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CRITICAL CARE - I

HEMODYNAMIC MONITORING IN PEDIATRIC INTENSIVE CARE

**** Anil Sachdev***
***** Preeti Anand***

Abstract: *Invasive hemodynamic monitoring is an essential monitoring system required to save critically ill children. Different methods are available to assess the cardiac function, state of the peripheral vasculature and tissue perfusion. Few methods are very simple and cheap like hourly urine output while others including pulmonary wedge pressure and continuous mixed venous saturation monitoring involve costly equipments and are highly technical and require skilled expertise. The critical care provider should thoroughly know the advantages and disadvantages of different available methods and their clinical utility.*

Keywords: *Hemodynamic monitoring, Pediatric intensive care, Invasive monitoring, Invasive pressure, Invasive pressure wave forms.*

Hemodynamic monitoring is the most vital and valuable of surveillance system which gives analysis of qualitative and quantitative data of cardiopulmonary function. The various systems of hemodynamic monitoring help determine therapies to support cardiovascular system in case of circulatory instability. The consumption of oxygen (VO_2) by tissues must be less than the oxygen delivery (DO_2) to the tissues and thus, a balance between DO_2 and VO_2 is of vital importance in critically ill patients. The key aim of resuscitative measures is adequate DO_2 to all tissues.[1] Also the monitoring of critically ill children helps in documenting hemodynamic stability and the lack of need for acute interventions. It also helps in identifying when measured variables vary from their defined baseline values.[2]

Hemodynamic monitoring can be noninvasive or invasive and continuous or intermittent. The non-invasive variables include body temperature, heart rate, systolic and diastolic arterial blood pressure and respiratory frequency. Other derived noninvasive variables include the electrocardiogram (ECG), pulse oximetry (SpO_2), expired CO_2 ($EtCO_2$), trans-thoracic echocardiography and noninvasive respiratory plethysmography.[2] The various invasive procedures include intravascular catheter insertion, transesophageal echocardiographic probe insertion and blood component analysis. This review article will deal with invasive and advanced hemodynamic monitoring.

Tissue dysfunction can be a guide to resuscitation and has led to the concept of "upstream" and "downstream" markers.[3] The "upstream" markers assess flow and pressure in the heart, vena cava, pulmonary artery and aorta. Upstream markers include systemic blood pressure, heart rate, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and cardiac output (Table I). The upstream end points of resuscitation do not reflect the severity of the microcirculatory injury nor the degree of tissue hypoxia and have been used to assess the hemodynamic status of critically ill patients.

Shock with end–organ dysfunction occurs at the capillary and tissue levels.[4] Various tools have been developed that follow alterations in the microvasculature of critically ill patients.[5] These have been described as ''downstream'' markers of resuscitation. The oxygen demands and metabolic needs of patients vary with different stressors and at different times. Monitoring of downstream variables helps determine the adequacy of cardiac output and perfusion pressure at a particular point in time. The currently available downstream markers include urine output, blood lactate, base excess, tissue carbon dioxide levels and mixed venous oxygen and carbon dioxide levels.[3] The downstream variables are markers of tissue perfusion and the adequacy of the resuscitation.

Upstream markers

Cardiac Output: Cardiac output is the most important hemodynamic upstream parameter. Echocardiography is a simple method to assess cardiac function. It uses ultrasound waves to assess the size of the heart chambers, ventricular contractility, valve function, and the flow can

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Table I. Hemodynamic monitoring markers

Upstream markers	Downstream markers
Blood pressure	Urine output
Heart rate	Blood lactate
Pulmonary capillary wedge pressure	Base excess
Central venous pressure	Tissue carbon dioxide
Cardiac output	Mixed venous oxygen and carbon dioxide levels

be assessed with the aid of Doppler.[6,7] Portable ultrasound devices have made the cardiac assessment easy.

Intravascular fluid and ventricular function assessments help in the management of critically ill patients.[6,7] For example, patients with features of tissue hypoxia and good left ventricular contractility may benefit from fluid administration. However, those patients with poor left ventricular contractility will probably benefit from inotropic agents. Ventricular chamber size can be estimated by calculating the ejection fraction.[6] Flow through the valves can be measured using Doppler imaging. This allows calculation of pulmonary artery pressures and cardiac output. The major advantages of this modality include portability, real time, non-invasive, easy to repeat monitoring and no radiation exposure. The difficulty with this technique is in the acquisition of adequate images in the correct plane, operator dependent interpretation of images. High degree of skill and experience and the cost of equipment are some other drawbacks.[3]

Invasive arterial pressure measurement

Arterial pressure is the input pressure for organ perfusion. Organ perfusion is usually dependent on organ metabolic demand and perfusion pressure. With increasing tissue metabolism, organ blood flow proportionally increases by selective local vasodilation of the small resistance arterioles.[2]

Invasive arterial measurement constitutes the gold standard for measurement in critically ill patients both in pediatrics and adults. With the help of PaO_2 patient's oxygen requirements can be titrated. The patient's requirement of inotropes can also be decided depending on the arterial blood pressure measured through arterial line.[8]

Invasive hemodynamic monitoring of vascular pressures is usually performed by the percutaneous insertion of a catheter into a vascular space and the pressure signals at the distal end of the catheter are sensed by the transducer and further amplified and displayed on the monitor screen numerically and as a waveform.[2]

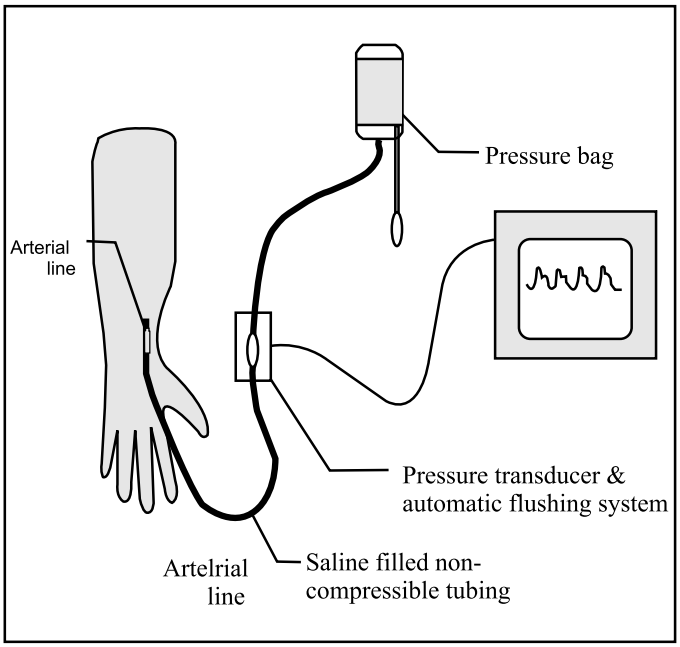

Fig.1. Invasive arterial blood pressure measurement system

Monitoring systems work on the principle of transmitting pressure changes from a column of uncompressible fluid to a mechanical transducer. The mechanical transducer is basically a displaceable diaphragm, which converts physical fluid displacement into a proportional electrical signal, which can be processed and displayed (Fig.1).[9,10] The three factors which need to be considered when using a transducer are (i) calibration, (ii) leveling and (iii) zero setting.[11]

Calibration involves applying a known pressure to the membrane and change in current is related to the applied pressure. To ensure proper functioning, the

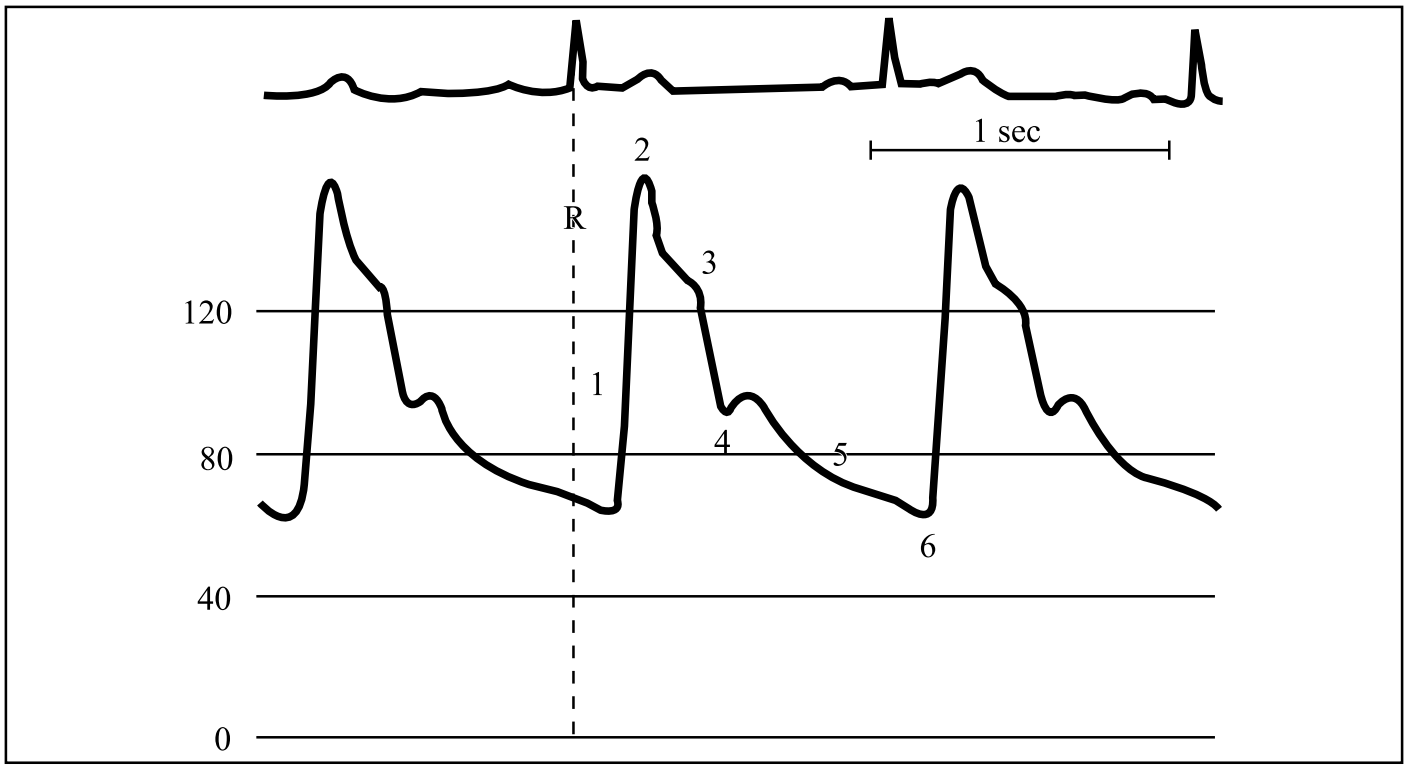

Fig.2. Normal arterial blood pressure waveform in relation to the electrocardiogram. 1 Systolic upstroke, 2 systolic pressure, 3 systolic decline, 4 dicrotic notch, 5 diastolic runoff, 6 diastolic pressure.

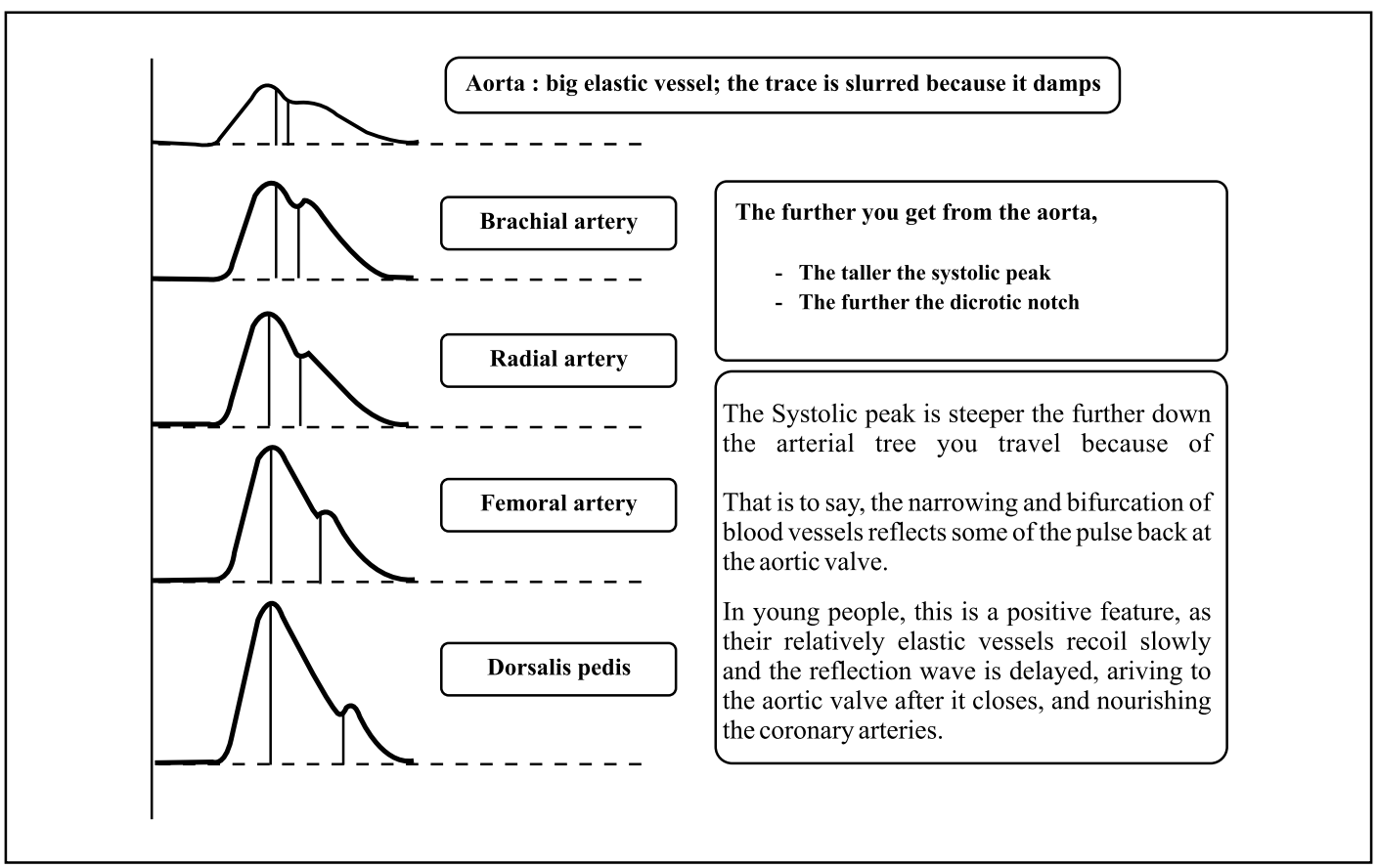

Fig.3. Changes in arterial waveform in different arteries

Table II. Indications for arterial catheter insertions

1. Synchronization of intra-aortic balloon counter pulsation
2. In systemic hypotension to monitor the effect of vasodilator drug infusions and to attain a target mean arterial pressure (MAP).
3. For rapid and repetitive arterial blood sampling
4. Helps in differentiating cardiac tamponade from respiration induced swings in the systolic arterial pressure
5. Helps differentiate hypovolemia from cardiac dysfunction.

response of the transducer must be linear in the range of measured pressures. Meaning thereby, that doubling the pressure doubles the voltage change in the range of the measured pressures.[11]

The next issue is the establishment of the ''zero'' value. The process of subtracting the atmospheric pressure is called ''zeroing''. The process of zeroing involves opening the fluid column on the measuring device to atmosphere and adjusting the electronics so that atmospheric pressure is the starting value or zero.[11]

The most confusing factor in hemodynamic measurements with fluid-filled catheters is the concept of leveling. It is generally accepted that for physiologic measurements, an appropriate reference point is the midpoint of the right atrium, because this is where blood comes back to the heart and this is also the pressure that provides the preload for the heart as a whole.[11] In adults, the midpoint of the right atrium is, on an average, 5 cm below the sternal angle or angle of Louis.[11] A more common leveling position often used in PICU is the mid-thoracic position at the level of the fourth rib. It is argued that the advantage of this position is that it is easier to teach and does not require a leveling device.[10,11] Measurements however, should be made in supine position only.

Other factors, which affect the quality of measurement, include the length, compliance, resistance and impedance of the system. This results in the alteration of the recorded signal. Bubbles in the tubing result in dampening of the pressure waveform. Other important factors include the frequency response of the system and the sampling rate.

The common sites used for arterial pressure monitoring are radial, femoral, and posterior tibial arteries. Less commonly used are the brachial and axillary arteries, especially in smaller infants.[2,11] Allen test must be done before arterial cannulation to check and ensure the collateral blood supply to the distal limb. The various indications for arterial catheter insertions are enlisted in Table II.[12]

The normal arterial waveform has an initial upstroke and peak, which represents left ventricular ejection (anacrotic limb) (Fig. 2). This is followed by brief decline in pressure until aortic valve closes and redirects back flow of blood into the aorta (dicrotic notch).

Systolic pressures measured in radial artery are 6 mm of Hg higher than those in brachial artery.[13] In absence of obstruction, pressures in dorsalis pedis artery are higher than femoral pressures. These differences are less significant in older patients and those with non-compliant vessels. The waveforms in various blood vessels have been shown in Fig.3. The Mean arterial pressure (MAP) does not vary along the course of the arterial tree and thus is a more accurate measurement of pressure in the aorta.[14]

Arterial catheter can lead to local infections of the surrounding skin and subcutaneous tissues. Thrombophlebitis, severe systemic infections and sepsis are other known side effects of arterial cannulations. Formation of hematomas, acute carpal tunnel syndrome, compartment syndrome, nerve injury, arterial thrombosis, formation of aneurysms and ischemia leading to necrosis of tissues including the thumb, fingers, and even the extremity have been reported.[15-22] A recent systematic review of a large number of cases showed that most of the complications were minor, including temporary vascular occlusion (19.7%) and hematoma (14.4%). Permanent ischemic damage, sepsis and pseudoaneurysm formation occurred in less than 1% of cases.[23]

Central venous pressure monitoring

Central venous pressure (CVP) is the pressure in the large central veins proximal to the right atrium relative to atmospheric pressure.[24] It reflects the amount of blood returning to the heart and the ability of the heart to pump the blood into the arterial system. In the ICUs, the CVP is usually measured using a fluid filled catheter (central venous line or Swan-Ganz catheter) with the distal tip located in the superior vena cava connected to a manometer, or more often to a pressure transducer of a monitor, displaying the waveform in a continuous fashion.[2] In order to correctly monitor the CVP, the reference level, the electrical transducer should be placed at the level of the right atrium.[24]

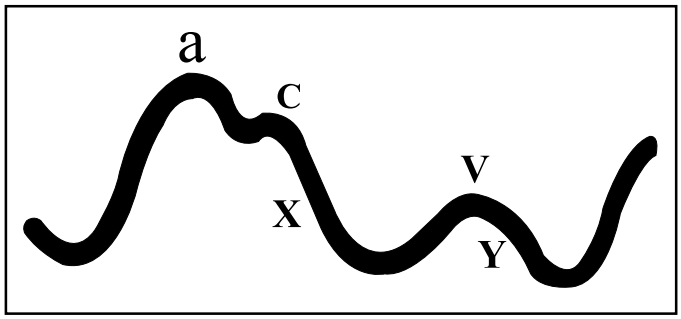

Fig.4. Normal central venous pressure waveform

The waveform for CVP depicts 3 ascending "waves" and 2 descents (Fig. 4). The "a" wave corresponds to the atrial contraction phase and the "x" descent corresponds to the atrial relaxation. The "c" wave, punctuates the x descent. It occurs during the ventricular contraction phase when the tricuspid valve closes and pushes into the atrium. The 'v' wave is seen as a result of continuous venous return to the right atrium against a closed tricuspid valve. The opening of the tricuspid valve during the end of ventricular systole resulting in filling of the ventricle from the atria results in the 'y' descent.

The CVP measurement is affected by many factors related to patient, equipment and technique[10,24] (Table III & IV). Since CVP is a low pressure system as compared to the systemic arterial pressure, it is more affected by the accuracy of leveling. Leveling should be checked whenever there is a unexplained rise or fall in the CVP reading. The CVP is often wrongly used to assess the intravascular volume status. Increase in cardiac output in response to volume resuscitation is unlikely if CVP is greater than 12 mmHg.[19] Studies have shown that CVP has a poor correlation with cardiac index, stroke volume, left ventricular end-diastolic volume, and right

Table III. Patient related factors affecting central venous pressure measurement

1. **Central venous blood volume**
   - Venous return/cardiac output
   - Regional vascular tone
   - Total blood volume.
2. **Tricuspid valve disease**
   - Regurgitation
   - Stenosis
3. **Compliance of the central compartment**
   - Right atrial compartment -
   - affected by myocardial or pericardial disease
   - Vascular tone
4. **Cardiac rhythm**
   - Atrial flutter
   - Junctional rhythm
   - Atrio-ventricular dissociation
5. **Intrathoracic pressure**
   - Phase of spontaneous respiration
   - Positive pressure ventilation
   - Positive end-expiratory pressure
   - Tension pneumothorax
   - Intra abdominal pressure
6. **Position of the patient**
   - Phlebostatic axis

Table IV. Technical and equipment factors affecting central venous pressure measurement

1. **Central venous line**
   - Tip position
   - Kinking
   - Air bubble/blood clot
   - Single or multiple lumens
   - Proximal or distal port
2. **Connecting tube and stop cock**
   - Kinking
   - Long length tube
   - Air bubble/blood clot
   - Motion artifact
3. **Transducer**
   - Type
   - Levelling
   - Zeroing

ventricular end-diastolic volume.[25-27] A high CVP implies that the patient will require a higher mean circulatory filling pressure (either by infusion of volume or by augmenting venoconstriction) to maintain right ventricular preload. In addition, the change in CVP to a fluid challenge is also a valuable assessment of ventricular compliance.[9] In reported series, some patients who had low CVP failed to respond to fluids and some patients who had high CVP responded to challenge of fluids.[28] However, there is no clinical evidence that CVP monitoring improves outcome in critically ill patients and attempts to normalize CVP in early goal directed therapy during resuscitation do not display any outcome benefits.[29]

Standard central venous catheters have risks that have been well described, including hematoma formation, vessel dissection, thrombosis, pneumothorax and even hemothorax and hemopericardium.[30,31]

Downstream Markers

Blood lactate: The body generates energy by metabolizing glucose to carbon dioxide via the Kreb's cycle. In hypoxic tissues, glucose is only partially metabolized and lactate is produced. In shock state, as the metabolic demands and oxygen deficit increases, more lactate is produced. Lactic acidosis can occur in muscles following vigorous exercise and can also be seen following a generalized tonic-clonic seizure.

Blood lactate is used as a "downstream" marker of tissue perfusion.[7] Blood lactate is an insensitive marker of tissue hypoxia.[32-35] If glycolysis occurs at a more rapid rate than is necessary for oxidative metabolism, some pyruvate may not be oxidatively metabolized in the Krebs cycle and will be converted to lactate. The result will be a concomitant increase in both pyruvate and lactate with an unchanged lactate/pyruvate ratio (L/P).[36,37] Lactate levels are a marker of illness severity rather than marker of anaerobic metabolism.[3] Along with the rate of production, the blood lactate level also depends on the rate of metabolism by the liver (Cori cycle). Lactate removal is decreased in critically ill patients due to decreased splanchnic blood flow and hepatocellular dysfunction.[3] Lactic acidosis must therefore be assessed in the proper clinical context before it can be used as a tool to assess downstream mitochondrial function. However, a blood lactate concentration in excess of 4 mEq/L is associated with a high risk of death.[38,39] The rate of lactate clearance has been proven to be a marker of good outcome.[40] The lactate clearance lags behind by many hours and thus cannot be used as marker of goal directed resuscitation.[41]

Venous oxygen saturation (SvO_2) and central venous oxygen saturation ($ScVO_2$)

Monitoring of the SvO_2 is used as a surrogate for the balance between systemic oxygen delivery and consumption during the treatment of critically ill patients.[42] In several diseases such as cardiopulmonary disease, septic shock, cardiogenic shock, and in patients after cardiovascular surgery, a low SvO_2 was associated with a poor prognosis.[43-45] In sepsis, an elevated SvO_2 is seen, secondary to maldistribution of flow (blood returning to the venous circulation without opportunity for oxygen transfer). Also, cellular hypoxia in sepsis leads to tissue dysfunction causing mitochondrial death and thus oxygen consumption by tissues is reduced.[46] This can also be due to changes in the macrocirculation.[47] Patients with sepsis can also present with a normal or low SvO_2. A low SvO_2 in sepsis is often associated with a low cardiac output and should trigger interventions, which increase oxygen delivery to the tissues and decrease tissue hypo-perfusion. However, measurement of SvO_2 involves placement of a pulmonary artery catheter with a risk/benefit relationship that is still a matter of controversy.[48-50]

The measurement of $ScvO_2$ on the other hand, requires the placement of a central venous catheter. Theoretically, measuring $ScvO_2$ reflects the degree of oxygen extraction from the brain and the upper part of the body. In healthy humans, the oxygen saturation in the inferior vena cava (IVC) is higher than in the superior vena cava owing to the increased metabolic demand of the brain. Because the pulmonary artery contains a mixture of blood from both the superior as well as the IVC, SvO_2 is greater than the oxygen saturation in the superior vena cava.[51] A reversal of this phenomenon is seen in septic shock. This effect is seen due to a decrease in mesenteric blood flow in septic shock, which leads to an increased oxygen consumption by these organs.[52,53] However several studies have been done which have shown a good correlation between $ScvO_2$ and SvO_2.[54,55] The Surviving Sepsis Guidelines stated that the use of SvO_2 and $ScvO_2$ is equivalent in the management of patients with severe sepsis and septic shock.[56] Rivers et al[57] demonstrated that in patients who had septic shock or severe sepsis admitted in the emergency department, an early and aggressive resuscitation guided by $ScvO_2$, CVP, and MAP reduced 28-day mortality from 46.5% to 30.5%.

Pulmonary arterial catheterization

The standard pulmonary artery catheter (PAC) has four lumens, which allow assessment of the patients' hemodynamic condition through direct intracardiac and

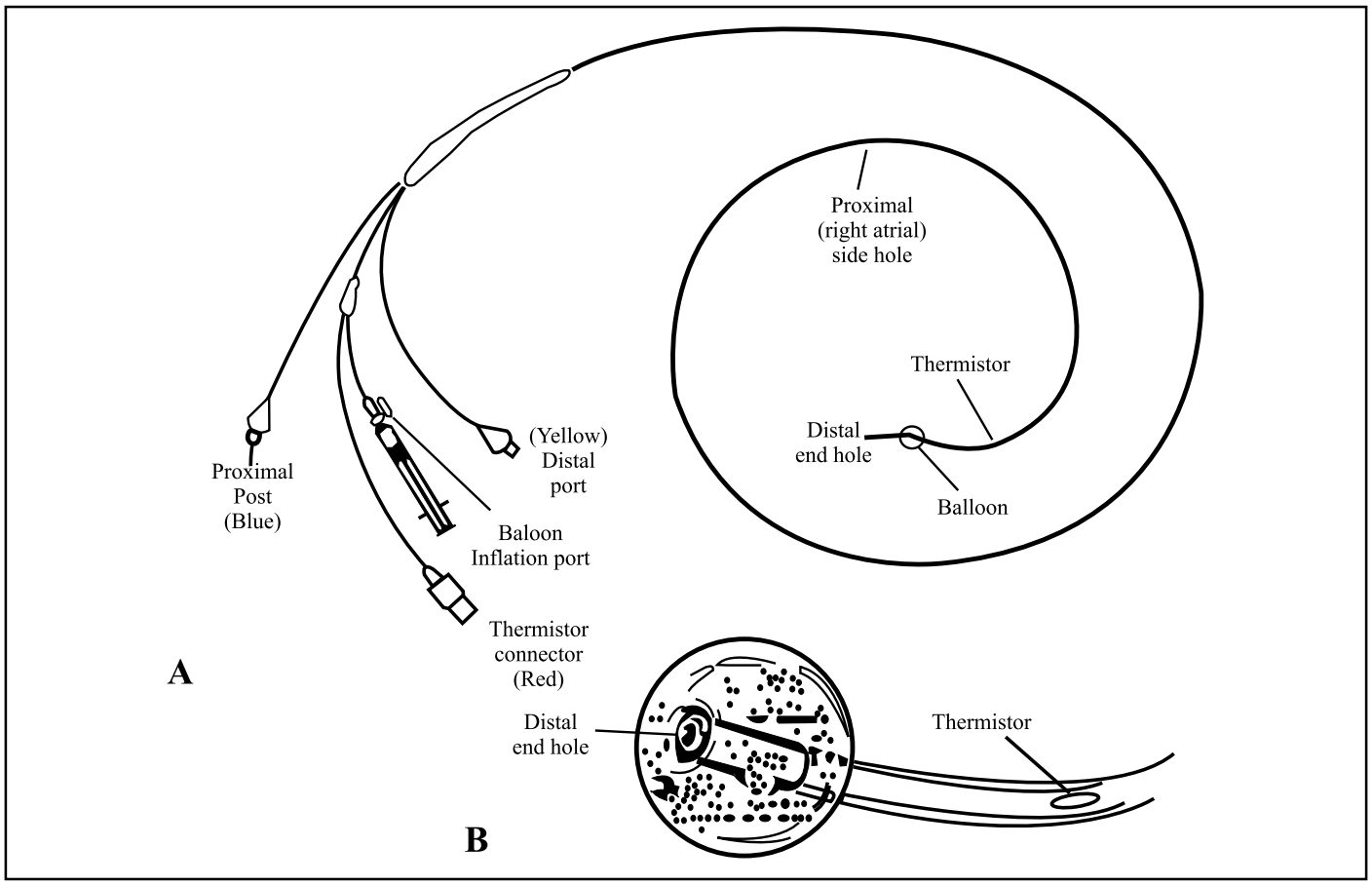

Fig.5. Pulmonary artery catheter

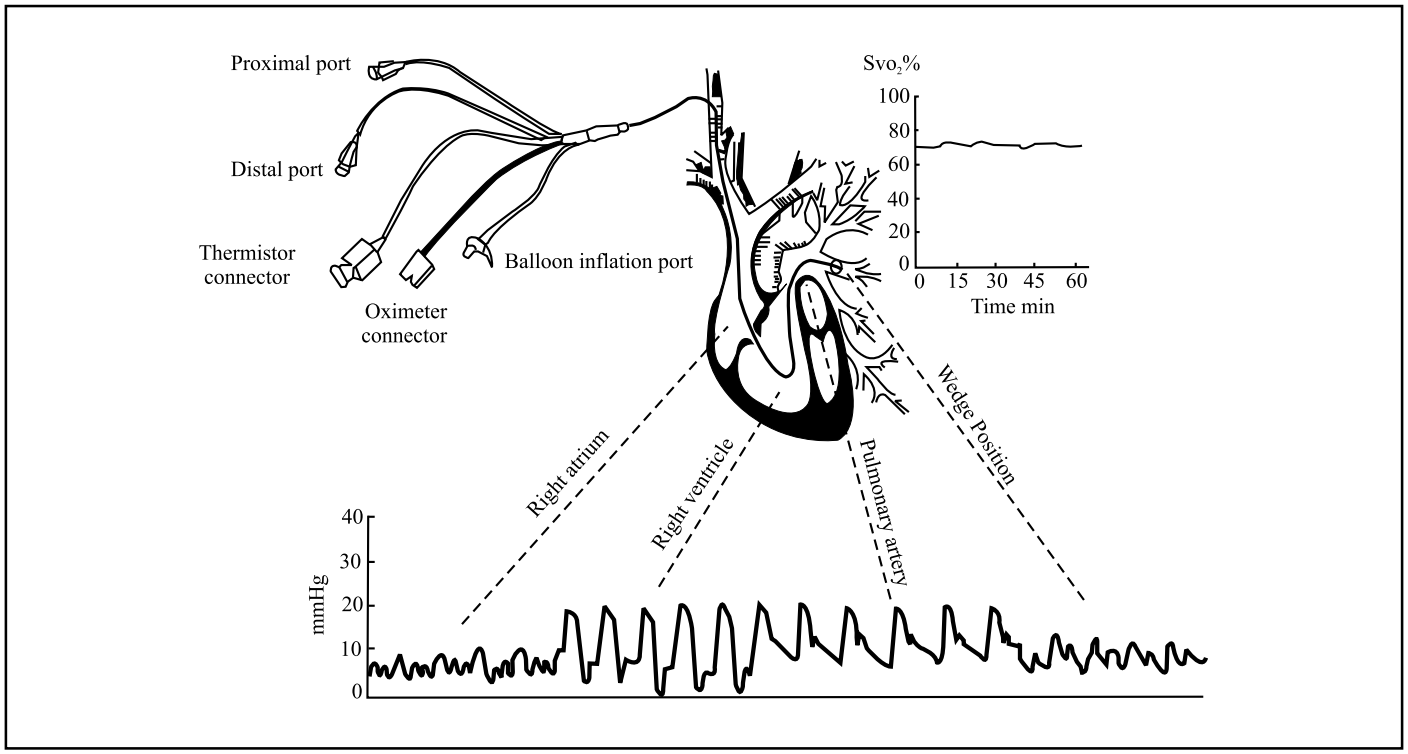

Fig.6. Pulmonary artery catheter insertion and values measured

pulmonary artery pressure monitoring (Fig.5).[58] The PAC directly measures pressures in the right atrium, right ventricle, pulmonary artery and pulmonary artery occlusion pressure; mixed venous oxygenation; and temperature (Fig.6). Other parameters, which can be calculated, include stroke volume, systemic vascular resistance, pulmonary vascular resistance, oxygen transport, oxygen consumption and oxygen extraction ratio.

Misinterpretation of the available hemodynamic data, limits the use of PAC.[51] Furthermore, the risks involved with the insertion of catheter include vascular inflammation and rupture, valvular rupture and arrhythmias thereby limiting the regular use of pulmonary artery catheters.

Newer monitoring devices

Pulse Contour Analysis: Pulse contour analysis finds its origin from variation in pulse pressure waveform. The pulse pressure is proportional to stroke volume and inversely related to vascular compliance. Thus, the greater the stroke volume, the greater is the amount of blood that must be accommodated in the arterial tree with each heartbeat and greater is the pressure rise and fall during systole and diastole, thus causing a greater pulse pressure. Therefore, pulse pressure waveform changes predictably with changes in the compliance of arterial wall and stroke volume. The compliance of vasculature can be calculated based on age, sex, ethnicity and body mass index (BMI).[59] The cardiac output is then calculated from the analysis of pulse contour using a complex proprietary formula (PulseCO, LiDCO, London, UK; PiCCO, Pulsion Medical Systems, Munich, Germany).[60] The pulse contour analysis is calibrated to an injection dilution method. Measurement of the cardiac output by pulse contour analysis corresponds to the cardiac output measured by other techniques. However, the use of vasoactive agents results in spurious changes in cardiac output.[61,62] A large pulse pressure/stroke volume variation (10% to 15%) is indicative of hypovolemia and predictive of volume responsiveness.[3]

Lithium is the contrast agent most commonly used with the injection dilution method for external calibration of pulse contour analysis devices (PulseCO, LiDCO).[60] The lithium may be injected via a central or peripheral vein. Stroke volume is calculated and compared with the stroke volume as determined by the dilution technique, and the cardiac output is then calculated. With beat-to-beat waveform analysis, cardiac output can be determined continuously.[61] In human studies a good correlation between thermodilution and lithium dilution has been reported.[61,63,64]

PiCCO (Pulsion Medical Systems) uses the aortic transpulmonary thermo dilution curve to calculate cardiac output (TP-TD). In this technique, a thermistor-tipped catheter is typically placed in the descending aorta via a femoral route. Iced saline (15 mL) is injected into a central vein and from the temperature change in the aorta, the cardiac output can be calculated and the pulse contour system calibrated.[65-66]

Gastric tonometry

Patients with deranged hemodynamics have flow distribution away from the gastrointestinal tract leading to tissue hypoxia. Studies have shown that changes in gastrointestinal mucosal pCO_2 mirrors changes in gastrointestinal oxygen uptake during progressive flow stagnation.[67,68] The PCO_2 of the stomach wall ($PgCO_2$) and sublingual tissue ($PsiCO_2$) have been demonstrated to increase predictably during both hemorrhagic and septic shock.[69-71] In a study in critically ill patients, Gutierrez and colleagues randomized ICU patients to a standard treatment group or a protocol group in which treatment was titrated to maintain the gastric intramucosal pH (pHi) greater than 7.35. They concluded that survival was significantly improved in the protocol subgroup whose initial pHi was greater than 7.35.[72] This study further supported the argument that the early detection and treatment of tissue dysoxia may improve the outcome of critically ill patients.

The logistic and practical difficulties of gastric tonometry have hindered its widespread use.[3] The advent of sublingual capnometry has resolved many difficulties associated with gastric tonometry. Sublingual capnometry is a non- invasive, simple, inexpensive technique, which provides information about the adequacy of tissue perfusion in critically ill patients.[69] The clinical experience with sublingual capnometry is limited and needs further studies to demonstrate the clinical utility of $PsiCO_2$ monitoring.

