Conventional angiography. No intracerebral filling at the level of the carotid bifurcation or circle of Willis. The external carotid circulation is patent, and filling of the superior longitudinal sinus may be delayed.

   1.2. Transcranial Doppler ultrasonography

      1.2.1. Ten percent of patients may not have temporal insonation windows. Therefore, the initial absence of Doppler signals cannot be interpreted as consistent with brain death.

      1.2.2. Small systolic peaks in early systole without diastolic flow or reverberating flow, indicating very high vascular resistance associated with greatly increased intracranial pressure.

   1.3. Technetium-99m hexamethylpropyleneamineoxime brain scan. No uptake of isotope in brain parenchyma (“hollow skull phenomenon”).

2. **Absence of bioelectrical activity of the brain**

   2.1. Electroencephalography. No electrical activity during at least 30 minutes of recording

   2.2. Somatosensory evoked potentials.

3. Decrease in cerebral oxygen consumption

Physiological changes accompanying brainstem death

1. Neurological

   1.1. Autonomic (see cardiovascular)

   1.2. Failure of the hypothalamic-pituitary axis (see endocrine)

1.3. Impairment of the temperature regulation center in the hypothalamus: poikilothermic, hypothermic

2. Cardiovascular

   2.1. Various manifestations related to the level of injury

   2.2. Cerebral, pons, spinal cord ischemia: vagal activation

   2.3. Medullary ischemia – “sympathetic storm”

   2.4. Catecholamine levels fall, relative hypovolemia

3. Pulmonary: pulmonary edema during catecholamine storm (deterioration in gas exchange hypoxemia)

4. Endocrine

   4.1. Neurogenic diabetes insipidus

   4.2. Sick euthyroid syndrome

   4.3. A degree of peripheral resistance to insulin

Management

It targets the changes that accompany BSD.

Nonspecific measures to maintain physiological endpoints in the potential organ donor:

- Systolic blood pressure ≥90 mm Hg
- Mean arterial pressure ≥60 mm Hg
- Central venous pressure ≤12 mm Hg
- Pulmonary capillary wedge pressure ≤12 mm Hg
- Cardiac index >2.5 L/min/m2
- Left ventricular stroke work index >15 g/m/m2
- Urine output >1 and <4 mL/kg/h Core temperature >35°C
- Hematocrit ≥25%
- Oxygen saturation >95% pH 7.35-7.45

In order to achieve the goals, crystalloids are preferred over colloids and dopamine over norepinephrine. Thyroid hormones play a role in excess catecholamine administration.

DELIRIUM

Delirium is a fluctuating change in consciousness and awareness, mainly characterized by an alteration of attention and organization of thinking associated with abnormal sleep–wake cycle, psychomotor activity, perceptions (e.g., hallucinations, illusions) and emotional behavior.

Incidence

- 32.3% prevalence – on admission
- ICU – 45-87%
  1. 4:5 – on MV
  2. 1:5 – high dependency unit
  3. 2:5 – geriatric
  4. 3:5 – fractured neck of femur
- duration until incidence
  1. Medical: 2-3 days
  2. Major trauma: 1-5 days
  3. Surgical (geriatric): ➔ 8 days
  4. In practice: as long as the precipitating factor

Types (minimum 2 in the last 24 h)

- **Hyperactive (better outcome, alcohol/drug withdrawal)**
  - Increased quantity of motor activity
  - Loss of control of activity
  - Restlessness
- **Hypoactive (most frequent, metabolic disturbances/hypoxemia)**

- Decreased amount of activity
- Decreased speed of action
- Reduced awareness of surroundings
- Decreased amount of speech
- Decreased speed of speech
- Listlessness
- Reduced alertness, withdrawal

- **Mixed**

Pathophysiology

Disturbed cholinergic activity (relative depression) vs. dopamine excess

Risk factors

- Age (more than 70 years)
- Previous history of psychiatric disease or cognitive impairment
- Visual or auditory impairment
- Alcohol, tobacco, drug or medication abuse or withdrawal
- Total dose of sedative drugs in ICU (benzodiazepines and opiates)
- Medication overdose (BZP, opioids – meperidine, anticholinergics, antihistaminics, antibiotics, corticosteroids, metoclopramide)
- Surgery (especially extracorporeal circulation, orthopedics)
- Infection or sepsis
- Coexisting medical condition (severe illness)
- Physical restrains
- Urinary bladder catheter

Diagnostic

Stepwise approach

1. Level of consciousness: sedation scales (see Pain)
2. Mental status: prerequisites
    - Responsive patient
    - Verbal stimulus/ interaction
    - 2 tools (see at the end of this chapter):
        - CAM-ICU: Confusion Assessment Method for the ICU
        - The Intensive Care Delirium Screening Checklist (ICDSC)

Treatment

1. Search and treat the underlying cause
2. Pharmacological approach

Haloperidol

- Butyrophenone
- D2 antagonist
- 2 – 10 mg every 30 min **or** 2-5 mg x 6h (0.5-2mg in the elderly) to a maximum dose of 20 mg/day
- TBI ??? (diffuse axonale injury with reduced dopamine turnover)
- Adverse effects
    - Neuroleptic malignant syndrome (10% mortality)
    - Torsade de pointes!!!

HEAD (TBI) AND SPINE TRAUMA IN THE ICU

TBI is a leading cause of mortality and disability.

Primary management (to avoid secondary brain injury) and referral to neurosurgical hospital is done by the EMT

- GSC score that is less than 9
- 2-point deterioration in GCS
- focal neurologic signs
- compound skull fracture
- basal skull fracture
- CT findings of mass lesion or diffuse axonal injury
- GCS score that is less than 15, persisting for more than 24 h

Posttraumatic ischemia initiates a cascade of metabolic events that lead to the surplus production of oxygen free radicals, excitatory amino acids, cytokines and other inflammatory agents responsible for edema and tissue distruction. TBI increase extracellular potassium levels and causes a decrease in extracellular magnesium having as a final result an intracellular Ca increase.

Coagulopathy resulting from TBI is thought to occur when hypoperfusion causes activation of the protein C pathway, thereby inducing alterations in the clotting cascade. It is more frequent with eztensive associated extracranial injuries.

Neurological monitoring

1. Standard measurements

    1.1. Neurological status (GCS, pupils, motor signs, brain-stem reflexes)

    1.2. ICP: is the cerebrospinal fluid pressure measured via a catheter in the ventricular system with its tip at the level of the Foramen of Monro without loss of fluid from the system (equivalent to ventricular fluid pressure, VFP).

    - Normal values < 15 mmHg in adult
    - Threshold for treatment 20 mmHg
    - Indication for monitoring

- GCS 3-8 & abnormal CT
- GCS 3-8 & normal CT
  - ♦ > 40 y
  - ♦ Posturing
  - ♦ Hypotension

1.3. Cerebral perfusion pressure – autoregulation impairement in early stage

CPP = MAP – ICP

Goal: 50-70 mmHg

2. Advanced measurements: look at cerebral oxygenation, cerebral perfusion, and metabolism giving a deeper insight into the various pathophysiological mechanisms involved and targeting therapy

Therapeutic goal: prevent ischemia

The most common preventable causes of cerebral ischemia are hypotension, hypoxemia, and intracranial hypertension.

Specific management

1. Surgery: often the primary treatment
2. Cerebral edema
   a. Standard
      - Adequate sedation and analgesia
      - Patient's head elevated at 15-30 degreas
      - Wound dressing and collars do not compress the jugular veins
      - CSF drainage
      - Mannitol: Serum osmolarity < 320 mOsm, Normal single dose 0.3g/kg over 15-20 min, Rebound: damaged blood brain - 168 -noppos and renal failure
   b. Second line
      - Hyperventilation: PaCO2 30-35 mmHg, for transtentorila herniation

- Barbiturates: titrated to control ICP
- Steroids: no part to play, studies underway
- Secondary decompresive craniectomy
- Hypothermia: 34°C, very minor fluctuations (0.2-0.5°C), slow and controlled rewarming (<0.2-0.5°C/h)

3. Seizures

   Risk factors for seizures:

   - GCS < 10
   - Cortical contusions
   - Depressed skull fractures
   - Wounds with dural penetration
   - > 24 h of coma
   - Posttraumatic amnesia

   1. Within 48 h of injury
   2. Prevention: phenytoin, carbamazepine

General management:

1. Early tracheostomy approach: 4-6 days post injury
2. Enteral nutrition should be started shortly after admission with the intention of reaching full nutritional intake by day 3 in ICU (more profound and - 169 -nopposed catabolic response).
3. Stress ulcer prophylaxy: there may be an increased risk of pneumonia, clostridium difficile colitis
4. Disturbances of sodium balance
   a. Hypernatremia: due to central - 169 -noppose inspidus and osmotic diuresis (mannitol)
   b. Hyponatremia

5. Control of blood sugar levels: maintain glycemia in the 150 mg/dL to 200 mg/dL (8.3– 11 mmol/L) range

6. Hematology/coagulation – venous thromboembolic disease

    a. Mechanical compression device on the leg

    b. LMWH should be considered after the first 3 days post injury (24h after hematoma stability)

Spinal Cord Injury (SCI)

It typically occurs in males at the peak of their productive lives. Most spinal injuries result from high-speed motor vehicle accidents. All patients sustaining major trauma, a fall from greater than ten feet, MVC, or noticeable injuries to the head or neck should be thoroughly evaluated for evidence of SCI warranting "spinal cord precautions"

- in-line immobilization,
- maintenance of neutral position,
- cervical immobilization with a rigid collar,
- use of backboards for transport

Management

1. Initial resuscitative efforts

2. Diagnostic studies

    a. Fine-cut helical computed tomography (CT) scan with coronal and sagittal reconstructions

    b. Plain radiographs

3. Further diagnostic studies will be dictated by the findings of the initial and secondary surveys

4. Pharmacotherapy

    a. Corticosteroids: reduction of the effects of secondary injury. Therapy must be initiated the first 8h postinjury (ie. Methylprednisolone). 1-3h: LD – 30mg/kg, infusion dose 5.4mg/kg/h x 23 h

3-8h: LD – 30mg/kg, infusion dose 5.4mg/kg/h x 48 h

b. Gangliosides: no benefit in humans

5. Hypothermia: conversion to a - 171 -noppo ASIA grade (studies underway)

6. ICU management

a. Respiratory: 18-38% mortality (tetraplegia)

Lesion below C4 – phrenic nerve continues to inervate the diaphragm. Patients with cervical SCI maintain their respiratory status for 24-48 h after admission. Abdominal stabilization (binder) for lesions below C5.

b. Cardiovascular – neurogenic/spinal shock

Incidence - 171 -nopposed for lesions above T6 (- 171 -nopposed vagal tone). In complete SCI, after a first period of areflexia and flaccidity (days to weeks) followed by hyper- tonia, exaggerated reflexes, and (in many cases) spasticity. The typical patient with SCI without associated vascular or visceral injury a mean arterial blood pressure of 80 mm Hg and a heart rate of 65 beats/min. Persistent bradycardia is a frequent finding and is often profound enough to produce hemodynamic compromise. The patient's blood pressure may respond to volume resuscitation, but often these patients require low-dose pressors (norepinephrine as first choice).

c. Urinary: atonic and flaccid urinary bladder. Over time it becomes an upper motor neuron bladder with small capacity. An indwelling Foley cath- eter is initially placed. After 3 to 4 days this is switched to intermittent bladder catheterization to maintain urinary volumes below 500 mL. Urinary tract infections are common. Long-term complications include chronic infections, obstructive urop- athy, and renal calculi; if left untreated, renal failure may develop

d. Integument: pressure sores. Maximum duration time of two hours for any single position. Although still immobile, patients should be supported with pressure-reducing mattress materials, such as foam, static air, alternating air, gel, water, low air loss, or air-fluidized support surfaces, with proper alignment of extremities and cushioning devices between legs and ankles.

e. Thromboembolic complications: prophylaxis as sooon as possible – combination of pneumatic compression stockings with low-molecular-weight heparin (enoxaparin) or adjusted-dose heparin.

f. Metabolic: Severe CNS injury causes a hypermetabolic response that peaks 5 to 12 days after injury and decreases to a level below pre-injury needs, depending on residual level of motor function.

Recovery depends on the functional complete or uncomplete neurologic deficit and it's evolution within the first 24 hours.

Autonomic Hyperreflexia

- Spinally mediated sympathetic reflexes in segments distal to the injury
- Typically start to reappear as early as three to six weeks after the injury
- Mostly in SCI patients with lesions above T6 – unopposed sympathetic discharge.
- Triggered by relatively minor autonomic stimuli, such as bladder distension 75% to 85% and fecal impaction 13% to 15%
- Manifestations: headaches, hypertension, sweating, reduced body temperature, strokes, pulmonary edema, myocardial ischemia
- Between 19% to 70% of SCI patients have at least one episode of autonomic dysreflexia in their lifetime and should always be anticipated when patients are scheduled for even small procedures, such as cystoscopy.

TAKE HOME MESSAGES

- The coma cocktail: dextrose 50 ml 50% (blood glucose before administration), oxygen, naloxone 0.4-2mg IV, thiamine 100 mg
- Coma is defined as an uninterrupted loss of the capacity for arousal
- The vegetative state is characterized by arousal without signs of awareness, a wakeful unconscious state
- When a patient in the ICU has altered consciousness, seizure should be ruled out and EEG performed
- Brain death is ***irreversible*** unconsciousness with complete loss of brain function, including the brain stem, although the heartbeat may continue
- Delirium is a fluctuating change in consciousness and awareness, mainly characterized by an alteration of attention and organization of thinking associated with abnormal sleep–wake cycle, psychomotor activity, perceptions (e.g., hallucinations, illusions) and emotional behavior

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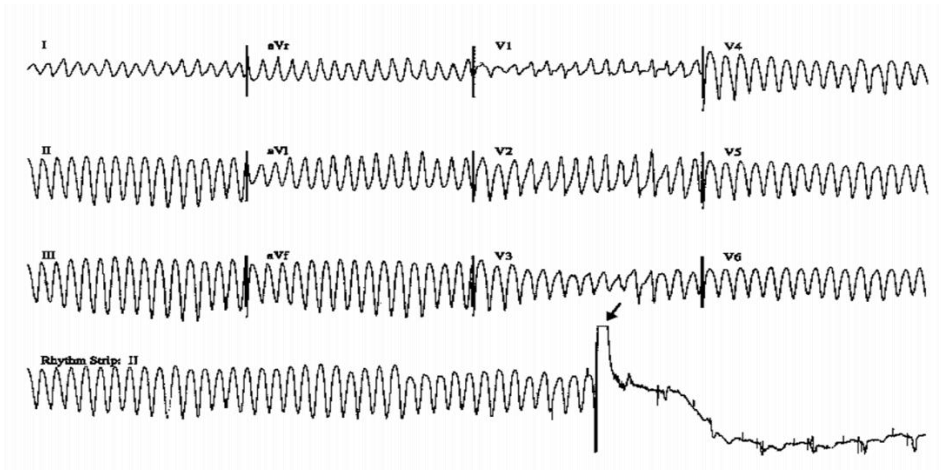
BASIC AND ADVANCED LIFE SUPPORT

Asist. Univ. Dr. Solomon Raluca

Prof. Univ. Dr. Azamfirei Leonard

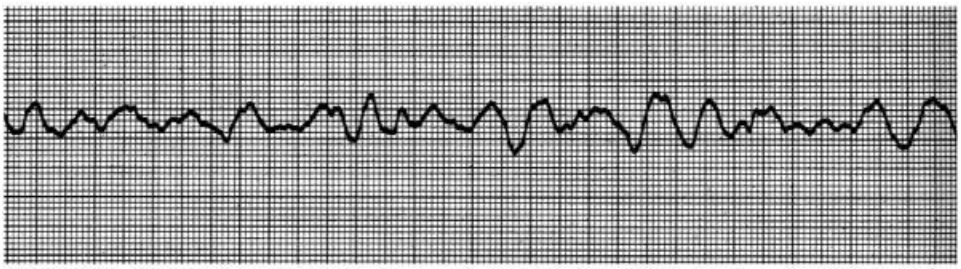
Sudden cardiac arrest is the sudden, unexpected loss of heart function, breathing and consciousness. Sudden cardiac arrest usually results from an electrical disturbance in your heart that disrupts its pumping action, stopping blood flow to the rest of your body. A common arrhythmia in cardiac arrest is ventricular fibrillation. On initial heart rhythm analysis, about 25–30% of outside hospital cardiac arrest victims have ventricular fibrillation (VF). It is likely that many more victims have VF or rapid ventricular tachycardia (VT) at the time of collapse but, by the time the first electrocardiogram (ECG) is recorded, the rhythm has deteriorated to asystole. The outcome of in-hospital cardiac arrest is very poor. The goal of treatment should always be to intervene early before the patient deteriorates to cardiopulmonary arrest.

Ventricular tachycardia

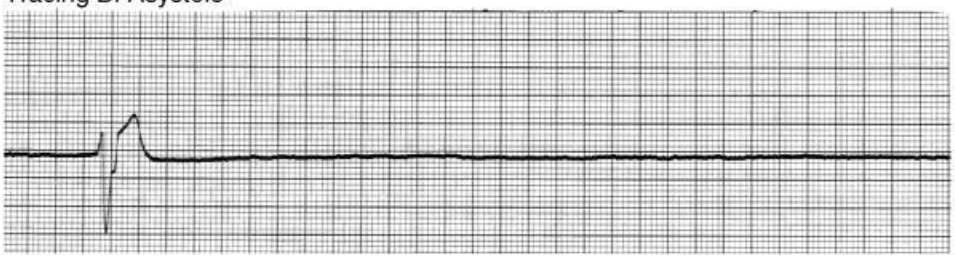


Picture 7

Tracing A: Ventricular Fibrillation

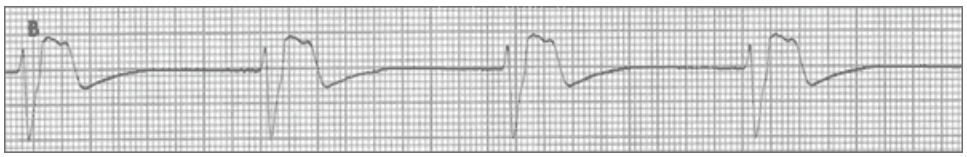


Tracing B: Asystole



Picture 8

PEA



Picture 9

Basic life support (BLS) includes:

- Recognition of signs of sudden cardiac arrest (SCA)
- Resuscitation (CPR)

When a patient has a cardiac arrest, basic life support can be provided to help their chance of survival. Essentially, you are providing chest compressions to pump blood from the heart and around the body, ensuring the tissues and brain maintain an oxygen supply. This will buy time to slow the rate of deterioration of the brain and heart. The primary function of basic life support is to keep a person alive until professional help can arrive. CPR should only be carried out in patients who have a reasonable chance of benefiting from it.