Near infra-red spectroscopy

Near infrared spectroscopy (NIRS) is a noninvasive optical technology that relies on the relative transparency of biological tissues to near infrared light (700-900 nm) to determine tissue oxygenation. It works on the hypothesis that as the oxygen delivery to the brain decreases, oxygen extraction from arterial blood increases and the oxygen saturation in cerebral venous blood decreases.[73] NIRS can be used as a continuous monitor of changes in cerebral oxygenation and blood volume by following changes in the blood concentrations of oxyhemoglobin (HbO_2) and deoxyhemoglobin. Evidence supports the conclusion that

near-infrared spectroscopy offers a favorable risk–benefit profile and can be effective and beneficial as a hemodynamic monitor for the care of critically ill patients.[74]

Points to Remember

- ***Upstream and downstream monitoring tools reflect the different physiological aspects of cardiovascular system.***
- ***The intensivist should remember the usefulness and pitfalls of all available hemodynamic monitoring tools.***
- ***The different invasive pressure waveforms help in understanding the physiological state of the cardiovascular system.***
- ***The critical care provider should not depend on a single parameter but take all the available hemodynamic variables into consideration and plan intervention.***

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NEWS AND NOTES

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CRITICAL CARE - I

SEPTIC SHOCK

**** Indumathy Santhanam***

Abstract: *The first protocol for septic shock published in 2002 by the American College of Critical Care medicine advised pushing up to 60 mL/kg in the initial minutes of resuscitation of shock due to sepsis. Faced with level I evidence that demonstrated increased risk of pulmonary edema in India and increased mortality in Africa these guidelines were modified. "The Surviving Sepsis Campaign guidelines-2012" now states that these recommendations are "appropriate only in resource rich regions with universal access to mechanically ventilated ICU beds". This review discusses the protocol used for early recognition of septic shock in the out-patient department and a step wise management of shock using clinical therapeutic goals in setting with limited access to mechanical ventilation and invasive monitoring.*

Keywords: *Septic shock, Pulmonary edema, Acute lung injury, CPAP triggers.*

In India, fever and infections are the most common causes for hospital visits amongst children whilst, the commonest cause of hospital mortality is serious sepsis. Fifty percent of deaths due to serious sepsis in developing countries[1] occur within the first 24 hours and these deaths are a result of shock. In these countries therefore, efforts must focus on early recognition of shock and energetic time sensitive, goal directed management in the emergency department.

Pathophysiology

Principles which help in recognition of septic shock in the pediatric emergency department: Local and systemic inflammatory response to microbes that traverse the epithelial and tissue barriers result in the systemic inflammatory response syndrome (SIRS). Fever or hypothermia, tachypnea and tachycardia are the cardinal clinical signs of SIRS. Sepsis is diagnosed when infection is suspected, proven or identified by visual inspection in patients having signs of SIRS. Severe sepsis is diagnosed when sepsis is associated with dysfunction of organs distant from the site of infection. It is interesting to note, that microbial invasion from the site of infection into the blood stream is not necessary to cause dysfunction of distant organs. It occurs due to, activation of the inflammatory cascade resulting in over expression of

Table I. Definitions of SIRS and different degrees of severity of sepsis[2,3]

Condition	Description
SIRS	Two or more of the following conditions: temperature > 38.5°C or < 35.0°C; heart rate of > 90 beats/min; respiratory rate of > 20 breaths/min or $Paco_2$ of < 32 mm Hg; and WBC count of > 12,000 cells/mL, < 4,000 cells/mL, or >10% immature (band) forms.
Sepsis	SIRS in response to documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection, eg, ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge).
Severe sepsis	Sepsis and at least one of the following signs of organ hypo-perfusion or organ dysfunction: areas of mottled skin; capillary refilling time> 3secs; urinary output of < 0.5 mL/kg for at least 1hr or renal replacement therapy; lactate >2 mmol/L; abrupt change in mental status or abnormal EEG findings; platelet count of < 100,000 cells/mL or disseminated intravascular coagulation; Acute lung injury (ALI)/ Acute respitatory distress syndrome (ARDS) and cardiac dysfunction (echocardiography).

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inflammatory responses. Excessive release of inflammatory mediators lead to acute lung injury (ALI)[4] and multiple organ dysfunction syndrome.

The International Sepsis Definitions Conference defined organ dysfunction only when sepsis was associated with any one of the laboratory variables shown in the Table I. Since, these facilities are not available on arrival in low and middle income countries, recognition and resuscitation of severe sepsis could be delayed. This article focuses on triage guidelines that assist early recognition of septic shock with or without pulmonary edema in the out-patient department.[5] It will also discuss a time sensitive goal directed protocol that is currently being used to resuscitate shock due to severe sepsis.

The following triage questions should be posed to mothers who bring children with fever with or without focus of infection.

1) History of inconsolable cry, lethargy, "more sleepy than usual", "not as usual" or posturing helps to detect cerebral hypoxia and shock due to severe sepsis.

2) In these children presenting with altered mental status, history of breathlessness especially in the presence of non-lung focus of sepsis, suggests the possibility of ALI (non-cardiogenic pulmonary edema) or pulmonary edema (PE) due to myocardial dysfunction.

It has been noted, that respiratory distress due to ALI is characterised by systemic components such as sepsis and shock.

When history of altered mental status and/or breathlessness is obtained, the rapid cardiopulmonary cerebral assessment should be performed to ascertain whether the child with fever and focus has additional features of SIRS, sepsis, or serious sepsis within the first minute of arrival (Fig.1).

Principles which assist in the management

Septic shock is characterized by decreased systemic vascular resistance (vasodilation) and increased cardiac index after adequate fluid resuscitation. In addition, several studies have revealed clear evidence of intrinsic depressed left ventricular performance that normalized within 10 days after the onset of septic shock.[6]

Sepsis induced myocardial depression causes increased pulmonary hydrostatic pressure. The latter causes the ultra filtrate of plasma to cross the pulmonary capillary membrane into the interstitium. In contrast, non-cardiogenic pulmonary edema due to sepsis results from permeability changes in the pulmonary capillary membrane.[7]

Large volumes of fluids are needed to resuscitate children with septic shock. But optimizing fluid balance in the presence of non-cardiogenic pulmonary edema is important to maximize patient outcomes. Although PE is not due to fluid overload, elevation in circulating blood volume and subsequent intravascular pressure can result in worsening of alveolar fluid collection and de-oxygenation.[8]

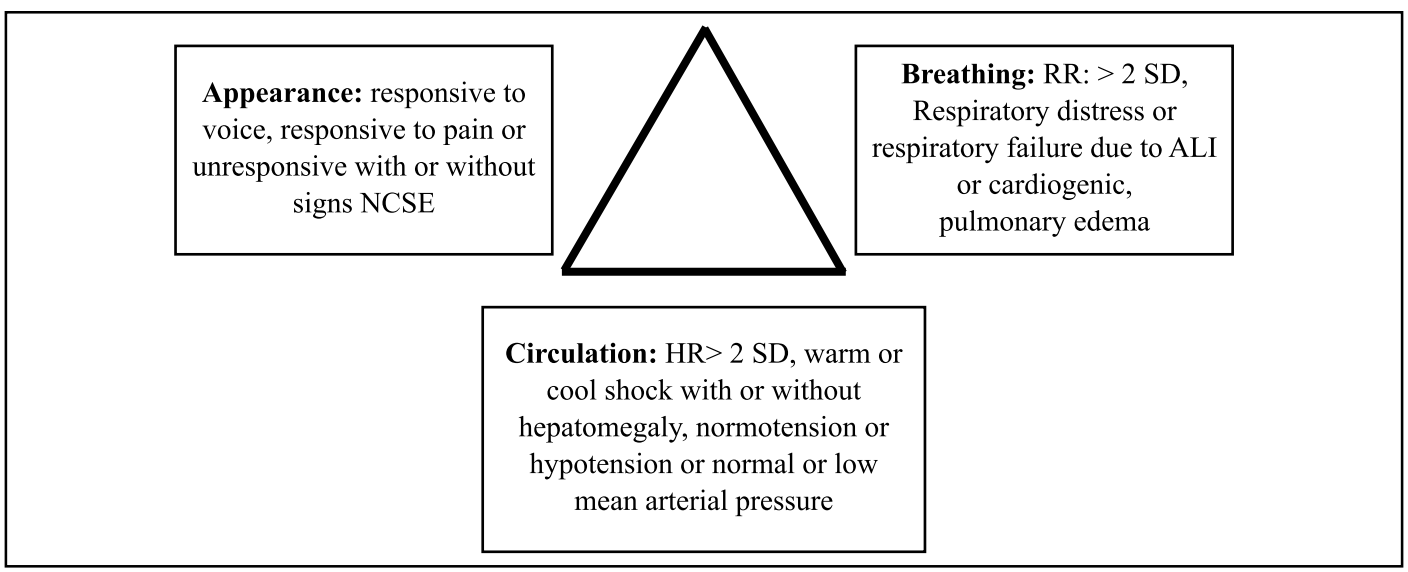

Fig.1. Serious sepsis is diagnosed when a child with fever >38^{0}C or hypothermia <36^{0}C with suspected, proven or visually seen focus of infection presents with the above physiological status[5]

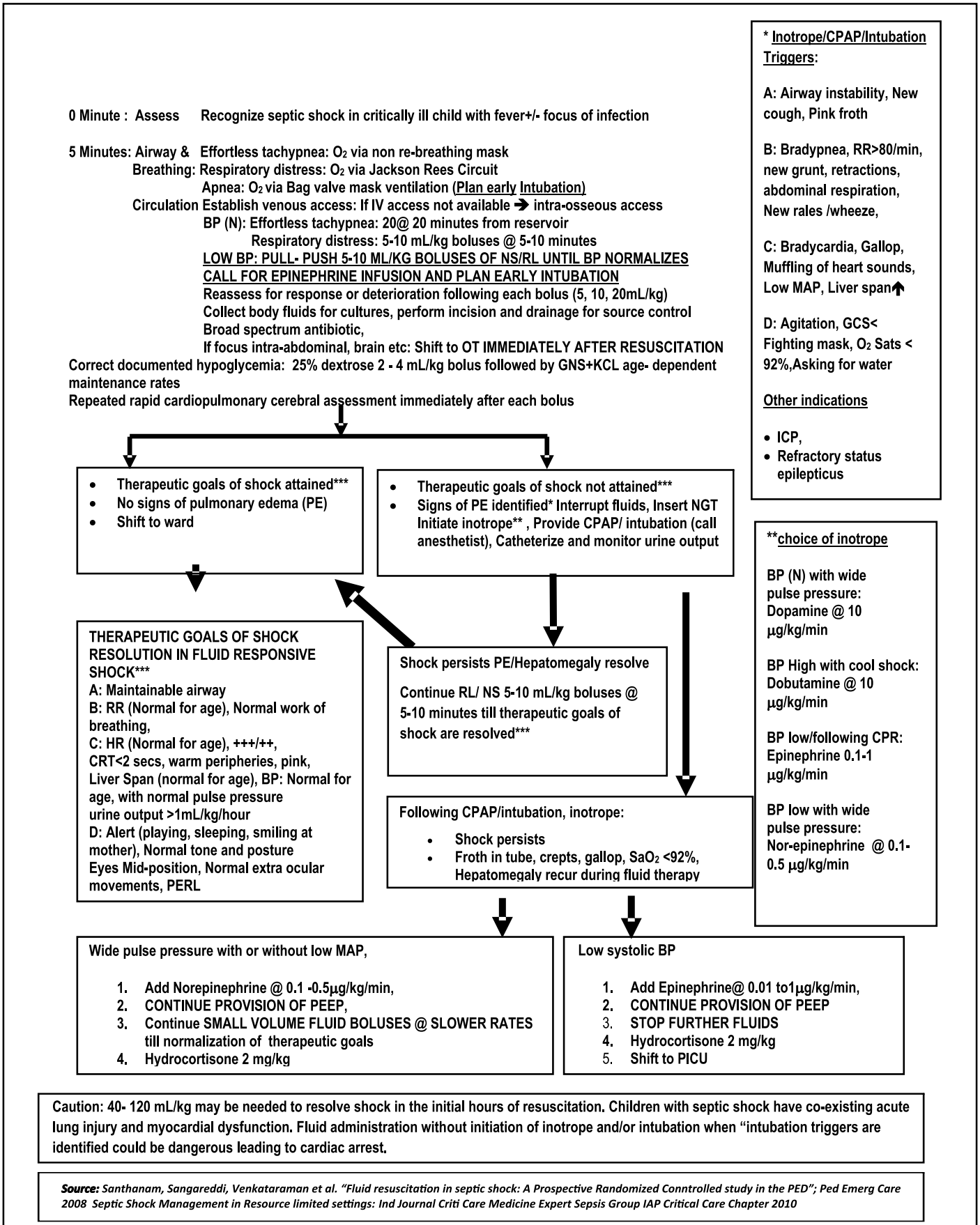

Fig.2. Septic shock protocol

PEEP is the most useful strategy in achieving successful oxygenation and ventilation in the presence of acute PE. The beneficial effects of PEEP in improving oxygenation result from increasing mean alveolar pressure, which opens up collapsed alveoli. This prevents further damage by reducing the repetitive opening and closing of the alveoli in a normal respiratory cycle.

Providing PEEP is one of the most difficult challenges in the management of shock due to sepsis in settings without universal access to mechanical ventilation. Acute PE, could worsen or become un-masked during fluid resuscitation of shock.[9] On the contrary, restriction of fluid boluses due to fear of pulmonary edema could lead to increased mortality.[10] Failure to recognize the development of PE or intubation triggers, failure to provide PEEP or inotropes during administration of fluid boluses, can also lead to increased mortality in children presenting with shock as demonstrated by the FEAST trial in severe sepsis.[11]

Adult studies have demonstrated the usefulness of noninvasive ventilation in the management of ALI. Randomized studies have shown lower rates of endotracheal intubation, barotrauma and reductions in mortality if these techniques are used early enough in the course of the disease.[12]

There is little data supporting the use of NIPPV in children with PE. However, use of a disposable flow inflating ventilation device in a large volume Pediatric Emergency Department during fluid resuscitation of septic shock has demonstrated a drop in mortality. This article is based on the data from this study.[9] Septic shock protocol (Fig.2).

Airway and breathing

- Provide oxygen through the non-rebreathing mask if the child with shock has effortless tachypnea.
- Administer oxygen through flow inflating ventilation device (Jackson Rees circuit) if the child has respiratory distress and shock.
- Initiate bag valve mask ventilation if child presents with bradypnea.
- Proceed to intubate at any step in the protocol if the child develops bradypnea, bradycardia or hypotension.
- Consider intubation when signs of pulmonary edema or cardiac dysfunction are noted during fluid resuscitation of septic shock.

Intubation should not be delayed till the child is moribund.[13] Despite lack of post resuscitation mechanical ventilatory facilities, intubation and manual ventilation offers a 50% chance of survival to children who need it, while failure to intubate would mean certain death.[9]

Circulation

- Secure two intra-venous lines simultaneously on arrival. If intra vascular access is not immediately obtained, an intra-osseous line should be urgently secured.

Normotensive shock[9]: Speed of fluid administration

Fluids should be administered in aliquots of 20 ml/kg over 20 minutes[9](Level A)

Small aliquots of 5-10 ml/kg over 5-10 minutes are administered if the child presents with pulmonary edema or respiratory distress and shock and larger aliquots of 20 mL/kg at the rate of 20 minutes if the initial assessment suggests effortless tachypnea with shock, viz. the increased respiratory rate is secondary to metabolic acidosis and lung parenchyma is normal.

In the Indian context, administration of larger volumes (60 ml/kg over 15 minutes) as recommended by the American College of Critical Care Medicine Surviving Sepsis Campaign guidelines 2012[14], will result in life threatening pulmonary edema. This is a major concern in our country where access to mechanical ventilators and advanced intensive care facilities are limited.

Fluid boluses should be administered until clinical therapeutic goals of shock resolution are attained.

Discontinuing fluid therapy based on achievement of some and not all the goals could result in inadequate resuscitation.[9] The individual components of the airway, breathing, circulation and disability is evaluated following every therapeutic intervention viz fluid bolus, intubation, initiating inotrope therapy or administration of an anti convulsant until therapeutic goals of correction of shock, pulmonary edema, cardiac dysfunction and seizures are achieved.

Resolution of shock is not complete until normalization of the following parameters are achieved.

Airway: consulable cry, verbalization in children who have not been intubated.

Breathing: RR (Normal for age), absence of grunt, retractions, normal thoracic respirations, no added sounds

Circulation: HR (Normal for age), pulses +++/++, CRT<2 secs, warm, peripheries, pink, liver span (normal for age), BP: normal for age, with normal pulse pressure, normal MAP, urine output >1mL/kg/hour

Disability: Alert, normal tone and posture, normal eye position, normal extra ocular movements in children who are not intubated. Pupils that react equally to light.

Clinical signs suggestive of myocardial dysfunction or pulmonary edema on arrival or its development during fluid therapy should be anticipated. If signs of pulmonary edema (intubation triggers) are noted during fluid therapy, further fluid administration is interrupted briefly.

Intubation triggers[9]

A: Froth, new cough, unstable airway

B: Increase or decrease in RR requiring respiratory support. Onset of grunt, retractions, abdominal pattern of respirations, new rales, new wheeze, cyanosis, O_2 saturations <92%

C: Bradycardia, gallop, increase in liver span from base line (hepatomegaly), shock not resolving at 60mL/kg, low BP, MAP <65m Hg.

D: Agitation, fighting the mask, combativeness, thirst

Other intubation triggers: seizures not resolving with 2 doses of benzodiazepine, features of ICP

During bolus therapy, if any one or a cluster of signs of deterioration viz. pulmonary edema are identified, fluid boluses are interrupted briefly.[9] Continuation of fluid bolus therapy when signs of PE have developed suggests the need for inotropes and provision of PEEP. Failure to provide PEEP could precipitate cardiac arrest.

A nasogastric tube is introduced and stomach is decompressed. An appropriate inotrope is initiated and CPAP ventilation is provided. If the airway becomes unmaintainbale, bradypnea supervenes, bradycardia, gallop is noted, BP falls or the child becomes unresponsive or starts convulsing, intubation must be performed using anesthetic drugs. Shock can worsen during or following intubation. Initiation of an appropriate inotrope infusion prior to intubation improves its safety profile. Further volumes may be safely administered to resolve shock after intubation and ventilation.[9] Failure to recognize signs of pulmonary edema during fluid resuscitation is dangerous. Continuance of fluid resuscitation without addition of inotrope or provision of continuous positive airway pressure (either non-invasively or following intubation) can result in cardiac arrest.

Following application of CPAP or intubation, the rapid cardiopulmonary assessment is repeated. If pulmonary edema (PE) and hepatomegaly have resolved but therapeutic goals of shock have not been achieved, boluses of 5-10 mL/kg should be continued till therapeutic goals of shock have been achieved. Flow inflating ventilation bags are used to provide CPAP during fluid therapy even after intubation. If after intubation, oxygen saturations fall below 92%, displacement, obstruction, equipment failure and pneumothorax must be urgently ruled out. Failure to do so can precipitate cardiac arrest in the intubated child!

In vasodilatory shock in severe sepsis, it is not uncommon for pulmonary edema to recur.

Development of froth, crepitations, de-saturation, gallop, muffling of heart sound, fall in mean arterial pressure, increase in liver span, herald the development of fluid refractory, dopamine un-responsive shock.

In these situations, addition of nor-epinephrine infusion at the rate of 0.3µg/kg/minute to 0.5µg/kg/minute and continuation of smaller fluid boluses until signs of shock and pulmonary edema are resolved improves outcomes.

Hypotensive shock suggests the presence of significant myocardial dysfunction and can progress to cardiac arrest within minutes.[5] The following unique steps are taken during resuscitation if hypotensive shock is noted either on arrival or during resuscitation:

- Assign one physician exclusively for managing the airway even if breathing and oxygen saturations look normal. He should be prepared to initiate bag mask ventilation since there is potential to progress to cardio respiratory arrest during resuscitation.
- Order ketamine, atropine and succinylcholine for urgent intubation. If IV access is not available, double the dose of ketamine, atropine and succinylcholine may be administered through the intra-muscular route.
- Administer the 1st bolus using pull push technique until BP stabilizes to the normal range.
- Administer small boluses of 5-10 ml/kg cautiously, with frequent assessments. Fluids could precipitate or worsen bradycardia in the failing heart.
- Dedicate one team member to initiate chest compressions if heart rate starts to fall.
- Order for epinephrine infusion simultaneously and initiate at 0.3 to 1 µg /kg/minute.

- Ensure that age appropriate bolus doses of epinephrine(0.1 ml/kg of 1: 10,000) are also available close at hand.

Unlike dopamine and dobutamine, epinephrine infusion should be initiated at the earliest along with the initial fluid resuscitation. Subsequently, when BP normalizes, dopamine may be initiated in addition to the adrenaline infusion. If BP is higher than normal for age, adrenaline infusion is gradually tapered to minimal rates. Sudden discontinuation of adrenaline infusion should be avoided since hypotension can recur.

Treatment and prevention of hypoglycemia

- Correct documented hypoglycemia with 2 ml/kg of 25% dextrose.
- Throughout resuscitation, glucose normal saline to which potassium has been added is infused at maintenance rates for age.

Treatment of sepsis

Blood and body fluids are collected for culture and a third generation cephalosporin is administered in the initial hours of resuscitation.

Obvious foci of sepsis should be drained even as resuscitation is in progress. If focus of sepsis is inaccessible the child is shifted to the OR at the earliest after stabilization. Avoid transferring to the ICU or ward without draining the focus of sepsis**.**

Steroids: Hydrocortisone (2 mg/kg) is administered intravenously for children who have been on steroid therapy in the recent past. It is also indicated when hypotensive shock is refractory to catecholamine infusion.

Blood transfusion: Blood transfusion is planned in a semi elective manner if hemoglobin is less than 10 gms/dL. Even in children presenting with massive bleeds or severe anemia complicating septic shock, isotonic fluids, inotropes and intubation should not be delayed while waiting for blood.

The physiological response of every critically ill child to resuscitative interventions is variable, un-predictable and occasionally anxiety provoking. In the initial hours of resuscitation in the ED, where radiological, biochemical evaluation and invasive monitoring are unavailable, it is imperative for the treating physician to remain by the bed-side and repeatedly perform the cardio pulmonary assessment, to accurately assess trends in patient's response and intervene appropriately.

Common errors

- Mistaking the flushed warm peripheries in the presence of abnormal mental status, tachypnea and tachycardia in a febrile child as normal. Recognize warm septic shock.
- Failing to note diastolic pressure. A diastolic pressure less than 50% of systole will help to recognize vasodilatory (warm) shock
- Diagnosing fever with altered mental status as central nervous system infection, atypical febrile fits or febrile encephalopathy.
- Failure to interrupt fluids, initiate inotrope and provide PEEP when signs of pulmonary edema are identified.

Points to Remember

- ***The protocol for septic shock can only provide a broad guideline where treatment needs to be individualized for the patient at hand.***
- ***Recognize septic shock by looking for evidence of decreased mental status and peripheral perfusion in any ill looking child with fever.***
- ***Altered level of consciousness in a febrile child could be due to septic shock. Correction of the hypoxia and shock often improves mental status in the ED.***
- ***Resuscitation should be continued till all therapeutic goals of shock and pulmonary edema are resolved.***

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CRITICAL CARE - I

INTRACRANIAL HYPERTENSION: PATHOPHYSIOLOGY AND APPROACH TO THERAPY

**** Suchitra Ranjit***

Abstract: *Intracranial hypertension is a medical emergency requiring prompt recognition and management. Etiology, pathophysiology, initial stabilization, specific management, monitoring and escalated therapy for refractory cases are discussed here. When treating ICP, clinicians should ensure an adequate cerebral perfusion pressure by maintaining a high normal mean arterial pressure for age. Cushing's triad is a late sign of intracranial hypertension. Systematic evaluation of underlying and associated problems is essential. Decision to do lumbar puncture (LP) in a comtose child is dictated by balancing the potential benefits of LP for early diagnosis of infection against the risks of herniation. Therefore if LP is decided, it must be performed with utmost care. One should remember the fact that absence of papilledema or normal CT scan in the acute phase, do not rule out raised ICP.*

Keywords: *Intra Cranial Pressure, Pathophysiology Approach.*

Increased intracranial pressure (ICP) is a pathological state which occurs in a variety of serious neurological conditions (Table I) all of which are characterized by addition of volume to the intracranial vault.

Pathophysiology

The intracranial pressure (ICP) and volume

Normal ICP varies with age. In the newborn, ICP averages 4.5 cm H_2O or 6 mmHg, and rises slowly with age. In normal adults, ICP is approximately 10-15 mmHg (1 cm H_20 = 1.3 mmHg). ICP of 20 mmHg or greater is considered abnormally elevated. In infants and young children (with open sutures and fontanelles), chronically increased intracranial volume may be compensated by the expansion of the intracranial vault. However, these do not provide protection for acute rapid increases in the intracranial volume. When the ICP is critically raised, herniation syndromes (uncal, central or medullary herniation) (Table II & III) can occur, which, along with hypoxic-ischemic damage from reduced Cerebral Perfusion Pressure (CPP), are the most important cause of death.

The volume of the intracranial vault is generally fixed in adults and most children. The contents of the intracranial vault in the normal condition include the brain, arterial blood, venous blood and cerebro spinal fluid (CSF) and are maintained at a relatively low ICP (Fig.1. Panel 1: normal). After an injury, swelling/edema/pathological tissue can increase within the brain (Fig.2. Panel 2: compensated). Compensatory mechanisms, including increased CSF absorption, extrusion of CSF into the spinal canal and extrusion of venous blood into the thorax, initially limit any changes in ICP. When these compensatory changes are exhausted (Fig.1. Panel 3: uncompensated), any further increase in intracranial volume is associated with concomitant increase in ICP that eventually can compromise arterial blood flow, ultimately leading to cerebral herniation.

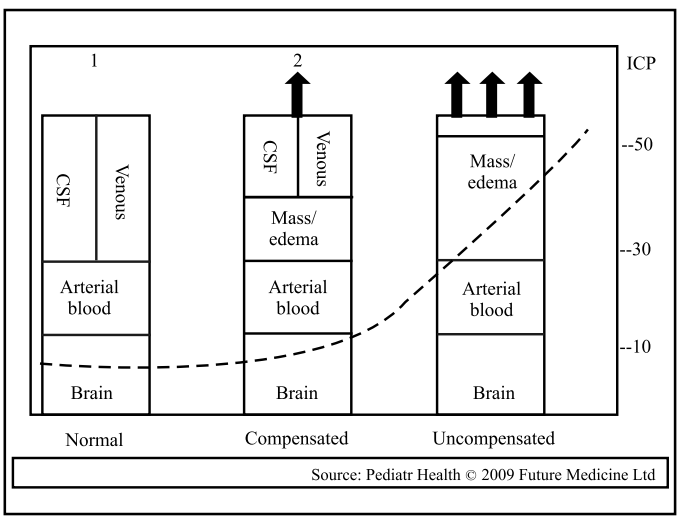

Fig.1. The Munro–Kellie Doctrine explains the relationship between intracranial volumes and intracranial pressure in physiological and pathophysiological conditions.

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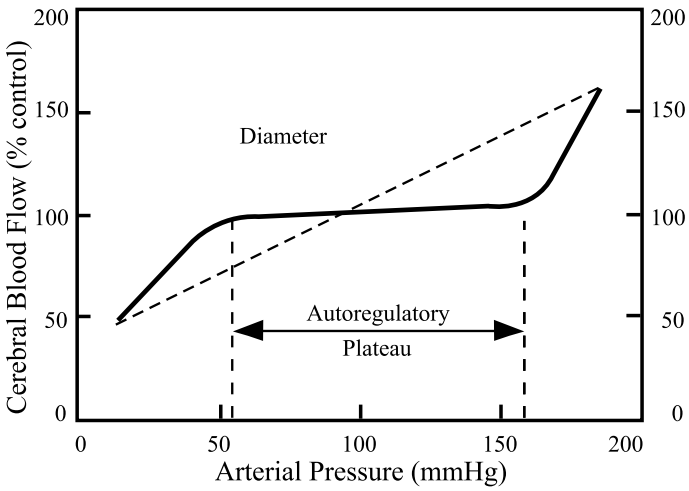


Fig.2. Cerebral autoregulation

Effect of Blood Gases on Cerebral Perfusion

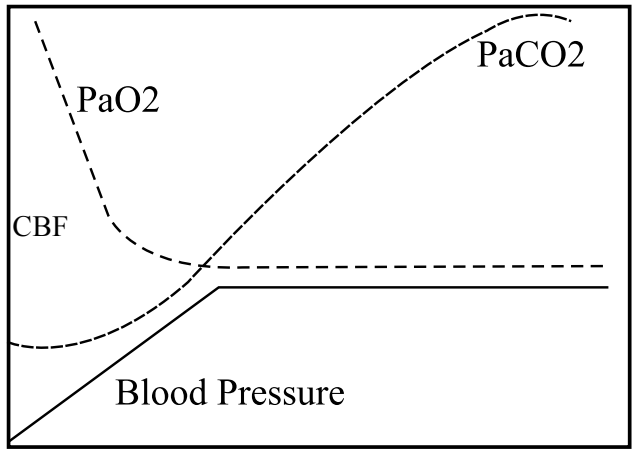


Fig.3. Physiological variables and ICP

Cerebral perfusion pressure (CPP): CPP is defined as the mean arterial pressure (MAP) minus ICP, and is a critical determinant of cerebral blood flow (CBF) and plays an important role in ICP management. CPP = MAP - ICP. Cerebral ischemia may result when CPP is lowered, either from raised ICP or lowered MAP (hypotension). Normally CBF is "autoregulated" at a constant level over a wide range of CPP (from 50 to 150 mmHg), (Fig.2). This means that even when a patient becomes hypotensive or hypertensive, the CBF autoregulates to remain constant and the neuronal perfusion remains normal. Autoregulation of this type is mediated by changes in arteriolar diameter and cerebrovascular resistance.

Note that within the limits of autoregulation, CBF is kept constant by changes in blood vessel caliber. When mean BP falls or rises, the cerebral blood vessels dilate and constrict respectively. The autoregulatory curve is shifted to the left in children and shifted to the right in patients with chronic hypertension. Autoregulation may be impaired by intracranial pathology such as head trauma.

Table I. Causes of intracranial hypertension

1. Increased brain mass

   Brain tumor

   Cerebral edema

- Vasogenic: Blood brain barrier defect which may be inflammatory or traumatic in origin resulting in increased vascular permeability.
- Cytotoxic: Neuronal swelling due to disruption of intracellular machinery and/or cellular membrane function. Cause may be traumatic, inflammatory or hypoxic-ischemic (eg, following cardiopulmonary arrest).
- Interstitial: Increased intraventricular pressure due to obstruction of normal CSF pathways (as in obstructive hydrocephalus).

2. Increased CSF volume

   Decreased absorption

   Obstructed CSF flow

   Overproduction of CSF

3. Increased intracranial blood volume

   Cerebral vasodilatation (hypoxia, hypercarbia)

   Obstructed venous flow

Table II. Signs of Increased ICP and Herniation: (Herniation syndromes)

Symptoms and signs which are sometimes present

- Headache
- Vomiting
- Papilledema is a late sign and rare in acutely elevated ICP.
- Sixth cranial nerve palsies

Signs which are almost always present

- Depressed level of consciousness (lethargy, stupor, coma)
- Hypertension, with or without heart rate changes (usually bradycardia, sometimes tachycardia)

When autoregulation is lost, CBF becomes "pressure-passive": i.e., the CBF is at the mercy of the patient's blood pressure. Systemic hypotension can lead to cerebral hypoperfusion and systemic hypertension can lead to cerebral hyperemia. The critical CPP for maintaining CBF in adults is approximately 50 mmHg. However, in the presence of intracranial pathology, the goal for CPP should be higher (at approximately 70 mmHg to avoid ischemia, and below 110 mmHg to avoid hyperemia). When treating raised ICP, it is important at all times to avoid any therapy that can cause systemic hypotension and consequent cerebral ischemia. Clinicians should ensure an adequate CPP by maintaining a high normal MAP for age.

Physiological variables that affect intracranial pressure: The following physiological variables that regulate CBF by causing acute changes in ICP (Fig.3). The $PaCO_2$ has a near linear relationship with CBF and within the physiological range, producing a 2-6% increase of CBF for each mmHg rise of $PaCO_2$. Changes in PaO_2 do not produce changes in CBF until the patient becomes hypoxic (PaO_2 < 60 mmHg), below which point the CBF increases steeply. The cerebral metabolic rate (expressed as cerebral metabolic rate for oxygen, $CMRO_2$) has a direct relationship with the CBF. Elevated temperature and seizures can markedly increase the $CMRO_2$ and thus cause massive surges in the CBF (up to 300 times).

Remember: The Cushing's triad consisting of bradycardia, hypertension and apnea is a very late sign of intracranial hypertension.

Therapeutic approach to a patient with suspected raised ICP

Therapy must be rapid and systematic and focus on the following aspects

A. Immediate stabilization (airway, breathing, circulation)

B. Control of ICP and CPP management

C. Monitoring in the PICU

D. Supportive management

E. Evaluation and treatment of underlying disorder

A. Stabilization of the patient's vitals is the priority: Assess the Airway, Breathing and Circulation (ABCs)

Patients with raised ICP will not be able to maintain or protect their airway because of altered mentation and loss of airway tone. Early control of the airway is paramount. Even if spontaneously breathing with normal gas exchange, early intubation, ventilation and deep sedation are often overlooked as key interventions for ICP control. Safe intubation is facilitated by the rapid sequence intubation (RSI) with deep sedation. Inadequate sedation during intubation causes coughing and gagging even in comatose children, thus further increasing ICP.

Indications for intubation in patients with coma and suspected raised ICP:

GCS ≤ 8 was the traditional teaching, although recent literature states that children with a GCS < 11- 12 should be intubated. Other indications include deterioration in the consciousness level, evidence of herniation, airway compromise and respiratory irregularities.

Drug regimen for intubation:

- Pre-medicate with lignocaine 1mg/kg for cough supression and to prevent ICP surges.

- Deep sedation with thiopentone (2-5mg/kg) or propofol (2-3mg/kg). If hypotensive, use the lower dose range for thiopentone along with rapid fluid resuscitation and vasopressor support.

- Analgesia with ketamine 1-2 mg/kg or fentanyl 2mcg/kg. Ketamine was thought to worsen ICP, however, recent literature supports neuroprotective role of ketamine. Hemodynamics are also well maintained.

- Muscle paralysis with vecuronium 0.1-0.2mg/kg

During the process of securing Airway and Breathing, assess for Circulatory status which may be compromised, especially during use of sedatives and also if the etiology is infectious. Also be aware that raised ICP may mask signs of shock such as tachycardia and hypotension. Rapid correction of shock with isotonic fluid resuscitation, followed by inotropic support may be required, aiming for a high normal mean arterial pressure for age.

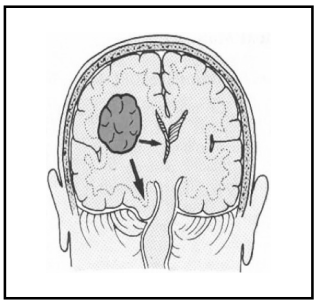
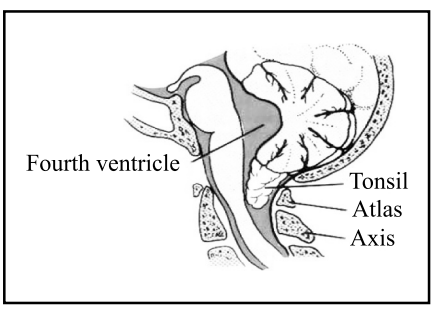
B. ICP and CPP management

Although clear guidelines for CPP targets in children are unavailable, guidelines suggest the following: Maintain ICP below 20 mmHg and CPP above 60mmHg in adolescents, CPP between 50-60 mmHg in children (1-12 years), between 40-50mmHg in infants.

ICP: Basic level therapy

Elevate head end of bed 30° with head in neutral position (promotes venous drainage from brain), unless patient is hypotensive.

Table III. Herniation syndromes

Type	Clinical hallmark	Causes
Uncal / lateral transtentorial Uncus of temporal lobe herniates downward medially through tentorium 	Ipsilateral 3rdCN palsy Contra-lateral motor posturing	Temporal lobe mass lesion
Central trans-tentorial Downward displacement of diencephal on thro' tentorium with pressure on brainstem	Coma with progression from bilateral decorticate to decerebrate posturing, pupils mid- position, poorly reactive	Diffuse cerebral edema. Acute hydrocephalus
Subfalcine Shift of affected hemisphere to opposite side	Coma with asymmetric (contralateral > ipsilateral) motor posturing	Convexity (frontal or parietal) mass lesion
Tonsillar /cerebellar (upward or downward) 	Sudden progression to coma with respiratory arrest and bilateral motor posturing in a patient with cerebellar signs	Posterior fossa / cerebellar mass lesion

Maintain deep sedation at all times. Pain, discomfort, agitation and coughing cause ICP elevation. Effective agents are continuous infusions of midazolam along with opioids (morphine or fentanyl infusion). Also give boluses of fentanyl 1-2µg/kg prior to suctioning and other noxious stimuli. Muscle paralysis not routinely used. Monitor core temperature. Maintain body temperature normal to mildly hypothermic. Fever is harmful. Control fever with paracetamol, tepid sponging and cooling blankets. Monitor for and aggressively treat fever and sepsis.

Ventilation strategy

- Maintain paCO2 35-40mmHg, paO2 > 60mmHg. Monitor with continuous capnography and pulse oximetry and frequent blood gases.
- Minimize PEEP. However, if PEEP required for maintenance of oxygenation, then oxygenation takes priority; PEEP up to 15 mmHg has not been shown to increase ICP.

Hemodynamic management

- Maintain euvolemia. Avoid hypotonic fluids (even RL is hypotonic). See fluid therapy. Mean arterial pressure (MAP) targets based on CPP goals, see above. If ICP monitoring unavailable in a patient with suspected intracranial hypertension, assume ICP of at least 20mmHg

Table IV. Causes of coma (TIPS from VOWELS)[1,9]

T	Trauma, head injury	Shaken baby syndrome: non-specific history, retinal hemorrhages.
I	Insulin, Hypoglycemia Intussusception* Inborn errors of metabolism	*Mental status changes may precede abdominal finding
P	Psychogenic	Common in adolescents
S	Seizures Shock, stroke Shunt	Post-ictal states, non-convulsive status may masquerade as undif ferentiated coma. Coma secondary to poor brain perfusion, arterial and venous infarcts Blocked or infected ventriculo-peritoneal shunts
A	Alcohol ingestion, abuse	
E	Electrolytes Encephalopathy	Disturbances of sodium, calcium, magnesium Hypertensive encephalopathy Reye syndrome, hepatic failure, urea cycle defects, lead encephal opathy
I	Infections of the CNS	Encephalitis, meningitis, malaria
O	Overdose, ingestion	Consider with unexplained loss of consciousness
U	Uremic encephalopathy	

and maintain MAP high normal with colloids and pressors at needed. E.g., in order to maintain CPP >60mmHg in an adolescent, a MAP of at least 80mmHg is necessary if the ICP is assumed to be 20mmHg. Noradrenaline can be used (via central line). If associated myocardial dysfunction suspected, an inotrope such as dobutamine should be added. CSF drainage via ventricular catheter is extremely effective as it permits both ICP monitoring and drainage. Osmotherapy: common agents like mannitol and hypertonic saline to be considered.

A. Mannitol is widely used and available. Given at 0.25-1.0 gm/kg/dose. Use high initial dose, provided hemodynamics is normal. Subsequent doses may be smaller.

Mannitol can be used PRN 4-6th hourly for acute increases in ICP. Dehydration must be prevented and serum osmolality must be maintained at <320 mOsm/L to prevent renal toxicity. With repeated use, mannitol may accumulate in injured brain and cause paradoxical increase in cerebral edema. It if preferable not to use mannitol > 48 hours. Intracranial bleed not a contraindication for mannitol.

B. Hypertonic saline: Acts like mannitol by causing fluid to shift from neurons and interstitial compartment to the intravascular compartment resulting in brain shrinkage. Additional advantage is ability to maintain circulating volume and thus the CPP. Maintain serum sodium between 145-160 mEq/L. Serum osmolality up to 360 mOsm/L is safe as the intra-vascular volume is well maintained. Hypertonic saline is more appealing than mannitol in patients with unstable or borderline hemodynamic status. It is given as initial bolus of 5-6 mL/kg over 10 minutes followed by continuous infusion at 0.1-1mL/kg/hr.

- As serum hyperosmolality can result in ADH mediated water retention, assess input-output and water balance with care. Euvolemia and must be maintained, and if the fluid balance is positive, consider restriction of fluids to 2/3rd whilst the patient is receiving 3% saline.

Maintain glucose in the normal range. Both hypo- and hyperglycaemia are detrimental. Steroids are most useful for vasogenic edema related to tumors, granulomas and abscesses. They are not useful for ICP related to infarcts, hemorrhage or trauma.

Table V. Summary of ICP treatment

A. Therapeutic measures to decrease cerebral blood volume	
1. Head elevation 15-30°C and in midline, avoid only if hypotensive	Promotes cerebral venous drainage.
2. Hyperventilation (PCO_2 < 35 mm Hg)	Decreases cerebral blood flow, has potential for cerebral ischemia if PCO_2 < 30 mm Hg
3. Minimize intra-thoracic pressure (PEEP).	Promotes cerebral venous drainage
4. Sedation and analgesia, particularly for noxious stimuli like tracheal suctioning : facilitated by sedative-narcotic infusions	Prevents spikes in cerebral metabolic rate and consequent reflex rise in CBF
5. Prevention of seizures, don't overlook non-convulsive seizures (NCS) not to be overlooked	Prevents rise in cerebral metabolic rate and consequent reflex rise in CBF
6. Maintain normothermia (35.5-37°C) . Hypothermia (33-35°C) if ICP refractory or severe.	Prevents rise in cerebral metabolic rate and consequent reflex rise in CBF. Hypothermia decreases $CMRO_2$ and thereby decreases CBF without causing ischemia
7. High dose barbiturates.	Lowers cerebral metabolic rate and decreases CBF without causing ischemia
B. Therapeutic measures to decrease CSF volume	
1. CSF withdrawal via an external ventricular drain (EVD).	One of the most effective methods of rapid reductions in ICP, can be drained until improvement in ICP or clinical signs noted
2. Decrease CSF production with acetazolamide	More effective in chronic communicating hydrocephalus, less useful in acute setting
C. Therapeutic measures to decrease brain volume	
1. Osmotherapy: • Mannitol • Hypertonic saline (3%)	Acts immediately by reducing blood viscosity and improving CBF. Later and more sustained effect is decreasing brain edema by establishing an osmotic gradient.
2. Steroids	Useful only in localized vasogenic edema such as that around tumors and abscesses.

Modalities of intracranial hypertension therapy may be classified according to the mechanism and predominant brain compartment that is targeted

Escalated therapy for refractory raised ICP

If despite the above treatments, the patient continues to show evidence of raised ICP, further measures to tackle refractory raised ICP must be instituted. Correct systemic factors (ventilation, pCO_2, hyponatremia, hyperthermia, etc). Repeated imaging may be necessary, specific surgically correctible lesions should be attended to.

Lower pCO_2 targets to 30-35 mmHg. Profound hyperventilation with PCO_2 of 25-30 mmHg maybe necessary as a short term measure in refractory ICP, bearing in mind the risk of inducing cerebral ischemia in the process.

High dose barbiturates, preferably with continuous EEG monitoring if available to be instituted. Thiopentone sodium is widely used in this setting , but has many adverse effects. Dose: Bolus 3-5 mg/kg followed by 1-5 mg/kg/hour. Profound hypotension is common. Invasive hemodynamic monitoring is mandatory (CVP, arterial line). Target high normal mean BP for age. If hypotension occurs, consider inotrope/pressor support. Thiopentone is immunosuppressive and can cause ileus and feed intolerance. Thiopentone can accumulate with prolonged infusions. Hence, if used > 48-72 hours, the drug can be abruptly ceased.

Decompressive craniectomy is to be considered in refractory intracranial hypertension. Moderate hypothermia (33-35°C) for 24-48 hours may be useful by decreasing cerebral metabolic rate of oxygen ($CMRO_2$) and thus decreasing CBF. Prevent shivering with muscle relaxants, cease feeds, monitor for infections and coagulopathy. Rewarm slowly and anticipate hypotension.

Surgical options

Early decompression of hydrocephalus if present is useful. Even when ventricles are not dilated, early insertion of a ventricular drain is useful as an ICP monitor and therapeutic modality (permits CSF drainage). If ICP is due to space occupying lesion, early resection is indicated. Decompressive craniectomy to be considered in refractory intracranial hypertension. Bilateral removal of skull flaps and lifting of dura allows decompression of the underlying brain and can prevent herniation and cerebral ischemia in some cases. Survival and functional outcome are best if performed early (with initial 36-48 hours of presentation) when medical treatments do not appearing to be working.

C. Monitoring during therapy of raised ICP in the PICU

Heart rate, invasive arterial blood pressure and CVP monitoring are useful. Intracranial pressure monitoring (ventricular, parenchymal or subdural) can be done if available.

Precise hourly fluid balance monitoring is required. An indwelling urinary catheter is usually necessary. ABG done 4 hourly, continuous capnography and pulse oximetry will optimise ventilation.

Blood glucose 1-4th hourly, electrolytes every 6-12 hourly, serum osmolality 12 hourly, BUN daily, hemogram and infection screen are other useful investigations.

Cranial imaging is done as necessary.

D. Supportive therapy in the ICU

Fluid management: Care shoud be taken to avoid hypovolemia, hypervolemia and hypotonic fluids. Hypovolemia worsens outcome in children with meningitis, malaria and severe head injury. Hypovolemia can lower the CPP and lead to worse ICP due to auto-regulatory vasodilatation. Avoid hypervolemia that can occur in the presence of SIADH and also in patients receiving hypertonic saline. Suspect if the serum sodium is low and fails to rise despite receiving hypertonic saline. Fluids may be restricted to 2/3rd, however euvolemia must be maintained at all times. The fluid infusion rates can be tailored based on perfusion indices, CVP, serum sodium, osmolality and urine output.

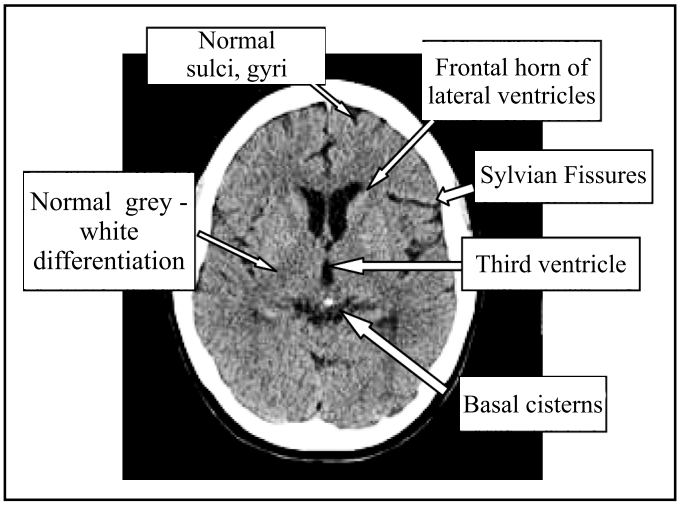


Fig.4. CT scan brain, normal

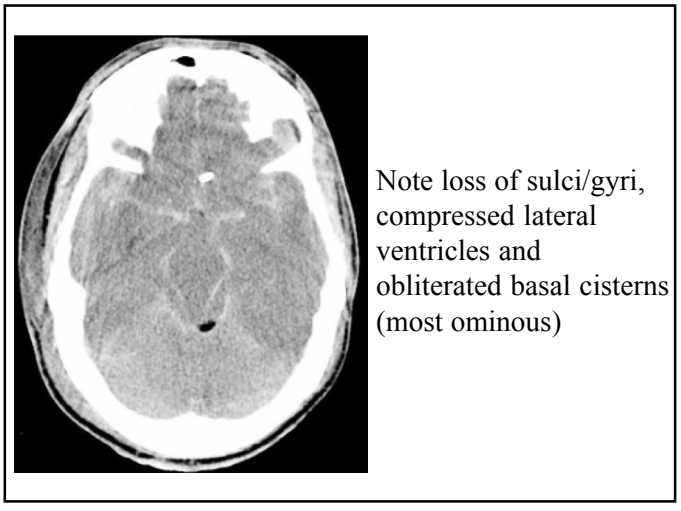


Fig.5. Severe cerebral edema

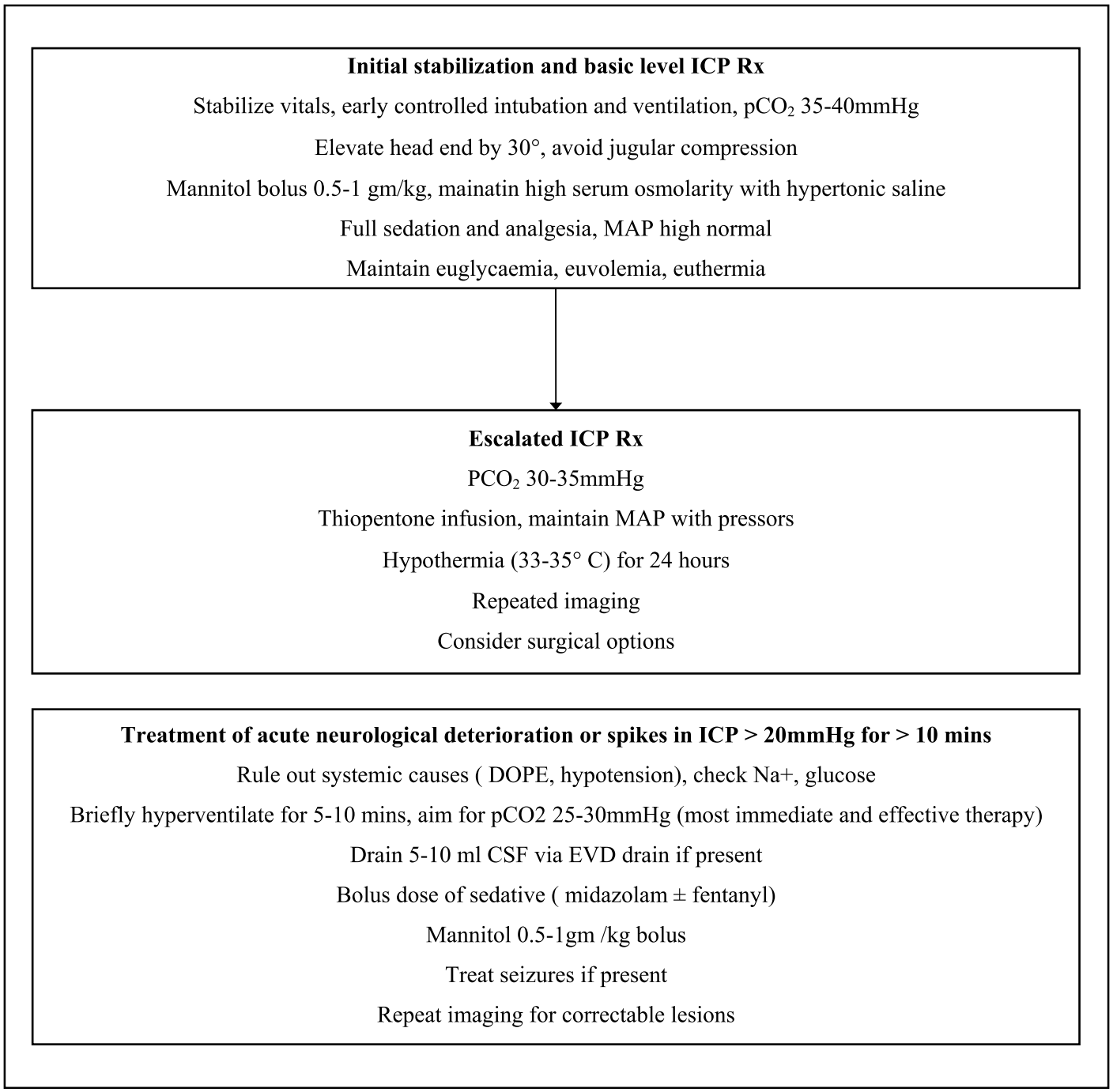


Fig.6. Sequential treatment approach to a patient with raised ICP

Free water must be strictly restricted: avoid hypotonic fluids such as 1/5th normal saline in 5% dextrose (such as Isolyte P) or ½ NS in 5% dextrose. The dextrose will be metabolized with a resultant hypotonic fluid that can aggravate cerebral edema and ICP. Isotonic fluids such as normal saline with added potassium is recommended. Maintain euglycemia. Add glucose to the maintenance fluid at sufficient concentrations to maintain serum glucose between 100-150mg%. Enteral feeds should be started at the earliest (isocaloric formula).

Anti-seizure medications

Convulsions can cause massive increases in CBF, consequent increase in ICP, can lead to secondary brain damage and may precipitate or be precipitated by cerebral herniation. Apart from generalized tonic-clonic seizures (GTCS), some comatose children may have non-convulsive seizures (NCS) manifesting with subtle signs such as eyelid twitching, eye deviation or nystagmus. A bedside EEG may be informative. If in doubt, empiric

treatment of seizures may be justified and can result in improvement of consciousness. Monitor drug levels of anti-convulsants and maintain therapeutic ranges.

E. Evaluation and treatment of underlying disorder. A variety of causes can lend on to coma in children (Table IV).

Neuro-imaging in suspected ICP

Urgent imaging is indicated in afebrile coma, the presence of focal signs or papilledema, as the diagnosis includes stroke, intra-cranial bleed, tumor or hydrocephalus. However, any child who does not have a very obvious metabolic/ toxic cause for the coma generally requires to be imaged.

A CT scan may provide information about the cause of altered mental status and the presence of intracranial hypertension, however a normal CT scan does not rule out raised ICP.

CT scan features of raised ICP are (Fig.4 and 5)

- Obliterated sulci and gyri
- Poor gray-white differentiation
- Compressed lateral ventricles
- Loss of basal cisterns (indicates imminent /established tentorial herniation)

An MRI may be more specific for early changes of herpes simplex encephalitis (where CT may be normal), posterior fossa and white matter pathology. A cranial ultra-sound may miss sub-dural collections or even extensive infarcts and a CT or MRI is an essential investigation in a deeply comatose infant even when the anterior fontanelle is open.

Lumbar puncture (LP) in a comatose child with suspected ICP

The potential benefits of early LP include making an early diagnosis of CNS infection and identification of the pathogen and drug sensitivities. Contra-indications for LP include signs of cerebral herniation, low GCS, focal neurological signs or cardio-respiratory compromise. In an unconscious child, the decision is controversial with some authors stating that the risk of herniation far outweighs the benefit of knowing the pathogen from an early LP. Therefore, if the decision for LP is taken, it must be performed with great care. As alluded to earlier, the absence of papilledema or a normal CT scan in the acute phase does not rule out raised ICP.

Choice of empiric anti-microbials

If a CNS infection is suspected in a febrile child presenting in acute coma and seizures, empiric anti-microbial should include acyclovir in addition to a third generation cephalosporin until further confirmatory tests are available.

The need for empiric anti-malarials and anti-mycoplasma therapy (IV macrolide) should be carefully assessed depending on the clinical context and the prevailing local epidemiology. Sequential approach of management of intracranial hypertension (Fig. 6) and summary of ICP treatment (Table V) are described.

Points to Remember

- ***Patients presenting with altered mental status and potential raised ICP have many challenging issues.***
- ***A systematic approach to stabilization and diagnosis may be rewarding in a large proportion.***
- ***The family needs to be counseled with honesty and sensitivity, explaining that survival and long term prognosis may be difficult to state with certainty, especially in the initial stages of illness.***

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Pediatric emergency medicine is the science which deals with a quick and accurate decision making in life threatening pediatric emergencies, especially in the golden first hour. The Pediatric Emergency Medicine Course (PEMC) guidelines given in this book are different from the western protocols as they are suitably modified according to the needs of our country, where access to advanced technology in diagnosis and therapy are scarce. The principles of pediatric emergency medicine practiced in a premier institution in our country have been put in an effective guideline format, so that it can be effectively practiced even in rural Institutions.

Organising chapters with learning objectives, assessment guidelines protocols, case scenarios, pharmacotherapy aspects, key points and common errors makes interesting reading. Highlighting the salient features including cautions is a unique way of emphasising the points to be remembered.

The topics are organized in such a way that the book covers normal anatomy, physiology, specific situations related to pediatric cases in the specific areas of the airway, breathing, circulation and disability which form the foundation of any resuscitation. It covers emergency management of conditions like septic shock / severe dengue, envenomation, poisoning and trauma. The book also includes issues like GI bleeds, diabetic keto acidosis. The description of conditions in Indian scenario make this book a boon to the pediatricians of our country.

Emergency case record and monitoring sheet brought out in the book are simple and at the same time comprehensive one. Photographs and line diagrams add to the value of presentation, convey rich information and lead to easy understanding.

Apart from giving guidelines on management of emergency, the book has made an useful contribution in giving guidelines for "Setting up pediatric resuscitation and emergency services" which will be of great help for the individual practitioners as well as institutions who wish to establish an Emergency Room. Inclusion of "Interpretation of chest x rays in critically children" apart from improving the knowledge, emphasises the importance of the same in the management of cases in emergency department.

Incorporating procedural sedation and management of pain, life saving procedures like pericardiocentesis spinal stabilization, description of various instruments, their technique and trouble shoots is appreciable.

Even annexure is being chosen and presented in such a way making every part of this book to be informative.

The presentation is so simple and complete that it can tutor even a beginner to tackle an emergency situation efficiently. This manual is worth possessing by every pediatrician, as anyone can face the emergency either in office practice or in an institution at any time.

Reviewed by:

Nedunchelian K

Emeritus Editor, IJPP

CRITICAL CARE - I

DISEASE SPECIFIC MECHANICAL VENTILATION IN PEDIATRICS

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Abstract: *Mechanical ventilation is a complex technique utilizing sophisticated and sometimes complex equipment. It can keep the most severely ill patients alive but simultaneously it can damage the lung and generate other unwanted complications. Mechanical ventilation can be seen as highly efficient technology but with a narrow therapeutic window. Although the technique has been available for children for last several decades, there are many gaps in knowledge of how best to apply the technique in specific situations. There is lack of data on mechanical ventilation in the pediatric population on how to ventilate children. Much of the knowledge applied to children in this area is handed down from adult intensive care research. The key to improving our application of mechanical ventilation is age and disease specific research and an increased understanding of safe ventilation practices leading to least disturbance in physiology and minimizing lung injury.*

Keywords: *Mechanical Ventilation, Pediatrics, Disease Specific, ARDS, PEEP.*

Over past ten decades, the use of mechanical ventilation has increased. Surgeons are getting more aggressive and operating on more sick patients. Oncologists are getting better at putting patients into remission, pediatricians are getting better at keeping even smaller infants alive.

Ventilator design principles - Breath delivery

A ventilator delivered breath can be described by its trigger, its gas delivery target and its breath cycling criteria. The trigger is what initiates the breath and is either a timer, which is a controlled breath or an effort, which is an assisted breath. The second component of breath is the gas delivery target or limit. On most ventilators, it is either a set flow or a set pressure that governs gas flow. Then there is the cycle- that is what turns the breath off.

The controlled breath is initiated by machine timer; whereas the assisted or supported breath is initiated by patient effort.

There are 2 ways to trigger the assisted or supported breath: the pressure trigger and the flow trigger. Originally, ventilators used the pressure trigger. The patient effort would produce a pressure drop in the ventilator circuit, which the ventilator responded to by supplying the gas. However the original machines were not very sensitive. In the late 1980s, the flow trigger was introduced. With the flow trigger, there is a continuous flow of gas running through the ventilator circuit, typically 5-20 L/min. if patient makes an effort, some of that flow is delivered to the patient which is sensed by the ventilator to trigger the breath. However, in today's microprocessor-based ventilators, the pressure trigger and the flow trigger have comparable sensitivity. Indeed, many ventilators have both, and whichever one activates first is the one that is used first.

There is no inherent difference in tidal volume with these 2 types of trigger mechanisms.

There are 3 common types of breath cycles. The breath reaches a set volume (i.e. a volume cycle breath, a set time (i.e. a time cycle breath) or a certain flow reduction (i.e. a flow cycle breath). Airway pressure usually functions as a backup cycle, which means that if the pressure exceeds certain limits, usually under the condition of an airway occlusion or active exhalation, the breath cycles off to prevent over pressurization. Newer ventilators have pressure release mechanism, so that if pressure starts to increase because the patient starts to forcefully exhale, for example, then instead of the breath turning off, the machine will allow the patient to exhale, thus providing relief.

Basic respiratory system mechanics

The respiratory system consists of the tracheobronchial tree and 300milion alveoli enclosed by the thoracic cage. Pressures are usually measured in the

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ventilator circuit (often referred to as airway pressure). This pressure is determined by gas flow and volume interacting with airway resistance and respiratory system compliance. By stopping flow, this circuit pressure equilibrates with alveolar pressure. This stop flow is commonly done at end inspiration and the resulting circuit pressure (surrogate indicator of alveolar pressure) is known as plateau pressure. When the stop flow is used at end expiration, the alveolar pressure reflects intrinsic positive end expiratory pressure (PEEPi). The pleural pressure can also be estimated with use of an esophageal balloon, although it is very rarely used.

Pressure, flow and volume

During a spontaneous breath, the inspiratory muscles are pulling the chest wall out and lung that is trying to collapse due to elastic forces. Consequently, the pleural pressure is negative. During a machine breath ventilator applies positive airway pressure, causing the alveolus to expand and push the chest wall outward. As a result the pleural pressure becomes positive.

If this patient develops pulmonary oedema, the lung will stiffen. There will be high peak and plateau pressures, but the pleural pressure will not change. So, this elevation in plateau pressure reflects an increase in lung stiffness, not chest wall stiffness. In non-homogenous lung disease (lung compliance with stiff lungs) some normal alveoli can rupture due to excessive plateau pressures leading to pneumothorax.

Stiff chest wall with normal lungs is responsible for driving up the pleural pressure due to direct transmission of pulmonary pressure to the pleura. Therefore higher pressure is used to overcome chest wall stiffness which can also cause airleak. Anasarca, ascites, obesity or chest bandages are the usual causes of low chest wall compliance.

Indications for mechanical ventilation

Indications remain essentially clinical, may not be always substantiated by objective lab parameters such as blood gas analysis.

Common indications include:

1) Respiratory failure
   a) Apnea / Respiratory Arrest
   b) Inadequate ventilation
   c) Inadequate oxygenation
   d) Chronic respiratory insufficiency
2) Cardiac Insufficiency /Shock

   Helps by eliminating work of breathing and reducing oxygen consumption
3) Neurologic dysfunction
   a) Central hypoventilation/ frequent apnea
   b) Patient comatose, GCS (Glasgow coma score) ≤ 8
   c) Inability to protect airway

Initial ventilator settings

One should always have the general idea regarding what initial ventilatory settings to choose when initiating the ventilation. Parameters to choose include:

Rate: Start with a rate that is somewhat normal; i.e., 15 for adolescent/child, 20-30 for infant/small child, 30-40 for a neonate, 40-50 for a premature neonate.

FiO_2: 1(100%) and quickly wean down to level<0.5. Depending upon oxygen requirement 0.5 may be a starting point for the FiO_2.

PEEP: 3-5 cm of H_20, higher (6-7cm) if ARDS, or low compliance disease, lower (2-3cm) if asthma, or high compliance disease.

Inspiratory time (I-time or I:E ratio): 0.3 to 0.4 sec for neonates, 0.5-0.6 sec for children,0.7-0.9 in older children. Normal I:E ratio=1:2-1:3.

Choose the mode: Control every breath (Assist control) if planned for heavy sedation and muscle relaxation or use SIMV when patient is likely to breathe spontaneously.

Pressure limited ventilation

Peak inspiratory pressure (PIP) is set depending upon the lung compliance and pathology

Neonates: Apnea 12-14cm, Hyaline membrane disease 18-22cm H_2O

Children: For normal lung 16-18cm, for low compliance 18-25cm H_2O, severe ARDS 25-35 cm may be required.

Volume limited ventilation

Tidal volume 8ml-10ml/kg with a goal to get 6-8 mL/kg expired tidal volume. Initial tidal volume at 10-12mL/kg may need to be set if leak present around endotracheal tube; in such patients pressure limited ventilation may be preferred.

Flow in most ventilators is set at 6-10 litres for the washout of the CO_2 from the internal ventilator circuit, tubings, etc. Flow less than 4L/min is not recommended. Following discussion includes cases and principles of ventilation based on disease specific pathophysiology.

Mechanical ventilation strategies

ARDS and Pneumonia

Case: A 5 year old, premorbidly well child weighing 15kg comes to emergency with 3 days of moderate to high grade fever and cough. He has been lethargic for the past 1 day and is not feeding well. Mother noticed that he is breathing fast since morning and has become dusky and unresponsive for the past 10 mins. On examination, he is unresponsive with a heart rate of 140/min, respiratory rate 60/min with retractions and head bobbing. He is peripherally cyanosed, saturating 80% in air and oxyhemoglobin saturations slowly increasing to 88% in 100% oxygen. Auscultation reveals bilateral extensive crepitations. The chest X-ray is suggestive of ARDS with bilateral diffuse infiltrates in lungs with no cardiac enlargement.Liver was not enlarged.

He was intubated and ventilated on PRVC(Pressure regulated Volume control mode). His initial settings were:

- Tidal volume 90 ml (6 mL/Kg expired tidal volume), set tidal volume of 120mL(8mL/kg)
- FiO_2: 1 (100%)
- Rate 25/min
- I:E ratio 1:2
- PEEP 6cm of H_2O
- On these settings his peak pressures were 36cm.

His saturations improved to 85% on the above settings and an ABG done showed pH 7.30, pCO_2 45mmHg, pO_2 47mmHg, HCO_3 20.4, BE –5 and O_2 saturation 85%. To improve his oxygenation, his PEEP was increased to 8cm H_2O and I:E ratio to 1:1. Following the intervention, his O_2 saturations improved to 89%. Two hours later his O_2 saturations were gradually down to 84%.ABG revealed pH 7.25, pCO_2 52mmHg, pO_2 42mmHg, HCO_3 19, B.E-5. A repeat chest x-ray was obtained revealing bilateral diffuse infiltrates. PEEP was further titrated in increments of 2cm to 12 cmH_2O over next two hours. His saturations improved to 95%.at this point his fiO_2 was decreased to (0.9)90%. His ABG revealed pH 7.29, pCO_2 49mmHg, pO_2 63mm Hg, HCO_3 22 B.E -2.

24hours later he had sudden deterioration with desaturation to 75% persistently despite 100% oxygen on the ventilator. Endotracheal tube was checked to be properly placed and not displaced or obstructed. Ventilator was working, but chest movement was less on the right side, with diminished breath sounds. At this point hand ventilation with C circuit bag (anesthesia bag) with PEEP was started with 100% oxygen. O_2 Saturations momentarily came up to 80 but then deteriorated again. His blood pressure was 80mmHg, fluid bolus was given and dopamine was started immediately with mild improvement only to 85mmHg.A tamponade situation such as tension pneumothorax was suspected and stat chest X-ray revealed right tension pneumothorax. Right thoracostomy tube was placed.In these emergency situations needle thoracentesis in 2nd intercostal space in mid clavicular line anteriorly can be tried if ches X-ray is not immediately available (Which is a common scenario!).

Goals of ventilation in ARDS

Ventilation should be delivered with minimal volutrauma to lungs (using low tidal volume: 6-7 mL/kg)[1], minimal tolerable inspired oxygen with PEEP (positive end expiratory pressure) to achieve PaO_2 55 to 80mm Hg and maximal tolerable arterial pCO_2(50 to 60 mm Hg) with arterial pH>7.25 (permissive hypercapnia)[2] and absence of metabolic acidosis. Conventional ventilation is the most readily available modality. Earlier, standard approach used to be: Volume ventilation with tidal volume 10 to 15 mL/kg with positive end expiratory pressure, adequate filling pressures with use of fluid and good cardiac contractility with inotropic support to prevent low cardiac output.

Problems with conventional 10 to 15mL/kg tidal volume and PEEP are: barotauma, volutrauma, air leak (pneumothorax), chronic lung disease, delayed recovery, poor cardiac output, prolonged ventilation and nosocomial infections.

In view of problems with conventional tidal volume ventilation: Low tidal volume strategy is recommended. (NIH ARDS Network study).[1] This was a prospective randomized multicenter trial of 240 patients with two groups using 12mL/kg vs 6 mL/kg tidal volume, PEEP 5 to 18 cm of H_2O, FiO_2 0.3 to 1. The study showed 25% reduction in mortality in 6mL/kg group. In another study, use of higher positive end expiratory pressure with lower tidal volumes (Open lung approach)[2,3] has been used with improved results. It is also important to note that without specific practices or strategies for initiating MV(mechanical ventilation) in young children, clinicians look to the above mentioned study, which provides a protocol for use of a low V_T, permissive hypercapnia, and

FiO_2 and positive end expiratory pressure (PEEP), despite the fact that children have not been studied by the ARDS Net.[1]

Gattinoni, et al in adults[4] and Marraro[5] in pediatric ARDS patients showed benefits of prone positioning in patients with ARDS with underventilated posterior zones. Prone positioning is being recommended although transient improvement in oxygenation occurs but no real effect on improving long term outcomes has been shown. Problems associated with prone positioning include difficulty in nursing management and monitoring (chances of accidental extubation, especially during X-ray examination and physiotherapy). Adult studies of ARDS do recommend prone positioning to offer mortality benefit.

Currently no good pediatric studies are available on use of prone positioning in ARDS patients and the effect on outcomes. It is reasonable to try prone positioning after PEEP titration.

Ventilation in severe asthma

Case: A 6 years male child presented with cough for 2 days, gradually worsening along with respiratory distress. On examination child has altered sensorium, SpO_2 83% in room air. History of multiple episodes of wheezing with relief after nebulisation was present indicating asthma. During this episode of wheezing there was no significant improvement. The clinical condition was treated with conventional medical management including continuous albuterol, steroids, magnesium and intravenous terbutaline. Subsequently child was intubated and started on mechanical ventilation. Initial arterial blood gas revealed pH 7.00, pCO_2 85, pO_2 43, Lactate 4.5.

Most children with status asthmaticus respond to medical therapy, and only two to six percent of those admitted to the hospital require care in an intensive care unit.[6-8] Out of these patients 8.5 to 33 percent require intubation and mechanical ventilation.[6-9]

Indication of intubation and mechanical ventilation:

- Altered sensorium/coma
- Increasing and decreasing pulsus paradoxus
- Respiratory and cardiac arrest
- Acute barotrauma
- Severe lactic acidosis (especially in infants)
- Refractory hypoxemia with increasing $PaCO_2$

The goals of mechanical ventilation are:

- To decrease the work of breathing and allow respiratory muscle rest.
- To ensure sufficient (not necessarily "normal") gas exchange until airway obstruction can be reversed.

Strategies of ventilatory support in childhood asthma

There is no uniform agreement about which ventilation strategies are optimal. A volume-cycled ventilation is preferred, because it is capable of maintaining more consistent alveolar ventilation in the face of high and potentially changing airways resistance. Lung hyperinflation should be avoided.

Recommended initial ventilator settings include:

Mode: controlled.

Inspired oxygen fraction = 1.0.

Tidal volume 6-8 mL/kg.

Respiratory rate 8 to 16 breaths per minute.

Inspiratory to expiratory (I:E) times should range from 1:3 to 1:5.

Positive end-expiratory pressure (PEEP) should be 2-3 cm water.

Measured pressure targets during mechanical ventilation include:

Peak airway pressure less than 45 cm water.

Plateau airway pressure less than 30 cm water.

Mean airway pressure less than 25 cm water

In our patient, child was placed on volume cycle ventilation with tidal volume of 8mL/kg, respiratory rate 14, PEEP of 4, plateau pressure less than 30cm of water. Along with maximum medical therapy subsequent ABG showed pH 7.28, pCO_2 65, pO_2 90, lactate 2.3.

Permissive hypercapnia

Persistent hyperinflation and high levels of airway pressure lead to pneumothorax and decreased cardiac output. To circumvent these adverse effects, strategies are aimed at intentional hypoventilation.[7,8,10] Increased levels of $PaCO_2$ (up to 90 mmHg) are tolerated as long as levels do not increase rapidly[11] and with acceptable pH> 7.2. The overall strategy of permissive hypercapnia has not been well studied in children, and its use cannot be unequivocally recommended without controlled studies.

Use of positive end-expiratory pressure

PEEP is generally kept to a minimum during the acute phase of mechanical ventilation in order to avoid dynamic hyperinflation[12] and development of excessive auto PEEP (intrinsic PEEP). However, there are two situations in which the addition of PEEP is beneficial:

a. During the recovery phase, when intrinsic PEEP lessens, potentially resulting in hypoxemia from worsened V/Q mismatch and/or atelectasis.

b. When "auto-PEEP" results in dynamic airways compression and inequality of ventilation. In this situation, extrinisic PEEP evens out the distribution of ventilation and improves the efficiency of pulmonary gas exchange.[13]

Refractory hypoxemia

In occasional patients with severe asthma, hypoxemia is a more problematic issue than hypercarbia. Readily treatable causes of hypoxemia should be sought, such as atelectasis, pneumothorax, frequent $\hat{a}_2$ agonist therapy and hypovolemia.