The actions linking the victim of sudden cardiac arrest with survival are called the "Chain of Survival"

- Early recognition of the emergency & team activation
- Early bystander (floor nurse/physician) CPR
- Early defibrillation
- Advanced life support
- Post resuscitation care – targets preserving function, particularly of the heart and brain, and restoring the patient's quality of life.

Immediate CPR can double or triple survival from VF outside hospital cardiac arrest victims. Following VF, cardiopulmonary resuscitation plus defibrillation within 3–5 min of collapse can produce survival rates as high as 49–75%. Each minute of delay before defibrillation reduces the probability of survival to discharge by 10–12%.

ADULT BLS SEQUENCE

Follow the algorithm:

1.Make sure you, the victim and any bystanders are **safe.** Initially you should assess if there is any danger in the situation either for you or for the patient.

2. Check for response - To check for response, tap the victim on the shoulder and ask, "Are you all right?"

3. Activate hospital CPR team/ shout for help

- Lone rescuer (floor nurse): calls CPR team alert /the ambulance service – gets a defibrillator & returns to provide CPR & defibrillation.
- 2 or more rescuers present: one rescuer begins CPR; second activates the CPR team & gets a defibrillator.

4. Positioning for CPR

- Place the victim supine; hard surface; face-up position.
- With an advanced airway (e.g, tracheal tube) if cannot be placed supine (e.g, during spinal surgery), CPR with the patient in a prone position.

5. Open the Airway:

- Head tilt– chin lift maneuver if no head or neck trauma.

- With suspected cervical spine injury, open the airway using jaw thrust without head extension.

Unconsciousness promotes upper airway obstruction. Relaxation of tongue and epiglottis facilitates its protrusion postero/inferiorly against glottis. The protrusion is exaggerated by head and neck flexing.

It may be treated with:

- airway manipulations
- supraglottic devices: airways, LMA
- tracheal intubation

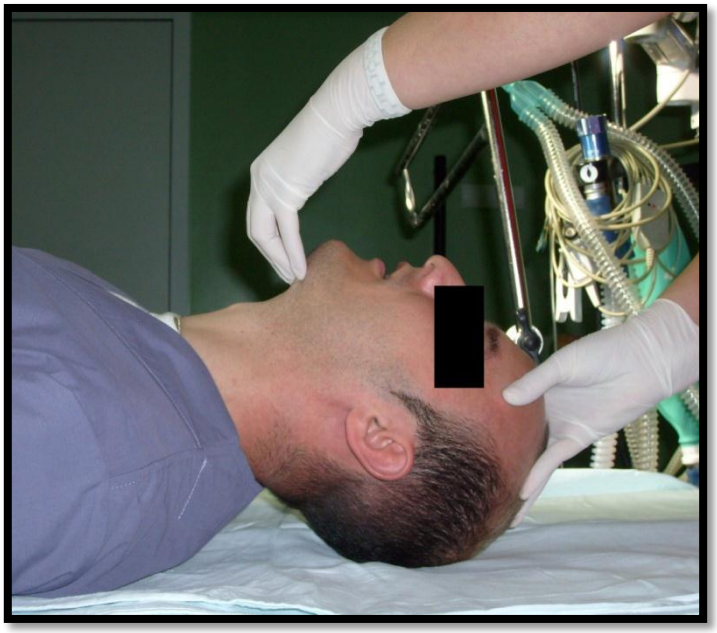
Ways to open the airway?

- Simple, non-instrumental opening
- Instrumental opening

Simple (non-instrumental) airway maneuvers - work by elevation of hyoid and thus tongue /epiglottis away from the pharynx. No need for finger sweep unless solid material can be seen in the airway

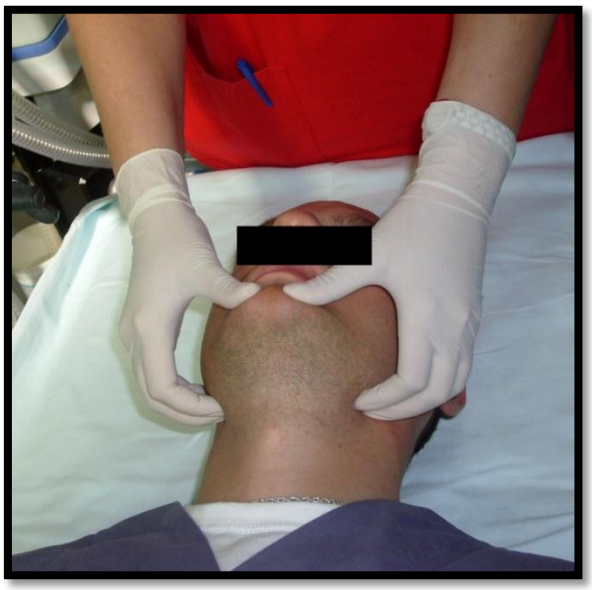
- Head tilting and chin lift - non-healthcare rescuers
- Jaw thrust - healthcare professionals
- A combination of them

Head tilt + chin lift



Picture 10

Jaw thrust



Picture 11

Simple (non-instrumental) airway maneuvers: contraindications

Procedure	Head tilt	Chin lift	Jaw thrust	Open mouth
Contraindi-cations	Neck fracture Basilar syndrome Infants	Same as head tilt	Dislocated jaw Awake patient	Less effective

Table 26

6. Check Breathing

- While maintaining an open airway, look, listen, and feel for breathing.

- Occasional gasps are not effective breaths.

- If *adequate* breathing not detected within 10 seconds

7. Give rescue breaths

Give 2 rescue breaths, each over 1 second, with enough volume to produce visible chest rise. This applies to all forms of ventilation (mask, device, etc.) during CPR.

Give rescue breaths – recommendations:

- During the first minutes of VF-SCA, rescue breaths are probably not as important as chest compressions.
- Provide effective chest compressions and minimize any interruption of chest compressions.
- Both ventilations and compressions are important for victims of prolonged VF SCA.
- Both are also important for victims of asphyxial arrest, such as children and drowning victims.
- During CPR cardiac output is 25% to 33%; oxygen uptake and CO_2 delivery to the lungs also reduced.
- During adult CPR tidal volumes of approximately 500 to 600 mL (6 -7 mL/kg) should suffice.
- Do not hyperventilate! Unnecessary and is harmful!

The Bag-Mask Device Description & use

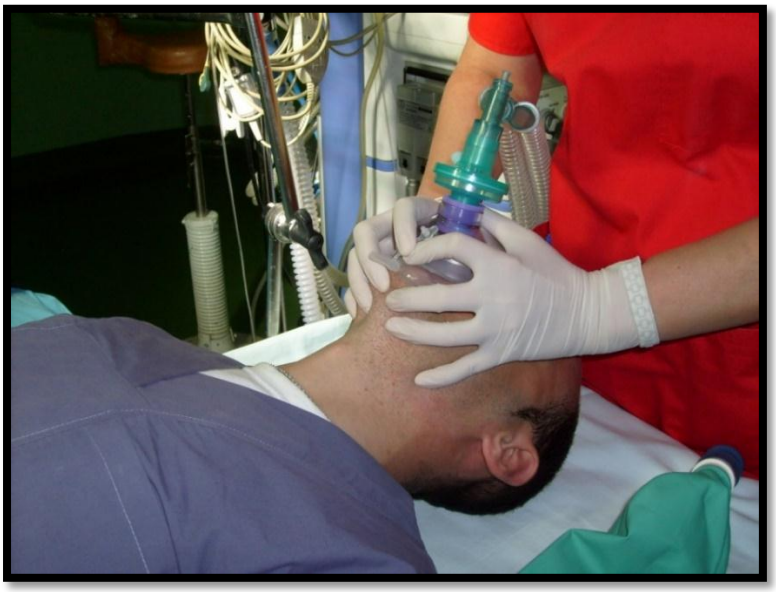
Picture 12

- The lone rescuer simultaneously opens the airway, holds the mask tightly against the patient's face, and squeezes the bag.
- The rescuer must also watch the chest rises.
- Bag-mask ventilation is most effective when provided by 2 trained and experienced rescuers.
- The rescuer delivers the breaths (8-10/min) during pauses in compressions and delivers each breath over 1 second.
- Supplementary oxygen: ideally the bag should be attached to an oxygen reservoir to enable delivery of 100% oxygen. Minimum flow rate of 10 to 12 L/min.

1 hand ventilation

Picture 13

Two hands ventilation



Picture 14

3 hands ventilation

Picture 15

Management of inadequate mask ventilation includes:

- Triple airway maneuver
- Naso/oropharyngeal Guedel airways
- LMA/ Esophageal-tracheal combitube
- Intubate the patient's trachea

Naso / oropharyngeal airways

- May help in completing the airway maneuvers and improving ventilation.
- Naso - Careful with coagulopathy/skull fracture.

oropharyngeal airways

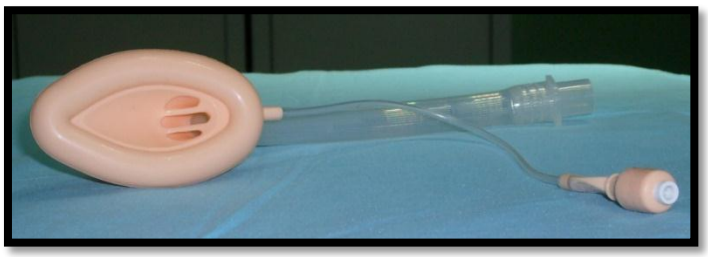
Picture 16

Ventilation with an advanced airway (TT, LMA, ETC)

- 2 rescuers no longer deliver cycles of CPR (compressions interrupted by pauses for ventilation).
- Compressing rescuer applies compressions at a rate of 100 per minute without pauses for ventilation:8-10 breaths/min.
- Change compressor & ventilator roles every 2 min.
- When multiple rescuers are present, they should rotate the compressor role about every 2 minutes.

Extraglottic devices

- Laryngeal mask airway – LMA



Picture 17

- Combitube – ETC

Infraglottic options

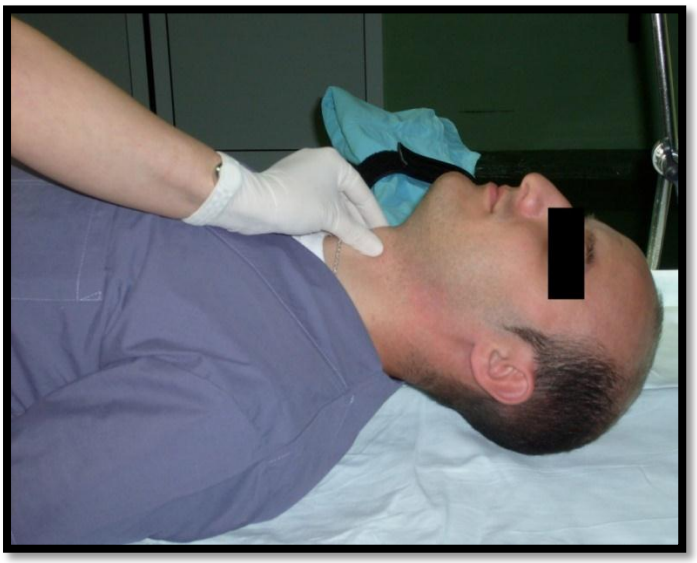
- Tracheal intubation
- Cricothyroidotomy

- Tracheostomy

Cricoid Pressure

- Pressure on cricoid pushes the trachea posteriorly, compresses the esophagus against the cervical vertebrae.
- Can prevent gastric inflation and reduce the risk of regurgitation and aspiration.
- Requires a third rescuer.
- Cricoid pressure should be used only if the victim is deeply unconscious (has no cough or gag reflex).

Cricoid Pressure



Picture 18

8. Pulse Check

- Deleted from training for lay rescuers.
- The healthcare provider should take no more than 10 seconds to check for a pulse.
- If not felt within 10 seconds, proceed with compressions

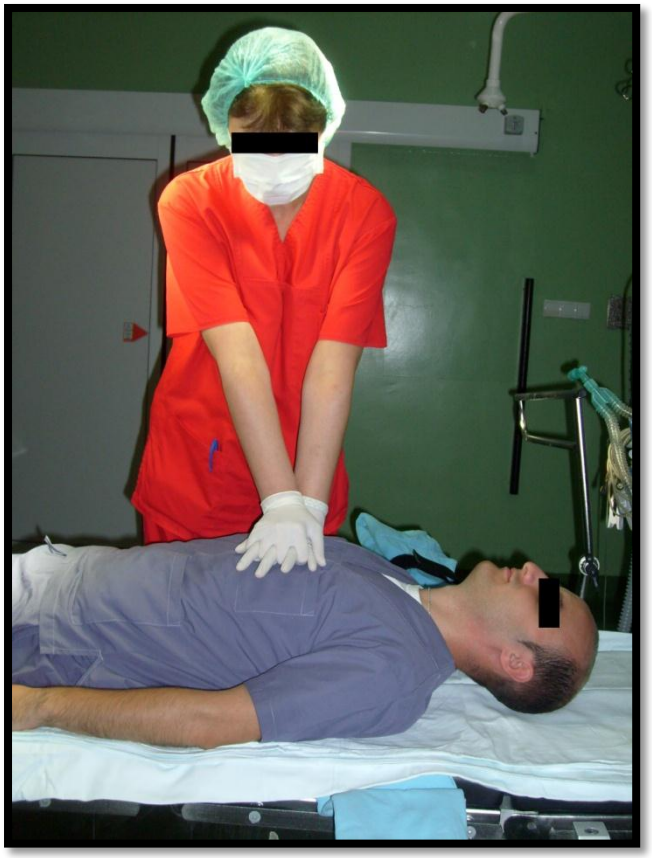
  Rescue breathing without chest compressions

- With palpable pulse who requires support of ventilation, give 10-12 rescue breaths/min.
- Reassess the pulse every 2 minutes.

9. Chest Compressions

- Create blood flow by increasing intrathoracic pressure and directly compressing the heart.
- If properly performed, can produce systolic BP of 60-80 mm Hg, diastolic 18 and mean at the carotid 40.
- In VF, chest compressions increase the likelihood that a defibrillation will be successful.
- Chest compressions are especially important if the first shock is delivered $\geq$4 minutes after collapse.
- "Effective" chest compressions are essential: "Push hard and push fast", rate 100/min, depth 4-5 cm, equal compression: relaxation.
- Supine on a hard surface (backboard or floor).
- Limit interruptions to no longer than 10 seconds except for specific interventions such as insertion of an advanced airway or use of a defibrillator.
- Patients should not be moved while CPR in progress.
- When 2 or more rescuers, reasonable to switch the compressor about every 2 minutes (or after 5 cycles of compressions and ventilations at a ratio of 30:2).
- Accomplish this switch in 5 seconds.

Chest compresions



Picture 19

Compression-Ventilation Ratio

- For adults 30:2 is recommended. In infants and children (<8 yr.) 2 rescuers should use a ratio of 15:2.
- The actual number (not rate) of chest compressions delivered per minute is determined by the rate of chest compressions and the number and duration of interruptions to open the airway, deliver rescue breaths, and allow defibrillator analysis.

Compression-Only CPR

- Some studies show rescue breathing is not essential during the first 5 minutes of adult CPR for VF SCA.

- Laypersons encouraged to do compression - only CPR if unwilling to provide rescue breaths, although the best CPR is compressions & ventilations.

10. Defibrillation

Survival rates is the highest when immediate CPR is provided and defibrillation within 3 to 5 minutes.

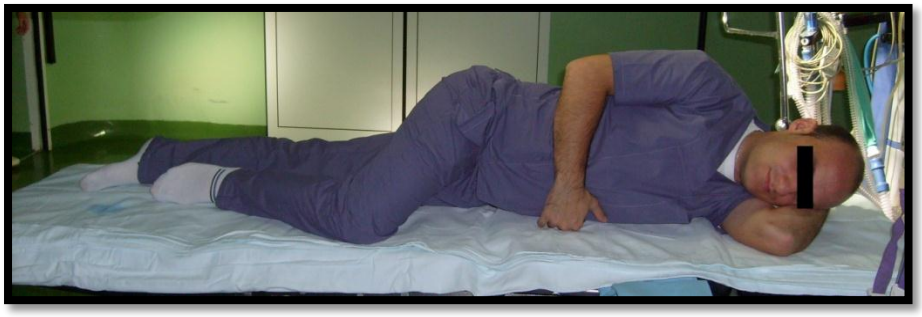
Automated External Defibrillator (AED)

- Some AEDs will automatically switch themselves on when the lid is opened
- Attach pads to casualty's bare chest
- Analysing rhythm do not touch victim
- Shock indicated: atand clear and deliver shock. After the shock was delivered, follow AED instructions, and immediately resume CPR 30:2 for 2 minutes; continue until the victim stars to wake up.
- No shock advised follow AED instructions and immediately resume CPR 30:2

AED Precautions:

- Water: If victim is in water, remove from water and place on dry surface, dry chest and make sure rescuer is not standing in water.
- Medication Patches: Remove any medication patches and clean area prior to applying AED pads.
- Implantable devices: Keep AED pads 3 cm away from any implantable devices such as a pacemaker, defibrillator or port.
- Hairy Chest: If the victim has a hairy chest, the AED pads may stick to the hair instead of the skin on the chest. If this happens the AED will prompt you to check the pads and press down firmly on each pad. If the AED continues to tell you to check the pads, quickly pull off the pads to remove the hair. If a lot of hair remains where you will put the pads, shave the area with a razor and apply a new set of pads.

If victim starts to breathe normally place in **recovery position**:



Picture 20

Continue resuscitation until:

- Qualified help arrives and takes over
- The victim starts breathing normally
- Rescuer becomes exhausted

Relief of Foreign-Body Airway Obstruction (Choking)

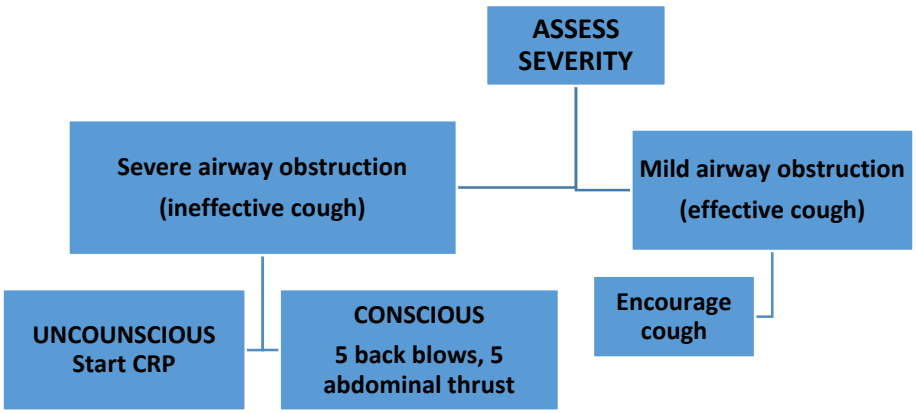


Diagram 1

- Mild obstruction: do not interfere
- Severe airway obstruction: 5 back blows, 5 abdominal thrusts

Abdominal thrust

Picture 21

- If ineffective: consider chest thrusts. Consider chest thrusts also for obese and late pregnancy.
- Abdominal thrusts are not recommended for <1 year.
- Finger sweep.
- If becomes unresponsive, begin CPR.

PEDIATRIC BASIC LIFE SUPPORT

Rescuers who have been taught adult BLS and have no specific knowledge of paediatric resuscitation may use the adult sequence, as outcome is worse if they do nothing. Non-specialists who wish to learn paediatric resuscitation because they have responsibility for children (teachers, school nurses, lifeguards), should be taught that it is preferable to modify adult BLS and perform five initial breaths followed by approximately one minute of CPR before they go for help.

Rescue breaths for a child over 1 year of age (as in [1]):

• Ensure head tilt and chin lift.

• Pinch the soft part of the nose closed with the index finger and thumb of your hand on his forehead.

• Allow the mouth to open, but maintain chin lift.

• Take a breath and place your lips around the mouth, making sure that you have a good seal.

• Blow steadily into the mouth over about 1–1.5 s watching for chest rise.

• Maintain head tilt and chin lift, take your mouth away from the victim and watch for his chest to fall as air comes out.

• Take another breath and repeat this sequence five times. Identify effectiveness by seeing that the child's chest has risen and fallen in a similar fashion to the movement produced by a normal breath.

Rescue breaths for an infant (as in [1]):

• Ensure a neutral position of the head and a chin lift.

• Take a breath and cover the mouth and nose of the infant with your mouth, making sure you have a good seal. If the nose and mouth cannot be covered in the older infant, the rescuer may attempt to seal only the infant's nose or mouth with his mouth (if the nose is used, close the lips to prevent air escape).

• Blow steadily into the infant's mouth and nose over 1–1.5 s, sufficient to make the chest visibly rise.

• Maintain head position and chin lift, take your mouth away from the victim and watch for his chest to fall as air comes out.

• Take another breath and repeat this sequence five times.

For both infants and children, if you have difficulty achieving an effective breath, the airway may be obstructed. No abdominal thrusts for choking infants. Risk because of the horizontal position of the ribs- upper abdominal viscera more exposed to trauma.

Chest compressions

For all children, compress the lower half of the sternum. To avoid compressing the upper abdomen, locate the xiphisternum by finding the angle where the lowest ribs join in the middle. Compress the sternum one finger's breadth above this; the compression should be sufficient to depress the sternum by at least one-third of the depth of the chest. Continue compressions and breaths in a ratio of 15:2.

Chest compression in infants (as in [1])

The lone rescuer compresses the sternum with the tips of two fingers. If there are two or more rescuers, use the encircling technique. Place both thumbs flat side by side on the lower half of the sternum with the tips pointing towards the infant's head. Spread the rest of both hands with the fingers together to encircle the lower part of the infant's rib cage with the tips of the fingers supporting the infant's back. For both methods, depress the lower sternum by at least one-third of the depth of the infant's chest.

Chest compression in children over 1 year of age (as in [1])

Place the heel of one hand over the lower half of the sternum. Lift the fingers to ensure that pressure is not applied over the child's ribs. Position yourself vertically above the victim's chest and, with your arm straight, compress the sternum to depress it by at least one-third of the depth of the chest. In larger children or for small rescuers, this is achieved most easily by using both hands with the fingers interlocked.

It is vital for rescuers to get help as quickly as possible when a child collapses:

• When more than one rescuer is available, one starts resuscitation while another rescuer goes for assistance.

• If only one rescuer is present, undertake resuscitation for about 1min before going for assistance. To minimise interruption in CPR, it may be possible to carry an infant or small child while summoning help.

• The only exception to performing 1min of CPR before going for help is in the case of a child with a witnessed, sudden collapse when the rescuer is alone. In this case, cardiac arrest is likely to be caused by an arrhythmia and the child will need defibrillation. Seek help immediately if there is no one to go for you.

Pediatric AED

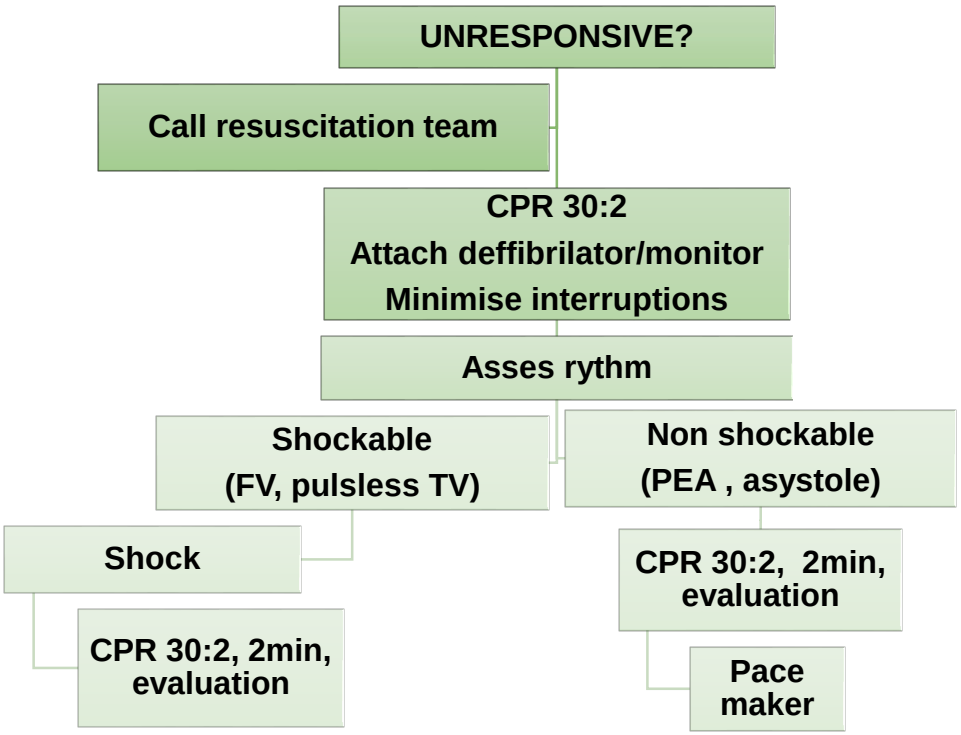
Automated external defibrillators (AEDs) are safe and successful when used in children older than 1 year of age. Purpose made paediatric pads or software attenuate the output of the machine to 50–75 J and these are recommended for children aged 1–8 years. If an attenuated shock or a manually adjustable machine is not available, an unmodified adult AED may be used in children older than 1 year. There are case reports of successful use of AEDs in children aged less than 1 year; in the rare case of a shockable rhythm occurring in a child less than 1 year, it is reasonable to use an AED (preferably with dose attenuator).

ADVANCED LIFE SUPPORT

Advanced cardiac life support, or ACLS, is a series of treatments used by medical professionals in an attempt to save a patient's life when cardiac arrest occurs. ACLS is a combination of medications and procedures performed in the event of cardiac arrest. Procedures involving airway, breathing and circulation, in addition to medications, are performed during ACLS.

Epinephrine, atropine, lidocaine, amiodarone and magnesium are drugs used, in accordance with AHA guidlelines, in ACLS. The medications should be given immediately after rhythm analysis during CPR to allow the drugs to circulate through the body during compressions. Never interrupt CPR to administer drugs.

Provide circulation and cardioversion (accomplished with an electrical shock) when performing ALS. Chest compressions manually provide circulation. A heart monitor allows rhythm analysis and provides a way to shock the heart. Cardioversion occurs when a heart rhythm that is irregular converts to a normal sinus rhythm. This is accomplished by certain medications and electric shock.



Picture 22

Plus:

- **Vascular access**
- **Oxygen**
- **Consider advanced airway ± capnography**
- **Intubation: CPR: 100/min, 10 ventilation/min**
- **Adrenaline 1mg every 3-5 min**
- **FV/TV: Amiodarone 300mg is also given after the third shock**
- **Causal treatment**

The most effective treatment for VF/VT is defibrillation. Early defibrillation results in better outcomes and should not be delayed by an attempt to gain intravenous access, secure the airway or perform cardiac compressions. However cardiac compressions and ventilation should be started if a defibrillator is not immediately available. For conventional monopolar defibrillator, use 360J for the first shock and

the subsequent shocks. For biphasic start with 150-200J. This can be escalated for subsequent shocks but continuing with the same energy is also acceptable

Delivery of drugs via a tracheal tube is no longer recommended – if intravenous access cannot be achieved, drugs should be given by the intraosseous (IO) route.

Several recent studies have failed to demonstrate any benefit from atropine in out-of-hospital or inhospital cardiac arrests; and its routine use for asystole or PEA is no longer recommended.

The recommended IV/IO dose of adrenaline in children for the first and for subsequent doses is 10 μgkg−1. The maximum single dose is 1mg. If needed, give further doses of adrenaline every 3–5 min. Intratracheal adrenaline is no longer recommended, but if this route is ever used, the dose is tentimes this (100μgkg−1).

Potential causes or aggravating factors for which specific treatment exists must be considered during any cardiac arrest. For ease of memory, these are divided into two groups of five based upon their initial letter: either H or T:

- Hypoxia
- Hypovolemia
- Hypo/hyperkalemia/metabolic
- Hypothermia
- Hypoglycaemia
- Thrombosis – coronary or pulmonary
- Tamponade - cardiac
- Toxins
- Tension pneumothorax
- Trauma

Administration of sodium bicarbonate during cardiac arrest and CPR or after ROSC is not recommended. Give sodium bicarbonate (50 mmol) if cardiac arrest is associated with hyperkalaemia or tricyclic antidepressant overdose; repeat the dose according to the clinical condition and the result of serial blood gas analysis.

Successful resuscitation requires teamwork. It is related to the interactions, knowledge, and skills of responders. There should be a team leader who is responsible for assessment /evaluation of the situation and delegation of duties.

Other responders should accept the delegated role and stay focused, while remaining aware of evolving resuscitation activities.

Components of CPR that affect hemodynamics are:

- Ventilation rate and duration
- Compression depth, rate and number
- Complete chest recoil
- Hands-off time.

Methods to improve the quality of CPR include:

- Education, training, assistance or feedback from biomedical devices & electronic monitoring.
- Continuous monitoring of the quality of CPR delivered and patient outcome up to hospital discharge.

TAKE HOME MESSAGES

- Following VF, cardiopulmonary resuscitation plus defibrillation within 3–5 min of collapse increases dramatically the survival rates. Each minute of delay before defibrillation reduces the probability of survival to discharge by 10–12%.
- The actual number (not rate) of chest compressions delivered per minute is determined by the rate of chest compressions and the number and duration of interruptions to open the airway, deliver rescue breaths, and allow defibrillator analysis.
- The only exception to performing 1min of CPR before going for help is in the case of a child with a witnessed, sudden collapse when the rescuer is alone. In this case, cardiac arrest is likely to be caused by an arrhythmia and the child will need defibrillation. Seek help immediately if there is no one to go for you.

References

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POISONING IN THE ICU

Dr. Cioc Adrian

Prof. Univ. Dr. Copotoiu Sanda-Maria

TOXIDROMES

A toxidrome describes clinical signs common to a number of toxins.

The toxidromes are:

- Anticholinergic (antimuscarinic)
- Cholinergic
- Adrenergic
- GABAergic
- Sodium and potassium channel blocker—related
- Serotoninergic
- Mixed

ANTICHOLINERGIC TOXIDROME

The anticholinergic syndrome is due to anticholinergic toxicity.

Anticholinergic toxicity is defined as antimuscarinic poisoning. It occurs when the acetylcholine postsynaptic muscarinic receptors are antagonized.

Characteristics of central anticholinergic toxicity include hallucinations, psychoses, seizures, and coma.

Anticholinergic syndrome can be summarized by the mnemonic:

- Mad as a hatter
- Hot as a hare
- Blind as a bat
- Red as a beet
- Dry as a bone

Antidote Considerations: Physostigmine, 1-2 mg or 0.02 mg/kg/dose. The dose can be repeated every 5-15 minutes until normal mental status is achieved or a maximum of 4 mg is administered in adults or 2 mg is administered in pediatrics.

CHOLINERGIC TOXIDROME

The cholinergic toxidrome is manifested by stimulation of both the muscarinic and the nicotinic receptors in both autonomic and central nervous systems.

Stimulation of the muscarinic receptors leads to the “classic” SLUDGE syndrome:

- Salivation
- Lacrimation
- Urination
- Diarrhea
- GI cramps
- Emesis
- In addition bronchoconstriction and/or bronchorrhea are commonly found.

Agents that cause a cholinergic toxidrome can be divided into two main groups according to their mechanism of action:

- Direct nicotinic receptor stimulation

  Plant alkaloids such as nicotine

  Nicotine-based insecticides

- Increased acetylcholine levels

  Organophosphates and carbamates

Organophosphates

Organophosphates are insecticides. These agents inhibit the enzyme acetylcholinesterase, which is responsible for the degradation of acetylcholine. The organophosphate binds to the enzyme, causing it to undergo a conformational change at its binding site to acetylcholine.

Atropine is an antidote to the muscarinic features of organophosphate toxicity, acting to competitively inhibit acetylcholine at muscarinic receptors but with no effect at ganglionic or neuromuscular nicotinic receptors.

The dose is 2 mg (0.05 mg/kg in children), repeated at 10- to 30-minute intervals until drying of excessive secretions occurs.

Pralidoxime is an oxime that reactivates acetylcholinesterase.

The dose is 1 to 2 g (25 to 50 mg/kg in children) given over 30 minutes, followed by an infusion of 200 to 500 mg/hour.

ADRENERGIC TOXIDROME

Sympathomimetic agents cause the adrenergic toxidrome. Neurological manifestations include hyperthermia, agitation, seizures, and coma. Cardiovascular effects include tachycardia, hypertension, peripheral vasoconstriction, arrhythmias, and myocardial infarction. Metabolic disturbances from increased circulating catecholamines cause elevation of glucose levels and the white blood cell count.

Common causes include:

- Cocaine
- Amphetamines
- Salbutamol
- Theophylline
- Pseudoephedrine
- Norepinephrine
- Epinephrine

No specific antidotes are available. Management consists of lowering body temperature and blood pressure and achieving central sedation, usually with a benzodiazepine and other supportive measures. Hypertension requiring pharmacological intervention is treated with a specific alpha-blocker or smooth muscle antihypertensive agent, such as nitroglycerine.

GABAERGIC TOXIDROME

γ-Aminobutyric acid, GABA, is a naturally occurring inhibitory neurotransmitter located in the central nervous system. The GABAergic toxidrome refers to the effects

of stimulation of the $GABA_A$ receptor. This action produces inhibitory neurotransmission by hyperpolarization of the neuron (influx of chloride ions).

Benzodiazepines and barbiturates, anticonvulsants such as valproate and to some degree, carbamazepine, general anesthetics, and ethanol produce GABA stimulation.

Flumazenil is a benzodiazepine antagonist that binds to the benzodiazepine receptor, displacing other benzodiazepine agonists, without neuroinhibitory effects. Thus, it antagonizes the neuronal depression caused by GABA stimulation at the $GABA_A$ receptor.

Criteria for Admission of the Poisoned Patient to ICU

- Respiratory failure
- Seizures
- Cardiac arrhythmia
- Hypotension
- Unresponsiveness to verbal stimuli
- Second- or third-degree atrioventricular block
- Emergent dialysis or hemoperfusion
- Increasing metabolic acidosis
- Tricyclic or phenothiazine overdose manifesting anticholinergic signs, neurologic abnormality, QRS duration >0.12 second, or QT duration >0.5 seconds
- Pulmonary edema induced by drugs or toxic inhalation
- Cerebral edema (from salicylate, lead, carbon monoxide)
- Drug-induced hypothermia or hyperthermia including neuroleptic malignant syndrome
- Hyperkalemia secondary to digitalis overdose

METHODS FOR DECONTAMINATION

Gastrointestinal Decontamination

For gastric lavage, an orogastric tube is passed, after which small volumes (200-300 mL) of liquid are administered and aspirated. Endotracheal intubation should precede this procedure in comatose patients (Glasgow Coma Scale <8 points).

Complications of the procedure include aspiration, laryngospasm, hypoxia, hypercapnia, mechanical injury.

Gastric lavage should not be employed routinely in poisoned patients. It should not be considered unless the patient has ingested a potentially life-threatening amount of a poison and the procedure can be undertaken within 60 minutes after ingestion.

Activated Charcoal

Activated charcoal is made when coconut shells, peat, wood, or other materials undergo controlled pyrolysis and are subsequently activated by heating in steam or air at high temperatures. Activation creates multiple internal pores and the small particle size necessary for adsorption. The particles have a large surface area and are capable of adsorbing poisons with varying affinities.

Contraindications to the administration of activated charcoal include decreased level of consciousness and unprotected airway, ingestion of caustic substances or hydrocarbons, gastrointestinal pathology (ileus).

Activated charcoal does not adsorb: lead, cyanide, hydrocarbons, caustics, lithium.

Single-dose activated charcoal should not be administered routinely in the management of poisoned patients. The effectiveness of charcoal decreases with time; the greatest benefit is obtained within the first hour after ingestion.

Dosage: 1 gram/kg administered orally or in a 1:10 ratio of activated charcoal to poison.

Toxins with Enhanced Elimination by Multiple Dosing of Activated Charcoal	
acetaminophen	sotalol
amitriptyline	theophylline
carbamazepine	
diazepam	
digoxin	
phenytoin	
propanolol	

Table 27

Cathartics (sorbitol or magnesium citrate)

Administration of a cathartic alone has no role in the management of poisoned patients. Routine use of a cathartic in combination with activated charcoal is not endorsed.

Whole-Bowel Irrigation

Whole-bowel irrigation consists of administration through a nasogastric tube of an osmotically balanced, polyethylene glycol–based electrolyte solution to decontaminate the entire gastrointestinal tract by physically expelling intraluminal contents.

Whole bowel irrigation has been advocated for certain intoxications, most particularly iron, lead, lithium, sustained-release or enteric-coated medications.

An adult infusion rate is 1.5-2 L/hour (500-1000 mL/hour in children). It may take 4-6 hours (or 3 L) for complete bowel irrigation until the rectal effluent is clear.

Contraindications include bowel pathology, unprotected or compromised airway, hemodynamic instability, and intractable vomiting. Whole-bowel irrigation should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs.

Urinary alkalinization

Urinary alkalinization is the administration of intravenous (IV) sodium bicarbonate to produce urine with a pH ≥ 7.5. The objective of treatment is pH manipulation, not forced diuresis.

Urinary alkalinization should be considered as first-line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urinary alkalinization also should be considered for patients with severe poisoning due to 2,4-dichlorophenoxyacetic acid or mecoprop (MCPP) poisoning.