Mechanical ventilation for cardiovascular illness

Case: An 18 month old boy presented with history of upper respiratory infection for three days with respiratory distress and poor feeding. He was diagnosed with cardiogenic shock with cardiomyopathy, presumably secondary to acute myocarditis. An echocardiogram revealed severely depressed left ventricular (LV) function and evidence of bilateral hazy lung fields with cardiomegaly. The patient was intubated and mechanically ventilated, initial settings on the ventilator were FiO_2 of 0.6, Tidal volume of 7mL/kg (PIP of 25mm) and PEEP of 5cm of H_2O, rate of 22/min, inspiratory time of 0.8 sec. Milrinone and epinephrine infusions were initiated. Over the next five days the patient's condition improved gradually. The epinephrine infusion was discontinued. A follow up echocardiogram demonstrated moderately depressed LV function-clearly improved from the initial study. The decision was made to extubate the patient. Two hours after extubation, the patient developed hypotension, tachycardia and poor peripheral perfusion.

Cardiorespiratory interactions: The heart

Preload and afterload can be affected by fluid administration and vasoactive agents, but they can also be significantly affected by MV.

The right side of the heart obtains its blood from outside the thorax and pumps it within the thorax. As the thorax is pressurized with PPV(positive pressure ventilation), the mean intrathoracic pressure in the chest increases. This can make it more difficult for the blood from the systemic venous circulation to return through the superior and inferior vena cava to the right atrium. The higher the mean intra thoracic pressure, the more difficult it is for blood to return to the right side of the heart. PPV will always decrease right ventricular (RV) preload; however, this effect is mostly not clinically significant.

In the majority of patients whose cardiac status is otherwise reasonably healthy, compensation for the decreased RV preload is fairly good. However, this is not necessarily so in critically ill patients. Those patients with significant lung injury requiring elevated PEEP or high MAP(mean airway pressure) during HFOV (High frequency oscillatory ventilation) must be monitored closely for signs of right side heart dysfunction related to decreased preload.

The left side of the heart obtains its blood from within the thorax and pumps it outside the thorax. Consequently, the effects of PPV on the left ventricle are the opposite of those on the right ventricle. As the thorax and lung pressurize, the lung may open to such a degree that blood is physically pushed forward into the left atrium, thus augmenting LV preload.

As the case mentioned above, deterioration after extubation is best explained by an increase in LV after load and patient with already depressed left ventricle had to generate a higher pressure to obtain the same systemic output. However, the patient's left ventricle was unable to maintain against that increase in afterload and resulted in poor cardiac output as demonstrated by hypotension and poor peripheral perfusion.

Unlike the effects of PPV on LV afterload, the effects of PPV on LV preload beyond the concept of thoracic pump augmentation can be somewhat variable because the effects of PPV on LV preload is generally based on the patient's intravascular volume status and on what has happened on the right side of the heart. If PPV is decreasing venous return to the right side of the heart, it is obviously going to decrease LV preload as well. The effects of this change in LV preload may be good or bad depending on the patient's place on the Frank-Starling curve. Thus, LV preload is complex as it can be largely affected by ventricular independence.

Cardiorespiratory interactions: The lungs

When the lungs are atelectactic, the large pulmonary vessels become tortuous and the resistance in the large vessels is elevated. As the lung is opened, these large vessels straighten and the resistance decreases. As the lung expands to normal lung volume and then becomes overdistended, the resistance in the large vessels is minimal.

When the lung collapsed, the resistance in the small vessels is very low. However, as the lung volume increases and the lungs overdistended, the resultant overdistended alveoli compress the surrounding capillaries, causing an elevation in the pulmonary vascular resistance (PVR) and a subsequent increase in RV afterload.

The total PVR will be highest at the extremes of alveolar overdistension and lung collapse and lowest at an optimal lung volume, which is approximated by functional residual capacity (FRC). The goals are to maintain an optimal lung volume and to avoid overdistension and collapse.

Ventilator management in post operative cardiac patient

Due to lack of randomized or non randomized controlled trials examining various ventilator strategies mechanical ventilation in the post operative cardiac patient remains challenging. Clinicians are forced to extrapolate from animal models, case series, or individual experiences. The ventilatory management of these patients requires an individualized approach.

The application of end-expiratory pressure to the post operative cardiac patient can have a significant negative effect on the circulatory state. However, the application of an "appropriate" level of end-expiratory pressure has substantial beneficial effects, especially in Fontan physiology. The level of "appropriate" positive end-expiratory pressure (PEEP) for lung disease in the Fontan patient remains unknown. Howell, et al demonstrated that in the non-Fontan patient pulmonary vascular resistance may fall at low levels of PEEP with subsequent increases at higher levels of PEEP.[14] In contrast, Williams, et al demonstrated in Fontan patients that pulmonary vascular resistance is increased at all levels of PEEP (3 to 12cm H_2O) and the cardiac index is decreased at high levels of PEEP (9-12 cm H_2O).[15] PEEP maintains functional residual capacity and increases PaO_2 after the Fontan procedure and also it has been demonstrated to have beneficial effects on arterial oxygenation, atelectasis and right-to-left shunting in children after a variety of cardiac operations.

Mechanical ventilation in the neurologically ill patient

Neurologically ill patients not only have the potential for primary lung pathology but also predominantly neurological concerns necessitating endotracheal intubation and mechanical ventilation. These include the following:

a. An adequate level of consciousness to demonstrate a central drive to breathe

b. Neuromuscular strength to maintain adequate ventilation and cough to clear the airway

c. An ability to swallow to manage the secretions, i.e.airway protection.

The Glasgow coma scale is a rapid bedside tool to assess level of consciousness. Intubation is typically necessary when GCS is 8 or less especially with traumatic brain injury.[16] Patients with an inadequate ventilatory effort, impending loss of airway due to neck or pharyngeal injury or neurological deterioration should be intubated.

Approximately 10-20% of people with acute spinal cord injury die before reaching medical care. About 3% of patients die during acute hospitalization.[17] Cervical spine injuries represent approximately 55% of all spinal cord injuries. The diaphragm is innervated from the levels of C3 through C5. For this reason, a common misconception is that respiratory failure does not occur if the cord injury is below the C5 level. The musculature of the chest wall, innervated at the thoracic level, assist in cough and deep inspiration by splinting the rib cage. Normally the diaphragm descends and the abdomen and chest wall should rise. Without intercostals innervations, during deep inspiration when the diaphragm descends and the abdomen rises, the chest wall will collapse. As a result, the patient is unable to deep breathe or cough effectively for adequate pulmonary toilet. Patients with high thoracic levels injury, especially if there is an accompanying aspiration or pre-existing pulmonary disease that requires clearance of secretions, may require early elective intubation.

Basic premises of intracranial pressure

To understand the impact of mechanical ventilation on the brain, it is important to be familiar with the basic premises of ICP. The Monro-Kellie hypothesis maintains that within the skull, a semi-closed box, are the brain, fluid (i.e. interstitial fluid, cerebrospinal fluid) and blood. Efforts to decrease the intracranial pressure include maneuvers to decrease the intracranial volume. Acutely, these include hyperventilation, which causes

vasoconstriction and thereby decrease blood volume; sedation, and osmotic therapy with mannitol or hypertonic saline, which draw the interstitial fluid from the brain. The extent to which these maneuvers decrease the pressure depends upon the intracranial compliance.

Another basic premise in dealing with brain injury is that the difference of mean arterial pressure and ICP is cerebral perfusion pressure. Adequate CPP is between 50-60mmHg. In traumatic Brain injury (TBI) a CPP less than 60mmHg is predictive of poor outcome.

Oxygenation: In neurologically injured patients, ventilator management strategies often include maintaining a partial pressure of arterial oxygen (PaO_2) 90mmHg or higher. In patients with high ICP and steepened cerebral compliance curves, episodes of desaturation and hypoxia are not well-tolerated. Even incrementally small changes in cerebral blood flow may increase the blood volume and are associated with elevated spikes in intracranial pressure.

Hypercarbia and hypocarbia: Hyperventilation to $PaCO_2$ of 25-30mm Hg can cause significant vasoconstriction and a reduction in cerebral blood flow. Cerebral autoregulation occurs in relatively intact brain, not in contusional or ischemic tissue. Vasoconstriction associated with hyperventilation may induce ischemia in certain areas.[18] In one trial, patients with severe head injury were randomized to either empiric hyper ventilation of $PaCO_2$ of 25mm Hg or ventilated to a $PaCO_2$ of 35mm Hg.[19] Patients kept normocapnic had better outcome as measured by GCS outcome score at 3 and 6 months although these differences equalized after 1 year. Secondary cerebral ischemia may occur with hyperventilation and should be avoided. Guidelines recommend against empiric hyperventilation and avoid $PaCO_2$ <30 if hyperventilation is necessary.

Temperature: While normalizing $PaCO_2$, it is essential to remember that muscle activity and warmer temperatures are associated with increase in metabolism and higher CO_2 production. Each increase of 1^0C increases the cerebral metabolic rate by 7%. If the cerebral metabolic rate goes up, so follows cerebral blood flow, blood volume, ICP and blood pressure. Consequently, in patients with fever or hypothermia, close attention to minute ventilation is essential.

The same principle regarding CO_2 applies to shivering. Shivering increases the metabolic rate of the muscles and so the CO_2 production. Sometimes shivering itself will increase the ICP and CO_2 as well.

The effects of PEEP on the brain: The effect of PEEP is relevant to ICP when it increases the right atrial pressure and superior vena cava pressure subsequently decreasing the venous outflow of the brain.[20] When the central venous pressure (CVP) is higher than the ICP, then CVP rather than ICP becomes the determinant pressure for CPP. PEEP also affects CPP. When the PEEP increases venous return to the heart and the mean arterial pressure decrease which subsequently decreases CPP.

The impact of ventilation modes: The different modes of ventilation can also affect the brain. For example, HFOV decouples oxygenation and ventilation. When using HFOV, oxygenation is determined by the mean airway pressure and the FiO_2. Lower oscillatory frequency and higher pressure amplitudes result in lower $PaCO_2$.

The effect of HFOV on ICP has been subject of a couple of studies. Mean airway pressure >30cm H_2O appears to increase ICP.[21] Higher airway pressures decrease the mean arterial pressure (MAP), which will decrease the CPP.

Neuromuscular disease: Ventilation strategy

Case: A 13 year old immunized female child weighing 30kg was admitted with complaints of sudden onset weakness of lower limbs with inability to stand and bear weight for 2 days. The next day she developed weakness of both upper limbs such that she could only move her arms in the bed. She started to have decreased volume of voice and complained of some tingling sensation in both legs. There was no history of fever, cough, loose stools, trauma alteration in sensorium or seizures. She had an episode of fever with cough 2 weeks back which lasted for 3-4 days.

On examination she was alert, conscious and oriented. Her heart rate was 110/min and respiratory rate 30/ min. She had shallow respiratory efforts with paradoxical respiration. CNS examination revealed quadriparesis with power in both lower limbs and upper limbs being 1/5 and 2/5 respectively. She had global areflexia. There was no objective sensory loss and no other focal deficits. She was diagnosed to have Gullian Barre Syndrome with respiratory muscle weakness supported by NCV(nerve conduction velocity) findings. She was ventilated for neurogenic cause of respiratory failure on SIMV mode of ventilation with the following settings:

- Tidal volume 200 ml (6 – 7 mL/kg)
- Rate 15/min

- FiO_2 : 0.4 (40%O_2)
- PEEP 3cm H_2O
- I: E ratio 1: 2

Her ABG on the above settings was within normal limits.

Chronic / Progressive neuromuscular disorder home ventilation

Most children with neuromuscular disease eventually require assistance with airway clearance and with breathing, especially during sleep. Techniques and devices for airway clearance and noninvasive ventilation that are commonly used in adults have been successfully adapted for use in infants and young children. Both physiological differences and small size of young patients with neuromuscular disease, however, can limit the applicability of such interventions or require special consideration. The appropriate time to begin airway clearance assistance are lacking for young children, and the role of early introduction of noninvasive ventilation to preserve or enhance lung growth and chest-wall mobility remains to be elucidated. Despite these issues, a greater number of children with neuromuscular diseases are living well past their second decade.

There is a typical sequence of events that leads to respiratory insufficiency and ultimately to respiratory failure[22,23] in cases like Duchene muscular dystrophy, spinal muscular atrophy etc. Initially respiratory muscle weakness leads to impaired cough and airway clearance, so these patients are prone to recurrent atelectasis and chest infections. Progressive inspiratory muscle weakness first causes nocturnal respiratory dysfunction, which is manifested by frequent arousals, sleep fragmentation and sleep-related hypoventilation. Subsequently, hypercapnia extends into the day time and frank respiratory failure ensues. The duration of this timeline can be expanded by interventions such as assistance with clearance of respiratory secretions and nocturnal mechanical ventilation.

Airway clearance in children with neuromuscular weakness

Assistance with airway clearance is a critical component in the care of children with neuromuscular disease, because of their propensity to develop mucus plugging and atelectasis with chest infections and their greater exposure to common viral respiratory illnesses. In fact, acute respiratory illness leading to respiratory compromise was found to be the most common cause of unplanned admission to a pediatric intensive care unit among children with neuromuscular disease. Manual assisted cough, breath stacking, manual and mechanical insufflation, and mechanical exsufflation with negative pressure have all been used to treat pediatric patients with neuromuscular disease.[24] The common goal of all of these interventions, used alone or in combination, is to increase the velocity of expiratory flow during a cough maneuver.

Mechanical ventilatory support

American[25] and European[26] guidelines suggest that patients with neuromuscular disease should receive ventilatory support when daytime hypercapnia (pCO_2>50mmHg) exists. Others have instituted nocturnal mechanical ventilation when the patient has sleep hypoventilation (pCO_2> 50 mm Hg) accompanied by oxyhemoglobin desaturation (< 92%) or a history of recurrent hospitalization for pneumonia or atelectasis.[27] Nocturnal noninvasive positive-pressure ventilation (NPPV) improves survival[28-30] and reduces the frequency of hospitalization,[27] even in children with progressive neuromuscular diseases. Nocturnal NPPV also improves diurnal gas exchange[29] and normalizes sleep-disordered breathing.[27] Nevertheless, the timing of institution of NPPV remains controversial. The role of mechanical ventilation in promoting lung growth, or at least preventing decline in function, in children with respiratory muscle weakness has not been fully explored. A multicenter study of the role of "preventive" NPPV in boys with Duchenne muscular dystrophy disappointingly found no evidence for preservation of lung function in those patients treated with NPPV.[31]

Two important factors in patient adherence with NPPV are patient-ventilator synchrony and the fit and comfort of the interface. Aside from the usual possible complications related to nasal mask ventilation described in adults, including skin irritation or breakdown, sinus and ear pain, eye irritation, gastric distention and excessive leak leading to inadequate ventilation, certain problems and complications are unique to infants and small children that can undermine adherence with therapy. There is a paucity of nasal interfaces commercially available for infants and toddlers. Often, nasal prong systems are adapted for use, but they leak around the prongs and the resistance across their narrow orifices reduces or eliminates small and weak children's ability to trigger and cycle assisted breaths, so patient-ventilator synchrony is compromised. The resistance across small prongs, coupled with the leak, can also simulate patient effort, causing some bi-level generators to auto-trigger when set in spontaneous/ timed mode. For such children, a common practice is to

wait for the child to fall asleep and then set the ventilator in a timed or control mode at a rate that overrides the patient's respiratory drive.[30]

Non invasive ventilation (NIV) and acute hypoxic respiratory failure (AHRF): Patients with varying co-morbidities like immune compromise and status asthmaticus

In a prospective, randomized trial conducted by Hlibert and colleague[32], intermittent NIV was compared to standard medical treatment for patients with AHRF who were immune-compromised. The study included 52 immunosuppressed patients in the early stage of AHRF with bilateral pulmonary infiltrates and fever. Patients were randomized into one of two groups. Group 1 received NIV via a full face mask with alternating three hours periods of spontaneous breathing. Group 2 received the standard medical treatment as per the institution which consists of supplemental O_2 without any ventilator support. The primary end points were rate of intubation, serious adverse events, ICU and hospital death. Results showed the group with NIV had a decreased rate of intubation (12 NIV patient vs 20 standard therapy patients), serious complications (13 vs 21), fewer ICU deaths (10 vs 18), and fewer hospital deaths (13 vs 21). Therefore, the patients in this study with AHRF who were immune- compromised did benefit from NIV.

Patients with severe asthma present in extreme respiratory distress; the use of invasive artificial airways and MV in this population can be especially problematic. Patients with asthma are poor candidates for intubation since manipulation of the airway may exacerbate the airway inflammation already existing in this population. Meduri and colleagues[33] provide a descriptive report of 17 adult inpatients with status asthmaticus treated over a 3 years period. All the patients received NIV with an acute care ventilator via full face mask. Their head of bed was elevated $\geq 45^0$, NIV pressure was set to deliver 7ml/kg of tidal volume. Patients were given a 'rest' period with no NIV every 4-6 hours. Their average length of NIV was 16±2 hours. Only two patients required sedation, none required endotracheal intubation and all survived, suggesting NIV may prove beneficial for treating patients with status asthmaticus.

Issues in prolonged mechanical ventilation- Tracheostomy

Tracheostomy should be considered when it becomes apparent that the patient will require prolonged mechanical ventilatory assistance after an initial period of stabilization. The patient should also be evaluated to determine if he/she will likely benefit from one of the following additional benefits associated with having a tracheostomy:

a. Need for less sedation than with a translaryngeal tube
b. Potential for improved respiratory mechanics as may result from decreased dead space.
c. Potential for psychological benefit from the ability to eat, speak, communicate, improve mobility or participate in physical therapy

The best time to perform a tracheostomy in a patient receiving MV was controversial in the past. The general consensus was that it was best to wait 21 days to do a tracheostomy. Today, with the availability and ease of performing a percutaneous tracheostomy and the psychological benefit to patients having one, tracheostomies are being performed earlier in the care process. One of the benefits of having a tracheostomy in place for prolonged ventilatory support is that weaning is much easier.

Points to Remember

- ***Volume control may be required if there is severe ARDS. Use 7-9 ml/kg tidal volume (6-8ml expired tidal volume)***
- ***Patients with asthma may be ventilated with pressure control with pressure support and low PEEP.***
- ***Patients with neuromuscular weakness (GBS) and raised ICP will require minimal settings to maintain normal ABGs and maintain pCO_2 30-35mmHg.***
- ***Permissive hypercapnea and permissive hypoxemia are practiced to minimize lung injury caused by mechanical ventilation.***

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CRITICAL CARE - I

PAIN AND SEDATION IN THE PICU

**** Soonu Udani***

Abstract: *All children who undergo pain and or anxiety in the course of treatment require adequate attention to alleviate their discomfort. There is a large number of sedatives and analgesics that can be used singly or in combination. In critically ill children, as opposed to stable children undergoing painful procedures, the issue is complicated by factors affecting organ failure, pharmacokinetics and tolerance as these agents need to be given, often in combinations, for prolonged periods. The possible combinations and their various uses in different situations in critical ill children in a Pediatric Intensive Care Unit (PICU) will be discussed here.*

Keywords: *Sedation, Analgesia, PICU.*

All of the nerve pathways essential for the transmission and perception of pain are present and functioning by 24 weeks of gestation.[1] To be free of pain and anxiety during any medical intervention is the right of every child. Analgesia and sedation an area formerly neglected is now the standard of care in good clinical practice. The child in a PICU is ill, in an unfamiliar, threatening environment; suffers loss of day-night and sleep-wake cycles, is separated from parents and may have fears of pain and even death.

Pain and anxiety lead to agitation and are associated with several serious consequences. Serious self- harm can occur from movement and displacement of devices. Self extubation has several problems including sudden death. Asynchrony during ventilation causes poor oxygenation and ventilation, increased work of breathing and even barotrauma. When we practice sedation and analgesia, besides alleviating pain, we also aim to allay anxiety for the proposed intervention and to provide amnesia for the unpleasant event.

Definitions[2]

Analgesia connotes the absence of sensibility to pain or noxious stimuli in the conscious patient. Sedation is the process of calming or allaying excitement or anxiety. Hypnosis is the state of minimal motor activity that seems similar to sleep. Amnesia is the impairment of memory caused by alteration in arousal, attention or mood. There are levels of sedation and increasing levels of expertise and preparedness would be needed as the sedation progresses from mild sedation to moderate sedation (procedural) to deep sedation to general anaesthesia.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Agitation is characterized by extreme arousal, irritability, excess motor activity driven by internal sense of discomfort such as disease, pain, anxiety and delirium. Anxiety is a sustained state of apprehension with accompanying autonomic arousal in response to a real or perceived threat while delirium is an acute, potentially reversible impairment of consciousness and cognitive function that fluctuates in severity.

Drugs

Hypnotic is a drug that tends to induce sleep, narcotic is a drug that induces drowsiness, sedative is one which produces sleep or stupor without analgesia, anxiolytic is a drug that calms or soothes without inducing sleep while analgesic is a drug that relieves pain. Many drugs have all of the first four properties but may lack any analgesia. Sedatives are commonly used and overused in the PICU. Adequate sedation begins with adequate analgesia and appropriate general measures. As there is often a change in metabolism, with liver and kidney involvement, pharmacokinetics may vary widely. Hence a structured approach to agitation (taking care of problems like hypoxemia) is required. The strategy needs to be re-evaulated daily for downward titration and protocols may need to be in place for weaning off sedatives. The sedation strategy for critically ill patients has stressed light sedation with daily awakening and assessment for neurologic, cognitive, and respiratory functions, ever since Society of Critical Care Medicine (SCCM) guidelines were presented in 2002.[3]

The final decision on the need or level of sedation and analgesia is always highly subjective. Pain-related

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behaviours (movement, facial expression and posturing) and physiological indicators (heart rate, blood pressure and respiratory rate) and the change in these parameters following analgesic therapy can be used with or without rating scales to judge effect (Grade of recommendation B).[3]

The Ramsay Sedation Scale (Table I) is the most often quoted and used scale as there seems to be some objectivity to it.[4]

Table I. Ramsay sedation scale

1. Anxious and agitated or restless, or both
2. Co-operative, oriented and tranquil
3. Responsive to commands only
4. Brisk response to light glabellar tap or loud auditory stimulus
5. Sluggish response to light glabellar tap or loud auditory stimulus
6. No response to light glabellar tap or loud auditory stimulus.

One of the most common indications for the use of sedatives and analgesics in critical care is during mechanical ventilation. 3-4 points in the scale would represent moderate sedation, the ideal level that is unlikely to compromise hemodynamics and respiratory drive. Deeper sedation may be required in patients on high, uncomfortable ventilator settings.

The reasons to sedate are several and includes

a) to relieve dyspnea and intractable coughing

b) for amnesia during critical illness and procedures.

c) to manage agitated patient from harming self by extubation or pulling at devices.

d) to facilitate invasive ventilation and improve synchrony.

e) to decrease oxygen consumption (VO_2) and (VCO_2) CO_2 release (especially with cardiopulmonary compromise).

f) to reduce unpleasant memories & post traumatic stress disorder (PTSS). In addition, extra pain relief is needed for the many intrusions like endotracheal suctioning and artificial devices like tubes and catheters, that invade the child.

The most common combination used is a benzodiazepine with an opiod.

Sedatives: Analgesics alone have little effect if the patient is anxious and cannot sleep. Combined with sedatives, the analgesic dose required reduces and the triple goals of anxiolysis, hypnosis and amnesia can also be met.

Benzodiazepines:(BDZ) are a unique class of drugs that provide all three. They also exhibit muscle relaxant and anticonvulsant effects but lack analgesic properties. They facilitate the inhibitory action of GABA. The ideal level of sedation varies but the RAS of about 3-4 is usually the aim. Deeper levels are needed for patients who are on controlled modes of ventilation, have significant hypoxemia or are on neuromuscular blocking agents. The right balance needs to be achieved and the risks of both, over and under-sedation are real.

Diazepam (DZ) is highly lipid soluble. The formulation is in propylglycol (PG) which produces thrombophlebitis and even metabolic acidosis, making it unsuitable for prolonged use. The lipid emulsion is expensive and not easily available. The elimination half-life varies widely.

Lorazepam (LZ) is 5-6 times more potent than DZ. It is very well absorbed by both the oral and intramuscular routes. Of the BDZs, it has the least drug interactions. It is also the least lipid-soluble and hence has a delayed onset and prolonged action. It is insoluble in water and formulated with polyethelene glycol (PEG) which has similar problems to PG in addition to hyperosmolar coma and nephrotoxicity.

Midazolam (MDZ) is between the two in potency. The onset is very rapid (2-2.5 mins). The cardiovascular and respiratory depressive effects are lower with continuous dosing as the peak levels attained are lower than with bolus dosing. MDZ is more titratable than LZ. Dosing at 0.05-0.2 mg/kg/h can be titrated under continuous monitoring. Continuous LZ in preference to MDZ has been studied for more prolonged sedation, as it is equally effective, longer acting, causes less hypotension, is lower in cost and results in a more rapid awakening after prolonged use.[5] Unwanted effects of the BDZ include venodilatation resulting in hypotension and third spacing, respiratory depression, withdrawal and paradoxical agitation which may be mistaken for withdrawal and the dose may be increased instead of decreased and replaced by another drug.[6] Dexmedetomidine (DEX) replacement has been used for BDZ withdrawal.[7]

Propofol: (2,6-diisopropylphenol) is an intravenous anesthetic agent which has been favourably compared with midazolam in the continuous sedation of patients

undergoing mechanical ventilation.[8] It has anxiolytic, hypnotic, sedative and amnestic properties at sub-anesthetic doses. It is also useful in rapid sequence intubation.

The use of propofol reduces the time needed for recovery of spontaneous respiration. It shortens the ICU stay and therefore may prove to have a better cost benefit ratio than MDZ despite being more expensive for the same level of sedation.[9,10] Rapid on off action is usual but after prolonged use over several days, recovery time may be prolonged to over an hour.[11] The rate of infusion is 1-3 µg/kg/hr for sedation. Higher doses are needed for status epilepticus (SE) and doses over 10 µg/kg/hr have been associated with greater hemodynamic side effects. As it reduces the cerebral oxygen consumption, it is also used in place of barbiturates for this purpose. EEG monitoring is essential to achieve burst suppression of the EEG and in higher doses, the EEG becomes isoelectric, although briefly.

Key benefits of propofol include rapid onset and offset of action, easy titration, metabolism independent of hepatic and renal function, sedative-hypnotic action with anxiolytic and amnestic properties. It is also a bronchodilator, anti-epileptic, muscle relaxant and anti-oxidant.

Problems with propofol are hypotension, hypertriglyceridemia, sepsis due to contamination as the solution should not be kept for >24 hrs due to the lipid content, pancreatitis, metabolic acidosis, adrenal insufficiency and immune dysfunction, cost and practically no benefit over midazolam in terms of earlier extubation and shorter stay. PRIS (Propofol Infusion Syndrome) defined as the occurrence of acute bradycardia resistant to treatment and progressing to asystole associated with propofol infusion. Bradycardia has to be associated with lipemic plasma, fatty liver enlargement, metabolic acidosis with base excess<10mmol/L, rhabdomyolysis or myoglobinuria. The syndrome usually leads to fatal cardiac and renal failure. Management includes stopping the drug, dialysis, carbohydrates and supportive care.

Because of the very dreaded PRIS, it remains a second line drug used for short durations of under 48 hours.

Dexmedetomidine (DEX), a highly selective á2 adrenergic receptor agonist and acts in the vasomotor center of the medulla, which decreases sympathetic tone. It also stimulates central parasympathetic outflow and decreases sympathetic outflow from the locus caeruleus of the brainstem and allows for increased activity of the inhibitory GABA neurons, which cause sedation, analgesia and natural REM sleep. It produces a normal sleep-like, cooperative sedation. The characteristic feature of sedation, together with a concomitant opioid sparing effect, may decrease the length of time spent on a ventilator, length of stay in ICU, prevalence and duration of delirium, as the evidence shown from several comparative studies. In addition, DEX has an excellent safety profile.[12] Other advantages include: maintenance of respiratory drive, rapid awakenings on stopping drug with some effect on analgesia as well with amnesia. Important in the crtically ill child, it has good hemodynamic tolerance if given carefully. Bradycardia and hypotension are two side effects that require continuous monitoring.

A loading dose of 0.5-1 µg/kg over 10 mins is given until sedated, followed by an infusion of 1 µg/kg/hr. A decrease of heart rate and blood pressure by about 10-15% is expected.[13] Titration for effect without deleterious effects is the key.

In burns patients, long term analgesia and sedation with frequent trips to the OR is required. Tolerance to the BZD and opiod groups develops and therefore DEX can be a useful analgesic/ sedative.[14]

Etomidate: This is an imidazole and is a short-acting IV hypnotic agent that provides anesthesia while maintaining hemodynamics and cerebral perfusion without raising ICP. These features make it useful as an agent for rapid sequence intubation in children with cardiac problems and head injury. The downside of this drug is that it is known to inhibit adrenal function by mainly impeding the enzyme 11β-hydroxylase. Even one single bolus of etomidate negatively influences adrenal function for at least 24 hours and therefore might increase risk of death.[15] Hence considerable caution should accompany the administration of etomidate in patients with septic shock. This drug is now not approved for prolonged sedation in critically ill patients and should be avoided totally in those at risk for adrenal insufficiency.[16]

A preview of the latest Clinical Practice Guidelines for the Management of Pain by American College of Critical Care Medicine (ACCM) suggests that the meta-analysis of moderate to high quality trials indicate that benzodiazepine sedation is associated with an increased ICU length of stay. The group has suggested that sedation strategies using nonbenzodiazepine sedatives (either propofol or DEX) may be preferred over sedation with BDZs (either MDZ or LZ) (Evidence+2B). However, since both these drugs are not clearly tried and tested for prolonged infusions in children, they cannot be recommended here.

Analgesic agents

Morphine:[17] The low cost, potency, analgesic efficacy and euphoric effect of morphine make it the ideal analgesic agent. The onset of action is 3-15 minutes and it's half life is 1.5-2 hours but in critically ill patients this would vary and therefore need titration. The loading dose is 0.02-0.05µg/kg followed by 2-5 µg/kg/hour. In hemodynamically unstable patients or if there is adverse histamine release or morphine allergy, hypotension and bronchospasm may occur.

Fentanyl: It is a synthetic opiate with excellent lipophilic properties and therefore a faster action. It is considered to be the most hemodynamically stable opioid. It also has 100 times greater potency of morphine but no euphoric effect. (Sufentanyl and Remifentanyl are 10 times as potent as fentanyl). They do not have any accumulation after infusions and are useful in induction for intubation or anesthesia. It is rapidly distributed to the peripheral compartments and has a half-life of 30-60 minutes. After a loading dose of 1-2 µg/kg, an infusion at the same dose per hour is usually adequate. There is a real prospect of drug withdrawal after prolonged use of opioids if the infusion is abruptly terminated. The drugs can be withdrawn either by gradual reduction in the infusion rate over 2-3 days or the infusion stopped and bolus doses of reducing amounts at increasing intervals can be adopted. Medications like chloral hydrate, DEX, oral clonidine and intermittent LZ alone or in combinations can be used if there is agitation suggestive of withdrawal.

Non-steroidal anti-inflammatory agents have no advantage over narcotics and can cause GI bleeding and add to the development of renal insufficiency. As the child is weaned off, analgesia alone is rarely required. IV preparations of paracetamol are available that can be given as continuous infusions or bolus doses.

Ketamine: It is a powerful analgesic agent which has a good safety profile when used in a variety of conditions. It has no hemodynamic depressive action and can be used in septic shock, cardiac disease and across all ages. The exception to its use is raised intracranial tension. The dose can be lowered and the dissociative reactions reduced when used with any BZ. It's a dissociative anesthetic that preserves respiratory drive and airway protective reflexes in moderate doses of upto 1.5µg/kg. It has mild sympathomimetic effects and therefore will preserve hemodynamics or will even raise blood pressure transiently. It is most useful for its powerful analgesic effects and almost complete amnesia. It is therefore useful in procedural sedation as well as in prolonged analgesia when combined with a BZ. It is also extremely useful in rapid sequence intubation in the PICU under several conditions as it is relatively cardiostable.[18] Side effects are, bronchial and salivary secretions, vomiting, transient laryngospasm, emergence reaction are the side effects. The route of administration is oral, IV or IM; and the dose for IM is 4-5µg/kg; IV is 1-2µg/kg and PO is 10µg/kg.

Neuromuscular blocking agents (NMBAs): These are adjuncts to sedation and analgesia and should NEVER be used on their own as they would result in tremendous anxiety and distress if adequate sedation is not achieved. The most common use of a muscle relaxant in the ICU is to facilitate mechanical ventilation.[19, 20] Other indications include control of ICP, control of muscle spasms and oxygen consumption.

Issues to be addressed before instituting NMBAs

1. Are there clear indications for initial and continued use?
2. Is there a pre-existing condition that may potentiate prolonged blockage. (Myasthenia, Guillane-Barre syndrome).
3. Is the patient on any other potentiating drug (steroids, aminoglycosides)
4. Is the electrolyte and metabolic status normal?
5. Is the patient normothermic?
6. Have all other methods for sedation and analgesia been optimized?

An ideal NMBA agent should have elimination independent of hepatic/renal function, cardiovascular stability, no interactions with other drugs, no accumulation over time, no active metabolites, rapid onset and offset of action and low cost.

But no agent meets all criteria. The aminosteroidal compounds include pancuronium, pipecuronium, vecuronium and rocuronium. Pancuronium is long acting, has vagolytic actions causing tachycardia and hypertension and has a prolonged half life in renal and hepatic failure. Atracurium and cis-atracurium are intermediate acting and do not depend on any end-organ metabolism for their elimination. Cis-atracurium is reported to be associated with the least incidence of neuromyopathy. Vecuronium, an intermediate acting agent has minimal cardiovascular side effects.

The assessment of the muscular response by visual, tactile or electronic means to a transcutaneous delivery of electric current meant to induce peripheral nerve

stimulation (PNS). PNS resulted in a significantly lower total dose and lower mean infusion rate of NMBA as well as a faster time to recovery of neuromuscular function and spontaneous ventilation.[21]

Administration: Continuous vs Intermittent: Continuous infusions provide greater comfort, consistent level of sedation, less agitation and anxiety. However, continuous infusions of sedative drugs in the intensive care unit may prolong the duration of mechanical ventilation and prolong the length of stay in the intensive care unit and the hospital. Neurologic assessment becomes difficult and daily interruptions in the infusions may help in reducing problems but may be associated with setbacks in ventilation and increased agitation.Strategies targeted at reducing the use of continuous IV sedation could shorten the duration of mechanical ventilation for some patients.[22]

Other problems seen with prolonged sedation, especially when coupled with neuromuscular blocking agents (NMBA) include cognitive impairment, critical care myoneuropathy and neuropathy pain induced immunosuppression when the child goes undertreated for the levels of sedation and analgesic required. In addition, chances of other complications like venous thrombosis, pneumonias and bedsores also increase.

When prolonged sedation is used, there is often tachyphylaxis to many medications used. Rotation of combinations sometimes helps to overcome the problem. However, before discarding a sedation, it is important to see if there is any cause for discomfort or pain, either endogenous or exogenous.

Last but not the least, sedation and analgesia don't always need to be in the form of medication. Allowing parents to stay with the child, talking to the child, a favourite toy, all can be very comforting. Topical oil/ moisturiser application to prevent itching and drying; taking care of lice in the hair; regular position change; changing soiled diapers promptly all will help. Avoiding loud noises; taking care of alarms promptly can help make their stay in the PICU less traumatic.

Combinations commonly used: with or without NMBAs are

i) MDZ + Morphine / Fentanyl or Morphine + PROP

ii) MDZ + Ketamine

iii) DEX / Morphine/Fentanyl + LZ/ MDZ with addition of chloral hydrate, lorezepam during weaning

Anaesthetists use the Bispectral index to monitor the depth of sedation/anesthesia. The result is read digitally as a number, or some monitors may show a graph. The validation of this system is not entirely clear in the PICU and much interference occurs with the other monitoring parameters that are constantly underway. The scale is read on 0-100, where[23]: a) 0 is deep sedation with flat line EEG with burst suppression at around 80, b) 100 is awake and responding to normal voice and only anxiolysis and c) 60 is about the stage where most ICU patients would be maintained. 80 would be where control for status epilepticus may be required.