Hemodialysis and Hemoperfusion
Indications:

- Patient deterioration despite intensive care management

Examples: phenobarbital, salicylates, methanol, lithium, ethylene glycol.

Drugs and Toxins Removed by Hemodialysis	
acetaminophen	formaldehyde
acetazolamide	fluoride
acyclovir	lithium
Amanita phalloides	metformin
carbamazepine	methanol
ethanol	
Ethylene glycol	

Table 28

Antidotes

Dextrose

Hypoglycemia can be the result of drug or toxin exposure, nutritional deprivation, or a medical complication (e.g., sepsis, hyperthermia).

Useful formula for hypoglycemia correction: volume (ml) dextrose 33% required= (120mg- actual glycaemia mg)*0.6. The actual glycaemia is measured in mg/dL.

Naloxone

Naloxone and naltrexone are competitive opioid antagonists that bind at the mu (μ), kappa (κ), and delta (δ) receptors and competitively prevent the binding of endogenous and exogenous opiates at these receptors. The duration of action of naloxone is 15 to 90 minutes.

Flumazenil

Flumazenil competitively antagonizes the pharmacologic effects of drugs that act on the benzodiazepine receptor.

Flumazenil also antagonizes the sedative effects of drugs other than benzodiazepines, such as zolpidem, cannabis, ethanol, promethazine, chlorzoxazone.

Physostigmine

Physostigmine inhibits acetylcholinesterase, the enzyme responsible for the metabolism of acetylcholine (ACH). ACH is an endogenous neurotransmitter that mediates action by binding to muscarinic and nicotinic receptors. In the poisoned patient, physostigmine is most frequently administered to treat anticholinergic

toxicity. Clinical signs of anticholinergic toxicity are listed on the front page of this chapter.

Complications of cholinergic crises (caused by excessive doses of physostigmine) include hypertension, arrhythmia, asystole, bronchorrhea, bronchoconstriction, seizures, and status epilepticus. Contraindications to physostigmine administration include reactive airway disease, peripheral vascular disease, intestinal or bladder obstruction, and treatment with a depolarizing neuromuscular blocking agent.

LIST OF POISONS AND CORRESPONDING ANTIDOTES

Poison	Antidote
acetaminophen	N-acetylcysteine
anticholinergic	physostigmine
benzodiazepines	flumazenil
Carbon monoxide	oxygen
cyanide	sodium nitrite/sodium thiosulfate
Ethylene glycol	ethanol, fomepizole
methanol	ethanol, fomepizole
organophosphate	atropine, pralidoxime
Opioids	naloxone

Table 29

ETHANOL INTOXICATION

It is a clear, colorless liquid with a pleasant odor and a burning taste, found in fermented alcoholic beverages.

The ethanol content of alcoholic beverages varies widely, but typical concentrations range from 40% to 55% in whiskey and related distilled spirits (40-60% in the indigenous tuica/palinca, a peer or plum distilled spirit), 10% to 15% in table wines, and 4% to 6% in most beers.

Between 2% and 10% of ingested ethanol is excreted intact by the kidneys and lungs, but the major fraction is metabolized by hepatic alcohol dehydrogenase to acetaldehyde. At high blood ethanol levels, a particular isoform of the hepatic

microsomal cytochrome P450 enzyme (CYP2E1) provides an additional, albeit normally minor, oxidative pathway for ethanol metabolism. This alternative pathway is inducible with chronic ethanol exposure.

Acetate can then enter the tricarboxylic acid cycle and ultimately be metabolized to carbon dioxide (CO_2) and water. Polymorphisms in the dehydrogenase enzymes can result in increased production rates or diminished metabolic clearance of acetaldehyde.

Metabolic conversion of ethanol to acetaldehyde and acetate by dehydrogenases raises the ratio of reduced nicotinamide adenine dinucleotide (NADH) relative to its oxidized form (NAD^+). This change in intracellular redox state favors conversion of pyruvate to lactate, by lactate dehydrogenase (LDH) and can thereby raise the blood lactate concentration.

The resulting increase in blood lactate level is usually small. However, the presence of lactic acidosis should prompt consideration of an alternative cause such as circulatory shock.

Acute intoxication can induce cardiac dysrhythmias, particularly atrial fibrillation, Wernicke-Korsakoff syndrome, chronic cerebellar ataxia, Marchiafava-Bignami syndrome, and central pontine myelinolysis.

Wernicke encephalopathy can manifest as lethargy, confusion, truncal ataxia, nystagmus, and ophthalmoplegia, whereas Korsakoff dementia manifests as retentive memory impairment, confabulation, and learning deficits.

In the absence of associated illness, mild to moderate intoxication requires no special treatment other than abstinence and a period of observation. Regardless of the degree of intoxication, withdrawal precautions are recommended for chronic imbibers, particularly those with a history of heavy chronic use or alcohol withdrawal manifestations.

Parenteral thiamine (50 or 100 mg) is given during the initial phase of management, regardless of the level of sensorium, to prevent or treat Wernicke-Korsakoff syndrome.

Dextrose-containing saline solutions are usually the fluid of choice to correct dehydration and prevent hypoglycemia. Dextrose administration is traditionally preceded by thiamine dosing.

ACETAMINOPHEN INTOXICATION

Acetaminophen causes liver toxicity. Toxic levels are more likely to occur with ingestions over 150 mg/kg. A small amount is metabolized by the P-450 enzyme system to a potentially toxic intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI). This intermediate is metabolized by glutathione to a nontoxic mercaptopurine product but only when an excessive amount of acetaminophen has been ingested, this pathway gets importance. In the face of an overdose glutathione can be used up, and when levels fall below 30% of normal, glutathione can no longer detoxify the acetaminophen intermediate, so toxicity develops.

N-acetylcysteine acts by donating a sulfhydryl group to detoxify the P-450—formed intermediate. It also replenishes glutathione stores. People at risk for acetaminophen toxicity are those with lowered glutathione stores, including alcoholic persons and those on medication that increases P-450 activity, such as phenobarbital.

The loading dose of *N*-acetylcysteine is 150 mg/kg in 200 mL of 5% dextrose given over 15 minutes, then 50 mg/kg in 500 mL of 5% dextrose is given over 4 hours, followed by 100 mg/kg in 1000 mL of 5% dextrose over 16 hours.

ETHYLENE GLYCOL INTOXICATION

Ethylene glycol is a clear, colorless, almost odorless, sweet-tasting, viscous liquid that is commonly used as the main constituent in most formulations of permanent automotive antifreeze.

The action of alcohol dehydrogenases converts ethylene glycol to glycoaldehyde, which can be converted further to glyoxal. Both glycoaldehyde and glyoxal are metabolized to glycolic acid, then to glyoxylic acid, and finally to oxalic acid.

The CNS manifestations of ethylene glycol poisoning can range from effects that are similar to those seen with acute ethanol intoxication, such as excitement, confusion, disorientation, and ataxia, to signs of CNS depression, such as lethargy, stupor, or coma. Nausea, vomiting, myoclonus, and seizures also can occur. The second phase manifests 12 to 24 hours after ingestion and consists of cardiorespiratory effects which may include dyspnea and a Kussmaul respiratory pattern secondary to metabolic acidosis or pulmonary edema. Tachycardia, hypotension, frank circulatory shock, coma, and death also can occur.

Ethanol or fomepizole is administered to slow the conversion of the glycol to toxic intermediates; sodium bicarbonate is given if there is significant metabolic acidosis (e.g., arterial pH < 7.30); and hemodialysis is used in cases of serious intoxication to speed elimination of the parent compound and toxic metabolites.

Intravenous ethanol (10% diluted in 5% dextrose) is given as a loading dose of 10 mL/kg over 30 minutes, followed by an infusion of 1.4 to 2.0 mL/kg per hour.

The loading dose of fomepizole is 15 mg/kg, with a maintenance dose 10 mg/kg every 12 hours for 4 doses followed by 15 mg/kg every 12 hours until ethylene glycol levels fall below 20 mg/dL.

METHANOL INTOXICATION

Methanol is a clear, colorless liquid having an alcoholic odor.

It is metabolized slowly to formaldehyde and then rapidly to formic acid.

Formic acid production can result in metabolic acidosis. Independent of the acidosis, formic acid inhibits cytochrome oxidase and has direct neurotoxic effects, particularly affecting the retina and optic nerves.

Clinical manifestations

- Nausea
- Vomiting
- Abdominal pain
- Hematemesis
- Coma
- Cerebral edema
- Seizures

Laboratory findings include high serum osmolal gap, high anion gap, metabolic acidosis with low bicarbonate, high hematocrit, high glucose, and high serum amylase.

Ethanol is to be considered an antidote for methanol intoxication, similar to ethylene glycol intoxication. Ethanol can be given orally, by gastric instillation, or by vein.

Like ethanol, fomepizole inhibits alcohol dehydrogenase. Fomepizole is given IV as a loading dose of 15 mg/kg, followed by 10 mg/kg every 12 hours for 4 doses and then 15 mg/kg every 12 hours.

Hemodialysis can effectively and more rapidly remove methanol and its toxic metabolites from the body.

ANTIDEPRESSANT OVERDOSE

Antidepressants include a wide range of drugs that act primarily in the central nervous system usually by affecting GABAergic, serotoninergic, NA, dopaminergic transmission.

We will refer only to tricyclic antidepressants because they account for most death-related antidepressant overdose.

Classification of antidepressants

Classification of Antidepressants
Tricyclic Antidepressants
Amitriptyline
Nortriptyline
Clomipramine
Monoamine Oxidase Inhibitors
Phenelzine
Tranylcypromine
Moclobemide
Selective Serotonin Reuptake Inhibitors
Citalopram
Escitalopram
Fluoxetine
Serotonin and Norepinephrine Reuptake Inhibitors
Venlafaxine
Desvenlafaxine
Duloxetine
Atypical Antidepressants
Bupropion
Mirtazapine
Reboxetine

Table 30

Antidepressants act to increase the extraneuronal concentrations of serotonin and/or norepinephrine in the CNS.

The TCAs, SSRIs, and SNRIs do this by inactivating transporters in the presynaptic neuron, thereby preventing the reuptake of these biogenic amines from the synaptic cleft.

MAOIs prevent the breakdown of 5-HT and NE after reuptake has occurred.

Most antidepressants block α_1-adrenergic, cholinergic, and histamine (H_1) receptors.

Tricyclic Antidepressants (TCA)

TCAs overdose account for the majority of deaths related to antidepressant overdose.

The clinical manifestations of toxicity may be divided into anticholinergic effects, cardiovascular effects, and central nervous system effects.

Clinical signs

- mydriasis
- dry mouth
- ileus
- urinary retention
- flushing
- seizures
- hypotension
- heart block
- arrhythmias

The diagnosis of TCA overdose should be suspected in any patient who presents with an anticholinergic toxidrome.

Treatment

Prevention of absorption can be accomplished by administration of activated charcoal. The administration of activated charcoal should be considered only in patients who present within 1 hour of a toxic ingestion.

Hemodialysis and charcoal hemoperfusion would be ineffective in removing TCAs and their active metabolites, because avid tissue and plasma protein binding leaves only a small fraction of free drug available for diffusion or adsorption.

Sodium bicarbonate is administered in order to antagonize the cardiovascular effects of TCA overdose, in order to maintain a ph of approximately 7.5.

ORGANOPHOSPHATES INTOXICATION

The primary toxicologic effects of organophosphates insecticides relate to their ability to phosphorylate acetylcholinesterase (AChE), thereby inhibiting the enzyme.

Two principal cholinesterases, red blood cell (RBC) cholinesterase (AChE), present in RBCs and nerve endings, and pseudocholinesterase (PChE), found primarily in liver and serum. Organophosphates and carbamates inhibit both cholinesterases.

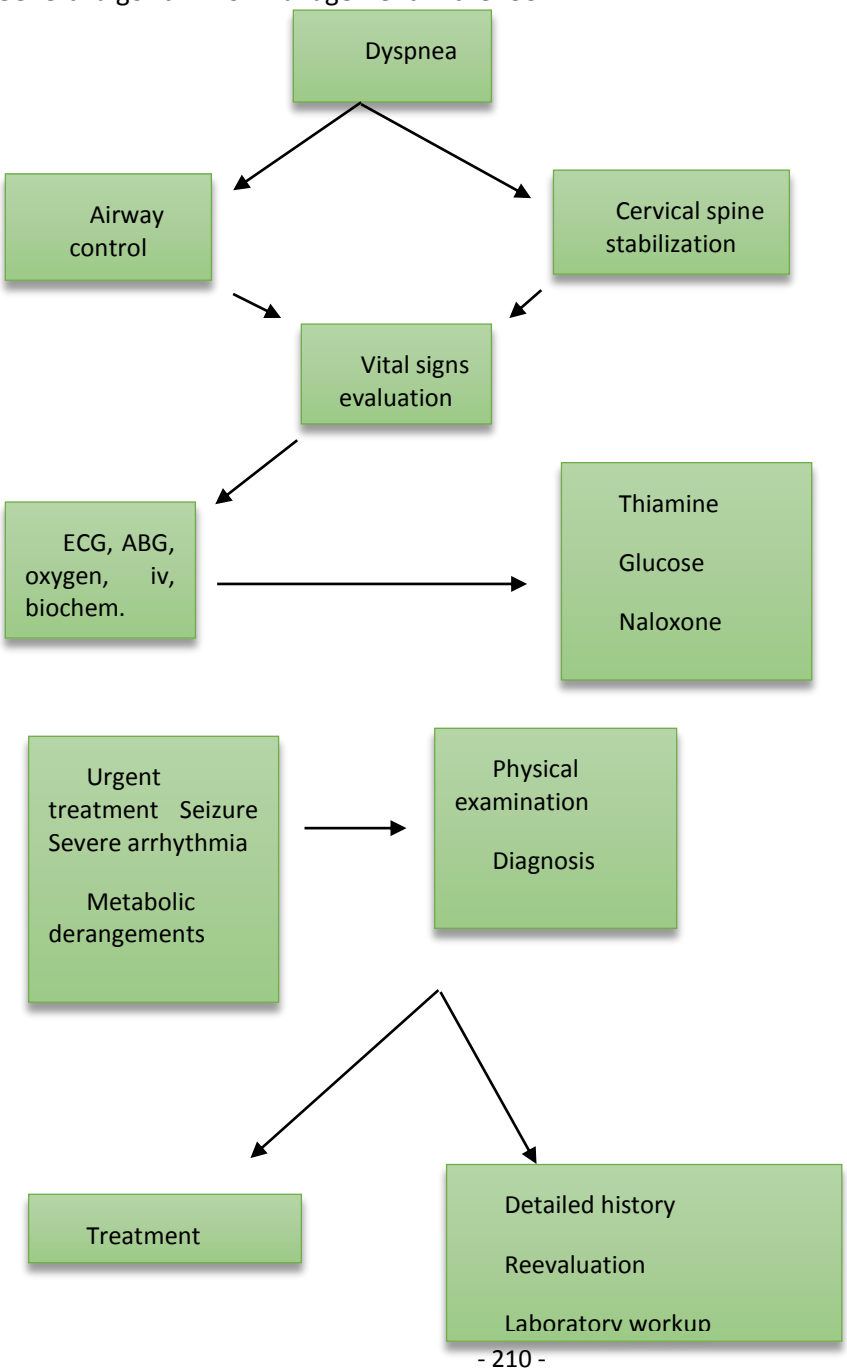
Clinical manifestations (cholinergic toxidrome)

- excessive mucous secretion
- noncardiogenic pulmonary edema
- seizures
- coma
- choreoathetoid movements
- salivation
- lacrimation
- urination
- emesis

Diagnosis of organophosphate poisoning typically requires a clinical picture of cholinergic symptoms, onset of symptoms within 12 hours of exposure, a 50% reduction of plasma and red blood cell (RBC) cholinesterase below baseline.

Atropine is the mainstay of treatment, and in some cases extremely large doses (>100 mg/d) may be required to reverse muscarinic symptoms. Critical care clinicians often administer an oxime such as pralidoxime (2-PAM), which regenerates AChE by reversing phosphorylation of the active site on the enzyme before the phosphorylated AChE has undergone aging.

General algorithm for management in the ICU



MUSHROOM INTOXICATION

1. Cyclopeptides Mushrooms

Examples: Amanita bisporigera, Amanita ocreata, Amanita phalloides, Amanita suballiacea, Amanita tenuifolia, Amanita verna, Amanita virosa , Conocybe filaris, Galerina autumnalis, Galerina marginatus, Galerina speciosissimus

Amanita Bisporigera

Picture 23

Amanita Ocreata

Picture 24

Amanita phalloides

Picture 25

Mechanism of Action

The mushrooms contain the cyclopeptides phallotoxins, amatoxins, and virotoxins. Only amatoxins are considered important in human poisoning and they can cause liver necrosis through inhibition of RNA polymerase II.

The clinical signs and symptoms follow 3 phases:

- Up to 24 hours post ingestion with an incubation period of 8 to 12 hours
- Remission after 72 hours post ingestion
- Renal and Hepatic adverse effects after 3 to 6 days post ingestion

Clinical signs and symptoms

- Hypotension, cardiomyopathy
- Encephalopathy, coma, seizures
- Nausea, vomiting, colicky abdominal pain, hepatitis, pancreatitis
- Coagulopathy
- Fulminant hepatic failure
- Acute kidney injury

Pharmacokinetics of cyclopetides

- Phallotoxin is not well absorbed though the gastrointestinal tract
- Toxins distribution volume is about 160-290 mL/kg
- The toxins are not protein bound
- The toxins are excreted in urine, feces, and bile
- The estimated lethal dose is 0.1 mg/kg; one Amanita cap may be lethal in an adult
- Amatoxins are extremely stable compounds, resistant to heat, drying, freezing, and not degraded enzymatically

The Meixner/Weiland test can be used to detect the presence of amatoxins.

Meixner Method:

- Squeeze one drop of juice from a fresh mushroom cap onto filter paper. Let it dry at room temperature and out of sunlight. Apply one drop of concentrated hydrochloric acid. A change to a blue color will indicate the presence of amatoxins

Treatment

- Gastric lavage may be performed if ingestion occurred within 1 hour
- Activated charcoal with cathartic are usually administered in the emergency department
- I.V. fluids are administered to correct hypovolemia, lactulose, neomycin are administered for hepatic failure
- Fresh frozen plasma may be needed to treat coagulopathy (INR >3)
- High dose Penicillin G (300,000-1,000,000 units/kg/day), silymarin, cimetidine, thioctic acid and N-acetylcysteine
- Dose of silymarin: 5 mg/kg I.V. infusion over 1 hour followed by 20 mg/kg/day continuous infusion for 6 days

Extracorporeal liver assistance methods utilizing albumin dialysate (molecular absorbent recycling system or MARS) has been utilized to remove protein-bound and water soluble substances in patients with liver failure and grade III or IV hepatic encephalopathy in cases of mushroom intoxication.

Charcoal hemoperfusion within 24 hours of ingestion is controversial. Orthotopic liver transplant may be necessary in the most severe cases.

2. Monomethylhydrazines Mushrooms

Examples: Gyromitra ambigua, Gyromitra brunnea, Gyromitra caroliniana, Gyromitra esculenta, Gyromitra fastigiata, Gyromitra gigas, Gyromitra infula, Helvella species, Sarcosphaera crasa

Gyromitra Infula

Picture 26

Picture 27

Gyromitra caroliniana

Picture 28

Sarcosphaera crasa

Picture 29

Mechanism of action

Gyromitrin present in the mushroom is hydrolyzed upon digestion to N-methyl-N-formylhydrazine and monomethylhydrazine. Monomethylhydrazine is an inhibitor of coenzyme pyridoxyl phosphate and gamma-aminobutyric acid in the central nervous system.

N-methyl-N-formylhydrazine depletes hepatic cytochrome P450.

Clinical signs and symptoms

- Seizures, coma, dizziness, delirium, fever
- Nausea, vomiting, abdominal pain, cramps, diarrhea
- Hemolytic anemia
- Nephritis, Hepatitis

Treatment

- Gastric lavage may be performed if ingestion occurred within 1 hour
- Activated charcoal with cathartic are usually administered in the emergency department
- I.V. fluids are administered to correct hypovolemia
- Pyridoxine 25 mg/kg I.V. for seizures

Lethal dose: Children: 10-30 mg/kg; Adults: 20-50 mg/kg.

3. Cholinergic Mushrooms

Examples: Clitocybe dealbata, Clitocybe dilatata, Clitocybe morbifera, Clitocybe rivulosa, Inocybe fastigiata, Inocybe geophylla

Clitocybe dealbata

Picture 30

Clitocybe dilatata

Picture 31

Inocybe fastigiata

Picture 32

Mechanism of action

- The mushrooms contain the compound muscarine which is structurally similar to acetylcholine and produces symptoms of cholinergic stimulation

Muscarine is not degraded by acetylcholinesterase enzyme, and therefore it accumulates.

Clinical signs and symptoms (cholinergic toxidrome)

- Bradycardia, hypotension, arrhythmias
- Delirium, dizziness, ataxia, somnolence, seizures, psychosis, euphoria, residual headaches, fever, coma, hallucinations, hyperthermia
- Vomiting, diarrhea, salivation
- Miosis, lacrimation

Treatment

- Gastric lavage may be performed if ingestion occurred within 1 hour
- Activated charcoal with cathartic are usually administered in the emergency department
- I.V. fluids are administered to correct hypovolemia
- Atropine 1-2 mg I.V. in adults or 0.05 mg/kg in children

Estimated lethal dose

- Muscarine: 40-180 mg;
- Toxic dose: 100 g or less of fresh mushrooms

4. Anticholinergic Mushrooms

Examples: Amanita cothurnata, Amanita crenulata, Amanita frostiana, Amanita gemmata, Amanita muscaria, Amanita pantherina

Amanita cothurnata

Picture 33

Amanita frostiana

Picture 35

Mechanism of action

- Inebriation syndrome is due primarily to the toxin ibotenic acid and its decarboxylation product, muscimol. Ibotenic acid is structurally related to the excitatory neurotransmitter glutamic acid while muscimol is related to the inhibitory neurotransmitter GABA

Clinical signs and symptoms

- Tachycardia, hypotension
- Delirium, dizziness, ataxia, somnolence, coma
- Vomiting, xerostomia
- Myoclonus
- Mydriasis

Treatment

- Gastric lavage may be performed if ingestion occurred within 1 hour
- Activated charcoal with cathartic are usually administered in the emergency department
- I.V. fluids are administered to correct hypovolemia
- physostigmine for life-threatening anticholinergic crisis (0.5-2 mg I.V. over a 5 minute period)

Toxic dose

- Ibotenic acid: 30-60 mg
- Muscimol: 6 mg

5. Psychedelic Mushrooms

Examples: Conocybe cyanopus, Conocybe smithii, Gymnopilus aeruginosa, Gymnopilus luteus, Gymnopilus spectabilis, Gymnopilus validipes, Panaeolus campanatuus, Panaeolus foenisecii, Panaeolussphinctrinus, Panaeolus subbalteatus, Pluteus salicinus, Psilocybe baeocystis, Psilocybe caerulescens, Psilocybe caerulipes, Psilocybe cubensis

Conocybe cyanopus

Picture 36

Gymnopilus spectabilis

Picture 37

Mechanism of action

- Contains psilocybin and psilocin which indole alkaloids similar to LSD and they are possible serotonin antagonists

Clinical signs and symptoms

- Tachycardia, flushing, hypertension, sinus tachycardia, Wolff-Parkinson-White syndrome
- Ataxia, chills, headache, dizziness, fever,
- seizures, visual hallucinations, psychosis
- Vomiting, urinary incontinence
- Methemoglobinemia
- Myalgias, paresthesias, hyperkinesis, rigors,
- Mydriasis

Treatment

- Gastric lavage may be performed if ingestion occurred within 1 hour
- Activated charcoal with cathartic are usually administered in the emergency department
- I.V. fluids are administered to correct hypovolemia
- Diazepam, midazolam, lorazepam for panic attacks, chlorpromazine for treatment of hallucinations

The mushroom images are downloaded mainly from Wikipedia and/or from sites that allowed downloading, interpreted as courtesy.

TAKE HOME MESSAGES

- The effectiveness of charcoal decreases with time; the greatest benefit is obtained within the first hour after ingestion
- Activated charcoal does not adsorb: lead, cyanide, hydrocarbons, caustics, lithium
- Administration of a cathartic alone has no role in the management of poisoned patients
- Urinary alkalinization should be considered as first-line treatment in patients with moderately severe salicylate poisoning
- Hemodialysis is effective for phenobarbital, salicylates, methanol, lithium, ethylene glycol

- Keep in mind the general approach of an intoxicated patient with unknown substance
- The earliest the clinical signs of mushroom toxicity, the best for the outcome

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ANESTHESIA

Dr. Cioc Adrian

Sef. lucr. Dr. Szederjesi Janos

DEFINITION OF ANESTHESIOLOGY

The American Board of Anesthesiology defines anesthesia as a discipline that is dealing with:

- Assessment, preparation and consultation of patients for anesthesia
- It provides relief and prevention of pain during and following surgery or therapeutic and diagnostic procedures
- Monitoring patients in the perioperative period
- Diagnosis, treatment of acute and chronic pain

The main goals of general anesthesia are:

- Amnesia
- Hypnosis
- Analgesia
- Muscle relaxation
- Control of homeostasis

PREOPERATIVE EVALUATION AND PREPARING

Introduction

The preoperative evaluation is the cornerstone to a safe practice of modern anesthesia.

The main preoperative goals are assessing the patient's coexisting diseases by taking the patient's history, addressing patients concerns and questions and explaining the course of anesthesia in order to relief the patient's anxiety. Care must be taken to evaluating the patient's current medication because some of the drugs might be best withheld in the morning of surgery (for example ACE inhibitors).

The patient's pathology usually influences the anesthetic plan. For example a patient considered with a full stomach implies utilization of rapid sequence induction for general anesthesia. Another important preoperative goal is obtaining the patient's informed consent and also explaining the potential risks associated with general or regional anesthesia techniques.

Preoperative evaluation of the surgical patient

- **Airway**

The airway is evaluated in order to anticipate a difficult intubation. The most widely accepted classification is the Mallampati classification.

Mallampati airway classification

Class	Direct visualization
I	Soft palate, fauces, uvula, pillars
II	Soft palate, fauces, uvula
III	Soft palate, uvular base
IV	Hard palate only

Table 31

Airway physical examination

1. Length of upper incisors
2. Interincisor distance
3. Shape of palate
4. Thyromental distance
5. Length of neck
6. Range of motion of head and neck
7. Visibility of uvula
8. Thickness of neck

Even if anesthesiologists often use the Mallampati classification, it has a low positive predictive value in identifying patients who are difficult to intubate.

In patients with Down syndrome or patients with rheumatoid arthritis, it is imperative to evaluate the cervical spine.

- **Pulmonary system**

A close pulmonary examination should be done in all patients, specially in those with history of tabacco use, shortness of breath, cough, wheezing, sleep apnea. Auscultation should be used to detect decreased breath sounds, wheezing, stridor or rales.

As indicated a chest X-ray should be performed or even functional respiratory tests in pacients with known COPD or asthma. It is important to educate patients to stop smoking 2-3 weeks before the planned procedure.

- **Cardiovascular**

The anesthesiologist should search for signs and symptoms of heart failure, uncontrolled hypertension (signs of end-organ damage), valvular disease and myocardial ischemia. In selected cases an ECG, echocardiography, stress test, should be performed preoperatively.

Diabetic patients are a special population because signs of myocardial ischemia might be obscured by diabetic polyneuropathy.

The examination of the cardiovascular system should include a preoperative blood pressure measurement, heart auscultation, peripheral vascular assessment. Auscultation of the heart and carotid area is mandatory because it is suggestive of aortic stenosis.

- **Neurologic System**

It should include testing of strength, reflexes, and sensation.

After a preoperative evaluation the patient should be assigned to the ASA physical status scale.

American Society of Anesthesiologists physical status classification	
ASA Class 1	No disease
ASA Class 2	Mild to moderate systemic disease
ASA Class 3	Severe systemic disease
ASA Class 4	Severe systemic disease that is life threatening with or without surgery
ASA Class 5	Moribund patient, submitted to surgery as a last resort
Emergency Operation (E)	

Table 32

SPINAL AND EPIDURAL ANESTHESIA

Introduction

Spinal anesthesia is accomplished by injecting local anesthetic solution into the subarachnoid space, confirmed by the presence of cerebral spinal fluid at needle insertion and by the rapidity of block development.

Epidural anesthesia is achieved by injection of local anesthetic in the epidural space.

Caudal anesthesia represents a special type of epidural anesthesia in witch local anesthetic is injected into the caudal space through a needle introduced through the sacral hiatus.

Compared to epidural anesthesia, spinal anesthesia takes less time to perform, causes less discomfort during the procedure, requires less anesthetic, and produces intense sensory, motor and sympathetic block.

Advantages of epidural anesthesia include a lower incidence of hypotension (less sympathetic block), the ability to produce segmental sensory block, less motor block (dose dependent). Additionally an epidural catheter provides the possibility of long term administration of anesthetic in combination with opioids.

Relevant structures

- **The subarachnoid space**

It is located between the arachnoid and pia mater and it contains the CSF formed mainly by the choroid plexus of the lateral, 4^{th}, 3^{rd} ventricles.

- **The epidural space**

It is located between the dura mater and the wall of the vertebral canal. It contains fat tissue, lymphatics, and blood vessels.

The depth of the epidural space is maximal (6mm) in the midline at L2 and is 4-5mm in the midthoracic region.

SPINAL ANESTHESIA

Spinal anesthesia is accomplished by injecting local anesthetic solution into the subarachnoid space.

Indications for spinal anesthesia

Spinal anesthesia is indicated for surgical procedures involving the lower abdominal area, perineum, and lower extremities.

Contraindications to neuraxial anesthesia

- Infection at the level of needle placement
- Mitral and aortic stenosis (lack of compensation after sympathetic block)
- Coagulation abnormalities (INR>1.5, aPTT>40s, Platelets <100K)
- Neurologic disease: increased intracranial pressure, multiple sclerosis
- Hypovolemia
- Patient refusal

Local anesthetics used for spinal and epidural anesthesia can be classified based on baricity. Hyperbaric solutions have a density higher than the CSF, hypobaric solutions have a density lower than the CSF. Isobaric solutions have the same density. The most widely used are hyperbaric and isobaric. With the hyperbaric solutions, height of the block can be controlled in the first minutes by patient position. The isobaric solutions tend to “stand” in one place. Isobaric solutions can be transformed to hyperbaric by addition of dextrose solution.

In order to prolong the action of local anesthetics adjuvants like vasoconstrictors and opioids are used.

Relevant physiology

The spinal block produces the following physiologic effects:

- First, blockade of small unmyelinated sympathetic fibers
- Second, blockade of larger myelinated sensory and motor fibers
- Important to remember that the sympathetic block usually exceeds the sensory block by 2-3 dermatomes, and the sensory block exceeds motor block by roughly the same number of dermatomes

- Little effect on the respiratory system unless the block has ascended so much that the intercostal muscles are blocked
- The intestines and ureters are constricted because of unopposed parasympathetic effect
- The cardiovascular responds with hypotension and bradycardia, due to sympathetic block

Technique

Prior to anesthesia, the patient should receive intravenous fluid (crystalloid 1000 ml or colloid 500 ml) in order to decrease the magnitude of hypotension.

In order to decrease patient anxiety a benzodiazepine should be considered usually 2-3 mg of midazolam would suffice. Sterile technique is mandatory.

Antiseptic preparation of the skin is performed (povidone iodine or clorhexidine solution), but contact with gloves and needles should be avoided because of the potential neurotoxicity of these solutions

Usually the patient is positioned in the sitting position. This position encourages flexion and facilitates recognition of midline structures.

In the sitting position if the patient receives a hyperbaric solution of local anesthetic and is being held for 5 min in this position the type of anesthesia is called “saddle block”. It is indicated for perineum procedures.

Lateral position is more comfortable for the patient and sometimes used when the sitting position is too uncomfortable for the patient or the pathology restricts it.

The interspace required for needle insertion is usually the 3-4th lumbar interspace. Some authors suggest that using a more caudal interspace might increase the chance of a failed spinal, but this must be weighed against the possibility of spinal cord injury if using a more rostral interspace. In most adults (98%) the spinal cord extends up to the L1-2 interspace.

There are 3 possible approaches to needle insertion: the middle technique, the paramedian or lateral technique and the Taylor technique. The middle technique is the most common one and consists of inserting the needle in the midline of the spine, at the top margin of the lower spinous process of the interspace. The needle is advanced through the skin until a distinct pop is felt (penetration of the ligamentum flavum) and then a few millimeters after which the guide is retracted and a free flow of cerebral spinal fluid is detected. Afterwards the local anesthetic is administered.

Local anesthetics used for spinal anesthesia				
Anesthetic	concentration	Dose (t10)	Dose (T4)	Duration (time)
Lidocaine	5%	40-50mg	60-75mg	45-75 min
Bupivacaine	0.5%	8-10mg	12-15mg	60-120min
Ropivacaine	0.5%	10-14mg	15-20mg	60-90 min

Table 33

Complications

Neurologic complications are either due to accidental needle puncture of neural tissue or the local anesthetic itself. Transient neurologic symptoms are reported after spinal block with lidocaine. In rare cases neurologic symptoms may arise from the development of hematoma or abscess.

Postdural puncture headache appears because of dural puncture and leakage of cerebral spinal fluid. For patients willing to accept, an epidural blood patch has a good chance in resolution of the headache. Usually 10 to 20 ml of patients' blood is aseptically injected into the epidural space at the level of spinal puncture. This technique has a 85-95 % chance of resolving the headache.

Hypotension is a common complication and is usually treated with vasopressors and fluid loading. Bradycardia may arise and responds very well to anticholinergic medication (atropine or glycopyrrolate).

Nausea usually appears after a rapid drop in blood pressure and reflects cerebral hypo perfusion.

Total spinal anesthesia is caused by very high block, excessive sensory, motor and sympathetic block and is usually associated with loss of consciousness. Treatment consists of hemodynamic, ventilatory support.

EPIDURAL ANESTHESIA

Epidural anesthesia is achieved by injection of local anesthetic in the epidural space.

Indications for epidural anesthesia

Epidural anesthesia is indicated for surgical procedures involving both lower and upper abdominal area, thoracic area, even cervical area although rarely used. The epidural is usually used to supplement general anesthesia for procedures involving the upper abdomen, or even the thoracic procedures.

The benefit of an epidural derives from the quality of analgesia, sparing of opioids, and the ability to control postoperative pain more effectively than opioids alone.

Continuous epidural analgesia is very effective and widely used for labor pain control usually in combination with epidural opioids.

Contraindications to neuraxial anesthesia

- Infection at the level of needle placement
- Mitral and aortic stenosis (lack of compensation after sympathetic block)
- Coagulation abnormalities (INR>1.5, aPTT>40s, Platelets <100K, risk of hematoma formation)
- Neurologic disease: increased intracranial pressure, multiple sclerosis
- Hypovolemia
- Patient refusal

Technique

The technique for lumbar and low thoracic are the same. The landmark is the midline, for the midline approach. Basically when the Tuohy needle enters the epidural space a loss of resistance is felt after which the anesthetic or catheter is advanced through the needle.

For the higher thoracic epidural the needle needs to be more angulated because of the angulation of thoracic spinal processes. For the loss of resistance technique the needle contains air or saline or both. Intermittent pressure is applied on the syringe plunger until the loss of resistance if felt. The hanging drop technique is also used and consists of placing a drop of saline at the hub of the Tuohy needle which will be absorbed when the epidural space is located.

Adjuvants of epidural consist of opioids, epinephrine, and bicarbonate.

Relevant physiology

Unlike spinal anesthesia, epidural anesthesia produces segmental block. The block spreads caudally and cranially as a function of dose and volume injected.

The site of action on the nervous system is the spinal nerve root.

The magnitude of physiologic changes regarding the sympathetic block for example is less compared to spinal anesthesia.

Diaphragm is unaffected by epidural unless the block ascends to C3-C5.

In summary the rest of physiologi changes are the same but less pronounced compared to spinal anesthesia.

Special considerations regarding epidural block

- The block is segmental, spreads both caudally and cranially from the site of injection.
- The dose is approximately 1-2ml per segment to be blocked.
- The site of injection is therefore an important factor in anesthetic spread
- Lumbar epidural in dose up to 10 ml often extend to sacral dermatomes but in some cases L5-S1 roots might be spared or patchy. The slow onset at L5-S1 level is due to the larger diameter of nerve roots
- The cranial nerves can't be blocked because the epidural space ends at foramen magnum
- The dural compression may lead to high subarachnoid pressure, requirering a higher mean arterial pressure to adequately perfuse the spine.

Complications

Besides the complications cited for spinal anesthesia, the complications after epidural anesthesia are:

- Epidural hematoma
- Accidental dural puncture
- Intravascular injection: produces cardiovascular collapse and neurotoxicity (seizures, coma)

- Intrasubarachoidian injection: produces total spinal anesthesia

GENERAL ANESTHESIA

The main objectives of general anesthesia are:

- Amnesia
- Hypnosis
- Analgesia
- Muscle relaxation

These objectives are achieved usually by a combination of drugs. There is no single agent that fulfils all the objectives.

The stages of general anesthesia are:

- Induction
- Maintenance
- Recovery

Induction is the period in time form the onset of hypnosis to the effective surgical anesthesia. The maintenance period is the time from effective surgical anesthesia to beginning of recovery. The recovery period is the time from discontinuation of anesthetic to regaining of consciousness.