Points to Remember

- ***Provide analgesia first with fentanyl, morphine, or possibly dexmedetomidine. Monitor analgesia adequacy if possible.***
- ***Avoid the adverse effects commonly associated with standard sedative medications.***
- ***Avoid midazolam accumulation by limiting the duration of use; practice at least daily interruption of drug or awakening the patient and targeting the lightest level of sedation possible.***
- ***Use drugs that you are familiar with and can control and tirtrate well***
- ***If propofol is used, avoid prolonged use***
- ***Monitor all patients for delirium, even those who are calm and not agitated.***
- ***Before hospital discharge, assess cognitive function in patients and consider neuropsychiatric follow-up for anyone who needs it.***

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NEWS AND NOTES

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CRITICAL CARE - I

DKA - CHANGING THOUGHTS

**** Poovazhagi V***

Abstract: *Changing thoughts pertaining to the diagnosis, monitoring, intravenous fluids and insulin therapy in Diabetic Keto Acidosis (DKA) are discussed in this article. Capillary blood ketone measurement using ketone meters is very useful in the diagnosis of DKA. Weight based intravenous fluid rates can be used from the precalculated fluid charts in DKA. Normal saline as the maintenance fluid is to be continued for at least 4-6 hours of initial therapy. Delay insulin infusion until 1-2 hours of fluid therapy. Oral rehydration fluids are advised if intravenous fluid therapy is not feasible. Subcutaneous rapid acting insulin analogs can be given 1- 2 hourly in DKA. Children on glargine insulin can continue the same along with intravenous insulin. Bed side capillary blood ketone measurements help to estimate recovery from ketoacidosis. Anticoagulant prophylaxis is advised in young children, especially with femoral lines. Hypertonic saline can be used as an alternative for treatment of cerebral edema in DKA.*

Keywords : *DKA, Pediatric, Cerebral edema, Insulin therapy.*

Diabetic ketoacidosis (DKA) is a common medical emergency encountered in children with diabetes mellitus (DM). Frequency of occurrence of DKA at the onset of diabetes mellitus varies from 15 to 70% and the rates inversely correlate with the incidence of Type 1 DM.[1] Appropriate fluid therapy and insulin are the main stay in DKA management. Guidelines by the International Diabetes Federation (IDF), the International Society for Pediatric and Adolescent Diabetes (ISPAD) and British Society for Pediatric Endocrinology and Diabetes (BSPED)[2,3] are currently followed in the management of DKA in most of the pediatric centers. Changing thoughts pertaining to the diagnosis, monitoring, intravenous fluids and insulin therapy in DKA are discussed in this article along with the DKA treatment protocol.

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Treatment protocol for diabetic ketoacidosis (DKA)

Biochemical criteria for diagnosis of DKA: Blood glucose ≥200mg/dL, venous pH <7.3 or bicarbonate <15mmol/L, ketonemia and/or ketonuria. Children with mild DKA usually tolerate oral fluids and can be started on subcutaneous insulin therapy and need minimal care. The following protocol is used in the treatment of moderate and severe DKA.

Emergency management: Pediatric life support guidelines have to be followed for airway, breathing and circulation. Two intravenous lines should be secured prior to therapy. Draw blood samples for glucose, ketones, electrolytes, urea, creatinine, complete blood counts, cultures, lactate, calcium and phosphate. Evaluate urine for ketones, deposits and culture sensitivity. An initial arterial blood gas analysis can be followed by 4th hourly venous blood gas analysis.

Infuse 10-20 mL/kg normal saline boluses over 60 minutes if in severe dehydration or shock. Do not exceed more than 30 mL/ kg fluid boluses.

Fluid therapy in DKA: Normal saline with potassium (K) 40 mEq/L is infused as follows. Fluid deficit in moderate and severe DKA is generally estimated to be 5-10% [2] and is corrected over 48 hours. Intravenous fluids should not be infused at a rate more than 1.5 to 2 times maintenance rate of fluid. Fluid calculation can be done by conventional method or the weight based recommendation of fluids.[2] Sample calculation by conventional method for a 20Kg child with severe dehydration is shown below:

Initial resuscitation with normal saline - 10mL/kg (200 mL) over one hour.

Deficit correction 8%. i.e 80 mL/kg NS (80 x 20) 1600 mL **plus** the maintenance fluid for 48 hours 3000 mL = 4600 ml **minus**

Initial bolus (4600 – 200mL) = 4400 to be infused over 48 hours =92 mL/hour.

(90mL/hr of 0.9% Saline with 40 mEq/L potassium and insulin infusion at 2 mL/hour).

Intravenous fluids should be changed to 5% dextrose containing ½ Normal saline with potassium if blood sugar falls < 250- 300 mg/dL. Maintain blood glucose between 200-250mg/dL while on insulin infusion.

Potassium concentration can be subsequently modified as shown in Table I.

Table I. Required concentration of potassium in IV fluid.

Serum K^+ level	Concentration of K^+ in IVF
< 3.5 mEq/ L	40 mEq/ L (2mL KCl/100mL)
3.5 – 4.5 mEq/ L	30 mEq/ L (1.5mL KCl/100mL)
4.5 – 5.5 mEq/ L	20 mEq/ L (1mL KCl/100mL)
> 5.5 mEq/ L	Potassium free fluid to be given

Insulin infusion is started after 1- 2 hours of fluid therapy at 0.1 unit/kg /hour. Add 100 units of regular (short acting) insulin to make up to 100 mL of 0.9% NaCl and flush out 50 mL of the solution slowly to prime the tubing with insulin.Infuse at 0.1ml/kg/hour to deliver 0.1unit/kg/hr of insulin. Document normal serum potassium levels before commencement of insulin infusion. Do not stop insulin infusion until acidosis has resolved. In case of persistent acidosis increase the dextrose content up to 12.5% before reducing insulin to 0.05unit/kg/hr to maintain blood glucose in the range recommended. If hypoglycemia (blood glucose <70 mg/dL) is encountered, stop insulin infusion , give dextrose bolus and restart insulin if blood glucose is more than 100mg/dL along with 7.5 %dextrose in 0.45% saline with potassium. If blood sugar is less than 100 mg/dL with persistent acidosis continue insulin at 0.1 unit /kg/hour while increasing the dextrose concentration of fluids to 12.5%. If hypoglycemia still persists then consider reducing insulin to 0.05units/kg/hr.

Monitoring in DKA

Hourly blood glucose and monitoring vital signs including the level of sensorium, 4th hourly electrolytes, 6-8 hourly urea and creatinine till normal are done till normal values are achieved. Bladder catheterization and gastric decompression may be needed. ECG monitoring for potassium is essential during therapy. Sepsis work up to be done for all children with DKA. If sepsis is suspected start on broad spectrum antibiotics until results are available. Fever is not a feature of DKA and it indicates infection. DKA may show increased white blood cell counts in the absence of infection (neutrophilia as stress response). Initial hyponatremia which is spurious due to hyperglycemia needs no correction. Blood ketone estimation may provide a valuable bedside information about the degree of keto acidosis.

Watch for cerebral edema, if encountered reduce intravenous fluids by one third, infuse 3% saline at 5 mL/kg over 20 minutes[2] or mannitol 0.5-1 g/kg over 30 minutes and repeat if necessary, intubate and optimally ventilate.

Consider switching over to subcutaneous insulin if blood ketones are less than 1 mmol/L, or blood pH more than 7.3 or the anion gap is normal. Stop the insulin infusion 1 hour after subcutaneous regular insulin or after 10 minutes if rapid acting insulin is given. Commence on subcutaneous insulin at 0.5-1 unit/kg/day depending on the age of the child in new onset DM or switch over to the previous insulin dose in children with established diabetes. Insulin should be given premeal three times daily and subsequently switched over to multiple daily insulin with intermediate and regular acting insulin. Multiple sessions of counseling with the primary care givers is an essential part of smooth transition to subsequent metabolic control. Psychosocial support needs to be undertaken in children with poor compliance to therapy.

Diagnosis of DKA

Blood ketones have been increasingly used to diagnose ketosis at bedside and it is superior to urine ketones as this directly measures β hydroxyl butyrate levels and correlates to ketogenesis. If an acid-base analysis is not available, the diagnosis of ketoacidosis can be made by bedside β-hydroxybutyrate (blood ketones) levels of 3 mmol/L or greater. It is recommended to monitor capillary blood ketones bedside using ketone meters during therapy especially in a setting of persistent acidosis. The rate of fall of ketones should be 0.5 - mmol/L/hour during therapy. Persistent acidosis despite normal ketones will indicate other etiologies like lactic acidosis, renal failure or hyperchloremic acidosis. Change over from insulin infusion to subcutaneous insulin is recommended if the blood ketone level is below 1 mmol/L.[3]

Intravenous fluid therapy

0.9 % saline boluses are recommended as initial therapy only if the peripheral circulation is decreased or if the child is in shock. It is recommended to be more cautious with the initial boluses of fluids in shock. A maximum of 30 mL/ kg is recommended in children presenting with shock.[3] Using early inotropes may be the

option if the initial fluid resuscitation exceeds 30 mL/kg. However in developing countries where sepsis is a significant factor there may be a rare indication for more fluid boluses. Subsequent fluid calculation is based on 5-10 % dehydration correction along with 48 hours of maintenance fluids to be given over 48 hours. Current recommendation is to use normal saline with added potassium for the first 4 - 6 hours of therapy. Weight based precalculated rates of intravenous fluids currently recommended in the management of DKA[2] is shown in Table II.

Table II. Infusion rate of fluids in the management of DKA

4 - 9 kg -6 mL/kg/hr,
10- 19 kg - 5 mL/kg/hr,
20- 39kg -4 mL/kg/hr,
40- 59kg -3.5 mL/kg/hr,
60- 80 kg – 3 mL/kg/hr.

Alternatively, fluids can be calculated conventionally according to the severity of dehydration along with 48 hours maintenance fluids. After reducing the amount of fluid boluses received, the fluid should be given over the next 48 hours. If appropriate intravenous fluids are unavailable or not feasible, arrange urgent transport to a facility that can provide intravenous fluid therapy. Give little sips (or small volumes through a syringe) of oral rehydrating solution (ORS) as frequently as possible. If vomiting does not occur after 1-2 hours, give ORS at a rate of 5 mL per kg body weight per hour.[2] In some cases it may be possible to insert a naso gastric tube and slowly rehydrate with ORS at 5 mL per kg body weight per hour. If ORS is not available, fruit juice and coconut water can provide some potassium. If the child cannot be transported immediately, start oral rehydration as above and give subcutaneous regular insulin 0.05 units/kg every 1-2 hours until transport to a centre with necessary facilities.

Potassium therapy

Total body potassium is depleted in children with DKA. If there is no hypokalemia start replacing potassium after initial volume expansion and concurrent with starting insulin therapy. Initial rate of potassium in maintenance intravenous fluids is 40 mmol/L and subsequently this can be modified according to the serum levels. If the patient is hypokalemic, start potassium replacement at the time of initial volume expansion and before starting insulin therapy. If potassium is used in rapid intravenous volume expansion the concentration should be 20 mmol/L.[2] The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol / kg / hr. If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced. If the patient is hyperkalemic, defer potassium replacement therapy until urine output is documented. ECG monitoring is useful if immediate serum potassium measurements are unavailable.

Phosphate therapy

Prospective studies have not shown clinical benefit from phosphate replacement.Severe hypophosphatemia in conjunction with unexplained weakness should be treated.[2]

Insulin therapy

Intravenous infusion of regular insulin(short acting) without boluses is the standard recommendation for DKA. Insulin infusion has to be started after 1-2 hours of commencement of fluid correction. Giving insulin prior to intravenous fluid therapy, increases the risk of hypokalemia. There is some evidence to show that cerebral edema is likely to occur if insulin is started in the first hour of therapy.[3] In children with hypokalemia initiation of insulin therapy should be delayed until serum potassium levels are corrected to normal levels .

For children who are already on long acting insulin (especially Glargine, Lantus), it can be continued at the same dose and time throughout the DKA treatment in addition to intravenous infusion of insulin and this shortens the length of hospital stay after recovery from DKA. For those on continuous subcutaneous insulin infusion (CSII) pump therapy, stop the pump when starting the treatment. Insulin therapy is recommended to be initiated with regular insulin at 0.1 unit /kg/hour. There is not much advantage by increasing the infusion rates beyond 0.1 unit /kg/hour as this is associated with increased risk of subsequent hypoglycemia. Continue intravenous infusion of insulin until resolution of acidosis as documented by blood ketones <1mmol/L or a normal anion gap or pH more than 7.3. Newer rapid acting insulin analogs (aspart or lispro insulin) given subcutaneously in the dose of 0.1 unit/kg every 1-2 hours is a safe and effective alternate therapy if IV insulin cannot be given in uncomplicated DKA.[4,5,6,7] While switching over from intravenous to subcutaneous insulin therapy the first subcutaneous injection should be given 15-30 minutes (with rapid-acting insulin) or 1-2 hours (with regular insulin) before stopping the insulin infusion. This overlap is essential to prevent rebound hyperglycemia.

Cerebral edema

Cerebral edema occurs in 0.68% to 13.2% of all DKA.[8] Cerebral edema accounts for 20-90% of all DKA deaths.10-20% of DKA survivors of cerebral edema have significant residual morbidity.

The pathogenic mechanisms of initiation and progression of cerebral edema in DKA are still controversial and risk factors for predicting cerebral edema were not consistently associated with its occurrence based on existing literature. New onset DM, younger age and longer duration of symptoms are the demographic factors associated with risk of cerebral edema. Based on the available epidemiological studies, greater hypocapnia at presentation, increased serum urea nitrogen at presentation, more severe acidosis, bicarbonate correction for acidosis, attenuated rise of serum sodium during therapy were found to be risk factors for cerebral edema.[1] The pathophysiology of DKA is still controversial and the following have been hypothesized. Cerebral ischemia and hypoxia, idiogenic osmoles related to the hyperosmolar state and fluid administration, rapid decline in blood glucose, bicarbonate administration, vasopressin and atrial natriuretic factor, cell membrane co transporters, aquaporin channels and proinflammatory cytokines due to ketotic state are likely to cause cerebral edema in DKA.[9] Hypertonic saline or mannitol is currently recommended in cerebral edema. Hypertonic saline (3 % saline) is infused at 5 ml/ kg over 20 minutes.[2] Restrict the fluids by one third[2] and rehydrate over a period of 72 hours rather than 48 hours.[3]

Use of bicarbonate: Bicarbonate should only be considered in children who are profoundly acidotic (pH< 6.9), in shock and in life threatening hyperkalemia. The recommended dose is 1-2 mEq/kg as an infusion over 60 minutes. The evidence to date does not justify the administration of bicarbonate for treatment of DKA, in the pediatric population, in view of possible clinical harm and lack of sustained benefits. There was no evidence of improved glycemic control or clinical efficacy with bicarbonate. There is retrospective evidence of increased risk of cerebral edema and prolonged hospital stay in children who received bicarbonate.[10]

Use of anticoagulant prophylaxis

There is a significant risk of femoral vein thrombosis in young and very sick children with DKA who have femoral lines inserted. Therefore consideration should be given to use anticoagulants in these children. Children who are significantly hyperosmolar might also require anticoagulant prophylaxis.[3]

Prevention of DKA

DKA is a preventable illness. Delayed diagnosis is an important cause for DKA at presentation in children with new onset diabetes.[11] Insulin omission is the important cause for DKA in children with established diabetes. Most often psychosocial reason is the cause for insulin omission. Sustained health education to the medical community and school personnel regarding the classical symptoms of diabetes and the significance of secondary nocturnal enuresis will reduce the incidence of new onset DKA.[12,13]

Points to Remember

- ***Bedside blood ketone measurement is useful in diagnosis and monitoring of children with DKA.***
- ***Fluid therapy in DKA should always precede insulin infusion in DKA.***
- ***Ensure normal serum potassium before starting insulin infusion.***
- ***Restricted fluid therapy as per protocol is essential in management of DKA.***
- ***Rapid analogs of insulin can be used 1-2 hourly if insulin infusion is not feasible.***
- ***Children on long acting insulin can continue the therapy during treatment of DKA.***
- ***Both new onset DKA and recurrent DKA are preventable in children with diabetes.***

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CLIPPINGS

Fish that feed on mosquito larvae for preventing malaria transmission

Adult anopheline mosquitoes transmit Plasmodium parasites that cause malaria. Some fish species eat mosquito larvae and pupae. In disease control policy documents, the World Health Organization includes biological control of malaria vectors by stocking ponds, rivers, and water collections near where people live with larvivorous fish to reduce Plasmodium parasite transmission. The Global Fund finances larvivorous fish programmes in some countries, and, with increasing efforts in eradication of malaria, policy makers may return to this option. We therefore assessed the evidence base for larvivorous fish programmes in malaria control.

Main objective was to evaluate whether introducing larvivorous fish to anopheline breeding sites impacts Plasmodium parasite transmission. Secondary objective was to summarize studies evaluating whether introducing larvivorous fish influences the density and presence of Anopheles larvae and pupae in water sources, to understand whether fish can possibly have an effect.

Selection criteria: Randomized controlled trials and non-randomized controlled trials, including controlled before-and-after studies, controlled time series and controlled interrupted time series studies from malaria-endemic regions that introduced fish as a larvicide and reported on malaria in the community or the density of the adult anopheline population. In the absence of direct evidence of an effect on transmission, we carried out a secondary analysis on studies that evaluated the effect of introducing larvivorous fish on the density or presence of immature anopheline mosquitoes (larvae and pupae forms) in community water sources to determine whether this intervention has any potential in further research on control of malaria vectors.

Authors' conclusions: Reliable research is insufficient to show whether introducing larvivorous fish reduces malaria transmission or the density of adult anopheline mosquito populations.

In research examining the effects on immature anopheline stages of introducing fish to potential malaria vector breeding sites (localized water bodies such as wells and domestic water sources, rice field plots, and water canals) weak evidence suggests an effect on the density or presence of immature anopheline mosquitoes with high stocking levels of fish, but this finding is by no means consistent. Whether this translates into health benefits, either with fish alone or with fish combined with other vector control measures is not known. Our interpretation of the current evidence is that countries should not invest in fish stocking as a larval control measure in any malaria transmission areas outside the context of carefully controlled field studies or quasi-experimental designs. Research could also usefully examine the effects on native fish and other non-target species.

Walshe DP, Garner P, Abdel-Hameed Adeel AA, Pyke GH, Burkot T. Larvivorous fish for preventing malaria transmission. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD008090. DOI: 10.1002/14651858.CD008090.pub2. Assessed as up to date: June 18, 2013.

CRITICAL CARE - I

ACUTE LIVER FAILURE IN CHILDREN

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Abstract: *Acute liver failure is a devastating clinical situation of rapidly deteriorating liver function which was normal before. The outcome of this catastrophic situation is greatly improved in the recent past owing to an early diagnosis, recognition of poor prognostic markers and a multi-disciplinary protocol based management. The imperative aspects being the early consultation of a pediatric hepatologist, appropriate and justified measures to manage the coagulopathy, encephalopathy and counseling for the possible need of a liver transplant.*

Key words: *Pediatric, Acute liver failure, Management, Hepatic encephalopathy and Liver transplantation.*

Acute liver failure is a devastating clinical situation of rapidly deteriorating liver function in a previously normal child. This may be associated with altered mentation, respiratory compromise and renal compromise in addition to the myriad manifestations of the liver dysfunction. The outcome had been universally dismal prior to era of liver transplantation with the survival rate estimated to be approximately 15%.[1] The one year survival rate with liver transplantation for ALF is currently greater than 65% while the 5-year survival rate is more than 50%.[2]

Definition

The most commonly used definition of acute liver failure is presence of any degree of encephalopathy with evidence of coagulopathy with INR >1.5 in a patient without pre-existing cirrhosis and illness duration of less than 26 weeks.[1] In children with Wilson's disease and autoimmune hepatitis sudden decompensation of liver function meeting the above criteria should be labelled as acute liver failure only if the total duration of illness is less than 26 weeks, else would be classified as acute on chronic liver failure as per "Pediatric acute liver failure study (PALF)" working group.[3] There are many terminologies in use based on the duration of illness, like fulminant, hyper acute, subacute liver failure. These terms are not of much significance as the prognosis and outcomes in these groups do not greatly differ from the acute liver failure group considering any hepatic decompensation of less than 26 weeks duration. Thus, only using the term of acute liver failure should suffice.[4]

Etiopathogenesis: In the Indian scenario amongst children, the most common etiologies are infective with hepatitis A being the most common. Drug induced hepatitis, particularly antitubercular drugs induced are important. Acetaminophen toxicity and mushroom poisoning have rarely been reported in our country as yet.[5] Even though the causes for acute liver failure may be myriad, the process involves the acute loss of liver cells. The loss of liver cell synthetic function and detoxification results in various manifestations. The coagulopathy and hypo-proteinemia can be attributed to less synthesis of hepatic proteins. The pathogenesis of cerebral edema and raised ICT are not clearly understood though multiple factors are involved. The factors implicated are osmotic disturbances, cerebrovascular dysregulation, metabolic disturbances and infections.

Table I. Grading of hepatic encephalopathy

Grade I: Changes in behavior with minimal change in level of consciousness
Grade II: Gross disorientation, drowsiness, possible asterixis, inappropriate behavior
Grade III: Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
Grade IV: Comatose, unresponsive to pain, decorticate or decerebrate posturing

Initial evaluation: Any child who has a clinical presentation of acute hepatitis and found to be having high liver enzymes should be evaluated with INR and for any subtle change in mentation as evidence of coagulopathy and encephalopathy respectively. Once the diagnosis of ALF has been ascertained, the child must be admitted in

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ICU for further management if grade II encephalopathy (Table I) sepsis or hemodynamic instability are present.

The initial evaluation is focused towards assessment of etiology and the need to transfer the child to a transplant facility. As the possibility of rapid progression is significant, for patients being treated in a non-transplant center frequent assessment for determining whether the transplant criteria are being met must be undertaken. Also early consultation with the transplant team and early transfer are critical.

The physical examination includes assessment of mental status, stigmata of chronic liver disease and liver span. The inability to palpate the liver is indicative of loss of liver volume due to massive hepatocyte necrosis. If the liver span is increased then it may be due to early acute viral hepatitis, Budd-Chiari syndrome or congestive heart failure. The initial investigatory workup is shown in Table II.

Table II. First line of tests in evaluation of acute liver failure severity and etiology

CBC
LFT, RFT, Blood sugar, serum electrolytes
PT/INR
ABG
Arterial ammonia and lactate
Cultures – blood, urine
USG Abdomen/CXR
Viral markers- anti HAV IgM, anti-HEV IgM, HBsAg, anti-HCV IgM
S.ceruloplasmin, S.copper, 24 hour urinary copper, KF ring
ANA, SMA, LKM, IgG
HIV
Amylase, lipase

After the clinical evaluation a battery of tests are needed to be sent to determine the sverity of the hepatic insult, parameters to be used in Kings college criteria as a prognostic marker and to determine the etiology of the liver failure. As a first line the tests mentioned in Table II are sent and thereafter if the etiology remains elusive or further evaluation is needed then subsequent tests need to be customized as per the situation.

The social and financial issues are intangible aspects of imparting care in ALF and during counseling of the parents the prognosis must be explained to help in deciding the line of management.

General management: The issues of prime importance, which are present in ALF irrespective of the etiology, are neurological dysfunction and coagulopathy. Fluid/ electrolyte management and infection control need special attention.

Neurological issues of concern are raised intracranial pressure, cerebral edema, encephalopathy, seizures and the additional complications due to sedatives administered.

Raised intracranial tension and cerebral edema are known to predict poor outcomes[6] and if severe, are taken as contra-indications for liver transplantation. Cerebral edema increases with worsening grade of encephalopathy. The brain injury caused may be permanent, with sequelae after recovery from acute liver failure.[7]

The encephalopathy grade can rapidly change and hence frequent monitoring is essential. Sudden deterioration of mentation can be attributed to either worsening of cerebral edema or intra cranial hemorrhage, the distinction can be confidently made only by a CT brain. Grade I encephalopathy can be managed in the ward while grade II should be admitted in the ICU and worsening from grade II is taken as an indication for intubation.

Anti-edema measures to be used include head end elevatioin, mannitol, hypertonic saline, inducing hypernatremia, hyperventilation, barbiturates and selective head cooling.

Mannitol is an osmotic diuretic and has been shown to correct raised intra cranial pressures in ALF[8] when used in the dosage of 0.5-1g/kg. It's not to be used as a prophylactic agent and when serum osmolarity is more than 320 mosm/L. The problems associated with enthusiastic use of mannitol are volume overload in a patient with renal compromise, hypernatremia and hyperosmolarity. Thus the current usage of this agent is restricted to worsening episodes of cerebral edema and intra cranial hemorrhage.

Hypernatremia with serum sodium between 145-150 mq/L which can be produced with 3% saline has been found to be protective against the development of cerebral edema[9] and has a potential benefit as a prophylactic measure.

Hyperventilation produces a carbon dioxide wash out which in turn causes cerebral vasoconstriction.

This decreased blood flow results in decreased intra cranial pressure. This effect is at best very transient and short lived though drop in pressure is significant.[10] Thus hyperventilation can only be recommended as an emergency option when sudden lowering of intra cranial pressure is required immediately as in impending herniation but has no role as prophylactic measure.

Barbiturate coma can be used when the above treatments measure are ineffective and the blood pressure needs close monitoring with this.[11]

Selective head cooling has been used an experimental modality in animals though extending it for practical use seems an attractive option.[12-15] The simple principle is that hypothermia will decrease the rate of metabolism and thus the deranged metabolic state in the brain that predisposes to development of cerebral edema can be circumvented.

Encephalopathy in addition to management as outlined above needs measures to reduce ammonia levels[16] due to its hypothesized role in pathogenesis. Ammonia levels of more than 200g/dL have been associated with worsening encephalopathy and herniation.[17] Lactulose administration is associated with increased survival[18] and has a role in decreasing ammonia levels as well. Grade II encephalopathy is taken as a threshold for prophylactic intubation as well.

Seizures may be seen in ALF. Prophylaxis for the same is not indicated though for management phenytoin may be used. Sedation should be avoided as far as possible and the choice of drug is not very clear. Propofol is often used on the grounds that its effect of decreasing the cerebral blood flow may also be beneficial in cerebral edema[19], though there are no robust studies to support this claim. At the same time the half life of propofol is prolonged in the setting of liver dysfunction.

Coagulopathy is universal in the setting of ALF. INR is prolonged due to decreased synthesis of clotting factors and in the presence of consumptive coagulopathy that may be present. Thrombocytopenia is also a frequent occurrence.[20] Correction of INR with blood products is fraught with many issues. These include fluid and protein overload, which may cause worsening of the cerebral edema and encephalopathy, in addition to the risks involved with transfusion of blood products. The correction of INR may also hamper in usage of the predictive scores that are used as deciding tools for the need for liver transplantation.

Platelets are to be transfused in the setting of bleeding or for doing a procedure with platelets less than 50,000/μL. In the absence of these platelets are not transfused till they fall to 10-15,000/μL.[20]

Clotting factors or FFP are to be transfused when INR is more than 7 or when an intervention is planned/active bleeding occurs. The role of factor VII infusion with FFP is under evaluation after having shown promising results in temporary correction of INR in small studies.[21]

For prevention of gastritis associated bleeding H_2blockers, PPI or sucralfate should be used.

Infection control is imperative as infections not only make the course more complicated but may also preclude transplantation as an option. As bacterial and fungal infections occur more frequently[22,23], scrupulous sepsis monitoring is essential. For the same purpose prophylactic antibiotics and anti fungals are used. Though this approach cannot be taken as a recommendation, it has sound practical reasoning to support it.

Fluid and electrolytes need to be aggressively managed as circulatory dysfunction is rather common in ALF setting due to the various inflammatory chemokines that are released. Also due to altered mentation oral intake is low and decreased circulatory volume may be co-existing. Continuous monitoring of vitals is imperative and vasopressor drugs are frequently required. Though either dopamine, epinephrine or nor epinephrine may be used, agents which cause peripheral vasoconstriction are avoided when cerebral edema or encephalopathy are present.

After initial volume resuscitation if needed fluid infusion rate is maintained at 2/3 of requirement. Sodium levels need to be maintained as per the need to achieve hypernatremia (serum sodium 145-155mEq/L). Hypokalemia aggravates hepatocyte injury and hence must be avoided.

Early enteral nutrition should be established and maintainence of euglycemia is essential.

Specific management based on etiology

Wilson's disease is suspected when ALF is associated with massive hemolysis. Renal function deterioration may be associated as well. The biochemical findings suggestive of Wilson's disease are of transaminases, alkaline phosphatase being in normal range and most suggestive is bilirubin: ALP ratio of >2.[24] Low serum ceruloplasmin is not specific as decreased hepatic synthetic function would be seen in any liver failure.

The treatment would be to decrease serum copper and inhibit further hemolysis.[24] Penicillamine is not recommended in the acute phase as there is a risk of hypersensitivity reaction. Also recovery from ALF in

Wilson's disease without transplantation is infrequent.[24] Hemofiltration, albumin dialysis or plasma exchange can directly decrease plasma copper especially when renal function is impaired.

Autoimmune hepatitis management in ALF would include giving trial of high dose steroids and simultaneously starting the work up for liver transplantation.[25] There are no specific prognostic factors that predict the outcome with steroid therapy in this clinical setting.

Drug induced ALF: There is no specific antidote for drug induced idiosyncratic reaction and steroids are not indicated unless an allergic reaction is suspected.

Acetaminophen toxicity is seen in the Indian context as well and the specific antidote is N Acetyl cysteinc(NAC).

Viral hepatitis induced liver failure commonly is due to either hepatitis A or E for which only general treatment is available and suffices. In cases with flare of HBV, lamivudine should be started and continued for at least 6 months to prevent a recurrence of flare.[26,27] In case of varicella and herpes induced liver failure acyclovir is used as specific therapy in addition to the general management.[28-30]

Table III. Poor prognostigators for non-acetaminophen acute liver failure

INR greater than 6.5; or,
Three of the following five criteria:
Patient age of less than 11 or greater than 40;
Serum bilirubin of greater than 300 micromoles per litre;
Time from onset of jaundice to the development of coma of greater than seven days;
INR greater than 3.5; or,
Drug toxicity, regardless of whether it was the cause of the acute liver failure.

Liver transplantation is the only modality of treatment when hepatocyte loss has occurred beyond a stage of regeneration or when the underlying disease process cannot be inhibited. Liver transplantation when done for ALF has survival rates at 5 years of more than 95%.[1,31] This has led to a radical change in the outcome of ALF. The main concern is transfer and posting the child for liver transplantation before transplantation becomes unfeasible. For this purpose Kings College criteria has been validated and used extensively and can be recommended as guideline to decide timing of liver transplantation.[9,32-37] APAP, acetaminophen; Prognosis (Table III and Table IV) INR, international normalized ratio.

Table IV. King's college criteria for liver transplantation in AHF

APAP* - associated AHF	All other causes of AHF
pH <7.3 or INR >6.5, serum creatinine >3.4mg/dl, and grade III-IV encephalopathy	INR >6.5 or Three of the following variables: 1. Age <10 or >40 years 2. Cause is nonA, nonB hepatitis or idosyn cratic drug reaction 3. Duration of jaundice before encephalo pathy >7 days 4. INR >3.5 5. Serum bilirubin >17.5mg/dl
APAP - Acetaminophen Paracetamol	

Points to Remember

- ***Acute liver failure is a life threatening condition. Appropriate management needs a multi-disciplinary approach.***
- ***Correct coagulopathy when indicated, not all deranged INR and thrombocytopenia need correction.***
- ***Hypertonic saline and not mannitol is better prophylactic agent for prevention of cerebral edema***
- ***Avoid sedation, if needed propofol is preferred.***
- ***Early consultation with a liver transplant team is beneficial***
- ***King's College criteria should be used in predicting prognosis and need for liver transplantation***

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CLIPPINGS

Is breathing retraining useful in the treatment of children with dysfunctional breathing/hyperventilation syndrome?

Dysfunctional breathing is described as chronic or recurrent changes in breathing pattern causing respiratory and non-respiratory symptoms. It is an umbrella term that encompasses hyperventilation syndrome and vocal cord dysfunction. Dysfunctional breathing affects 10% of the general population. Symptoms include dyspnoea, chest tightness, sighing and chest pain which arise secondary to alterations in respiratory pattern and rate. Little is known about dysfunctional breathing in children. Preliminary data suggest 5.3% or more of children with asthma have dysfunctional breathing and that, unlike in adults, it is associated with poorer asthma control. It is not known what proportion of the general paediatric population is affected. Breathing training is recommended as a first-line treatment for adults with dysfunctional breathing (with or without asthma) but no similar recommendations are available for the management of children. As such, breathing retraining is adapted from adult regimens based on the age and ability of the child.

Objectives: To determine whether breathing retraining in children with dysfunctional breathing has beneficial effects as measured by quality of life indices and whether there are any adverse effects of breathing retraining in young people with dysfunctional breathing.

Selection criteria: Randomised, quasi-randomised or cluster-randomised controlled trials were included. Observational studies, case studies and studies utilising a cross-over design were excluded. The cross-over design was considered inappropriate due to the purported long-lasting effects of breathing retraining. Children up to the age of 18 years with a clinical diagnosis of dysfunctional breathing were eligible for inclusion. Included children with a primary diagnosis of asthma with the intention of undertaking a subgroup analysis. Children with symptoms secondary to cardiac or metabolic disease were excluded.

Any type of breathing retraining exercise was considered for inclusion in this review, such as breathing control, diaphragmatic breathing, yoga breathing, Buteyko breathing, biofeedback-guided breathing modification and yawn/sigh suppression.Programmes where exercises were either supervised (by parents or a health professional, or both) or unsupervised were considered. Also considered relaxation techniques and acute episode management as long as it was clear that breathing exercises were a component of the intervention.

Any intervention without breathing exercises or where breathing exercises were not key to the intervention were excluded.

Authors' conclusions: The results of this systematic review cannot inform clinical practice as no suitable trials were identified for inclusion. Therefore, it is currently unknown whether these interventions offer any added value in this patient group or whether specific types of breathing exercise demonstrate superiority over others. Given that breathing exercises are frequently used to treat dysfunctional breathing/hyperventilation syndrome, there is an urgent need for well-designed clinical trials in this area. Future trials should conform to the CONSORT statement for standards of reporting and use validated outcome measures. Trial reports should also ensure full disclosure of data for all important clinical outcomes.

Barker NJ, Jones M, O'Connell NE, Everard ML. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in children. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD010376. DOI: 10.1002/14651858.CD010376.pub2. Assessed as up to date: October 16, 2013.

CRITICAL CARE - I

POLYTRAUMA

**** Anitha VP***

Abstract: *Major polytrauma in children results in higher mortality compared to adults. The mechanism of injury defines the associated injuries. Prompt resuscitation, which begins within the "platinum half-hour" and continued in dedicated PICUs will improve outcomes. Primary survey should include cervical spine stabilization and hemorrhage control with routine ABCDE. Emphasis on airway management with alternative plan in case of difficult airway has been defined. Focus has also shifted to damage control resuscitation including permissive hypotension and damage control surgery. CT scan can be the "tunnel of death" for unstable patients. FAST has replaced it as the bedside diagnostic of choice.*

Key words: *Pediatric polytrauma, Damage control, Resuscitation.*

Major pediatric trauma, though not the leading cause of childhood mortality in our country, has high mortality and morbidity. There can be varying levels of severity, with morbidity increasing with severity. About 50% of deaths occur at the scene of accident, and another 25 % within 24 hours due to massive hemorrhage or severe TBI.[1] It is this group who will benefit from appropriate care, which should ideally begin with prompt pediatric emergency medical services[2], who transport the child to pediatric ICUs, where a multispeciality team can manage the critically ill child. Mortality results, most often, due to unsecured airway and inadequate ventilation and to a lesser extent from delayed volume resuscitation.

Mechanism of injury and patterns

The mechanism of injury predicts the injury pattern. Children can be a victim of motor vehicle accidents either as an occupant or as pedestrian. The Waddell triad[3] defines the major areas injured: pedestrian trauma results in injuries to head, torso and lower extremities, while occupant injuries include head, face, neck in unrestrained passengers and cervical-spine injuries, bowel trauma and chance fractures of spine in restrained passengers. Bicycle riders sustain injuries to head (unhelmeted), upper limbs and upper abdomen (contact with handlebar). Falls account for another major cause; high falls (from 2nd storey and higher) are associated with serious head injuries, long bone fractures and intrathoracic and intra-abdominal injuries, resulting in higher mortality. Drowning, burns and child abuse account for rest of the causes.

Pathophysiology[3]

The effects of injury are related to the velocity of the impacting object applied to the small body mass of the child. In addition, the increased elasticity of immature bones results in increased soft tissue injuries.

The body's physiologic response to trauma is a reflex increase in vasomotor tone in response to hemorrhage and catecholamine mediated increase in cardiac output, to maintain perfusion of vital organs. Other responses include release of angiotensin by kidneys, cortisol and aldosterone by the adrenals and vasopressin by the posterior pituitary. Local compensatory mechanisms, in the presence of diminished blood volume, help to contract circulation. Tissue injury activates cascades of complement, cytokines and other mediators. In severe injury the stress response can be profound and result in a hypermetabolic state. Inflammation results in systemic inflammatory response syndrome and multiorgan dysfunction. Stress hyperglycemia is associated with poor outcome due to a shift to anaerobic metabolism with increased lactate production and brain tissue acidosis.

Initial assessment

Emergency services: Resuscitation of the pediatric trauma victim should begin as soon as possible, to maintain vital signs during the "platinum half-hour" in order to improve outcomes. Specialized trauma teams with trained paramedics who can reach the victim in time are not available in most parts of our country. With the present scenario it is best to "scoop and run" the child to the nearest centre with facilities to manage the patient (as against the "stay and play" principle of stabilization before transport).

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Transport: Transporting from the site or between healthcare facilities, though fraught with risks, must be undertaken in an equipped ambulance by pediatric trauma/ transport teams capable of maintaining airway, ventilation and circulation.

Scoring systems[4] are useful to stratify risk and predict outcome in critically injured children. Various studies comparing one against another have been conducted. The "Pediatric Trauma Score" has been found useful in the field (Table I), while "Modified Injury Severity Scale," an anatomic scale incorporating GCS, has been validated after admission to PICU.

Primary survey is completed by exposing the patient fully. The conventional management priority ABCDE can be modified to PDABCDE (Table II).[5]

One must not wait to complete primary survey to intervene and manage life threatening problems. The Broselow tape is handy in choosing appropriate size of airway equipment and drug doses.

Airway and cervical spine stabilization: All patients resuscitated should receive oxygen supplement through NRM. Airway should be maintained with modified jaw thrust (avoiding head tilt), while immobilizing C-spine manually, followed by application of semirigid collar and back board. An oropharyngeal airway of appropriate size can be utilized after clearing secretions and blood with a wide bore suction (Yankaeur). Intubation is better done with RSI, assuming a full stomach. Nasal and blind intubations are contraindicted in children. An orogastric tube is recommended to decompress stomach, until basal skull fractures have been ruled out.

Indications for intubation are as follows:

- Apnea or central hypoventilation,
- Upper airway obstruction
- To protect upper airway and major maxillo-facial trauma
- Respiratory insufficiency
- GCS < 8 or drop in GCS > 2 from baseline, raised ICP
- Status epilepticus

When difficult airway is anticipated or intubation attempts fail, instead of a wide, confusing plan B, a stratified 5 level approach is recommended (Table III).

If airway is not secured and adequate ventilation ensured all other efforts will be rendered futile. While immobilising C-spine is a priority, clearing it is not. It has been proved that it is difficult to obtain the 3 views of neck X-ray in a critically ill patient. CT scan of the neck can be included while getting one of the brain, after stabilizing vitals. CT console has been termed "tunnel of death" for the unstable patient.

Breathing: Usual causes of respiratory failure in trauma are central hypoventilation, pneumothorax, hemothorax, flail chest, lung contusion. These conditions can be differentiated at bedside by clinical examination findings aided by the increasingly useful ultrasound. One must not wait for X-ray to drain a tension pneumothorax; or an ABG before intubation. Ensure adequate minute ventilation and oxygenation by providing positive pressure ventilation.

Table I. Pediatric trauma score

Component	2	1	-1
Patient weight	> 20 kg	10 – 20 kg	<10 kg
Airway	Normal	Maintainable	Unmaintainable
Systolic BP	90 mmHg Palpable radial pulse	50 -90 mmHg Palpable femoral pulse	< 50 mmHg
CNS	Awake	Obtunded/LOC	Coma/decerebrate
Open wound	None	Minor	Major/penetrating
Skeletal	None	Closed	Open/multiple

A PTS between 12 and 9 was considered as moderate trauma, between 8 and 4 as severe trauma, between 3 and 1 as a high risk of death and between 0 and -6 as improbable survival. A PTS score < 9 warrants admission to PICU.

Table II. Management priority on trauma

P	Protection with personal protection equipment (PPE facial shield+conventional mask, gown and gloves)
D	Decision–to initiate, continue or discontinue trauma resuscitation (such as fatal injuries with decapitation or torso truncation or OHCA
A	Airway: Maintenance of patent airway with cervical spine control (head and neck immobilization)–a new 5-level of DAM and DIM
B	Breathing: Ensure adequate breathing or provide positive pressure ventilation
C	Circulation: Check circulation, stop external bleeding, IV lines+blood work, identify internal bleeding to control hemorrhage (to prevent lethal trauma triad by DCR & MTP as indicated)
D	Decompression of intra-cranium
E	Extremities (adequate exposure but prevent hypothermia): After controlling exsanguinating external limb bleeding the priorities return to C and D above

[OHCA: Out-of-hospital cardiac arrest; DAM: Difficult airway management; DIM: Difficult intubation management; DCR: Damage control resuscitation; MTP: Massive transfusion protocol.]

Table III. Five levels of DAM / DIM (difficult intubation management)[5]

Levels	Devices / Procedures
1.	Conventional direct laryngoscopy (DL)
2.	Gum elastic bougie (GEB)
3.	Video-assisted airway management (VAAM)
4.	LMA or iLMA (intubating LMA)
5.	Surgical airway–cricothyrotomy (needle for children and open for adults) followed by tracheostomy

Circulation: Though discussed here, by now at least two wide bore lines should have been accessed and isotonic fluid boluses commenced. If peripheral access is unsuccessful, intraosseous access in non injured limb or central vein or cut down by competent personnel must be accomplished without delay. Shock assessment has shifted from the static model of classifying hemorrhage based on blood volume lost, to a more dynamic model of monitoring the response to initial IVF resuscitation with division into rapid, transient and non-responders to indicate the status of any on-going bleeding, volume loss, need for transfusion and operation as well as the possibility of non-hemorrhagic causes of tension pneumothorax and pericardial tamponade contributing to non-response as summarized in Table IV.

The lethal triad of trauma are hypothermia, coagulopathy and acidosis[6] (which forms a vicious cycle) and is related to massive transfusion in uncontrolled bleeding. One of the recent approaches to combat this is the damage control resuscitation (DCR) comprising of three major components:

1. Permissive hypotension
2. Hemostatic resuscitation
3. Damage control operation / surgery (DCO / DCS)

Permissive hypotension aims to defer or restrict the fluid resuscitation until hemorrhage is controlled to minimize the risk of hydrostatic dislodgement of the temporary clots in bleeding vessels prior to operation to stop the internal bleeding. Regarding the choice of fluid, no difference in outcomes have been demonstrated whether isotonic crystolloids or colloids like dextran, starch or albumin were used. Colloids, on the contrary, can worsen coagulopathy. Volume is restricted to 10 mL/kg aliquots and if > 20 mL/kg is required, surgical intervention will most likely be needed. Blood should be ordered as the third bolus. If time does not permit a full cross matching, a partial cross match or ABO and Rh type specific, uncrossmatched blood is still preferable to O negative, uncrossmatched blood.

Hemostatic resuscitation targets blood replacement by packed red cells together with high ratio of plasma and platelet concentrate at the early point when massive blood transfusion is anticipated so as to minimise the coagulopathy (related to dilution of platelet and coagulation factors) and to improve survival. While studies have proved that 1:1 ratio of FFP and PRBC transfusion decreases mortality, there is no specific recommendation

Table IV. Response to initial IVF resuscitation in trauma shock[5]

Response	Rapid	Transient	Non - response
Blood loss	10 – 20 %	20 – 40%	> 40%
On going bleeding	Nil	Yes	Heavy/+possibility of non hemorrhagic shock causes
Replacement	Sufficient	Insufficient	Difficult to stop bleeding immediately
Need blood	Low	High	Very high
Need operation	Low	Likely	High

regarding platelet transfusion. The threshold in the presence of bleeding warrants transfusion of 0.1-0.2 units/kg of platelet concentrates. The risks of transfusion associated acute lung injury (TRALI), which has emerged as the leading cause of transfusion associated mortality must be borne in mind. Cryoprecipitate must be transfused when the fibrinogen level is <100 mg%. Aprotinin and aminocaproic acid can decrease transfusion requirements, so also recombinant activated factor VII.

Damage control surgery (DCS)[5] aims to restore or optimize the physiology instead of definitive anatomical repair. The principles can be summarized as follows:

1. Bleeding control
2. Decontamination
3. Quick body cavity closure to rewarm patient
4. Planned re-operation for definitive repair when physiology normalized

Until the patient is taken up for surgery, external sources of hemorrhage should be compressed by direct pressure. While tourniquet techniques are not advocated, "life over limb" approach warrants it. Potential sites of concealed hemorrhage include hemithorax, retroperitoneum, pelvis and thigh compartments.

FAST (focused assessment with sonography in trauma) and E-FAST (extended FAST) must be included in the primary survey. This point of care investigation is reliable, reproducible, noninvasive and minimizes time to diagnose life threatening injuries, the only disadvantage being unable to identify hollow viscus and retroperitoneal injuries. If pelvic fracture is suspected based on bruise or hip joint line tenderness, pelvic binders must be applied to prevent dislodgement of clot, which can worsen the bleed, the other purpose is in limiting the pelvic volume to create tamponade effect to reduce bleed.

Disability: Assessment of neurological status by GCS and pupillary response will identify conditions requiring intubation and neurosurgical interventions. Minor injuries without ongoing bleed or signs of increasing cerebral edema can be managed in the PICU with raised ICP protocol. Extradural or subdural hematomas with midline shifts and increasing ICP have to be evacuated urgently, while uncontrollable intracranial hypertension may benefit from decompressive craniectomy.

Exposure: Hypothermia worsens coagulopathy and acidosis and increases oxygen consumption. Minimize its effects by warming fluids and blood products while limiting exposure.

Monitoring: The child should be frequently re-assessed and vital signs monitored for any deterioration in sensorium (drop in GCS), respiratory or circulation parameters. The heart rate is the most sensitive indicator of volume status and cardiac output. Urine output can be used as a surrogate for tissue perfusion of other vital organs. Chest tube drains must be quantified periodically, as also soaked dressings. Serial ABG, lactate, base deficit and mixed venous saturation provides information about adequacy of resuscitation.

Secondary survey: Consists of "SAMPLE" (signs and symptoms, allergies, medication history, past medical history, last meal, events leading upto present condition) history and a detailed head to toe examination to identify all the injuries sustained and manage them appropriately. Re-assessment and resuscitation must continue through the secondary survey. A systematic palpation will reveal areas of tenderness, crepitus indicating fractures; subcutaneous emphysema points to disruption of airways; an engorged jugular vein may suggest cardiac tamponade (with muffled heart sounds) or tension pneumothorax, while a flat vein suggests open sucking wound causing pneumothorax. A distended abdomen indicates intra abdominal bleed. The back is often overlooked; the patient must be log rolled to examine the back. Perineal discoloration or swelling

Table V. Acute management of life-threatening injuries and hemodynamically unstable pediatric patients.[7]

Severe traumatic brain injury	Operation, decompression
Chest trauma with hemo-/tension-pneumothorax	Thoracostomy tube, operation
Abdominal trauma with presence of free intra-abdominal fluid	Damage control laparotomy, "Packing"
Pelvic trauma	Pelvic binder, sheet wrap, external fixation Ongoing bleeding: Embolization, pelvic tamponade
Extremity trauma with active bleeding	Compression bandage, vascular clamp, operation, "life before limb"
Hemorrhagic shock	Volume substitution therapy, transfusion, coagulation factor replacement, warm blanket

Table VI. Goals in the management

- Regaining sufficient cardiovascular function
- Reversal of coagulopathy
- Normalization of body core temperature
- Early decision regarding the therapeutic approach (..treat first what kills first")
- Minimizing blood loss

can be seen with pelvic disruption. Blood at the meatus or suspected pelvic fractures are contra indications to bladder catheterisation.

Investigations should include serial hematocrit, blood type and cross match, urea, creatinine, electrolytes, amylase, lipase, liver enzymes (which will pick occult pancreatic and hepatic injuries). Coagulation profile is often abnormal after resuscitation. Urinalysis can identify hematuria seen with renal injury. Appropriate skeletal X rays and CT scan of affected areas should be obtained after stabilisation.

Definitive management

A multidisciplinary team of surgeons, pediatricians, intensivist including physiotherapist during rehab are involved in the care of the patient. Table V shows the acute management of life threatening injuries. Table VI shows the priority goals in management. The child is kept NPO till abdominal injuries are ruled out and for anticipated procedures requiring anaesthesia. Analgesia should be provided for fractures, procedures and wound dressing. Fluids are given at two-thirds maintenance rates (high incidence of SIADH), dextrose is rarely needed (stress hyperglycemia). Stress ulcer prophylaxis with PPI or H_2 blockers must be prescribed.

Penetrating wounds and open wounds are contaminated and treated as infected (only indication warranting antibiotics). Tetanus prone wounds require tetanus toxoid, with or without tetanus immune globulin. Avoiding secondary injuries like hypoxia and hypotension, treating seizures aggressively, maintaining euvolemia, normoglycemia, normocarbia and sodium in normal to high normal range improves outcome.

Indications for immediate operative intervention in pediatric trauma[8] is given in Table VII.

Most solid visceral injuries can be managed non operatively. Fractures should be fixed within 24 hours to limit SIRS and infection risk

Child abuse: When the history of injury does not correlate with the pattern and physical examination, non accidental trauma must be considered.

Table VII. Indictions for surgery

- Persisting shock due to on-going intra abdominal bleed or massive hemothorax
- Massive air leak or salivary drainage from chest tube
- Peritonitis
- Rigid silent abdomen
- Evisceration
- Ruptured diaphragm

Outcome

Despite the severity of the injuries sustained and the impact of the injuries on short-term outcome results, the long-term outcomes are very satisfactory.[9] Degree of disablement in pediatric polytrauma patients does not correlate with the quality of life. Patients are apparently able to adjust to their disabilities. Every effort must be taken with a positive approach to achieve these results.

Complications

Post traumatic stress disorder (PTSD) is diagnosed when symptoms of persistent hyperaroused state, avoidance of reminders of event, unwanted recollections persist for more than a month following traumatic event. Trauma related infections usually involve wounds, CNS and abdomen; most often they are nosocomial and related to catheters and VAP (ventilator associated pneumonia).

Thrombo embolic events are less common in children, not warranting routine prophylaxis; however deep vein thrombosis and pulmonary embolism require anticoagulation after detailed discussions.

Prevention

Discussion of trauma is incomplete without mentioning preventive aspects; use of simple yet effective gadgets like helmets, seat belts and restraints, speed guards and strict adherence to road safety rules must be emphasized at the community level at every opportunity. Balconies should have high parapet walls and children should be monitored in the playgrounds.

Future direction

While PICUs in our country are in their adolescence, pediatric emergency medicine is in its infancy. With growth of more pediatric hospitals, the dream of dedicated trauma teams who reach the patient within the platinum half hour will become a reality.

Points to Remember

- ***Secure airway early in unstable patients.***
- ***Adhere to damage control resuscitation.***
- ***Prefer E-FAST to identify thoracoabdominal pathology in unstable children.***
- ***CT scans should be performed only after stabilization.***

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CRITICAL CARE - I

PERIOPERATIVE CARE IN PICU

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Abstract: *The perioperative period is laden with rapid and dynamic changes in physiologic condition. Anticipation of hemodynamic events and good care are the key to success. Postoperative mortality continues to be high in high-risk population when they undergo surgical procedures. Additionally, patients who undergo high risk corrective procedures or complex palliative surgeries may experience considerable morbidity that further challenges the intensive care physician to improve care and outcome.*

Key words: *Perioperative care, PICU, Critical care.*

Perioperative care must be approached in an organized, timely manner, with attention to the acute nature of the patient's changing physiology. There are crucial physiologic, diagnostic, medical and surgical priorities and differences between caring for infants and children compared to adults. Although there are a number of guiding principles, the unique nature of each surgical condition mandates both specific expertise and careful titration of care at the bedside. Here, key physiologic and management issues have been discussed for children in the PICU during and after surgery.[1]

Although the incidence of serious postoperative complications in healthy children undergoing ambulatory surgery is relatively low (<1%), some minor postoperative problems occur commonly. These common anesthetic and surgical postoperative problems can be classified into early and late, depending on their time of onset. In many instances, the family will call on the primary care physician, rather than the surgeon or anesthesiologist, to diagnose and treat these problems. The primary care physician must therefore be aware of the existence of and recommended treatment for these complications.[2]

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A careful preoperative examination of the child and the child's medical record, mainly done by the anesthesiologist, enables to assess the general state of health and to identify the presence of chronic, acute and intercurrent diseases. From this knowledge, appropriate sub speciality consultation can be sought, the operative medical condition can be optimized for surgery and anesthetic plans can be made. Supplementary oxygen should be given to all children on arrival in the PICU.[3]

For preoperative fasting (NPO orders), the patient's size, age and general medical condition as well as the scheduled time of surgery must be considered.[4] The younger the child, the smaller are the glycogen stores and more likely is the occurrence of hypoglycemia with prolonged period of fasting. For this reason, the fasting time is reduced in the infant and young child. In general, solid food and milk products are 8 and 6 hours, respectively, before surgery; breast milk withheld for 4 and clear liquids for 2 hours before surgery. Liquids such as apple or grape juice may be encouraged upto 2 hours before the induction of anesthesia (Table I).

Table I. NPO Guidelines for elective surgery in infants and children

Substance	Minimum hours of fasting
Solid food	8
Commercial formula	6
Milk/milk products	6
Citrus juices	6
Breast milk	4
Clear liquids	2

Pulmonary gas exchange deteriorates during general anesthesia primarily because of reduction in the functional residual capacity and resultant airway closure and atelectasis. It is not uncommon for an infant or a child to have obstruction after extubation. Optimal patient position may be enough to correct the problem. Pneumothorax, silent aspiration and pulmonary edema can be considered if respiratory compromise persists. The incidence of post intubation croup was reported to be about 1%. This is

reported to have decreased with or without leak around the tube at or above 20 to 25cm of water positive airway pressure.[4]

Some children may be continued on mechanical ventilation post operatively in view of airway control, abnormal lung function, reduction of oxygen delivery needs or assurance of stability during immediate post-operative period. Monitoring of ventilation and pulmonary adequacy is accomplished by physical examination, non-invasive monitoring of oxygen saturation and end tidal carbon dioxide. Volume ventilation with effective tidal volume of 8 to 10ml per kilogram measured at the endotracheal tube, a respiratory rate of 15 to 30 breaths per minute and positive end expiratory pressure (PEEP) of 3 to 5 cm of water is appropriate for most children with normal lung compliance.[4]

The most frequent complications of general anesthesia are postoperative nausea and vomiting, which is the most common cause of delayed discharge from the PICU and unanticipated hospitalization after outpatient surgery. The cause of these adverse effects is multifactorial, with factors such as predisposition (previous history of postoperative vomiting, susceptibility to motion sickness), the anesthetic drugs or techniques used, the procedure being performed, the skill of the anesthesiologist providing the anesthetic and motion playing an important role. Certain surgical procedures, such as strabismus surgery, middle ear surgery, orchidopexy, and umbilical hernia repair, are associated with a greater than 50% incidence of postoperative vomiting. Similarly, the perioperative use of any opioid is associated with a high incidence of postoperative nausea and vomiting even when general anesthetic drugs associated with a lower incidence of nausea, such as propofol are used. The treatment of post-operative nausea and vomiting is the same as that used for viral gastroenteritis. A cooling-off period of 2 to 4 hours is followed by sips of clear fluids that contain sugar and salt (oral rehydration solution). Each sip is separated by several minutes. Giving fluids or solids prematurely only aggravates the problem. Finally, an antiemetic can be used either prophylactically or to treat the problem once it develops. The most commonly used antiemetic, includes benzamides (metoclopramide), serotonin antagonists (ondansetron), phenothiazines (prochlorperazine, promethazine) and antihistamines (hydroxyzine, diphenhydramine). Nausea and vomiting that persists beyond 12 to 24 hours is unusual and requires evaluation to determine the state of hydration and possible necessity of intravenous rehydration and to rule out alternative conditions. In rare instances, excessive air swallowing in the postoperative period may lead to acute gastric dilation in young children. Recognition of the characteristic distended abdomen and gastric splash, if present, should be followed by nasogastric decompression.[2]

Children are prone to disorientation, hallucinations and at times, uncontrollable physical activity during emergence from general anesthesia. This hyper excitable, hyperactive state is sometimes referred to as emergence delirium and occurs most commonly if a patient awakens in pain after receiving a potent vapor anesthetic (eg, halothane, sevoflurane, isoflurane, desflurane). Other causes include sensory deprivation (eye bandages, eye lubricant); residual anesthetic; awakening in a strange environment (the PICU) and the perioperative use of ketamine. Regardless of cause, before discharge from the PICU, most of the disorientation, hyperactivity, excitability and hallucinatory visual disturbances should be completely resolved. PICU treatment for these phenomena may include small doses of analgesics (eg, fentanyl) or flumazenil, if midazolam was administered. In some instances, atropine may be responsible for this reaction, in which case it will be accompanied by other features of anticholinergic syndrome (flushed cheeks, mydriasis, and low-grade fever). This reaction may be treated by administration of physostigmine, an anticholinesterase that crosses the blood-brain barrier and reverses the central nervous system effects of atropine by potentiating the action of acetylcholine at nerve terminals. The prevalence of such anticholinergic reactions has been reduced since the replacement of halothane with sevoflurane as the primary gas for mask anesthetic induction in children. Sevoflurane does not cause the bradycardia seen with halothane, making routine use of atropine unnecessary in pediatric anesthetic practice, except that used to counteract the muscarinic effects of anticholinesterase administration for reversal of non-depolarizing muscle relaxant.[2]

Even with the most careful attention to maintaining normothermia, patients frequently arrive in the PICU with lowered body temperature. Usually covering the patient with warm blankets is sufficient, but radiant warming lamps and conductive warming blankets should be used in extreme cases.[4] Postoperative fever has several possible causes, which can be remembered as the 4 Ws: wind, wound, water and walker (Table II). Pyrexia (rectal temperature greater than 101.2°F [38.5°C]) within 24 hours of surgery and general anesthesia is common and usually caused by atelectasis. Postoperative atelectasis has many causes. Endotracheal intubation, inhalational general anesthetics and the use of non-humidified gases all depress ciliary motion within the tracheal-bronchial tree and

Table II. Common causes of postoperative fever

Site	Etiology	Time	Incidence	Sign Symptoms	Diagnosis	Therapy
Wind (lungs)	Atelectasis	24-48 hr	Very common	Cough, shortness of breath, retractions	Examination, chest x-ray	Cough,deep breathing, incentive spirometer
Wound (operative site)	Infection	<24 hr-7 days	Rare	Pain, erythema, induration	Examination, wound cultures	Antibiotics, open wound
Water (urinary tract)	Urinary tract infection	3-5 days	Very rare	Dysuria, hematuria	Examination urinalysis, culture	Remove indwelling catheter, antibiotics
Walker (legs)	Deep-vein thrombosis	>3 days	Extremely rare	Swelling, heaviness of lower extremities, superficial venous congestion, palpable cord	Examination, duplex Doppler, venogram	Bed rest, elevation, heparin (Coumadin), thrombolytics

thereby interfere with normal pulmonary clearance mechanisms. Atelectasis occurs when these factors are combined with small tidal volume breathing, somnolence, splinting caused by pain and cough suppression caused by pain or opioid analgesics. Early ambulation, deep breathing and coughing can be extremely helpful in alleviating or preventing atelectasis and postoperative fever. Indeed, this feature may be one of the important medical advantages of ambulatory surgery because patients are more likely to be up and about when they are at home rather than in the hospital.[2]

Other causes of postoperative pyrexia are rare. Most patients with low-grade postoperative fevers require only a physical examination to differentiate between a septic and non-septic process. Extensive (and expensive) diagnostic workups are rarely indicated. Indeed, in most patients, fever in the early postoperative period is so common that it can be regarded as a normal response to operative trauma and general anesthesia. Other unusual causes of postoperative fever include urinary tract infections, dehydration, infected intravenous access sites, thyroid storm, pheochromocytoma and malignant hyperthermia. Urinary tract infections do not usually produce symptoms in the immediate postoperative period. Rather, they are a cause of late postoperative fever, usually occurring 3 to 5 days after operation. These children generally are symptomatic and complain of dysuria. Infants may have hematuria. The fever associated with malignant hyperthermia usually starts intraoperatively. Wound infection as a cause of fever is rare. The post-operative day on which a given wound infection becomes apparent and the local signs of sepsis produced by the infection vary according to the organism and the concomitant use of antibiotics (Table III). As a general rule, the earlier the onset of wound sepsis the more destructive and life-threatening the infection will be. Most wound infections do not usually become apparent until the 5th to 10th postoperative day. The rare exceptions are beta-streptococcus, Clostridium difficile and Clostridium perfringens (welchii) infections. These organisms produce wound infections that can become apparent within 24 to 48 hours of surgery. Clostridium and streptococcal wound infections are life threatening. In most instances, children with these infections develop high, spiking fevers (temperatures of 102.2° to 105.8°F [39°C to 41°C]), become irrational and may even develop jaundice. The surgical incision site is red, warm, and intensely painful on palpation. Additionally, vesicle formation, wound crepitance, and an exudate may be present. Obviously, patients who develop this type of wound infection require immediate hospitalization and treatment.Malignant hyperthermia may be seen initially during the post-anesthetic period.[2]

There is a higher incidence of anesthesia associated risk in infants and young children as compared to adults. As much as 4.7/1000 pediatric patients end up in a cardiac

Table III. Postoperative wound infections

Onset (Postoperative Day)	Usual Pathogens	Wound Appearance	Other Signs
1-3	Clostridium welchii	Brawny, hemorrhagic, cool, Occasional gaseous crepitance, Putrid dishwasherexudate, Intense local pain	High standard fever (temperatures of 39°C-40°C), Irrational behavior, Leukocytosis (white blood cell count >15,000/mL), Occasional jaundice
2-3	Streptococcus	Erythematous, warm, tender, Occasionally, hemorrhagic with blebs, Serous exudate	High, spiking fever (temperatures of 39°C-40°C), Irrational at times, Leukocytosis (white blood cell count >15,000 mL), Rare jaundice
3-5	Staphylococcus	Erythematous, warm, tender, Purulent exudates	High, spiking fever (temperatures of 38°C-40°C), Irrational behavior at times, Leukocytosis (white blood cell count 12,000-20,000/mL)
>5	Gram-negative rods	Erythematous, warm, tender, Purulent exudates	Sustained low-grade to moderate fever (temperatures of 38°C-40°C), Rational behavior, Leukocytosis (white blood cell count 10,000-16,000/mL)
>5	Symbiotic (usually anaerobes plus gram-negative rods)	Erythematous, warm, tender, Focal necrosis, Purulent, putrid exudates	Moderate to high fever (temperatures of 38°C-40°C), Leukocytosis (white blood cell count >15,000/mL), Occasional jaundice Mentation variable

arrest post anesthesia as compared to 1.4/1000 adult patients.[4]

All pediatric patients experience pain if untreated. Treatment of pain in the PICU depends on the patient's medical condition and surgical procedure. Morphine (0.025 - 0.05 mg/kg) or fentanyl (0.5 - 1 mg/kg), given in incremental doses can be used to achieve an analgesic state in patients recovering from general anesthesia.[4]

Perioperative fluid losses consist of hypotonic and isotonic components. Fluid requirements are higher in fever. For every 1 degree rise in temperature, about 10% more fluid is necessary. Intraoperative fluid deficits may result from exposure of large areas of tissue, as in abdominal and thoracic surgery, as well as from blood loss. In young infants the fontanelles, the eyes and the tongue are good indicators of volume deficit. Blood pressure and heart rate may remain normal even when the fluid deficit is as high as 10% of body weight. Intraoperative fluids must be replaced, both preoperative deficit and intraoperative hypotonic and isotonic deficits. When hypotonic solutions are administered, there is concurrent loss of sodium and therefore, administering of balanced salt solutions is the better choice. Similarly, acute dilution hyponatremia may occur when the postoperative infusion is immediately changed to hypotonic saline or glucose solutions.[5]

Persistent bleeding is defined as bleeding and bloody ooze that continues for more than 6 to 8 hours after the surgery or a need to change a blood-soaked wound dressing more than twice in the first 6 to 8 hours after surgery. It almost always indicates inadequate hemostasis and is usually due to a superficial skin arterial bleeding site, although coagulopathy might also be responsible. Until the bleeding site is investigated and controlled by the operating surgeon or the surgeon's designee, direct digital pressure applied to the wound will slow or stop the flow of blood.[2] Hemoglobin concentration may not accurately reflect blood loss in the perioperative period. Children have a robust neuro-hormonal response that maintains cardiac output and blood pressure. Unfortunately, tachycardia can be a misleading sign because it is non-specific response. Children at this stage will respond to prompt treatment with fluid boluses. If the early physiological signs of compensation are unrecognized, shock will progress. Therapy during late stages of compensated and uncompensated shock frequently requires airway and breathing management as well as resuscitation with both volume and blood. After 40ml/kg of lactated Ringer, whole blood or packed red blood cells should be administered.[1]

Risk factors for post-operative renal failure include preoperative renal dysfunction, prolonged surgery time, low cardiac output and cardiac arrest. Post-operative sepsis and nephrotoxic drugs can cause further damage to the kidneys. The indications for peritoneal catheter placement in the ICU include the need for renal support and the need to reduce intra-abdominal pressure from ascites that may be compromising mechanical ventilation.[6]

Critically ill children have decreased caloric intake and increased energy demand after surgery. Total parenteral nutrition can provide adequate nutrition in the early hyper catabolic phases of the early post-operative period. Upper gastrointestinal bleeding and ulcer formation may occur following the stress of surgery.[1]

Cardiac rhythm disturbances and blood pressure fluctuations tend to be less problematic in infants and children recovering from anesthesia post-surgery, than in adults. Bradycardia is typically a response to medications. Assessment of a child following cardiac surgery begins with review of preoperative and operative findings. All patients should have continuous monitoring by ECG, systemic arterial blood pressure (invasive or noninvasive), oxygen saturation by pulse oximetry and respiratory rate. Intra cardiac or transthoracic left atrial catheters are essentially helpful in the management of patients with ventricular dysfunction or coronary artery perfusion abnormalities. Low cardiac output syndrome can be treated with newer strategies such as atrio-biventricular pacing for patients with complete heart block or prolonged intra-ventricular conduction delays and asynchronous contraction.[6]

In pediatric neurosurgery, the assessment of adverse events and risk factors of morbidity and mortality is rare and little is known about the complications of surgical events. Children undergoing neurosurgical procedures may presumably have more complications when compared to adults. Hyponatremia may occur in up to 20% of cases and reach up to 50% of neurosurgical patients making it the most common electrolyte disturbance in patients undergoing neurosurgery. Severe hyponatremia may result in cerebral edema. Hyponatremia is attributed to either SIADH or salt-losing brain syndrome. In SIADH, due to an excess ADH secretion, the patient should be kept in fluid restriction (including volumes administered in medications) of approximately 70 mL/100 kcal and, depending on volume status; loop diuretics (furosemide) and/or increased sodium supply may be prescribed. In the salt-losing syndrome, volume replacement with an isotonic solution and increased sodium supply are mandatory, given the severe dehydration risk.[7]

The resection of suprasellar tumors extending to the pituitary stalk can cause loss of pituitary function and consequent impairment in antidiuretic hormone secretion resulting in diabetes insipidus. Intranasal desmopressin, an ADH synthetic analogue, should be replaced within the first postoperative hours to avoid the described metabolic complications. Postoperative hyperglycemia is common due to surgical stress and release of insulin counter-regulatory hormones. Postoperative meningitis is an important cause for morbidity and mortality after craniotomies. One of the seminal studies on local and systemic antibiotics in preventing infections used an intraoperative regimen of antibiotic prophylaxis consisting of intramuscular gentamicin or tobramycin, intravenous vancomycin and streptomycin irrigation solution, with no postoperative antibiotics.[7] Though the incidence of seizures in the ICU has dramatically declined in recent years, we treat seizures aggressively when they do occur, using benzodiazapines, phenobarbital or phenytoin.[1]

Multiple organ failure (MOF) occurs most frequently in the perioperative setting secondary to prolonged shock or ongoing ischemia, DIC, primary organ failure, a persistent nidus of inflammation/infection, trauma, toxin or drug toxicity. Prevention and supportive care remains the key to limiting the development of MOF.[1]

Critical care expertise is essential to optimize the outcome of our most seriously ill infants and children with surgical conditions. In general, pediatricians know about infants and children, and "medical" issues, and surgeons know about "surgical/technical" issues. If a collaborative relationship is formed, the patients will receive the best of both sets of knowledge.

Points to Remember

- ***There are crucial physiologic, diagnostic, medical and surgical priorities and differences between caring for infants and children compared to adults. Unique nature of each surgical condition mandates both specific expertise and careful titration of care at the bedside.***
- ***Post-surgery airway maintenance and ventilation must be monitored continuously as pulmonary gas exchange deteriorates during general anesthesia resulting in airway closure.***
- ***Post anesthesia complications like disorientation, hyperactivity, excitability, and hallucinatory visual disturbances should be completely resolved before discharge from the PICU.***
- ***Postoperative fever has several possible causes can be remembered as the 4 Ws: wind (atelectasis), wound (infection), water (urinary tract infection), and walker (deep vein thrombosis).***
- ***All pediatric patients experience pain if untreated.***
- ***Total parenteral nutrition can provide adequate nutrition in the early hyper catabolic phases of the early post-operative period.***
- ***Cardiac rhythm disturbances and blood pressure fluctuations tend to be less problematic in infants and children recovering from anesthesia post-surgery, than in adults.***
- ***Multiple organ failure (MOF) occurs most frequently in the perioperative setting secondary to prolonged shock or ongoing ischemia, DIC, primary organ failure, a persistent nidus of inflammation/ infection, trauma, toxin or drug toxicity.***

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GENERAL ARTICLES

ANTIBIOTIC THERAPY: RIGHT CHOICE RIGHT RESULT

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Abstract: *Though awareness of bacterial infections is increasing and better diagnostic techniques such as culture, rapid diagnostic tests (RDTs) and molecular tests help to make a correct diagnosis, rampant antibiotic use to treat any fever and even cough, cold and diarrhea has not reduced. Today, we are facing a dual problem of limited antibiotics in our armamentarium and increasing antibiotic resistance which is affecting the entire globe. A scientific knowledge of antibiotics like when ,why, which to use and even knowing their pharmacodynamics is of prime importance for successful therapy of bacterial infections.*

Keywords: *Bacterial infections, Antibiotics use, Pharmacodynamics.*

Antibiotics have radically improved the prognosis of infectious diseases. Infections that were almost invariably fatal are almost always curable if treatment is started early. Antibiotics are amongst our most valuable resources, but their indiscriminate use is threatened by the emergence of resistant strains of bacteria. Rational antibiotic use not only requires accurate diagnosis and appropriate antibiotic choice but also correct dose and duration of therapy.

When a child develops signs and symptoms consistent with a bacterial infection, the clinician must first decide if the child's illness is caused by an infection or other inflammatory process and subsequently whether an infection is likely to be caused by a microorganism that is susceptible to antibiotic therapy. The choice of antibiotic also requires consideration of safety profile of the drug. Inappropriate antibiotic therapy given to a child with a viral infection exposes the child needlessly to the toxicities inherent to the antibiotic, adds to the selective pressure driving antibiotic resistance in bacteria and also increases cost of the therapy.

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The selection of optimal antibiotic therapy for presumed bacterial infection is based on deduction of balance, benefits, and risks of specific therapy for the child.

A number of questions are to be asked and answered before commencing antibiotic therapy as only a right choice in right circumstances will give a right result. They revolve around identifying potential or presumed pathogens and considering the relative merits of antimicrobial agents for specific pathogens and circumstances.

1. Is an antibiotic necessary?

Neither all fevers are due to infection and nor all infections are due to bacteria.[1] There is no evidence that antibiotics will prevent secondary bacterial infection in patients with viral infection. The treatment of certain infections might be better achieved with other means, such as surgery:eg debridement of local cellulitis in CA-MRSA infections of the skin.

2. Predict the organism

At the outset one has to define the site of infection. Bacteria are tropic for tissues locally following invasion; certain species have a proclivity for causing certain infections. Examples are S aureus and S pyogenes for cellulitis, osteomyelitis, septic arthritis. H influenzae, M catarrhalis, S pneumonia for AOM and Group A Streptococci for acute tonsillitis. On the other hand, certain pathogens can almost be dismissed in some circumstances when the site of infection is identified. Examples are S aureus / S pneumoniae for UTI.[2]

3. Consider the host

Whether the host is healthy with intact immunity or does the host have defect in granulocyte number or function or a (B/T) B or T cell defect is important. Even for an immunocompetent child, a recent surgical procedure, or an indwelling catheter or prolonged ICU stay can have variety of relatively non pathogenic commensals be causative pathogens, mandating therapy with an antibiotic that provide activity against a much broader range of organisms. A child with G6PD deficiency cannot be given sulphonamides. One has to be careful while selecting the antibiotic and frequent adjustments in doses of the drug needs to be done in a child with hepatic or renal failure.[3]

4. Age of the child

Certain infections are common in certain age groups which helps in predicting the etiologic agent. The perfect example is in cases of pneumonia where Gram neg organisms are at the top of the list in newborns whereas S pneumoniae and H influenzae become common organisms in young infants and toddlers. and atypical organisms responsible for causing walking pneumonia are almost ruled out in first 3 years of life.[4] This knowledge is of great help in selecting the right antibiotic so as to get the right result. Even though viral pneumonias are very common causes in all the age groups the distinction cannot be made confidently of the viral/bacterial etiology and hence all children with pneumonia are to be treated with antibiotics.[8]

5. Perform diagnostic tests and interpret them with clinical picture

Every effort should be made to prove the etiology of the infection and obtain an isolate for susceptibility testing. The Gram stain is perhaps the simplest, least expensive and most useful of the rapid tests because it provides clues to the pathogen (eg. swab in neonatal conjunctivitis), pathogenesis (eg. aspirate in polymicrobial lung abscess), or interpretation of culture results (eg.tracheal secretions in pneumonia). An error in processing or interpreting the Gram stain must not lead to ineffective therapy. Obtaining blood culture for bacteremia and to diagnose enteric fever and a urine culture for the diagnosis of UTI should be a part of standard of care everywhere. However certain care needs to be taken while interpreting the results of these culture results. Infection should be diagnosed clinically based on multiple data points and infections are not diagnosed by culture alone.[5]

Mistakes commonly made by clinicians in diagnosing infection are:

- Base their diagnosis on a single positive data point when other data points are negative.
- React to a positive culture when there is no clinical evidence of infection.
- Use serial cultures to determine when infection has resolved.
- Obtain cultures randomly when clinical suspicion of infection is low.