The induction can be accomplished by using several drugs for example: volatile anesthetic, propofol, thiopental, etomidate, ketamine.

The usual scheme for general anesthesia induction is as follows:

- A benzodiazepine for amnesia: midazolam (0.03 mg/kg), can also be included as a premedicant before induction
- A hypnotic agent: propofol (1-2.5 mg/kg), thiopental (3-5 mg/kg), ketamine (1-2 mg/kg)
- Analgesia: opioids, fentanyl (1-5 μg/kg)
- Muscle relaxation: roccuronium (0.6-1.2 mg/kg)

A special induction scheme is the fast induction technique used for patients considered to have a full stomach.

The sequence is as follows:

- Hypnotic agent: propofol or thiopental or etomidate or ketamine
- Muscle relaxant: roccuronium, atracurium, vecurronium

After oro-thracheal intubation, an analgesic is administered.

The stages of volatile anesthetic induction are as follows:

1. CNS depression, analgesia, lack of consciousness
2. Excitement (delirium)
3. Surgical anesthesia- the ideal stage of anesthesia
4. Medullary paralysis and death

THE ANESTHESIA DELIVERY SYSTEM

The anesthesia delivery system includes the gas machine and the breathing circuit.

The gas machine has evolved to incorporate complex modules that monitor a wide range of physiological parameters like ECG, pulsoximetry, heart rate, end tidal concentration of expired gases (CO_2, volatile agents) as well as inhaled concentration of gases (O_2, volatile agents), blood pressure non-invasively as well as invasively. Complex alarm systems are also present in order to signal apnea, arrhythmias, asystole, hypotension, or breathing system disconnection or leakage. Exhaled gases are either returned to the patient after removal or CO_2 by a chemical absorbent or scavenged from the system and returned to the atmosphere.

Modern anesthesia machines are also equipped with a fail-safe valve and an oxygen analyzer designed to prevent delivery of hypoxic gas mixtures. Flow meters either mechanical or electronic are used to precisely measure and control gas flow.

The vaporizer

A vaporizer is needed because most of the volatile anesthetics are liquids at room temperature and atmospheric pressure. The boiling point of an anesthetic is the temperature at which the vapor pressure of the anesthetic exceeds the atmospheric pressure. This is an important physical concept because, for example, desflurane (a volatile anesthetic) evaporates at room temperature so a special vaporizer needed to be constructed (boiling point of desflurane is 23.5^{o}C at 1 atm, vapor pressure 664 mmHg at 20^{0}C).

Properties of vaporizers:

- Agent specific: only calibrated for a single agent
- Variable bypass
- Flow over
- Temperature compensated

Types of vaporizers:

- Variable bypass
- Measured flow

Variable bypass

Fresh gas enters the vaporizer. The concentration dial setting splits this fresh gas into bypass gas (does not enter the vaporization chamber) and carrier gas (enters the vaporization chamber to become saturated). These two flows rejoin at the vaporizer outlet. The splitting ratio of these two flows depends on concentration dial setting.

The output of all variable-bypass vaporizers is constant at fresh gas flow between 250ml/min and 15 L/min. the output is constant over a wide range of temperatures 20-35^{0}C.

ANESTHETIC BREATHING SYSTEMS

The breathing system connects the gas machine to the patient's airway. And has the purpose of conducting the gases in and out of the patient.

The breathing systems can be classified in several ways:

1. traditional
    - Open
    - Semi open
    - Semi closed
    - Closed

Type	Reservoir bag	Rebreathing	Type
1. Open	No	No	Bag and bottle
2. Semi-open.	No	Partial	Bag and bottle with occlusive packing
3. Semi-closed without absorption.	Yes	No	Bain, modified Jackson Rees, Ayre's T piece. Lack, Magill
3. Semi-closed with absorption.	Yes	Partial	Carbon dioxide absorbers with leak
4. Closed.	Yes	Complete	Carbon dioxide absorbers with no leaks

Table 34

2. modern

- Non-rebreathing
- Partial rebreathing
- Non-rebreathing (unidirectional or bidirectional)

Modern classification

A. Non-rebreathing systems

It is a simple system that utilizes non-rebreathing valves or valve.

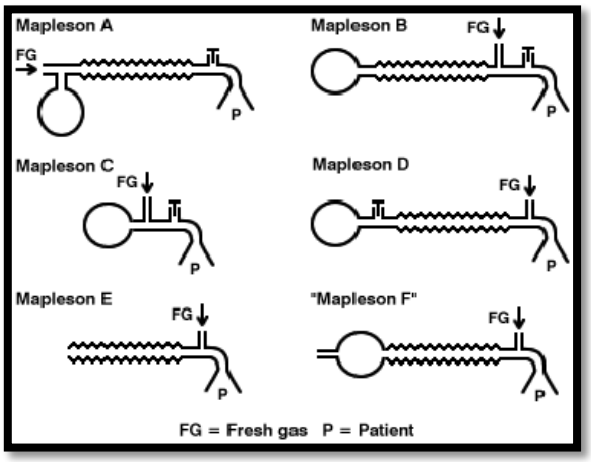
The valve opens during the inspiration and occludes the expiratory limb of the circuit. During the expiration the inspiratory valve closes and gas escapes through the expiratory limb. The inspiratory limb usually contains a reservoir bag which has a capacity of 1.5-2L and has the purpose of meeting the high inspiratory demand of

a spontaneous breathing patient (example Tidal volume 600 ml delivered in 1 sec equals 36L/min inspiratory flow rate)

B. Partial rebreathing systems

The main characteristic of these systems is that CO_2 elimination is achieved by flushing of new fresh gas rather than the presence of a unidirectional valve. Some rebreathing is possible especially if fresh gas flow is not adequate to patient's minute ventilation as outlined below. These systems were classified by Mapleson into 6 categories A…F.

Mapleson Classification



Picture 38

The Mapleson systems are classified in order of increased fresh gas flow that prevents rebreathing.

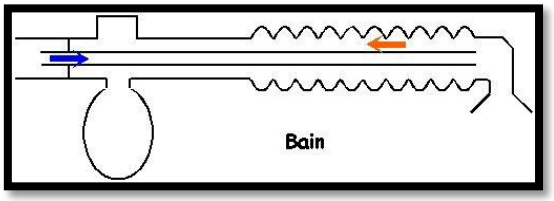
Mapleson A system requires 0.8-1 times the patient's minute ventilation.

Mapleson B and C require 1.5-2 times the patient's minute ventilation.

Mapleson D, E, F require 2-3 times the patient's minute ventilation.

The Bain system which is a modification of the Mapleson D system and the Rees T-piece which is a modification of the Mapleson F system are still being used today.

The Bain system utilizes a coaxial arrangement of tubing as shown:



Picture 39

The Rees modification of the Mapleson F system consists of adding a double-ended reservoir bag to the circuit. It is important to note that the reservoir bag should approximate the patient's tidal volume or else rebreathing could occur.

C. Non-rebreathing systems

The breathing systems described before utilize a high fresh gas flow in order to prevent rebreathing of CO_2. This implies a high consumption of volatile anesthetic and therefore more expensive. In non-rebreathing systems the exhaled gases are passed through an absorbent, CO2 is removed, after which O2, and volatile is added in order to maintain optimum concentration. In this manner we can use a lower fresh gas flow during controlled ventilation and use considerably less volatile anesthetic.

CO_2 can be removed from the system by a chemical reaction with bases such as NaOH or Ca $(OH)_2$ as detailed below.

$CO_2 + H_2O = H^+ + HCO_3^-$

$NaOH + H^+ + HCO_3^- = Na_2CO_3 + 2H_2O$

$Na_2CO_3 + Ca(OH)_2 = CaCO_3 + 2NaOH$

Ca hydroxide is added in order to regenerate soda lime NaOH. The soda lime is capable of absorbing 25L of CO_2 per 100 g.

Practical considerations of the above chemical reactions:

- They are exothermic reactions meaning energy (heat) is produced
- The reaction changes the ph. of the soda lime which allows the use of indicator dye
- It produces water

Granule size is important for two reasons, too large a granule size produces a small surface contact overall, too small a granule size results in very high resistance to gas flow. Optimal size is 1.5-5mm diameter.

The downside of the above chemical reactions is the heat produced. This heat encourages other chemical reactions which maybe produce toxic compounds. Desflurane, enflurane and isoflurane react with dry soda lime to produce minute amounts of carbon monoxide.

Sevoflurane may react with soda lime in order to produces 5 degradation compounds, the most important being Compound A.

PHARMACOLOGIC BASIS OF GENERAL AND REGIONAL ANESTHESIA

General Anesthetics

INTRAVENOUS ANESTHETICS

Propofol

Propofol is an intravenous anesthetic widely used for general anesthesia and sedation in the intensive care unit

Physicochemical properties

It is an alkylphenol with hypnotic properties. It is insoluble in aqueous solutions and formulated as an emulsion. The solution appears milky-white with a ph of 7 with a concentration of propofol of 1%

Pharmacodynamics

The mechanism of action of propofol is through potentiation of Chloride current in the $GABA_a$ receptor.

In the central nervous system, it produces hypnosis and it does not have any analgesic properties. Besides hypnosis, propofol reduces cerebral blood flow and cerebral metabolism, favorable effects in patients with increased intracranial pressure.

On the cardiovascular system, propofol produces hypotension and has a negative inotrope effect on the heart. Vasodilation appears in both arterial and venous beds. Exaggerated responses to induction doses appear in hypovolemia or elderly patients.

It reduces the minute volume, by effecting both tidal volume and respiratory rate. Given in sufficient amounts it can cause transient apnea. It also lowers the airway reflexes, a desirable effect during laryngoscopy and intubation.

Pharmacokinetics

Propofol is metabolized in the liver and the resulting compounds are eliminated by the kidneys. The lungs play an important role in extra hepatic metabolism sites of propofol, as much as 30% of the induction dose being metabolized bye the lungs.

Ketamine

It is an intravenous general anesthetic, which unlike the other intravenous has potent analgesic effect.

Physicochemical properties

Ketamine is a phencyclidine derivative, partially water-soluble, highly lipid soluble.

Pharmacodynamics

The mechanism of action is inhibition of N-methyl-D-Aspartate receptor.

In contrast to the other intravenous anesthetics, ketamine increases the cerebral blood flow and cerebral metabolic rate and oxygen consumption, but it has potent analgesic effect. In summary it is a hypnotic with analgesic properties.

It stimulates the sympathetic system, thus blood pressure and cardiac output are increased. The cardio stimulatory effects can be blunted by benzodiazepines, opioids or volatile anesthetics.

Ketamine does not produce significant respiratory depression, airway reflexes remain intact, and bronchodilation occurs, but stimulates secretions (which can be abolished by atropine administration prior to ketamine).

Emergence reactions might be unpleasant, and include vivid dreams, hallucinations. These effects can be blunted by administration of benzodiapines (midazolam, diazepam)

Pharmacokinetics

Like other intravenous anesthetics, ketamine is metabolized bye the liver. The termination of effect after a bolus dose is not due to liver metabolism, but to redistribution of the drug from the central compartment.

Thiopental

Belongs to the barbiturates class of drugs. The barbiturates consist of thiobarbiturates like thiopental and oxybarbiturates like methohexital.

Physicochemical properties

Thiopental is formulated as a sodium salt, it is very alkaline in solution, having a ph. of 10.

Pharmacodynamics

Thiopental produces hypnosis, sedation, it reduces the cerebral metabolic rate and oxygen consumption. It constricts the cerebral vessels being the first choice anesthetic in patients with increased intracranial pressure. It is also considered in patients with epileptic seizures that do not respond to conventional therapy.

Thiopental lowers the blood pressure by its, vasodilation properties but to a lesser degree that propofol. Exaggerated responses to induction doses appear in hypovolemia or elderly patients.

Regarding the respiratory system, thiopental reduces tidal volume, lowers the minute ventilation and may cause apnea after a bolus induction dose. Suppression of airway reflexes is not as profound as with propofol.

Pharmacokinetics

Barbiturates undergo hepatic metabolism and excretion by the kidneys and through the bile. A unique property of barbiturates is hepatic enzyme induction. They may stimulate the aminolevulinic acid synthetase, and porphyrin production. Therefore thiopental is contraindicated in acute intermittent porphyria.

VOLATILE ANESTHETICS

Modern volatile anesthetics are halogenated (with chloride and fluorine) hydrocarbons.

Examples of volatile halogenated anesthetics: Halothane, Isoflurane, Sevoflurane, Desflurane.

Volatile anesthetics produce central nervous system depression by their actions on specific ion channels, having enhancing function on inhibitory ion channels like the GABA receptor and blocking function on excitatory ion channels like NMDA receptor.

Physicochemical properties

The volatile halogenated anesthetics are liquids at ambient temperature.

Vapor pressure definition

Molecules escape from a volatile liquid to the vapor phase, creating a "saturated vapor pressure" at equilibrium. Vapor pressure increases with temperature and is

independent of atmospheric pressure, it depends only on the physical characteristics of the liquid, and its temperature.

Halothane, Isoflurane and Sevoflurane are delivered by a variable-bypass vaporizer while Desflurane requires a heated vaporizer because of its chemical and physical properties.

Desflurane has a vapor pressure of almost 700 mmHg at 20^0C (that means near boiling point at room temperature). In order to deliver an accurate anesthetic concentration, the special vaporizer heats the desflurane (39^0C) until the pressure reaches 2 atm.

Potency

Potency of volatile anesthetics is measured by MAC. **MAC** represents the minimal alveolar concentration which suppresses movement to surgical incision in 50% of patients. 99% of patients should not move to surgical incision at 1.3 MAC of volatile anesthetic. It is important to notice that MAC's are additive.

MAC is a measure of potency between volatile anesthetics. 1.15 % (1MAC) isoflurane is equipotent to 6% (1 MAC) sevoflurane.

The MAC required to produce amnesia is 0.6 MAC, the MAC required to block the sympathetic response is 1.8 MAC.

Factors affecting MAC

Factors increasing MAC	Factors decreasing MAC
Drugs (amphetamine, cocaine, ephedrine, ethanol)	Benzodiazepines, intravenous anesthetics, opioids, lithium
Age, Hyperthermia, Hypernatremia	Age (elderly patients)
	Anemia, Hypercarbia, Hypothermia

Table 35

Pharmacodynamics

Overall inhaled anesthetics decrease the blood pressure by a vasodilation effect and decreased myocardial contractility. Herat rate increases accordantly to compensate for the decrease in blood pressure. Desflurane causes a transient increase in sympathetic stimulation in the absence of opioid administration.

Inhaled anesthetics decrease the tidal volume and increase respiratory rate. Sevoflurane and halothane are nonpungent and cause minimal irritation of the airways.

Inhaled anesthetic increase cerebral blood flow and decrease cerebral metabolic rate, causing “luxury perfusion”. At high MAC they can increase the intracranial pressure.

Inhaled anesthetics produce skeletal muscle relaxation, with exception of nitrous oxide, and enhance the action of neuromuscular blocking drugs.

Complications

- Malignant hyperthermia; all volatile anesthetics can cause malignant hyperthermia
- Liver dysfunction
- Nephrotoxicity; Compound A; a byproduct of sevoflurane degradation in alkaline absorbers
- CO (carbon monoxide) production in dry absorbents because of soda lime reaction with inhaled anesthetics

LOCAL ANESTHETICS

Local anesthetics are used to provide regional anesthesia and can be classified as aminoesters and aminoamides.

They act at the level of the nervous system by blocking the Na (sodium) fast channels, thus inhibiting depolarization (preventing achievement of threshold potential) and nerve impulse conduction.

They are both lipid soluble, made up of a benzene ring connected to an amide or an ester group. Aminoesters are metabolized by plasma cholinesterase, and aminoamides by hepatic carboxylesterases.

Classification of local anesthetics

AMIDES	ESTERS
Bupivacaine	**Chlorprocaine**
Lidocaine	**Tetracaine**
Ropivacaine	
Mepivacaine	

Table 36

Lipid solubility may augmented by increasing the ph o the solution e.g making the anesthetic solution more alkaline.

Additives that increase local anesthetic activity:

- Epinephrine; beneficial effects include decreased system absorption, increased block duration, direct analgesic action due to alpha 2 receptor stimulation
- Alkalization
- Opioids
- Alpha 2 adrenergic agonists

Complications

- Systemic toxicity: results from excessive absorption and high plasma levels, sometimes from accidental intravascular injection.
- Central nervous system toxicity: manifested clinically as circumoral numbness, tingling, vertigo, tinnitus, seizures, and coma. The onset of seizures underlines

the selective depression of inhibitory pathways in the central nervous system, leaving excitatory pathways unopposed.

- Cardiovascular system toxicity: high plasma concentration of local anesthetics can produce profound hypotension and depressed myocardial contractility, even cardiac arrest. Cardiac toxicity can be attenuated by administration of Intralipid solution.

- Allergic reactions

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking drugs are used in anesthesia in order to provide muscle relaxation, prevent movement and facilitate surgical exposure, oro-tracheal intubation, and mechanical ventilation.

Classification of neuromuscular blocking agents based of mode of action and duration of action	
Depolarizing agents	
Succinylcholine	Short acting
Nondepolarinzing agents	
Pancuronium	Long acting
Vecuronium	Intermediate acting
Rocuronium	Intermediate acting
Atracurium	Intermediate acting
Cisatracurium	Intermediate acting
Mivacurium	Short acting

Table 37

Mode of action

Neuromuscular blocking agents (NMBA) exert their action at the level of neuromuscular junction, by blocking the nicotinic acetylcholine receptor, thus preventing muscular contraction. They act by either sustained depolarization at the postjunctional membrane, activation of the receptor, or by binding and inactivation of the nicotinic acetylcholine receptor.

NMBAs are quaternary ammonium drugs that resemble acetylcholine.

Chemical classification of nondepolarizing NMBAs	
Aminosteroid	**Benzylisoquinolinium**
Pancuronium	Atracurium
Vecuronium	Cisatracurium
Rocuronium	Mivacurium

Table 38

Succinylcholine is the only depolarizing agent in use today and the shortest acting. It is metabolized by plasma cholinesterase at a very fast rate.

Succinylcholine side effects
Cardiac arrhythmias
Fasciculation
Hyperkalemia
Myalgia
Myoglobinuria
Increased intracranial pressure
Increased intraocular pressure
Increased intragastric pressure

Table 39

Nondepolarizing NMDBs act by competing with acetylcholine and are classified as long acting, intermediate and short acting as described above.

By blocking the acetylcholine receptor depolarization cannot occur, and muscle paralysis develops.

Pharmacokinetics

Nondepolarizing NMBDs are quaternary ammonium drugs, highly ionized and therefore water soluble. Because they are highly ionized they cannot pass the blood brain barrier, renal tubular and gastrointestinal epithelium or placenta.

Because of their chemical properties they cannot pass the placenta, blood brain barrier, the renal reabsorption is minimal and cannot be administered per os. Rocuronium is eliminated by the liver, mivacurium metabolized by plasma

cholinesterase, atracurium and cisatracurium metabolized via Hofmann degradation.