The following steps are useful to avoid this:

First step:Determine whether culture represents real pathogen or colonizer. Colonizer is any organism actually present in or on patient, but does not invade tissue or cause clinical disease. Contaminant is any organism growing in culture that is not actually present in or on the patient, but came from the environment directly to the culture medium.

Second Step: Every positive culture needs to be interpreted with respect to other data points. Example: A wound culture taken from a clean appearing, granulating wound that is not painful, has no purulence in a patient with no fever and a normal WBC is a colonizer and should not be treated.

6. Importance of local antibiotic resistance data

Resistance patterns vary from country to country, from hospital to hospital in the same country and even from unit to unit in the same hospital with time! Regional/ country data are useful only for following trends, NOT guide empirical therapy. eg.Though multidrug resistant enteric fever was very rampant all over the country, recent data shows the re-emergence of sensitivity even to first line drugs like cotrimoxazole, amoxicillin and chloramphenicol in many parts of the country. These factors help the clinician in deciding the antibiotic therapy.

Regardless of which population is under study, however,a range of susceptibilities is always present;some organism are relatively more susceptible and others more resistant to specific agents.The hospital antibiogram is widely available tool that allows the clinician to asses the current local resistance pattern for each pathogen and each antibiotic.

The probability that the antibiotic selected for empiric therapy will be effective against the presumed pathogen is directly related to the proportion of susceptible pathogen infecting the patient in that location.

7. Pharmacodynamics and pharmacokinetics of the drug

In the treatment of meningitis, adequate antibiotic concentration in the CSF are critical for cure. The concentration of aminoglycosides in CSF following intravenous infusion is likely inadequate as single antibiotic therapy to treat meningitis caused by Gram-negative pathogens, despite the fact that CSF concentrations are roughly 20% of those available in serum. In contrast, although CSF concentration of penicillin is only 5% of that achievable in serum ,the high serum concentration leads to adequate CSF concentration if the pathogen has exquisite susceptibility to penicillin. Within the predictable tissue penetration of antimicrobial

agents there is considerable variability among children receiving the same dose of drug. For example, antibiotic concentration in the middle ear space can be in adequate in a low but predictable percentage of children given the same mg/kg oral dosage. However, unlike acute otitis media, the clinician cannot risk inadequate dosing for even one child with meningitis.[6]

The pharmacodynamic properties of an antibiotic describe how exposure of the antibiotic to the pathogen leads to a bacteriostatic or bactericidal effect and are important in designing an antibiotic dosing regimen. Aminoglycosides kill bacteria in a concentration dependent fashion. Therefore, it is desirable to achieve the highest concentrations possible at the site of infection. Unfortunately, the maximum safe serum concentration is limited by risk of toxicity. For other antibiotic classes, such as penicillins, achieving tissue concentration above the minimum inhibitory concentration for that pathogen for 30-40% of the dosing interval is associated with microbiological and clinical cure. For this class of antibiotic, a higher concentration of penicillin at the infected tissue site is not associated with more rapid sterilization of tissues or better clinical outcome, although higher serum concentrations would likely be safe.[7]

In treating any child, the practitioner must assess the seriousness of the infection and the risk of injury or death if the antibiotic is not effective. For the infections that are bothersome like impetigo but not life threatening, achieving the cure rate of 70-80% with a safe and inexpensive antibiotic is often acceptable, especially if use of an alternative agent to achieve a 98% success rate has excessive risk of toxicity or high cost. For other infections that cause a degree of suffering or risk of organ damage eg. pyelonephritis or acute otitis media, the cure rate of 80-90% is often desirable. For serious life threatening infections eg. bacterial meningitis or septicemia in a neutropenic child, a cure of 100% must be achieved.[8]

Empiric therapy is selected based on presumed pathogens at site of infection, the local resistance patterns of presumed pathogens as outlined above and the desired cure rates selected by the clinician. In general the sicker child demands treatment dosages and antimicrobial activities associated with a higher rate of cure. Therefore, antibiotics with appropriately broad antibacterial activities at the highest tolerated dosage are selected for empiric therapy. Less critically ill children may not require broad spectrum agents as empiric therapy, particularly if culture results can provide information within 48-72 hrs on most appropriate narrow spectrum antimicrobial therapy the risks of delayed appropriate therapy are acceptable to the clinician and the family.[9]

Empiric therapy for meningitis in first two months of life consist of ampicillin plus an aminoglycoside or third generation cephalosporin because the possible causative agent includes Listeria monocytogenes, group B streptococci and Escherichia coli.

Once the pathogen is identified, a narrow spectrum agent can frequently provide the same degree of bacterial eradication and clinical efficacy with decreased toxicity and decreased selective pressure and decreased cost. For example, initial therapy with carbapenem agent for ventilator associated pneumonia can be narrowed to the cefotaxim if the pathogen isolated is susceptible Klebsiella spacies rather than Pseudomonas aeuruginosa. For an outpatient with a cutaneous abscess presumed to be caused by S aureus, empiric clindamycin can be replaced by oral first generation cephalosporin or a β lactamase stable penicillin if the organism is not MRSA.

Definitive, convalescent outpatient therapy of serious infections initially treated in the hospitals can be acceptable if the risks of complications the infection are negligible, parents and child can adhere to well defined management plans and can return to hospital quickly for any infection or therapy related problems. High dose β lactam therapy for bone and joint infections is one of the best evaluated step-down therapies of invasive infection.

As a rule only free, nonprotein bound drug is active in eradicating pathogens. In general, the plasma protein binding of aminoglycosides and quinolones is low whereas binding is low to very high for beta lactam agents. A high degree of protein binding precludes the use of sulfa drugs, ceftriaxone, nafcillin in jaundiced neonates because the potential competitive displacement of bilirubin from albumin facilitates the diffusion of bilirubin into the brain.

Most bacterial infections occur in the interstitial tissue fluid. For such infections, serum concentration of antibiotics generally predicts response adequately.

The unique properties of antimicrobial agents must be considered when the site of infection is intracellular because many antibiotics do not penetrate eukaryotic cells. β lactam antibiotics, for example, are almost exclusively confined to plasma water and the interstitial fluid space. Such localization explains some discrepancies between apparent in vitro activity and therapeutic ineffectiveness;

Intracellular pathogens include Listeria monocytogenes, Salmonella, Brucella, Legionella,

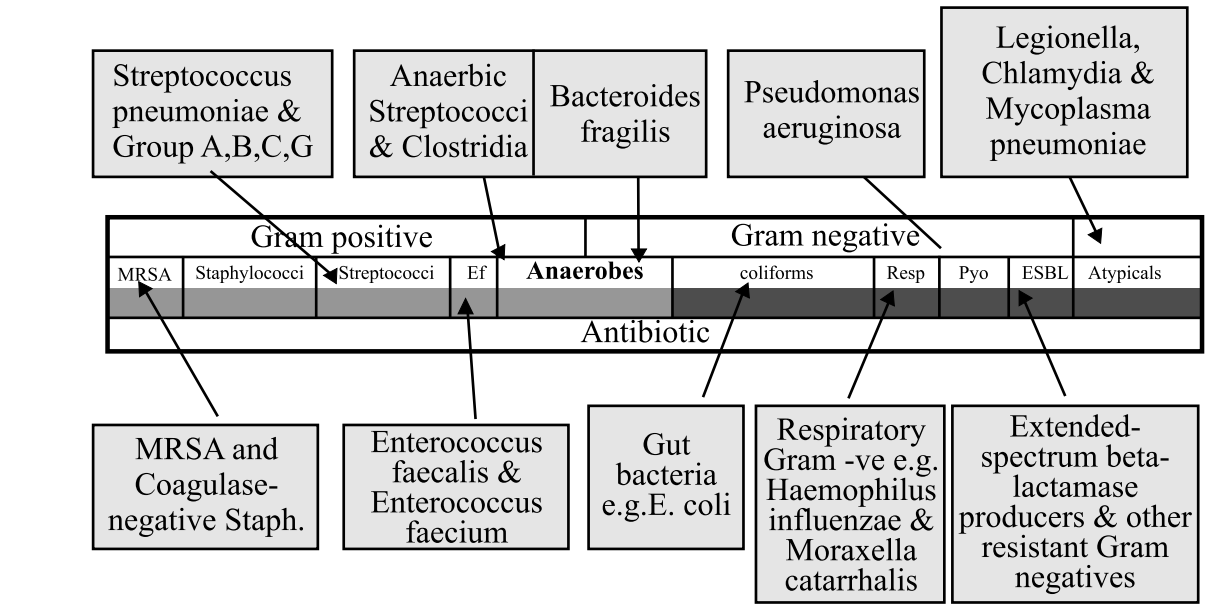

Fig.1. Antibiotic spectrum[11]

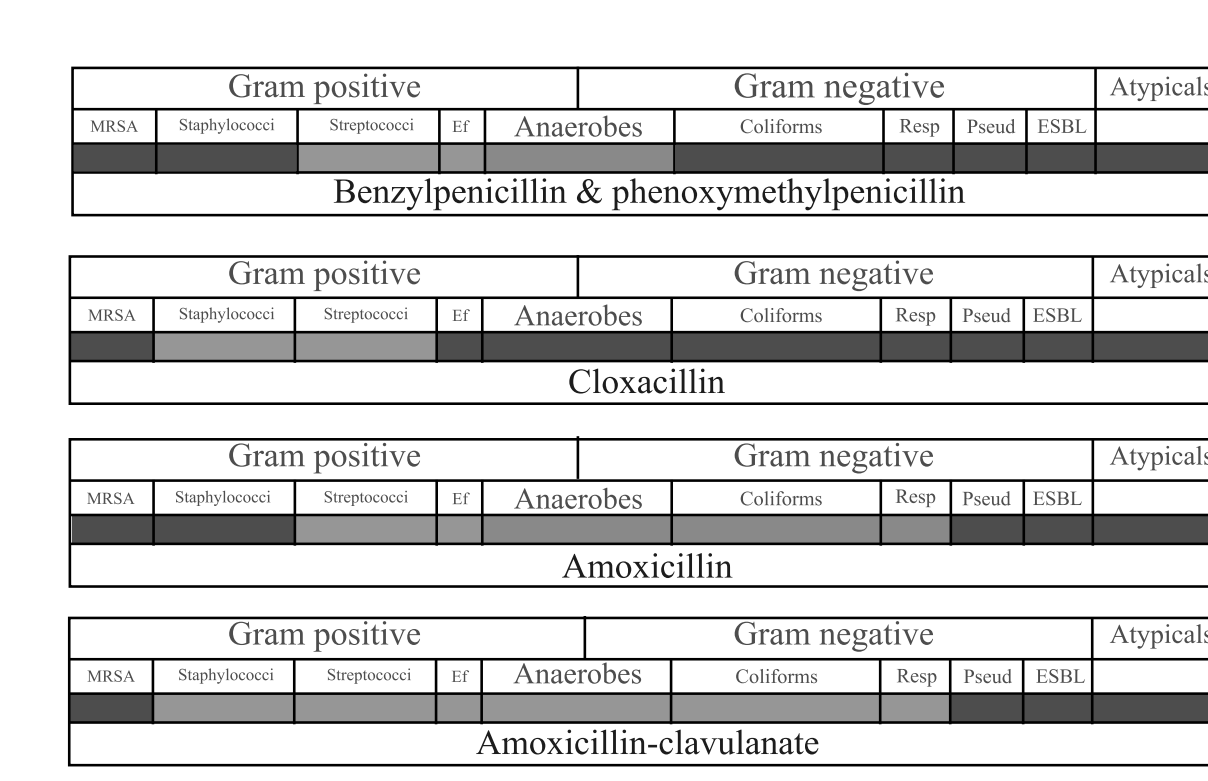

Fig.2. Penicillins[11]

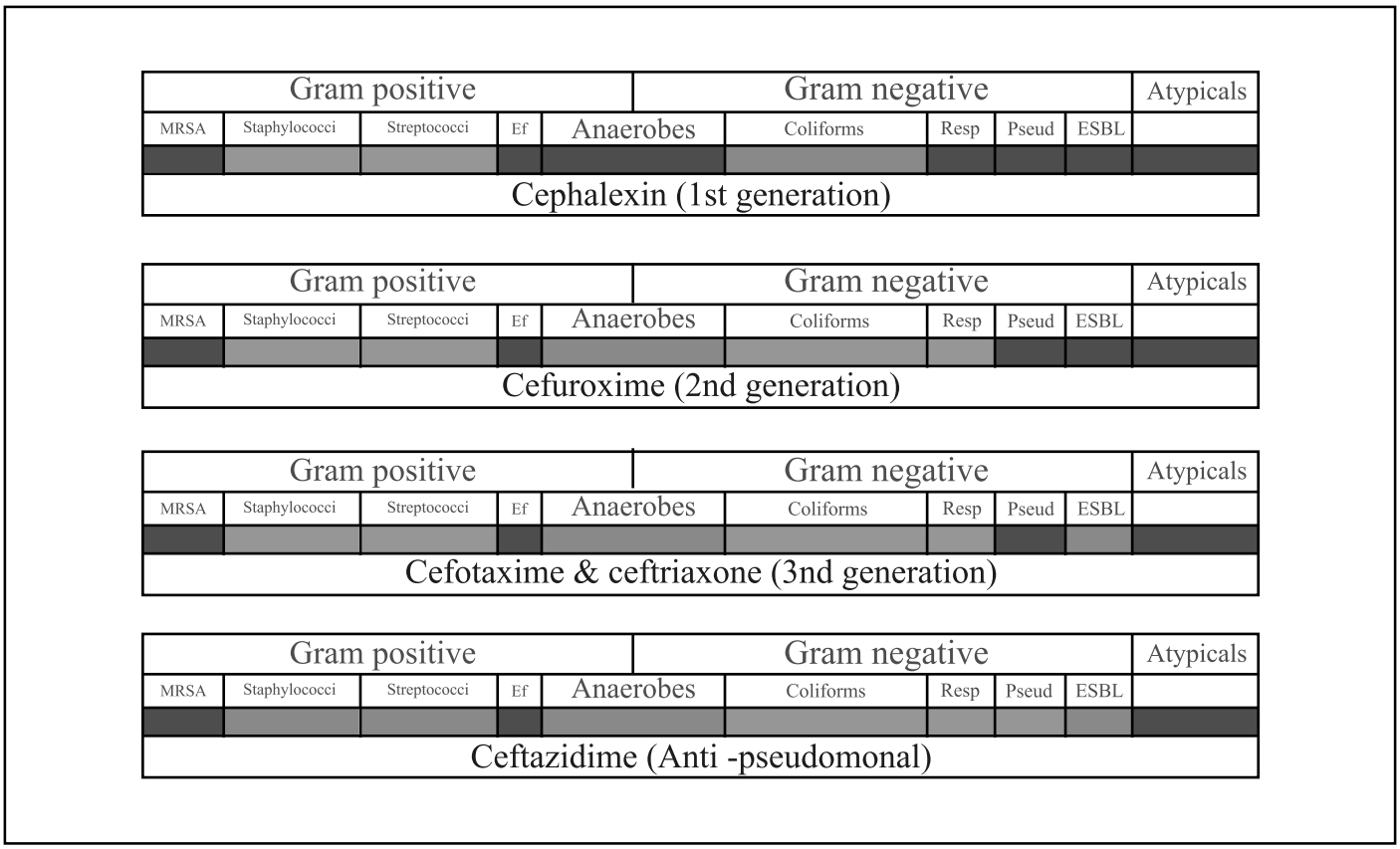

Fig.3. Cephalosporins[11]

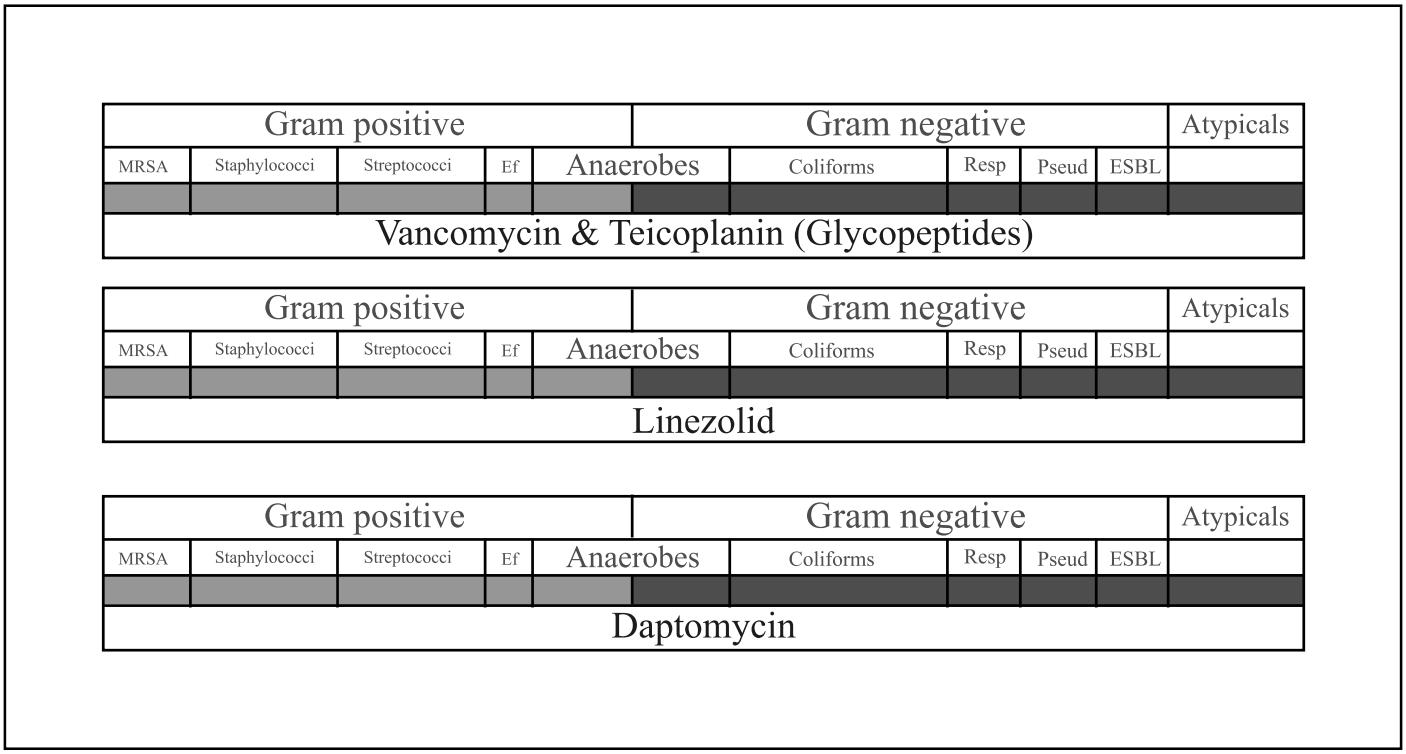

Fig.4. MRSA cover

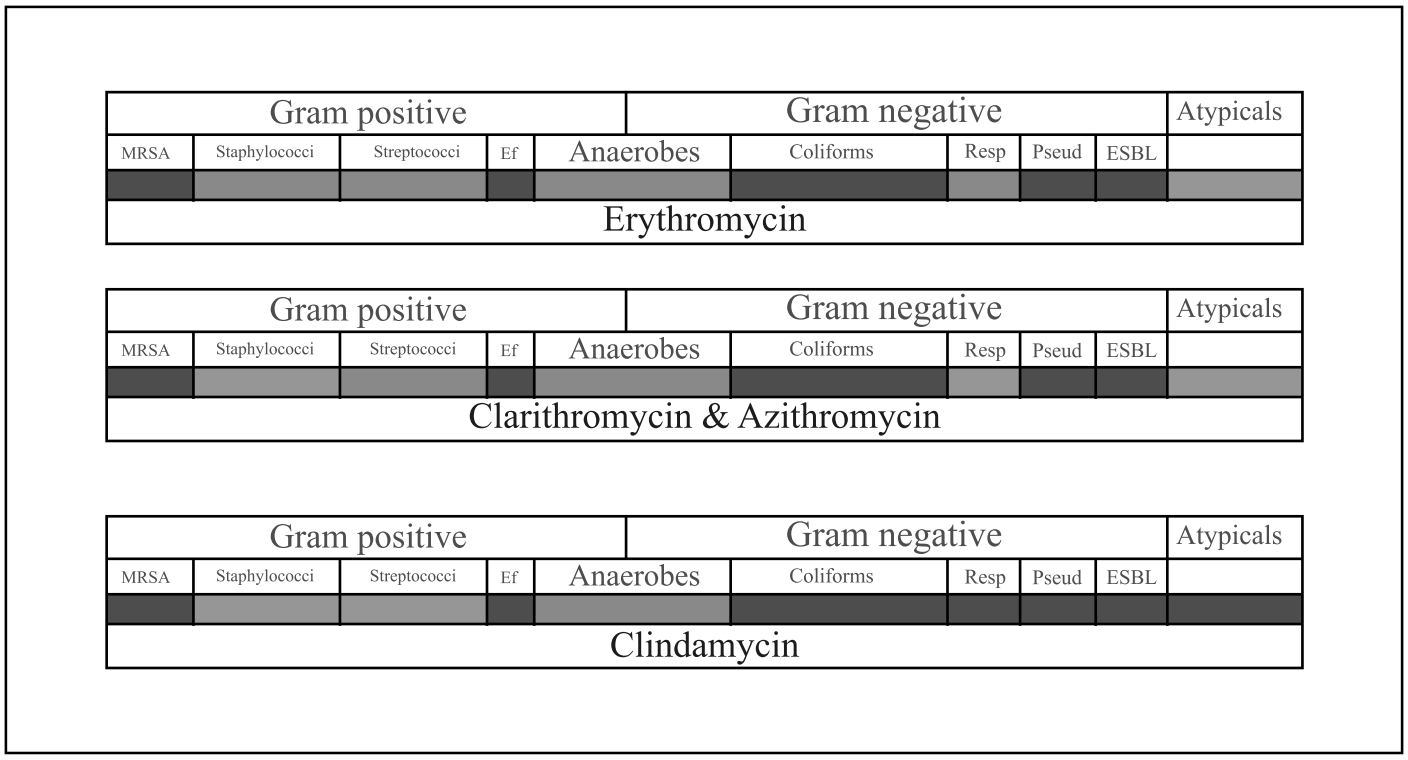

Fig.5. Macrolides and Clindamycin[11]

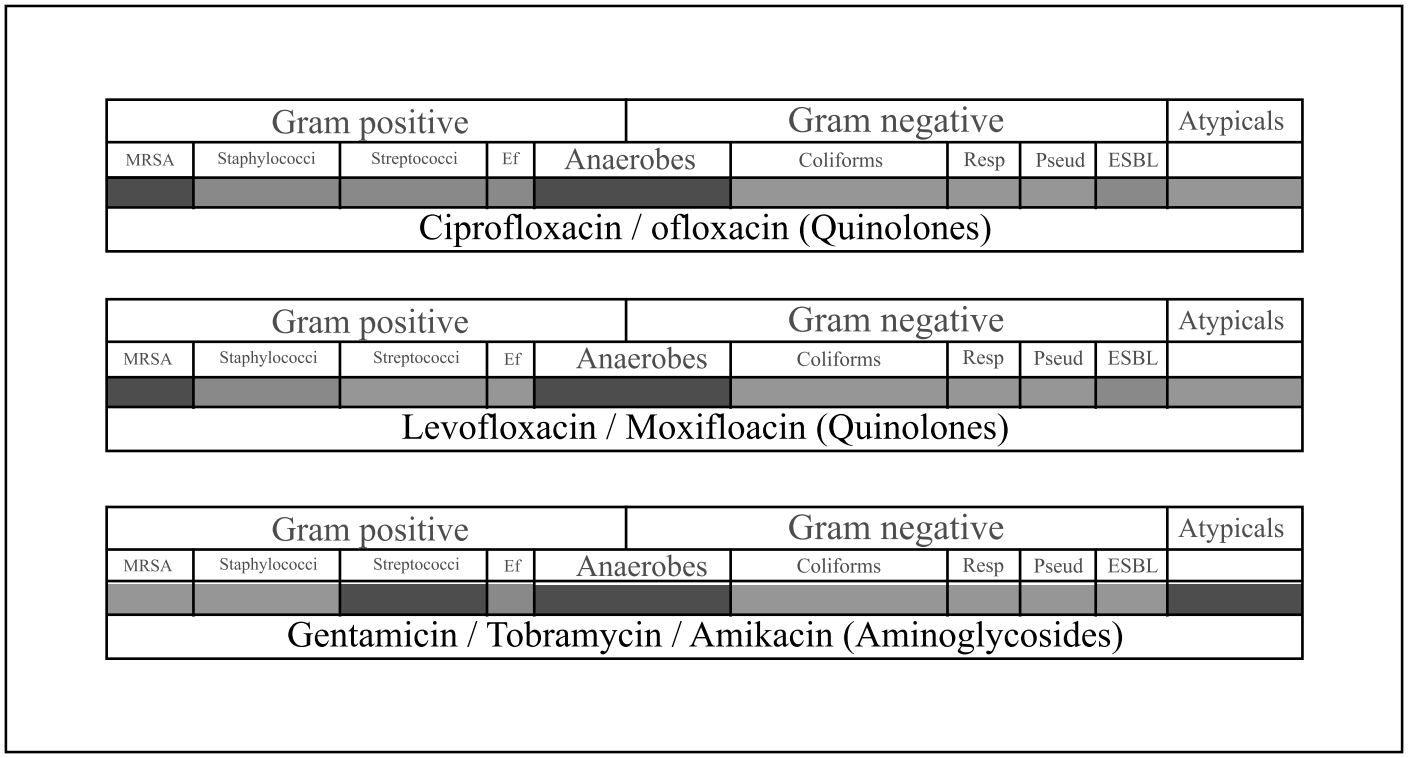

Fig.6. Quinolones and Aminoglycosides[11]

Mycobacterium, Rickettsia and Toxoplasma, as well as persisting infections with S aureus and E.coli.

Cellular accumulation of drug dose not necessarily translate into efficacy against intracellular organisms; efficacy depends on whether the microbe and the drug are at the same intracellular site, how avidly the drug is bound and the molecular charge of the intracellular antibiotic.

Aminoglycosides accumulate slowly in intracellular lysosomes and mitochondrial organelles, where they bind irreversibly and thus have no antibacterial effect. Quinolones have a large volume of distribution and a high tissue to serum ratio and low affinity intracellular binding; much of the quinolone body load is thus present intracellularly. For azithromycin, an even more dramatic intracellular location of antibiotic has been documented, particularly within phagocytic cells. The pharmacokinetic properties and intracellular accrual of azithromycin are responsible for unique applications and short courses of therapy; at the same time, it is noteworthy that drug concentration in serum, CSF and the aqueous humour of the eye are almost negligible.

The synergy is present when at least a fourfold reduction in the MIC of each antibiotic occurs when the agents are combined as compared with the MIC of each antibiotic tested separately.[10]

A classic example of synergy of targeted activity at consecutive metabolic steps is represented by the combination of a sulphonamide with a dihydrofolate reductase inhibitor such as trimethoprim. The resulting inhibition of consecutive steps in the folic acid pathway result in a significantly reduced MIC and can also enhance the drug's bactericidal capacity.

Some instances of antibiotic resistance eg. to aminoglycosides, can be due to a permeability barrier that precludes the drug reaching the intracellular target site. Agents that act on the cell wall eg. β lactam agents and vancomycin, could enhance the entry of an aminoglycoside; unless the drug is rendered ineffective by aminoglycoside modifying enzymes or the resistance occurs at the ribosomal level, a combination would be expected to be synergistic.

The superior clinical efficacy of combination over single-drug therapy has been documented in only limited clinical settings. For the treatment of enterococcal endocarditis, penicillin alone, which provides only bacteriostatic activity against enterococci, results in an unacceptable relapse rate. The addition of an aminoglycoside such as streptomycin or gentamicin results in clinical cure rates comparable with the rates attained in the treatment of endocarditis caused by penicillin susceptible streptococci.

Rifampin has synergistic bactericidal activity with teicoplanin against methicillin sensitive and methicillin resistant S aureus, with vancomycin against coagulase negative staphylococci and with ampicillin against Listeria.

Conclusion

A prerequisite of knowledge of type of bacterial infection, indications of antibiotic use and its pharmacodynamics is a must for the desired result. To combat the menace of rising antibiotic resistance, it is a primary responsibility of the clinician to stop antibiotic abuse and use right antibiotic, in right dose for right duration to get the right result.

Antibiotic spectrum of some commonly used antibiotics in pediatric practice are shown in Figs 1 to 6:[11]

Points to Remember

- ***Identify potential or presumed pathogens causing the infection and consider the relative merits of antimicrobial agents for specific pathogens and circumstances.***
- ***Certain bacteria can be predicted from certain infections.eg S aureus and S pyogenes for cellulitis, osteomyelitis and septic arthritis and similarly some can be dismissed from certain infections like S aureus/S pneumonia from UTI.***
- ***Age of the child is important parameter for predicting the organism even without bacteriological diagnosis. eg Gram neg organisms are most important cause of pneumonia in neonatal age whereas S pneumoniae and H influenza are commoner after age of 3 months.***
- ***Though culture and susceptibility tests are of great value in diagnosing bacterial infection and choosing the right antibiotic, the results need to be interpreted with caution keeping the entire clinical picture in mind. e.g. aymptomatic bacteriuria.***
- ***A very sick child may demand a broad spectrum antibiotic as empiric therapy to begin with, treatment can be deescalated if organism with narrow spectrum antibiotic susceptibility can be identified. In a less sicker child a more cautious approach in choosing antibacterial therapy and even delay (if acceptable) is worthwhile.***

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CLIPPINGS

Use of a powder mix of vitamins and minerals to fortify complementary foods immediately before consumption and improve health and nutrition in children under two years of age

Deficiencies of vitamins and minerals, particularly of iron, vitamin A and zinc, affect approximately half of the infants and young children under two years of age worldwide. Exclusive breastfeeding until six months of age and continued breastfeeding for at least two years are recommended to maintain children's adequate health and nutrition. After six months of age, infants start receiving semi-solid foods but the amount of vitamins and minerals can be insufficient to fulfil all the requirements of the growing baby. Micronutrient powders (MNP) are single-dose packets of powder containing iron, vitamin A, zinc and other vitamins and minerals that can be sprinkled onto any semi-solid food at home or at any other point of use to increase the content of essential nutrients in the infant's diet during this period. This is done without changing the usual baby diet.

Objective was to assess the effects and safety of home (point-of-use) fortification of foods with multiple micronutrient powders on nutritional, health and developmental outcomes in children under two years of age.

Selection criteria: Randomised and quasi-randomised trials with either individual or cluster randomisation were included. Participants were children under the age of two years at the time of intervention, with no specific health problems. The intervention was consumption of food fortified at the point of use with multiple micronutrient powders formulated with at least iron, zinc and vitamin A compared with placebo, no intervention or the use of iron containing supplements, which is the standard practice.

Authors' conclusions: Home fortification of foods with multiple micronutrient powders is an effective intervention to reduce anaemia and iron deficiency in children six months to 23 months of age. The provision of MNP is better than no intervention or placebo and possibly comparable to commonly used daily iron supplementation. The benefits of this intervention as a child survival strategy or on developmental outcomes are unclear. Data on effects on malaria outcomes are lacking and further investigation of morbidity outcomes is needed. The micronutrient powders containing multiple nutrients are well accepted but adherence is variable and in some cases comparable to that achieved in infants and young children receiving standard iron supplements as drops or syrups.

De-Regil L, Suchdev PS, Vist GE, Walleser S, Peña-Rosas J. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD008959. DOI: 10.1002/14651858.CD008959.pub2. Assessed as up to date: August 10, 2011.

DRUG PROFILE

ANTI HYPERTENSIVES

**** Jeeson C Unni***

Abstract: *Hypertension in children and adolescents is increasing and its rational management is more intensely researched now than ever before. Remediable causes of hypertension needs to be identified and appropriate remedial measures (surgery for coarctation of aorta, renal artery stenosis, pheochromocytoma) undertaken. Pharmacotherapy is reserved for control of hypertension before such intervention and for essential hypertension and for conditions where such interventions are either not fully curative or not producing expected results. An attempt is made to detail antihypertensives licensed for use in children and adolescents.*

Keywords: *Antihypertensives, Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, Calcium channel blockers, Beta-blockers, Central alpha agonist, Peripheral alpha antagonist, Diuretics, Alpha adrenergic blockers, Essential hypertension, Chronic kidney disease, Renovascular hypertension, Pheochromocytoma, Hypertensive emergencies*

Prevalence of childhood hypertension is on the increase over the years, mainly due to the childhood obesity epidemic and increasing stress.[1] Small surveys among school children in India suggest a prevalence ranging from 2-5%.[2] It is also known that the risk of mortality due to cardiovascular causes increases as blood pressure rises.[3,4] Hypertension and prehypertension in children and adolescents is associated with LVH and pathologically elevated left ventricular mass index values[5] and increased coronary intima media thickness.[6] Further, a lack of awareness of normal, prehypertensive and hypertensive levels for Indian children and poor blood pressure taking behavior among pediatricians in our country result in gross under-diagnosis of childhood hypertension. Since hypertension causes multiple end organ damage – IHD and resultant LVH and CCF, peripheral vascular disease, cerebral hemorrhage and stroke, renal failure and proteinuria – it is important to understand its natural history, diagnose it early and treat effectively so as to prevent or delay complications.[7] This article will deal with the effective use of antihypertensives in children and adolescents.

* Editor-in-Chief,
IAP Drug Formulary,
Cochin.

Definitions

Normal BP: Systolic or diastolic BP < 90th centile for gender, age and height.

Pre hypertension: Systolic or diastolic BP between 90th and 95th centile.

Hypertension: Systolic or diastolic BP exceeding 95th centile on 3 separate occasions. This is further subdivided into 2 stages Stage I: Systolic or diastolic BP > 95th centile and up to 5 mm above the 99th percentile and Systolic or diastolic BP values 5mm or more above the 99th percentile. Indian Pediatric Nephrology Group and Indian Academy of Pediatrics, endorse the guidelines on definition of hypertension proposed in the Fourth US Task Force Report on Hypertension.[8,9] For infants, systolic BP needs to be monitored and normative data from the "Second report" should be used for defining hypertension.[10] All children with prehypertension and hypertension are advised therapeutic lifestyle changes (TLC). Prehypertension is evaluated once in 6 months while weekly evaluation is recommended for Stage I and Stage II hypertension.

Indication for pharmacotherapy

a) Secondary or Stage II hypertension

b) Prehypertension or Stage I hypertension associated with co-morbid conditions (renal or cardiac disease; diabetes mellitus)

c) Stage I hypertension with end-organ disease (symptomatic hypertension, LVH, hypertensive retinal changes)

d) Stage I hypertension that fails to respond to 6-12 months of TLC

Principles of treatment

The goal for treatment is reduction of blood pressure to levels <95th percentile, unless comorbid conditions or target-organ damage is present, when it should be lowered to <90th percentile.

Commonly used medications in children include ACEI, calcium channel blockers (CCB), vasodilators, β blockers and thiazide diuretics.

Therapy is initiated with one agent, at an appropriate dose and the dose is increased until the desired blood pressure is achieved. If the highest dose is not effective or if there are side effects, a drug from a different class is added or substituted.

Medications with a longer duration of action (once, twice daily dosing) are preferred for better compliance and less side effects.

Dose adjustment of antihypertensive medications need not be made more frequently than every 2-3 days.

Oral antihypertensives

The various antihypertensives licensed for use in children and adolescents, as enumerated in the IAP Drug Formulary, are classified and detailed with dosages and relevant comments in Table I.