Pharmacodynamics

- NMBDs cause minimal cardiovascular depression (hypotension), largely due to histamine release (atracurium, mivacurium)
- Bronchoconstriction may appear due to histamine release
- If administered for long periods of time they may cause the syndrome called Critical illness myopathy and polyneuropathy

Antagonism of nondepolarizing neuromuscular blocking drugs

Antagonism of these drugs is achieved by administration of anticholinesterase drugs, namely neostigmine. Neostigmine is administered during spontaneous recovery from neuromuscular block. Neostigmine acts by inhibiting the degradation of acetylcholine by acetylcholinesterase, thus increasing the availability of acetylcholine on the nicotinic receptor. To minimize the parasympathetic overstimulation atropine is administered concurrently.

OPIOIDS

Opioids have an important role in anesthesia practice, being the drugs that provide analgesia.

Mechanism of action

Opioids produce analgesia by interacting with opioid receptors throughout the central nervous system.

Pharmacokinetics

Most opioids are metabolized at the liver with exception of remifentanyl, which is metabolized by plasma esterases, and eliminated by the kidneys.

Opioid receptors			
	Mu (μ)	Delta (δ)	Kappa (κ)
Endogenous ligand	endorphin	enkephalin	dinorphin
Agonist	Morphine Fentanyl Sufentanyl	Deltorphin	Pentazocine
Antagonist	Naloxone	Naloxone	Naloxone
Supraspinal analgesia	Yes	Yes	yes
Spinal analgesia	Yes	Yes	yes
Ventilatory depression	yes	No	Yes
Sedation	Yes	No	Yes
GI effects	Yes	No	Yes

Table 40

Pharmacodynamics

- Central nervous system: supraspinal analgesia, sedation, euphoria, miosis (stimulation of Edinger-Westphal nucleus), nausea and vomiting (stimulating chemoreceptor trigger zone in aria postrema), cough suppression
- Cardiovascular: hypotension, bradycardia (increased vagal tone), less than other anesthetics.
- Respiratory system: ventilatory depression
- Gastrointestinal system: delayed gastric emptying, ileus and constipation, increased biliary pressure
- Other: pruritus, muscle rigidity, urinary retention, depressed cellular immunity

Opioid agonists: Morphine, Fentanyl, Sufentanyl, Meperidine, Pentazocine, Remifentanyl

Clinical indications

- Postoperative analgesia
- Analgesia as a part of balanced anesthesia
- Analgesia as a part of total intravenous anesthesia (TIVA)

- Labor analgesia and as an additive to spinal, epidural anesthesia

ANESTHESIA AND COEXISTING DISEASE

The following chapter will outline in summary some of the particularities regarding anesthesia and coexisting disease with reference to anesthesia and caridiovascular disease and pulmonary disease.

Management of anesthesia in patients with ischemic heart disease

The preoperative management of patients with ischemic heart disease includes:

- determining the extent of ischemic heart disease and any previous interventions (PTCA, coronary artery bypass graft)
- determining the severity of the disease
- reviewing medical therapy

In stable patients undergoing elective surgery, independent predictors of major cardiac complications have been described in the **Lee Revised Cardiac Risk Index**

Cardiac Risk Factors in Patients Undergoing Elective Major Noncardiac Surgery	
High-risk surgery	Abdominal aortic aneurysm
1 point	Peripheral vascular operation
	Thoracotomy
	Major abdominal operation
Ischemic heart disease	History of myocardial infarction
1point	History of a positive exercise test
	Current complaints of angina pectoris
	Use of nitrate therapy
	Q waves on electrocardiogram
Congestive heart failure	History of congestive heart failure
1 point	History of pulmonary edema
	History of paroxysmal nocturnal dyspnea
	Physical examination showing rales or S_3 gallop
	Chest radiograph showing pulmonary vascular redistribution
Cerebrovascular disease 1point	History of stroke
	History of transient ischemic attack
Insulin-dependent diabetes mellitus 1point	
Preoperative serum creatinine concentration > 2 mg/dL 1 point	

Adapted from Lee TH, Marcantonio ER, Mangione CM, et al: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999

1. Points 0: Class I Very Low (0.4% complications)
2. Points 1: Class II Low (0.9% complications)
3. Points 2: Class III Moderate (6.6% complications)
4. Points 3: Class IV High (>11% complications)

The reason for risk stratification is to identify patients at increased risk to manage them with pharmacologic and other perioperative interventions that can lessen the risk and severity of perioperative cardiac events.

Perioperative use of β-blockers has been shown to reduce perioperative cardiac morbidity and mortality.

In patients in whom β-blockers are contraindicated, α_2-agonists can be used to decrease perioperative cardiac injury.

ACE inhibitors, statins, aspirin, and insulin are beneficial in the perioperative period as well as glcose-insulin-potassium infusion.

The challenges during induction and maintenance of anesthesia in patients with ischemic heart disease are:

- to prevent myocardial ischemia by optimizing myocardial oxygen supply and reducing myocardial oxygen demand
- monitor for ischemia and to treat ischemia if it develops

The use of Ketamine during induction of anesthesia is not a viable choice because the associated increase in heart rate and systemic blood pressure transiently increases myocardial oxygen requirements.

Myocardial ischemia accompany the sympathetic nervous system stimulation that results from direct laryngoscopy and tracheal intubation.

Laryngotracheal lidocaine, intravenous lidocaine, esmolol, and fentanyl are useful for blunting the sympathetic stimulation evoked by tracheal intubation.

Volatile anesthetics may be beneficial in patients with ischemic heart disease by decreasing myocardial oxygen requirements and preconditioning the myocardium to tolerate ischemic events.

Muscle relaxants with minimal or no effect on heart rate and systemic blood pressure (vecuronium, rocuronium, cisatracurium) are attractive choices for patients with ischemic heart disease.

Management of anesthesia in patients with aortic stenosis

The obstruction to ejection of blood into the aorta imposed by aortic stenosis leads to:

- Increase in left ventricular pressure
- Increase oxygen consumption
- Myocardial remodeling causing concentric myocardial hypertrophy

Severe aortic stenosis appears when transvalvular pressure gradients are higher than 50 mm Hg and an aortic valve area is less than 0.8 cm^2.

Management of anesthesia in patients with aortic stenosis includes the prevention of hypotension and any hemodynamic change that will decrease cardiac output.

Anesthetic Considerations:

- Maintain normal sinus rhythm
- Avoid bradycardia or tachycardia
- Avoid hypotension
- Optimize intravascular fluid volume

General anesthesia is often selected in preference to epidural or spinal anesthesia because the sympathetic blockade produced by regional anesthesia can lead to significant hypotension.

Induction of anesthesia can be accomplished with an intravenous induction drug that does not decrease systemic vascular resistance (etomidate).

Maintenance of anesthesia can be accomplished with a combination of volatile anesthetic and opioids.

Neuromuscular blocking drugs with minimal hemodynamic effects are selected.

Management of anesthesia in patients with chronic obstructive pulmonary disease and asthma

COPD is characterized by the progressive development of airflow obstruction that is not fully reversible.

It includes chronic bronchitis with obstruction of small airways and emphysema with destruction of lung parenchyma, loss of elasticity, and obstruction of small airways.

Pulmonary function tests reveal decreases in the FEV_1/forced vital capacity (FVC) ratio and even greater decreases in the forced expiratory flow between 25% and 75% of vital capacity.

A history of poor exercise tolerance, chronic cough, or unexplained dyspnea combined with diminished breath sounds, wheezing, and a prolonged expiratory phase predict an increased risk of postoperative pulmonary complications.

Preoperative preparation of patients with COPD includes:

- smoking cessation
- treatment of bronchospasm
- eradication of bacterial infection

Indications for a preoperative pulmonary evaluation typically include

- hypoxemia on room air or the need for home oxygen therapy without a known etiology
- bicarbonate more than 33 mEq/L or PCO_2 more than 50 mm Hg
- a history of respiratory failure due to a problem that still exists
- severe shortness of breath attributed to respiratory disease
- planned pneumonectomy
- difficulty assessing pulmonary function by clinical signs
- distinguishing among potential etiologies of significant respiratory compromise
- suspected pulmonary hypertension

Regional anesthesia is suitable for operations that do not invade the peritoneum and for surgical procedures performed on the extremities. Lower intraabdominal surgery can also be performed using a regional anesthesia technique.

General anesthesia is the usual choice for upper abdominal and intrathoracic surgery.

General anesthesia is often provided with volatile anesthetics that also produce bronchodilation.

Opioids may be less useful than inhaled anesthetics for maintenance of anesthesia in patients with COPD because they can be associated with prolonged ventilatory depression because of their slow rate of metabolism or elimination.

During induction and maintenance of anesthesia in asthmatic patients, it is necessary to suppress airway reflexes to avoid bronchoconstriction in response to mechanical stimulation of these hyperactive airways.

When general anesthesia is selected, induction of anesthesia is most often accomplished with an intravenous induction drug.

Skeletal muscle relaxation is usually provided with nondepolarizing muscle relaxants. Drugs with limited ability to evoke the release of histamine should be selected.

Antagonism of neuromuscular blockade with anticholinesterase drugs could precipitate bronchospasm secondary to stimulation of postganglionic cholinergic receptors in airway smooth muscle. Such bronchospasm does not predictably occur after administration of anticholinesterase drugs, probably because of the protective bronchodilating effects provided by the simultaneous administration of anticholinergic drugs.

TAKE HOME MESSAGES

- The main goals of general anesthesia are amnesia, hypnosis, analgesia, muscle relaxation, control of homeostasis
- The main preoperative goals are assessing the patient's coexisting diseases by taking the patient's history, addressing patients concerns and questions
- The airway is always evaluated in order to anticipate a difficult intubation
- Spinal anesthesia is indicated for surgical procedures involving the lower abdominal area, perineum, and lower extremities
- Epidural anesthesia is indicated for surgical procedures involving both lower and upper abdominal area, thoracic area, even cervical area
- The anesthesia delivery system includes the gas machine and the breathing circuit
- Propofol is an intravenous anesthetic widely used for general anesthesia and sedation in the intensive care unit
- Ketamine administration is considered in patients with shock
- Etomidate is administered in patients with hemodynamic instability
- Modern volatile anesthetics are halogenated (with chloride and fluorine) hydrocarbons

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PAIN

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DEFINITION

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Note: The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli that cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience. Experiences that resemble pain but are not unpleasant, e.g., pricking, should not be called pain. Unpleasant abnormal experiences (dysesthesias) may also be pain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.

ACUTE AND CHRONIC PAIN

Pain can be put into five categories

1. Acute: a normal and time related response to trauma and other 'noxious' procedures, including pain related to medical procedures and acute medical condition. Tissue injury plays a key role.
2. Pain that is progressing towards chronic pain, but this progression may be prevented (subacute pain). Transition from acute to chronic is the time from tissue healing (1-2 months) to the 6-month time point that currently defines the presence of chronic pain. Ongoing nociception and neuroplastic changes are incriminated.

3. Recurrent pain – cyclical basis

4. Chronic non-cancer pain. It arises from maladaptive changes in the central nervous system. The cause of the ongoing pain seems to be the overactive glia. There is no definitive treatment and it has to be recognized as a disease on it's own right.

5. Cancer pain- occurs regardless of the stage, and in survivors it is a result of side effects of curative treatment. Cancer patients with persistent pain have major differences in treatment options and needs compared with people with non-cancer pain.

EVALUATION OF PAIN

The evaluation of pain is mandatory in the postoperative period (intensity, treatment's efficacy and side-effects). It should be performed at rest and at mobilization (kinetotherapy, cough, first mobilization) in an instantaneously and a non-retrospective way.

The evaluation scales are unidimensional and the patient assesses the pain's intensity.

1. Visual analog scale (VAS)

    a. It is the reference.

    b. It consists of a nongraded scale on the side of the patient and a graded one on clinician's side. The patient is instructed to position the line (cursor) between two points: no pain and maximal pain, thus the physician being able to quantify the intensity of pain.

    c. It is simple but incomprehensible foe 10% of the patients.

2. Numeric Pain Rating Scale (NPR)

    a. The patient gives a note to his/hers pain from 0 to 10.

        0 = no pain; 10 = worst possible pain; 5 = moderate pain

3. Simple Verbal Scale (SVS)

        0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain

Action I warranted for VAS> 30, NPR > 3, SVS>1.

For the pediatric and less cooperant geriatric patient there is a facial scale (Wong Baker). The physician has to explain to the person that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit.

Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can image, although you don't have to be crying to feel this bad. The patient is asked to choose the face that best describes how he is feeling.

Picture 40

As for the behavioral pain assessment we have the DoLoPLUS scale, a little to complex for everyday practice. There is a simplified one:

Level 1 – calm patient, no verbal or behavioral pain manifestation

Level 2 - no verbal or behavioral pain manifestation

Level 3 – extreme pain manifestations – extreme agitation, cries, prostration, immobility, and protective body postures

SEDATION – SCALES

When opiates are used for the treatment of pain, regardless of the site of administration, the level of sedation should be monitored. Failure to meet goals of proper sedation and analgesia has deleterious sequele that are associated with an increase in adverse events, poor outcomes, longer ICU stays and economic effects.

Ramsey Scale

Sedation level	Description
1	Anxious and agitated
2	Cooperative, tranquil, oriented
3	Responds only to verbal commands
4	Asleep with brisk response to light stimulation
5	Asleep without response to light stimulation
6	Non responsive

Table 42

Richmond Sedation Agitation Scale

Target	Description
+4	Combative, violent, danger to staff
+3	Pulls or removes tube(s) or catheters; aggressive
+2	Frequent nonpurposeful movement, fights ventilator
+1	Anxious, apprehensive, but not aggressive
0	Alert and calm
-1	Awakens to voice (eye opening/contact) >10 sec
-2	Light sedation, briefly awakens to voice (eye opening/contact) <10 sec
-3	Moderate sedation, movement or eye opening. No eye contact
-4	Deep sedation, no response to voice, but movement or eye opening to physical stimulation
-5	Unarousable, no response to voice or physical stimulation

Table 43

Simplified Sedation Scale

0: alert

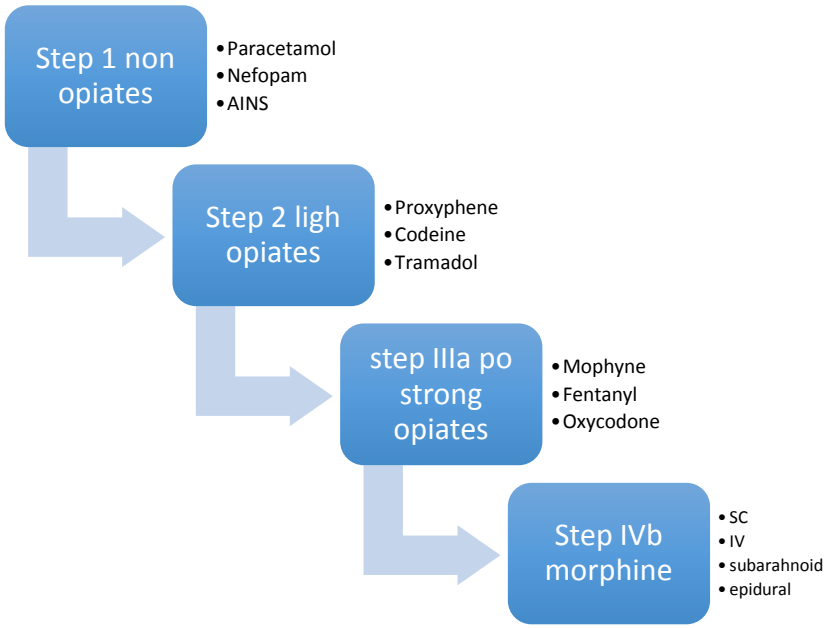
1: intermittently asleep, instant response

2: asleep with brisk response to verbal stimulation

3: asleep with brisk response to physical stimulation

ACUTE PAIN MANAGEMENT

The WHO pain ladder pertinent to pain treatment is organized as follows:



Picture 41

Paracetamol

- Unknown mechanism of action
- Minimal 15 min infusion
- Dosage:
    - Adults and adolescents > 50 kg:
        - 1000 mg every 6 h or 650 mg every 4 h
        - A maximum single dose of 1000 mg, a minimum dosing interval of 4 h, and a maximum daily dose of acetaminophen of 4000 mg per day.
    - Adults and adolescents < 50 kg:
        - 15 mg/kg every 6 h or 12.5 mg/kg every 4 h
        - A maximum single dose of 15 mg/kg, a minimum dosing interval of 4 h, and a maximum daily dose of acetaminophen of 75 mg/kg per day.
    - CrCl < 10 ml/min administer every 8 h

- Limited, low-dose therapy is usually well tolerated in hepatic disease/cirrhosis

- Treatment starts 30-60 minutes before the end of the procedure
- A loading dose of 2g is recommended

AINS

- Reversible inhibition of COX
- IV ketoprofen 4 x 50 mg (max 5 days)
- Adverse effects
  - Coagulation: platelets function alteration

    Elective surgery and chronic treatment

    T1/2 long: stop 7-10 days before procedure (oxicams, naproxen)

    T1/2 short: stop 24 h before procedure (ibuprofen, ketoprofen)
  - Gastric: ulcer
  - Renal: ↑ vascular resistance, ↑ K^+, Na and water retention
  - Pulmonary bronchospasm: history of asthma, nasal polyps or aspirin allergy

Nefopam

- Monoamine oxidase reuptake inhibitor
- Contra-indications
  - < 15 years
  - urinary retention
  - glaucoma
- Side effects: perspiration, nausea, vomiting, tachycardia, sedation, acute urinary retention
- Dosage:
  - 20mg/4h iv
  - 80-120 mg/24 h iv
- Morphine sparing effect
- Mowers postoperative shivering threshold (treatment 0.15mg/kg)

Tramadol

- Light opiate effect by inhibition of serotonin and noradrenalin reuptake
- Side effects: nausea, vomiting, dysuria, urinary retention, convulsions
- Partially antagonized by setrons (anti emetic treatment)
- The association tramadol-morphine is to be avoided (antagonists)
- Contra-indications
    - < 15 years
    - MAOI treatment
    - Non controlled epilepsy
    - Pregnancy, breast feeding
    - Severe hepatic insufficiency
- Dosage:
    - 50-200mg x 2-4/day (1-1.5mg/kg)
    - 2 mg/kg intraop then 6-10mg/kg/24h
    - Half dose in renal and/or hepatic insufficiency

Nalburphine

- Central agonist-antagonist
- Antidote: naloxone
- Used mostly in obstetrics and pediatrics
- Dosage:
    - Adult: 10-20mg/6h
    - Child: 0.2mg/kg every 4-6h

Fentanyl

- Mostly chronic pain
- Bolus 10-20 μg (see PCA)

Morphine

- Recipe:
  - 1st bolus of 5mg IV (CI: heavy sedation, respiratory depression, severe renal/hepatic insufficiency)
  - Titration of 2-3 mg every 5-7 min until goal reached (NPR<3)
  - Maximal dose 10-15 mg in opioid naïve patients (to limit acute tolerance and hyperalgesia)
  - PCA relay
- Antidote: naloxone (titration od 40μg boluses)
- Adverse effects: respiratory depression, nausea, vomiting, urinary retention, constipation, pruritus, sedation
- Opioid dependent patient:
  - Daily morphine: at least 2 x heroine dose
  - Multimodal analgesia
  - !!! Adjuvants (clonidine, gabapentin)
  - PCA: increased risk of addiction
  - Ketamine: increased risk of addiction

Pentazocine (Fortral)

- Recipe:
  - 30 mg IV/IM/SC q3-4hr (not to exceed 30 mg/dose IV or 60 mg/dose IM/SC)
  - Not to exceed 360 mg/day IV/IM/SC
- Renal impairement:
  - CrCl 10-50 mL/min: 75% of regular dose
  - CrCl<10 mL/min: 50% of regular dose
- Hepatic impairement
  - Use lower dose or avoid in liver disease
- IV incompatibititie

- Additive: aminophylline, amobarbital, pentobarbital, phenobarbital, sodium bicarbonate
- Syringe: glycopyrrolate, heparin, pentobarbital
- Y-site: nafcillin

Meperidine, Pethidine (Mialgin®)

- No benefit in billiary colic or acute pancreatitis
- Caution:
  - Atrial flutter or other supraventricular tachycardia
  - Convulsive dosorders or patients receiving drugs that are known to predispose patients to seizures
- CI:
  - Patients who are receiving monoamine oxidase (MAO) inhibitors or those who have received MAO inhibitors in the past 14 days
  - Patients with renal insufficiency (creatinine clearance less than 50 ml/min)
  - Patients with untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture
- Dosage:
  - SC: 50-150 mg x 3h as needed
  - IV: slow push starting dose of 25 mg, increasing in 25 mg increments to a maximum of 100 mg x 2-3h as needed
  - Maximal dose 600mg/24h
  - Maximal duration: 48h
- IV incompatibilities
  - Additive: aminophylline, amobarbital, floxacillin, furosemide, heparin, morphine, phenobarbital, phenytoin, Na bicarb(?)
  - Syringe: heparin, morphine, pentobarbital
  - Y-site: acyclovir(?), allopurinol, amphotericin B cholesteryl sulfate, cefepime, cefoperazone, doxorubicin, furosemide (may be compatible at lower concentrations), idarubicin, imipenem/cilastatin, minocycline, nafcillin(?)
  - Not spec: diazepam

Ketamine

- Anti NMDA
- 1/10 induction dose = analgesic properties
- Recipe:
    - Bolus 0.15-0.5 mg/kg after induction (hallucinations, premedication with BZD)
    - Relay 0.125-0.25 mg/kg/h if surgery > 2h
    - Stop 30 min before the end of the procedure
    - ? Associated to morphine in PCA

Gabapentin

- Ca channel blocker
- Administered preoperatively
    - Morphine sparing effect
    - ↓ Chronic pain
    - Sedation and anxyolysis
- CI: allergy, breastfeeding, lactose deficiency, glucose/galactose malabsorbtion
- Dosage:
    - 1200mg 1h before surgery
    - 900mg: old patients, renal insufficiency

Clonidine

- Centrally acting α_2 adrenergic agonist
- Caution in hemodynamic instability
- Prolongs the effect of analgesia together with a local anesthetic
- 30 μg/h as adjuvant

Postoperative analgesia

Keyword: anticipation

- premedication: gabapentin, AINS

- perioperative:
  - ketamine
  - paracetamol ± AINS ± Nefopam
- Localregional analgesia/infiltration as soon as possible
  - Lidocaine:
    - Open/laparoscopic abdominal surgery, prostatectomy
    - Bolus 1.5-2mg/kg, than continuous infusion 1.5-2mg/kg, stop 1h before the administration of any local anesthetic (regardless of it's site of administration)
  - PCA (patient controlled analgesia)
    - Principle: what you need is what you gain
    - Drugs administered by the patient: bolus ± continous infusion, in response to the real time pain
    - Parameters:
      - Bolus
      - Continous infusion
      - Lock-out interval: the time allowed between two consecutive doses
      - Maximal dose (1, 2, 4h): for combined therapy

PCA dosing regimen

Drug	Bolus	Lockout interval	Continous rate
Morphine (1mg/ml)	0.5-2.5 mg	5-10	0.01-0.03 mg/kg/h
Fentanyl (10 μg/ml)	10-20 μg	4-10	0.5-1 μg/kg/h
Alfentanyl (0.1mg/ml)	0.1-0.2 mg	5-8	-
Sufentanyl (2 μg/ml)	2-5 μg	5-10	0-8 μg/kg/h
Meperidine (10 mg/ml)	5-25 mg	5-10	10 mg/h
Tramadol (10 mg/ml)	10-20 mg	5-10	10-20 mg/h

Table 44

TAKE HOME MESSAGES

- The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment
- Pain is always subjective
- Experiences that resemble pain but are not unpleasant, e.g., pricking, should not be called pain

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ETHICS IN THE ICU

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Ethics in the ICU evolved from a translation of human ethics directly from the outside the walls world to the inside. The inside is a virtual space where the stakeholders are also the players of the life sustaining games: the critically ill patients, the caregivers, the patients' families and health interests' representatives and the hospital managers. Within these boundaries, we all should preserve life and patients' well being by promoting their health.

Sometimes some of the stakeholders are confronted with previously unmet issues, some of them end of life problems:

- Who should be informed as to the patients' status while they are incapacitated?
- Who should decide as to the treatments offered by the ICU team?
- When is a futile treatment to be avoided and who decides as to the futility?
- Should the team refrain from installing an organ sustaining treatment or not?
- When to accept a treatment withdrawing considered futile or unnecessary battery by the medical team?
- What happens when the patients' of families' values collide with those promoted by the ICU?
- Is my diagnosed brain dead child, parent really dead?
- What happens to our dear ones if we oppose treatment?
- Would a media alert if unsatisfied or despaired as to the patients' evolution do some good?
- The desperate and prematurely grieving families consider that the medical teams under perform or overdo. How should they react to fix their critical issue?
- The medical team should approach closer and more intensely my dear one. All the other patients can wait.
- Once in the ICU one is at least half dead.

- Those white coats will harvest the organs of my beloved despite he/ she being alive or will accelerate his/her death. They will cut any chance of survival for the best outcome of some undeserving well positioned individuals.
- They are not considering the best of my son's interest, but their institutional interests which money driven.
- I'm afraid they will resuscitate the hell of me even if I oppose a wrongful life.
- I'm afraid they will let me die because I am considered unworthy to be treated since I am a homeless, an alcoholic and I have nobody to care for me or to sue them.
- Helpless as I am now, they will start experiencing on me despite my will or their commitment. They will reject my treatment if I refuse enrolling in their studies.
- I feel bad when awaking in the ICU and it is completely their fault. I will refuse to cooperate to teach them well.
- If we do not accept their treatment offers they will let down my beloved.
- They should keep him/her alive no matter his/her will until the lawyer fixes the last will.
- They keep my beloved physically refrained. This is torture and torture is unacceptable.

At least half of the aforementioned lines belong to families and former critically ill patients. They reflect the main ethical problems we are confronted with: respecting the patients' autonomy, doing good and not harming, observing justice and a right material distribution. Often patients demand the right to a good death and (rarely enough) they ask to be euthanized. Thus you can have a panoramic picture as to the ethical and moral challenges in the ICU. Moreover, treatment is expensive for an uncertain outcome. Therefore, the ICU manager has to consider distributing not uniformly the resources, but justly and justified.

In a society where responsibility is a key issue, such as ours, decisions are taken in a process of *shared decision making*. This means that the physician is supposed to offer the best suitable and feasible treatment options and alternatives. The surrogate decision maker is thus mandated to represent the patients' interests and the patient' will, to express a substituted judgment, to convey an understanding of "what the patient would want". When the patients' preferences are unknown, one should use the best interest standard. This is a presumed understanding of what a reasonable person would expect. And the ultimate responsibility as to a reasonable plan belongs to the attending physician. When the attending physician disagrees with the patients or surrogates, communication with the families, second opinions

or further information will certainly help. A trial of time-limited continued therapy may bring about resolution. Supportive services could also help: clergy, social services, psychiatric consultation, ethics consultation, palliative care.

EUTHANASIA

Euthanasia is banned generally in the world. Our penal code states that it is considered murder and is punished as such. Differences between active and passive euthanasia vanished as passive euthanasia (letting the patient die in a futility context) is not considered euthanasia anymore. There are a few organisations offering euthanasia to terminally ill patients in countries where this is still legal, but it is an unethical approach according to our general moral values. With the existing means to fight pain and suffering, such painful decisions should be marginal.

ASSISTED SUICIDE

Assisted suicide is not an option for Christians. Many European countries forbid assisted suicide. In the UK, the law currently forbids assisted dying, but come uncertainty exists as to what actually constitutes “assistance’’. Cases are prosecuted on an individual basis, bearing in mind a predefined set of factors. It is our duty to make the patients approaching end of life aware as to the palliative care. Attempts to carry out assisted dying have to be discouraged and we should explore additional support to improve the patients’ quality of life. Embarking on a slippery slope with undesirable consequences is one of the risks of accepting assisted dying. Assisted suicide is a notion overlapped by assisted dying.

WITHHOLDING AND WITHDRAWING LIFE-SUSTAINING TREATMENT

Withholding means refraining from instituting life-supporting treatment to the critically ill. It might appear as a consequence of an advance directive, as an option of a patient’s while still conscious or as a demand of the family or the surrogate decision maker instituted with the power to decide for the patient in question. The consequence is demise or, in rare cases, survival with different sequels.

Withdrawing is consistent with removal of the life-sustaining technology or treatment once instituted. The conditions and consequences of removal are similar with the previous. People are undecided as to the ethical differences among the two situations, although doctors tend to see no difference at all. There are protocols and guidelines on performing withdrawal procedures, but in our country it is still an avoided practice, mainly when it comes for mechanical ventilation. Doctors are less hesitant when it comes for renal replacement therapies.

INFORMED DECISION MAKING

Autonomy is a core principle in the majority of the European countries and in the USA. It is part of the respect due to the person and for the values and wishes of the individual. Decisions as to his future have to be made only by involving him. If not incapacitated for some reason, he must be well informed, free of coercion and competent in order to make decisions as to his treatment options. The commonest situation in the ICU is to ask for a surrogate since the patients are comatose. Even then, confidentiality prevents us from unrevealing unnecessary confidential information to the surrogates, such as the state of HIV status. When the surrogate's decision is conflicting with the known patient's wishes or there are suspicions of felony or crime, the risk management team should approach the problem or it should be directed to the ethics committee for consultation prior to acting.

DNAR

Do not attempt resuscitation orders are a limited form of advance directive and are known as "code status". They are sometimes sought on admission to the ICU. Their content must be explicitly formulated, understood by the surrogate decision maker and by the doctor. The patient can and should reconsider his position according to the actual health condition. These orders may be suspended for certain well documented reasons. The DNAR status is based on sound rationales: CPR has such a low likelihood of producing the desired outcome that it is effectively "futile"; there would be an unacceptable quality of life after CPR; there is already an unacceptable quality of life, and cardiopulmonary arrest would be a welcome deliverance. Postresuscitation issues must be addressed when discussing a DNAR order. Insufficient information as to the limits of resuscitation and the possible outcome will limit the capacity of the patients' to make informed decisions. Accepting a DNAR directive equals acknowledging the limits of medical science.

THE RIGHT TO A GOOD DEATH

This is a novel concept promoted towards the end of the last century. Considering the respect for the person and promoting autonomy in decision making, the advocates of this privilege deemed as a "right" ask for death with dignity, with minimal pain and limiting complex suffering. Debatable as it is, the concept is more frequent in developed countries and less accepted within the orthodox coordinates. Enforcing our invasive and aggressive management to these patients equals battery or assault.

WRONGFUL DEATH

There are surrogates who may sue the physicians for the way they handled the demise of their beloved. Refusal to accept a DNAR order by the attending physician followed by a shorter or longer period of survival in a debilitated state or in a condition the patient would have wanted to avoid at all price, may degenerate into a wrongful death accusation.

COMMUNICATION ISSUES

Communication failure is considered to be one of the main causes of conflicts in the ICU and of consecutive claims. When it comes for families, a five step approach is promoted to improve communication. The acronym for this approach is VALUE. V – value family statements; A – acknowledge family emotions; L – listen to the family; U – understand the patient as a person; E – elicit family questions.

Difficult communication tasks may be approached by using the "Ask, Tell, Ask" model. The first step consists in asking the patient or the surrogate to describe his understanding of the medical disease and prognosis. The second step is to explain in a simple straightforward language what we understand about the medical disease in cause and prognosis. The final step would be to assess the patient's understanding by politely demanding him to explain in his words what he was just told. The addressing language is codified in the sense that it must be clear, polite and not patronising.

CONFLICT OF INTEREST

Conflict of interest may manifest at all levels in the ICUs. The cause is a nonalignment of the stakeholders to the same interest. The solution is disclosure or patient referral. Mediation is sometimes a way out. The most mirrored conflicts of interests are raised by clinical research sponsored by the industry. However, this is one of the fields best regulated by national and international policies.

ETHICS INTERVENTIONS

Ethics committees have to be instituted in health facilities in order to assist with difficult situation based on ethical grounds. It is best for the final outcome to include clergy in the committee, as flexible as possible, according to the specific cases' confession. The composition of the committees depends on the policy of the hospital and on the accreditation requirements.

ORGAN DONATION

Organ donation in the ICU is connected to brain death and organ donation after cardiac death. Brain death is a clinical condition characterised by irreversibility and is due to brainstem death. Interruption of the brain dead management leads to irreversible cardiac arrest. The un harvested organs die. At the end of the day it is a terrible waste as numerous lives on the waiting list depend on organ donation.

Organ donation after cardiac death (DCD) was first regulated in the USA, in 1993, at the University Of Pittsburgh Medical Centre (UPMC). Thus challenging situations, such as patients' and families' requests of participating to organ donation after first electing withdrawal of life sustaining treatment were comprised in a concrete model for the use of cardiopulmonary criteria to determine death for the purposes of organ procurement. All accredited institutions have to develop and standardise DCD policies al over Europe as well.

The DCD donors are classified according to the Maastricht category in four. Category 1 comprises cardiac arrest outside the hospital, no resuscitation attempted, but the condition is uncontrolled. Category 2 is cardiac arrest followed by unsuccessful resuscitation, either inside or outside the hospital, still uncontrolled. Category 3 is cardiac arrest after planned withdrawal of life-support technology, the single case of controlled condition. The 4th category is cardiac arrest in a brain-dead patient awaiting organ procurement, uncontrolled condition. There are several remaining issues regarding DCD donations: how to best identify potential DCD donors in order to avoid failed donations; how to optimize DCD donor management, which leaves very little room for error; how to best standardize DCD procurement protocols to ensure a multidisciplinary effort and reproducible results. The major threat for the outcome is the warm ischemic insult.

RESOURCE ALLOCATION

Resource allocation quotes usually the actual truisms of economics: the supply of goods and services is finite and insufficient to meet the demands. We live in a market based economy that allocates many resources on the basis of ability to pay, but the strategies differ according to the political principle of allocation. Common and necessary, the allocations are stigmatised by the media and society on the grounds of promoting inequity, on suspicions of wrongful allocation and discrimination, much spiced by emotional flavours. The seven principles at the basis of resource allocation are: autocracy defined by "to each according to the will of one"; democracy – to each according to the will of the majority; equality – to each according to an equal share; lottery – to each according to en equal chance; capitalism – to each according to the ability to pay; personal worth – to each according to their contribution to the community; utilitarianism – to each so that the utility of the community is maximized.

One of the stringent issues that surfaces on a daily basis is the case of “the last bed in the ICU”. In large community hospitals, mixed ICUs face difficult bed allocation situations: pressure from the Emergency Department, “surprises” in terms of admissions agreed upon by other clinics on behalf of the ICU without even warning the intensivist as to the immediate future plans, enforced admissions by managers. Thus a doctor may have to make choices as to whom to give the last bed in the ICU. E.g.: the intensivist is asked to admit a young patient in a metabolic coma he knows he could reverse or an old conscious preterminal patient with an acute condition requiring mechanical ventilation. The last patient faces the prospect of a short term painful evolution, but is short of breath, cyanotic and in desperate need of air. Facts: the young one is comatose, already intubated and ventilated in the ED, but needs continuous intensive care treatment and assistance best provided by the intensivist. The old one offers a really dramatic picture and will soon die if not helped by the intensivist. Knowing that the age is not an ethical issue, the intensivist has to decide rapidly and act consecutively.

He decides to admit the old dyspnoeic patient, intubate and ventilate him while alleviating his distressful symptoms and leaves the young one in the ED visiting him frequently and providing a qualified nurse to care for him. Meanwhile, he urges the discharge of other patients. He could not have been able to do this if not having been helped by the ED colleagues. A blocked ICU is often the cause of ethical challenges to the intensivist.

The best way to handle these decisions is to prevent them. Thus, public, explicit triage and discharge criteria developed in collaboration with ICU users well in advance of the actual decisions are essential for fair and efficient use of the existing resources.

A very important reason we are under constant scrutiny is the fact that the outcome of the critically ill is so difficult to predict. Scores were developed and applied, but a patient may be found at the extremes of the Gauss curve. Thus predicting the outcome becomes a statistic game, flawed as such. The most valued are the models based on physiologic derangement, such as the family of the APACHE (Acute Physiology and Chronic Health Evaluation) scores, the MPM (Mortality Probability Models and the SAPS (Simplified Acute Physiology Score) successive generations. The premise is that as illness deepens, the physiologic variables deviate from the normal value. The scores and their applicability must be understood so that the outcome considerations become reasonable.

The key word for caring in the ICU is empathy. Burn-out can blunt it, thus giving room for lack of interest and dehumanisation.

We will finish with quoting Cory Franklin: “Unlike the emergency room, the ICU doesn’t lend itself well to shift work.

Do not practice critical care with an eye toward avoiding lawsuits. The best strategy for avoiding lawsuits is to work hard, act in good faith, and establish a good rapport with patients and families. Occasionally, doing the right in the ICU means making people upset.”

TAKE-HOME MESSAGES:

1. Ethical principles for the ICUs are the same as in other fields of medicine, although the challenges are steep and constantly renewed.

2. Different approaches within the frame of the law and the good clinical practice should be offered to our critically ill patients according to their culture and values in their best health interest.

3. The patients’ values and demands have to be respected, but they should not undermine our medical rational thinking.

4. Ethics are under constant pressure, the change is to be welcome provided it does not impede on general human values and survival interests.

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