Choice of antihypertensive

The approach to selection of drugs for treatment of hypertension in children and adolescents has been reviewed by the Indian Pediatric Nephrology Group, Indian Academy of Pediatrics.[8] Start with a CCB or an ACEI or an adrenergic β-blocker. The ACEIs, ARBs and CCBs have the strongest data to support their use in pediatric patients.[12] A study suggests that ACEI monotherapy was significantly more effective in controlling hypertension in children CCB.[13] If the BP remains >95th percentile, a combination therapy comprising of either an ACEI+CCB or ACEI+thiazide diuretic or beta-blocker+CCB may be tried. Combinations minimize the side effects by allowing administration of lower dosage of different agents. The above mentioned combinations are derived by selecting drugs with complementary mechanisms of action. However, there are very few studies of use of these combinations in children.[14] Unsatisfactory control of BP despite combination therapy in adequate doses is an indication for using additional drugs. Prazocin/β-blocker/ thiazide may be added to ACEI+CCB and other drugs like clonidine, labetalol, hydrallazine or minoxidil may also be added to this combination according to the expertise of the pediatrician.

Use of antihypertensives in specific conditions

Essential hypertension: Either ACEI or CCB may be used to initiate therapy. However, if these 2 groups of drugs are not tolerated by the child, α-blockers is recommended.[15]

Acute post-infectious glomerulonephritis: Sodium restriction, diuresis usually with IV frusemide, and pharmacotherapy with CCB, vasodilators or ACEI are standard therapies for control of the transient hypertension in this condition.[16]

Chronic kidney disease: Initiate with ACEI, since these agents also reduce proteinuria and retard progression of renal damage.[17] Give a reduced dose if there is a 30-35% increase in serum creatinine or there is hyperkalemia. Therapy with either a CCB or α-blocker is considered in severe renal failure (GFR <30 mL/min/1.73 m^2). Prazocin, labetalol, clonidine, hydralazine or minoxidil may also need to be added for control of hypertension in CKD.

Renovacular hypertension: Treatment includes angioplasty, surgery and medications. Avoid ACEI in bilateral renovacular disease and use cautiously in unilateral disease as drugs acting on rennin-angiotensin axis may reduce GFR and precipitate renal failure.[18] Initiate with CCB or α-blocker

Hypertensive emergencies: May be associated with hypertensive encephalopathy, including seizures. Controlled reduction in blood pressure over 72–96 hours is essential; rapid reduction can reduce perfusion leading to organ damage.[19] Treatment should be initiated with intravenous drugs; once blood pressure is controlled, oral therapy can be started. It may be necessary to infuse fluids particularly during the first 12 hours to expand plasma volume should the blood pressure drop too rapidly.

Controlled reduction of blood pressure is achieved by intravenous administration of labetalol or sodium nitroprusside. Esmolol is useful for short-term use and has a short duration of action. In less severe cases, nifedipine capsules can be used. In resistant cases, diazoxide is given intravenously, but it can cause sudden hypotension. Other antihypertensive drugs which can be given intravenously include hydralazine and clonidine. Commonly used drugs for hypertensive emergencies are detailed in Table II.

Pheochromocytoma: The mainstay of treatment of pheochromocytoma is surgical removal of the tumour. However, surgery should not take place until there is adequate blockade of both α - and β-adrenoceptors. α-blockers are used first to control the hypertensive episodes in phaeochromocytoma. Once alpha blockade is established, tachycardia and heart irregularity may be controlled by the cautious addition of a β-blocker; a cardioselectiveβ-blocker is preferred. Phenoxybenzamine, a powerful α-blocker, is effective in the management of

Table I. Oral Antihypertensive Medications[11]

Agents	Dose; frequency	Comments
Angiotensin converting enzyme inhibitors (ACEI)		
Captopril	The starting dose is 0.1 mg/kg/dose; it is gradually increased to 0.5-1 mg/kg/dose three times a day (increase after every 4 to 5 doses). Maximum dose is 2 mg/kg/dose. BP and renal parameters should be monitored when up titrating the dose. Captopril is the preferred ACEI in young infants, requires dosing every 6-8 hr.	Avoid in neonates (particularly preterm and sick neonates) due to the risk of renal failure, anuria and hypotension. Risk of marked hypotension if volume depleted. Use smaller doses in neonates. Use cautiously if GFR <30 ml/min/1.73 m^2; avoid in renal artery stenosis or outflow tract obstruction. Use carefully in coarctation of aorta. In patients with evidence of prior renal disease, urine should be tested for protein monthly for first 9 months of treatment. Anaphylactoid reaction can occur during dialysis with high-flux polyacrylonitrile membranes.
Enalapril	Neonate - Oral 0.1mg/kg/24hr in 1-2 doses (max 0.4mg/kg/24 hr); IV 5-10 microgm/kg/dose every 8-24 hr. 1month-12yr - Oral 0.1-0.5mg/kg/24hr in 1-2 doses; IV 5-10 microgm/ kg/dose every 8-24 hr. 12-18 yr Oral 2.5-5 mg/24hr and titrate to max 40 mg/24hr. Beyond infancy, enalapril is preferred ACEI.	Same as for captopril. Severe hypotension may occur particularly following the first dose. Patient should be observed every 15 min.
Lisinopril	Adolescent: Initially, 10 mg PO once daily. The usual dosage range is 20-40 mg PO once daily. Lower dosage may be necessary in patients with renal impairment and in those receiving diuretics. In patients with a creatinine clearance of less than 30 ml/min, initiate therapy with 5 mg PO once daily. Maximum daily dose is 80 mg/day. Children > 6 yrs: starting dosage is 0.07 mg/kg PO once daily (up to 5 mg/day). Adjust dosage based on blood pressure response. Doses > 0.61 mg/kg/day PO or > 40 mg/day have not been studied in pediatric patients.	Lisinopril and Ramipril are new ACEI that may be given once daily and have fewer side effects. Lisinopril is not recommended in children with GFR < 30 ml/min/1.73 m2. Children < 6 years: recommended. Lisinopril is removed by hemodialysis. For patients receiving dialysis, the initial recommended dosage is 2.5 mg PO once daily. Maximum 40 mg/day.
Ramipril	Children - 1.5mg/m^2/24 hrs once daily. Adolescents-2.5 mg once daily. Adjust dosage to achieve proper blood pressure response, up to max of 20 mg/day. But more studies are required in children before it is used in pediatrics.	Contraindications include diabetes, heart or blood vessel disease esp renal artery stenosis, autoimmune disorders like lupus or scleroderma, renal impairment, hepatic illness, hypotension, previous swelling of the tongue, face, or lips with difficulty breathing, difficulty swallowing, hoarseness, or tightening of the throat, allergic reaction to lisinopril, other ACE inhibitors, insect venom, foods, dyes, or preservatives. Monitor serum potassium, creatinine.

Table I. Oral Antihypertensive Medications[11] (Contd.,)

Agents	Dose; frequency	Comments
Angiotensin receptor blockers		
Losartan	Adolescents: Initially, 50 mg PO once daily, unless the patient is volume-depleted. The maintenance dosage range is 25-100 mg/day PO, given in 1-2 divided doses. Maximal effects generally occur within 3-6 weeks. The addition of a diuretic has a greater effect on lowering blood pressure than increasing the losartan dosage beyond 50 mg/day. The addition of hydrochlorothiazide 12.5mg to losartan 50 mg daily results in an additional 50% reduction in diastolic and systolic BP. A modest reduction in blood pressure (up to 3 mmHg) is achieved by increasing the daily dose of losartan from 50 to 100 mg. When volume-depletion is suspected (e.g., patients taking diuretics), initiate therapy with 25 mg PO once daily. Children >= 6 years: The usual recommended starting dose is 0.7 mg/kg PO once daily (up to 50 mg/day). Individualize dosage to attain blood pressure goals. Doses > 1.4 mg/kg/day (or > 100 mg/day) PO have not been studied.	Side effects: hyperkalemia, impaired renalfunctions; anemia, neutropenia – nut unlike captopril cough is infrequent.
Calcium channel blockers (CCB)		
Amlodepine	6yrs - 100-200 microgram/kg daily once increased if required to maximum of 10mg. (6-15kg 1.25mg, 15-25kg 2.5 mg, >25kg 5mg).	Nifedipine and amlodipine are effective CCB for children. The availability of long acting preparations permits once or twice daily dosing
Nifedipine	Hypertensive crisis/ angina - Sublingual/oral pierce the capsule and pour contents sublingually /into mouth -250-500 microgm/kg as single dose. Hypertension/ angina - < 12 yr 0.2-0.3mg/kg/dose and 12-18 yr 5-20mg/kg/dose 3 times daily (max 3mg/kg/day).	Oral: if liquid preparation required for young children, liquid can be aspirated from capsules using asyringe. However, different brands of nifedipine 5 and 10mg capsules contain different amounts of liquid. Aspirated liquid dose should be covered in foil and administered immediately as nifedipine is very light sensitive. Rather than remove liquid from capsules, some pediatric units crush the nifedipine retard tablets and administer immediately; this may alter the modified release action. Some units have found that the retard tablets may require three times daily dosing, even if swallowed whole. Note that when nifedipine is given sublingually, only a small amountis

Table I. Oral Antihypertensive Medications[11] (Contd.,)

Agents	Dose; frequency	Comments
		absorbed sublingually. He observed effects are actually due to swallowing of the drug with subsequent rapid oral absorption. Side effects: Headache, flushing, dizziness, tachycardia, rash, gum hyperplasia. May increase intracranial pressure.; at higher doses: lower extremity edema, erythema.
Isradipine	0.15 - 0.8mg/kg/day; tid	
Beta-blockers		
Atenolol	0.5 - 2 mg/kg/day; od-bid	Renal failure: No dose adjustment is required in patients with a creatinine clearance >35ml/minute/ 1.73sqm. If creatinine clearance 10-35ml/minute/ 1.73sqm give 50% dose, <10ml/minute/1.73msqm give 30-50% dose and adjust according to response.
Metoprolol	Children 0.2-0.4 mg/kg/day initially, gradually increase to a maximum of 1 mg/kg/day in two divided doses and adolescents 100-450mg/24hr in 3-4 divided doses. IV 5mg every 2 min for 3 doses.	
Propanolol	Newborn 0.25-0.5mg/kg, < 12 yr 0.25-1mg/kg 3 times daily and >12yr 80-160mg 2 times daily. Max in newborn 2mg/kg/day and in children increase weekly as required to usual dose 1-5mg/kg/day.	Sleep disturbances with propranolol, metoprolol; hyperlipidemia. Avoid β–blockers in asthma, heart failure, advanced heart block, sick sinus syndrome, cardiogenic shock; blunts symptoms of hypoglycemia
Labetalol	Oral - 1 mth–12 yrs 1–2 mg/kg 3–4 times a day; 12–18 years initially 50–100 mg twice daily increased if required at intervals of 3–14 days to usual dose of 200–400 mg twice daily (3–4 divided doses if higher); max.2.4g daily. IV - 1 mth–12 years 250–500 micrograms/kg as a single dose, max. 20 mg;12–18 yrs 50 mg over at least 1 minute, repeated after 5 minutes if necessary, max. total dose 200 mg.	Useful in patients refractory to other medications. Severe hepatocellular damage reported after both short-term and long-term treatment. Appropriate laboratory testing needed at first symptom of liver dysfunction and if laboratory evidence of damage (or if jaundice) labetalol should be stopped and not restarted. Avoid in liver disease. May cause hypoglycemia in dialysis patients.
Central alpha agonist		
Clonidine	5-10 microgram/kg /day in 2-4 divided doses (max 0.9 mg/kg/day);	Abrupt cessation may cause rebound hypertension; sedation; can intensify depression. IV 2-6 microgram/kg as single dose
Peripheral alpha antagonist		
Prazosin	1 mth - 12yr 10-15 microgm/ kg/dose 2-4 times daily (max 0.5mg/kg/day) and 12-18 yr 0.5mg/dose 2-3 times daily (max 20mg/day)	May cause 'first dose' hypotension, syncope – give 1st dose at bedtime and monitor

Table I. Oral Antihypertensive Medications[11] (Contd.,)

Agents	Dose; frequency	Comments
Vasodilators		
Hydralazine	<12 yr 0.75 mg/kg/day in 2-3 divided doses and 12-18 yr 50 mg in 2 divided doses. Increase if needed to max dose of 7.5mg/kg/day or 200mg/day. IV bolus over 20min - < 12 yr 100-500 microgm/kg and > 12yr 5-10 mg as single dose. May be repeated upto 4-6 times daily. IV infusion - <12 yr 12.5 - 50 microgm /kg/hr and > 12 yr 3-5 mg/hr. In hepatic and renal impairment start with small doses or increase interval between doses.	For hypertension refractory to other drugs. Fluid retention, headache, tachycardia, palpitation are frequent side-effects. Occasional side-effects include, blood disorders e.g. anemia, leucopenia, thrombocytopenia, neutropenia; prolonged treatment (>6 months) may provoke a lupus erythematosus-like syndrome.
Minoxidil	<12yr 0.2mg/kg (max 1mg/kg/day) and 12-18yr 5mg (max 100mg/day - rarely need to give more than 50mg/day). The dose may be given 1-2 times daily.	Headache, palpitation, fluid retention, congestive heart failure; pericardial effusions, hypertrichosis with minoxidil
Diuretics		
Frusemide	Newborn 1-2mg/kg/day in 2 divided doses; 1 month-12 yr 1-2mg/kg/dose and 12-18 yr 20-40mg/dose 2-3 times daily.	Monitor electrolytes, fluid status periodically Thiazides: dyslipidemia, hyperglycemia, hyperuricemia, hypokalemia, hypomagnesemia Loop diuretics: metabolic alkalosis, hypokalemia, hypercalciuria
Spironolactone*	1 - 3 mg/kg/day; in 2 divided doses	*Use cautiously with ACEI, angiotensin receptor blockers
Metolazone	2.5-5 mg/day for adolescents, 0.2-0.4 mg/kg/ day in children	
Hydrochlorothiazide	Neonates and infants - Oral 2 - 4 mg/kg/24hr in 2 divided doses.; >6 months - 12 yr 2 mg/kg/24 hr in 2 divided doses; 12-18 yr 12.5 - 100 mg/24hr	
Amiloride*	0.4 - 0.6 mg/kg/day; qd	

Table II. Drugs in treatment of hypertensive emergencies

Drug	Dosage	Remarks
Sodium nitroprusside	Start with a low dose - IV infusion 500nanogm/kg/min, increased in increments of 200nanogm/kg/min according to improvement in symptoms, status of BP, filling pressures, to max of 10 microgm/kg/min. (max 4 microgm/kg/min if used for longer than 24hrs. For continuous IV infusion in Glucose 5%, infuse via infusion device to allow precise control; protect infusion from light.	Acts within 30secs, peaks in 2 min, subsides 2 min after cessation. Blood pressure is measured at least every 15 minutes; pupillary reflexes, visual acuity and level of consciousness are also monitored. Two IV lines should be maintained, one for drug infusion and the other for saline infusion (if the blood pressure were to fall precipitously). Loss of pupillary reflex to light is an early indicator of retinal vascular ischemia, requiring immediate infusion of normal saline. Patients receiving nitroprusside at doses exceeding 2-3 mg/kg per minute for longer than 48hr are at risk of cyanide toxicity, and even earlier if there is hepatic or renal dysfunction.
Labetalol	IV - Newborn - 500 microgm/kg/hr - adjust every 15 min as per response; max 4mg/kg/hr 1-12yr – start with 0.5-1mg/kg/hr - adjust every 15 min as per response; max 3mg/kg/hr 12-18yr – 30-120mg/hr - adjust every 15 min as per response	Acts within 2-5min, subsides 5-10min aftercessation. IV infusion - dilute to a conc. of 1 mg/ml in 5% glucose or glucose saline; if fluid restricted may be given undiluted, preferably through a central venous catheter. Hypertensive encephalopathy – reduce BP to normal in 24-48hrs (rapid reduction – cerebral infarction, blindness, death). If child having seizure, reduce rapidly but not to normal levels
Nifedepine	Oral - 0.1-0.25 mg/kg; max 10mg	Acts within 5-10min, peaks in ½-1hr and lasts for 2-6hrs. Sudden reduction of BP leading to arrhythmias, syncope, cerebrovascular accidents and myocardial infarction (seen in adults) are uncommon in children. However, one needs to be aware of possibility that response to short acting nifedipine might be inconsistent and unpredictable (requiring more than one dose) or uncontrolled (sudden fall of blood pressure).
Glyceryl trinitrate (Nitroglycerine)	IV infusion – Neonate – 0.2 - 0.5mcg/kg/min (usual dose reqd 1-3 mcg/kg/min). The initial dose is 0.5mcg/kg/min IV, it is up titrated depending on the response (1mcg/kg/min once in 30min), to a maximum of 10mcg/kg/min. Not to exceed 200 mcg/min. Monitor BP and heart rate. Tolerance may develop.	Acts within 2-5min, subsides 5-10min aftercessation. For continuous IV infusion, dilute to max. conc of 400 µ/ml (but concentration of 1 mg/ml has been used via a central venous catheter) with 5% Glucose or Normal saline. Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used. Neonatal intensive care, dilute 3 mg/kg body-weight to a final volume of 50 ml with infusion fluid; an IV infusion rate of 1 ml/hour provides a dose of 1 µ/kg/minute.
Nicardipine	Continuous IV infusion initially 500 nanogm/kg/min followed by maintenance infusion of 1-3 microgm/kg/min	For IV infusion, dilute to a conc of 100 µg/ml with 5% Glucose or Normal saline; to minimise peripheral venous irritation, change site of infusion every 12 hours

Table II. Drugs in treatment of hypertensive emergencies (Contd.,)

Drug	Dosage	Remarks
Esmolol	1-18yr – initial IV 500µg/kg over 1 min followed by IV infusion 50µg/kg/min for 4 min (reduce rate if BP or heart rate is low). May repeat loading dose and inctdrease maintenance infusion by 50µg/kg/min increments; Could repeat until effect obtained or max of 200µg/kg/min reached.	Give through a central venous catheter; incompatible with bicarbonate

phaeochromocytoma but it has many side-effects. It may be given for children 1-18 yrs age; orally at 0.5–1 mg/kg twice daily adjusted according to response and as IV infusion at 0.5–1 mg/kg daily adjusted according to response; occasionally up to 2 mg/kg daily may be required. Do not repeat dose within 24 hours. Idiosyncratic profound hypotension within few minutes of starting infusion and convulsions following rapid IV infusion have been reported occasionally; postural hypotension with dizziness and marked compensatory tachycardia, lassitude, nasal congestion and miosis are more commonly encountered.

Conclusion

Rational and effective use of antihypertensives in children and adolescents needs a lucid understanding of approach to diagnosis, identification of cause and its use in emergencies. Each condition associated with hypertension has specific pharmacotherapeutic recommendations and this article attempts to highlight these guidelines.

Points to Remember

- ***Screening and early diagnosis and identification of cause, if any, of hypertension in childhood is emphasized***
- ***ACEI or CCB may be used to initiate therapy in essential hypertension***
- ***ACEI is preferred for initial therapy of hypertension associated with CKD since these agents also reduce proteinuria and retard progression of renal damage***
- ***Initiate with CCB or beta-blocker in renovascular hypertension prior to surgery and avoid ACEI in bilateral disease***
- ***Treatment for hypertensive emergencies should be initiated with intravenous drugs (controlled reduction of blood pressure is achieved by intravenous administration of labetalol or sodium nitroprusside); once blood pressure is controlled, oral therapy can be started.***
- ***Surgery for pheochromocytoma should not take place until there is adequate blockade of both α- and β- adrenoceptors.***

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CLIPPINGS

Eating and drinking in labour

This review looked at any restriction of fluids and food in labour compared with women able to eat and drink.

Objective was to determine the benefits and harms of oral fluid or food restriction during labour.

The review identified five studies involving 3130 women. Most studies had looked at specific foods being recommended, though one study let women choose what they wished to eat and drink. The review identified no benefits or harms of restricting foods and fluids during labour in women at low risk of needing anaesthesia.

Selection criteria: Randomised controlled trials (RCTs) and quasi-RCTs of restricting fluids and food for women in labour compared with women free to eat and drink.

Authors' conclusions: Since the evidence shows no benefits or harms, there is no justification for the restriction of fluids and food in labour for women at low risk of complications. No studies looked specifically at women at increased risk of complications, hence there is no evidence to support restrictions in this group of women. Conflicting evidence on carbohydrate solutions means further studies are needed and it is critical in any future studies to assess women's views.

Singata M, Tranmer J, Gyte GML. Restricting oral fluid and food intake during labour. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD003930. DOI: 10.1002/14651858.CD003930.pub3. Assessed as up to date: July 9, 2013.

DERMATOLOGY

HENOCH-SCHONLEIN PURPURA - REVISITED

**** Anandan V***

Abstract: *Henoch-Schonlein purpura (HSP) is the commonest childhood vasculitis with male preponderance (2:1) and winter predilection with a peak incidence between 4-6 years, first reported in 1801 by William Heberdon, clinically presenting as palpable red spots, joint pains, abdominal pain, with or without blood in the urine and stools frequently preceded by fever and malaise. Renal damage by an immune complex glomerulonephritis is a serious long term complication which warrants early diagnosis, appropriate management and a vigilant watch to avoid long term morbidity.*

Key words: *Palpable purpura, Arthritis, Arthralgia, Hematuria.*

Henoch-Schonlein purpura [HSP] which is also known as IgA immune complex vasculitis, anaphylactoid purpura. Purpura rheumatoide is the commonest childhood leucocytoclastic vasculitis first described by William Heberdon in 1801, clinically presening as bloody spots over the shins, abdominal pain, blood in the urine and stools associated with subcutaneous edema.

It was Johann Schonlein in 1837 found the association of purpura and joint pain and described as 'Peliosis rheumatica,' later in 1868 Eduard Henoch, Schonleins student documented the association of purpura, joint pain, gastrointestinal system and later he observed the renal involvement.[1]

Epidemiology

The incidence of HSP varies between 10 - 20.4 per 1,00,000 children.[2] It has stated that the peak incidence is between 4-7 years with male preponderance of 2:1 even though female preponderance has been reported. It has been observed that children less than 2 years of age with HSP have less incidence of renal involvement.

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HSP is more common in the winter, autumn and spring than the summer, which supports the view that an infectious trigger may have a role in its pathogenesis[3] and one study has documented that HSP could be precipitated by Group A and β hemolytic streptococcus which has been the commonest organism cultured in up to 36% of those tested in one series.[4]

HSP has reported following measles, mumps, rubella (MMR), pneumococcal, influenza, meningococcal and hepatitis B vaccinations.[5]

Clinical features

Skin manifestation is almost the presenting feature of HSP preceded by constitutional symptoms like fever, malaise and myalgia.

Characteristic cutaneous presentation of HSP is painless, non tender, palpable purpura ranging from petechiae to ecchymoses commonly over the shin and around the joints of the lower limbs preferably over the extensor aspects, less commonly involving the upper limbs and face, usually sparing the trunk. In 2% of the children bullous lesions may be seen indicating the severity of the disease. A retiform pattern within lesions is characteristic but need not be present always.

50-75% of HSPs do have GI involvement. Even though the commonest presentation is the colicky pain[6] it is not uncommon to present with vomiting, and bloody stools. Massive GI bleed has been reported in 2% of HSPs which has been attributed secondary to bowel vasculitis. Intussusception, pancreatitis, hydrops of the gall bladder, protien losing enteropathy has been reported as complications.

Arthralgia or arthritis is the presenting symptom in 15-25%, but a retrospective analysis has shown that 80% at an average had some form of joint involvement in the form of pain, swelling and restriction of joint mobility. It is interesting to note that joints of the lower limbs are involved more often than the upper limbs. Renal involvement is around 20-60% in HSP, manifesting as hematuria, proteinuria, nephritis, nephrotic syndrome and hypertension around 4-12 weeks.[7]

Less common manifestations are non-specific headache, mental depression, hyperactivity and seizures has been reported. Even though pulmonary complications are not so very common in children, diffuse alveolar hemorrhage [DAH] has been reported.[8] In 24% of children with HSP, orchitis has been reported.[9] The activity of HSP is evidenced by an increase in serum IgA, TNF-α IL-6, IL-8, TGF-β, vascular endothelial growth factor (VEGF).

Pathology

Skin biopsy is not warranted as a routine, as the clinical presentation is adequate for the diagnosis, but however it is mandatory in atypical presentations.

Histopathological examination of the skin exhibits a leucocytoclastic vasculitis with peri nuclear infiltration of polymorphs and mononuclear cells. There may be necrosis of small blood vessels and platelet thrombi. IgA is found in most purpuric lesions and can also be found in non-affected areas. Direct immunofluoresence (DIF) of the lesional and perilesional skin reveals IgA, C3 and fibrin in dermal blood vessel walls.

Immuno pathologically it has been documented that abnormal deposition of IgA. However in HSP there is predominantly deposition of polymeric IgA1 isotype in skin, gastrointestinal and glomerular capillaries.[10]

Diagnosis

Even though the diagnosis of HSP is straight forward the European League against Rheumatism (EULAR) and Pediatric Rheumatology European Society (PReS) has put forward the criteria's for the diagnosis of HSP such as, palpable purpura which is mandatory in the presence of at least one of the following diffuse abdominal pain/Acute arthritis or arthralgia/ Renal involvement in the form of hematuria and/or proteinuria/ biopsy showing predominant IgA deposition.

Differential diagnosis

Differentials are thought only when the HSP is atypical and the appropriate differentials would be, Wegener's granulomatosis, polyarteritis, isolated cutaneous leucocytoplastic vasculitis and Systemic lupus erythematosus (SLE) .Septicemia could also be entertained if the child is very sick.

Acute hemorrhagic edema of infancy (AHEI) is considered a variant of HSP[11] which is characterized by large purpuric lesions and edema of face and extremities in which the histology is identical but only 30% have IgA deposition and has rarely internal associations.

Management

Investigations

Full blood count to exclude thrombocytopenia; most often thrombocytosis is found in HSP. Anemia may be present but is usually an indicator of GIT hemorrhage or severe hematuria.

Erythrocyte sedimentation rate (ESR) is elevated in approximately 60%, but is a nonspecific inflammatory marker.

IgA levels are elevated in 25-50% of patients.

C3 and C4 are decreased in circulation in 15-20%.

ANA, dsDNA to rule out SLE.

Albumen levels are diminished in cases of nephritic syndrome and/or protein-losing enteropathy which may occur.

Renal function is obviously very important and assists in identifying some with a rapidly progressive glomerular disease.

Antineutrophil cytoplasm auto antibodies (ANCAs) of the IgA subtype have along with antistreptolysin O titres (ASOT) been shown to be elevated in some studies but are of little prognostic or diagnostic assistance.

Occult faecal blood is seen in 25%.

Factor XIII plasma levels can be measured in atypical cases and are decreased in the majority, even prior to purpura formation.

Skin biopsy is a useful diagnostic tool in atypical cases and reveals a typical leucocytoclastic vasculitis with necrosis of the vascular wall and inflammatory cell infiltrate, accompanying IgA dermal deposition.

Treatment

Skin HSP resolves spontaneously and requires no treatment except for the supportive measures, but when the presentation is bullous then prednisolone-1mg/kg/day for 2 weeks is effective.[12] Dapsone 1mg/kg is found to be useful as a steroid sparing agent.[13] Colchicine and aspirin is a useful combination to treat skin and joint involvement.[14]

When there is going to be other system involvement it is always better to plan the treatment in coordination with the concerned specialist.

Prognosis

HSP by itself is a self limiting disease but recurrences have been reported in more than 30% of the cases. The long term prognosis depends on the involvement of the renal system. In general the renal involvement and the decrease in the factor X111 at the onset heralds poor prognosis.[15] Mortality is less than 1% in a reported series.[16]

Conclusion

Henoch-Schonlein purpura [HSP] is the commonest childhood leucocytoclastic vasculitis primarily affecting the skin but has ramifications over other systems undergoes spontaneous resolution with or without steroids and has a recurrence among one third of the sufferers which requires vigilant follow-up for at least six months if there is no renal involvement Long term follow-up is advisable for renal complications if there is an alteration in the renal functions at the onset. The use of steroids is controversial but studies are available to support the usage of steroids has reduced the morbidity as far as the skin, joint, and gastrointestinal system but with no effect on renal system. ACE inhibitors do find a place in the management of proteinuria and hypertension. Methotrexate, mycophenalate mofetil and immunoglobulins has been used in small groups with variable success.

Future

Plasmapheresis, anticoagulants, fibrinolytics and Factor X111 therapies in combination with immunomodulators and biological like Rituximab is expected to revolutionize the future therapy of Henoch-Schonlein purpura.

Points to Remember

- ***Henoch-Schonlein purpura [HSP] is the commonest childhood leucocytoclastic vasculitis self resolving.***
- ***Steroids reduce the morbidity.***
- ***Renal involvement should be ruled out and should be followed up.***
- ***High index of suspicion and a thorough knowledge is essential to rule out the differentials.***

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SURGERY

CONGENITAL LUNG CYSTS: AN OVER VIEW

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Abstract: *As lung cysts are space occupying lesions, familiarity with normal variations and potential pathologic abnormalities in lung is necessary during evaluation of infective chest conditions that produce respiratory distress and airway problems. Background knowledge of this pathology, facilitates expeditious work up of the case, paving way for precise treatment.*

Keywords: *Congenital pulmonary airway malformation, Congenital lobar emphysema, Bronchogenic cyst, Bronchopulmonary sequestration.*

Definition

Congenital lung cysts are lesions that are present during prenatal / postnatal period, prior to an inflammatory, traumatic insult or can occur if there is an anomalous blood supply to them .[1]

Embryology and developmental pathology

Congenital lung cysts are developmental in origin. Hence it is imperative that the normal lung development is understood. Fetal lung development involves 5 stages.

The primitive tracheal and lung bud arises as a diverticulum of foregut during the 3rd week of gestation. The 5 stages of lung development are given in Table I.

Pseudo glandular stage occurs between 7 and 16 weeks. This stage is called airway phase because bronchial air ways develop during this time.

Canalicular stage occurs between 16-24 weeks. This stage is called airspace phase, because alveolar air spaces develop. The lining epithelium of alveolus has two types of cells. They are type 1 and type 2 pneumocytes. Surfactant production occurs from type 2 pneumocytes. Airway exchange is possible at this stage.

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Saccular stage occurs between 24-36 weeks. Alveolar multiplication happens resulting in increased alveolar numbers.

Alveolar stage occurs from birth up to 8 years of age. There is a ten fold increase in the number of functioning alveoli.

Table I. Stages of lung development

1-Embryonic
2-Pseudoglandular
3-Canalicular
4-Saccular
5-Alveolar

Pulmonary development is regulated by master genes, the most important being HOXB5 genes. Growth factors like TGEF also contribute to lung development. Hormones like glucocorticoids and thyroid hormones contribute to the normal pulmonary organogenesis.

Lung cysts classification: 1. Congenital and 2. Acquired. The types of congenital lung cysts: are (a) Congenital pulmonary airway malformation (CPAM), (b) Congenital lobar emphysema (CLE), (c) Bronchopulmonary sequestration and (d) Bronchogenic cysts.

Congenital pulmonary airway malformation (CPAM)

This was earlier commonly described as "congenital cystic adenamatoid malformation (CCAM)". Development of lung beyond canalicular stage is affected. This results in the formation of air spaces (cysts) which are devoid of alveoli. Saccular and alveolar stages do not occur.

Antenatal diagnosis: Routine prenatal ultra sonogram (USG) at fifth month identifies fetal cystic lung masses. USG will demonstrate multiple large cysts, multiple small cysts and numerous tiny cysts which may appear solid. Presence or absence of hydrops fetalis, fetal ascites and pleural fluid can also be detected by prenatal USG.

Antenatal intervention: This is done based on the following factors (1) gestation <24 weeks and (2) presence of hydrops fetalis.

Predictor of fetal hydrops: CCAM volume ratio (CVR) is a good predictor for the possible development of hydrops.It is the ratio of fetal lung volume to fetal head circumference. If the measured value is greater than 1.6, it is a good predictor of impending fetal hydrops.[2] If these factors are not present, gestation is allowed to continue on expectant lines and post natal management is planned as per the merits of the case.

Fetal intervention: Thoraco amniotic fetal shunting is done if large cysts are present. Direct fetal surgery in the form of fetal lobe resection is performed if cystic lesions are small.

Post natal management: CT chest is an important investigation prior to surgery (Fig.1). In case of disappearing lung masses by USG, CT chest should be done which will detect the lesion which was undetected by USG.[3]

The timing of surgical intervention depends on patient's condition. Child should be stabilized before contemplating surgery because lung resection is a major procedure. With the advent of skilled anesthetic techniques, surgical skills and neonatal care, neonatal surgical lobe resection is a safe procedure. Even in an asymptomatic child, surgery should never be denied.

The commonly involved lobes are left lower lobe and right middle lobe (Fig.2). The following types of CPAM are recognized based on the surgical specimen which is of prognostic value[4] (Table II).

Risk of malignancy: CPAM harbors dysplastic epithelium and hence prone for malignant transformation. The following malignancies are proved to occur in children and young adults. They are rhabdomyosarcoma, pleuropulmonary blastoma, bronchoalveolar carcinoma and squamous cell carcinoma.[5] Hence a surgical resection is warranted even in an asymptomatic child.

Table II. Stocker's classification of lung cyst[4]

Type 1- Large multiple cysts, most common type, good prognosis.
Type 2 - Small multiple cysts, good prognosis.
Type 3 - Numerous micro cysts appear solid, associated with hydrops, poor prognosis.
Type 4 - Variant of type 1 peripherally situated large cysts, risk of pneumothorax, good prognosis.

Congenital lobar emphysema (CLE)

The fundamental cause in CLE is hyperinflation of lobe due to air entering on inspiration and limited expulsion on expiration resulting in air trapping and over inflation of the lobe producing space occupying lesion effect on mediastinal structures.

Etiopathology

a) Intrinsic causes: Can be bronchial or alveolar

Bronchial causes: Presence of intrinsic weak bronchial cartilage produces ball valve effect. During expiration they collapse causing air trapping and over inflation.[6]

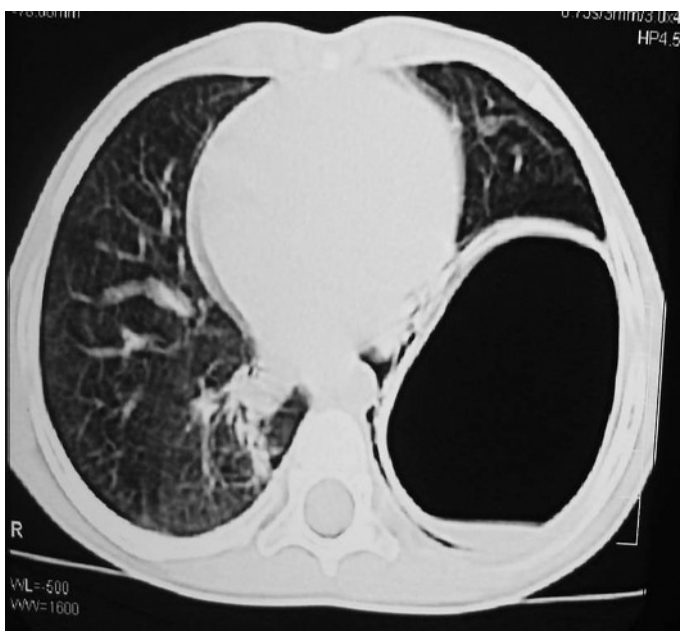

Fig.1. CT chest showing left lower lobe CPAM

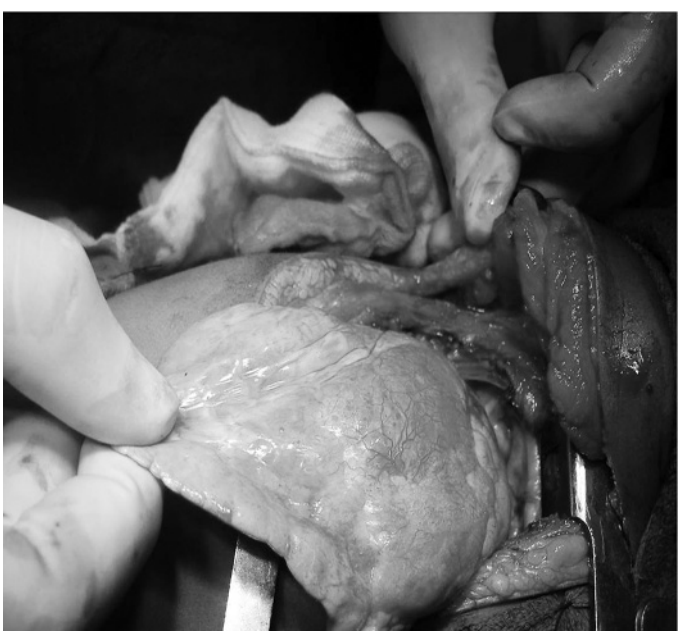

Fig.2. Left lower lobe CPAM

Alveolar causes: The terminal bronchiole tends three times more alveoli, thereby producing numerous alveoli (Poly alveolar lobe of Reid) which allow air trapping and over inflation of the lobe.[7]

b) Extrinsic causes: Abnormal pulmonary artery, cardiomegaly, compressing the bronchus.

Diagnosis

a) Prenatal diagnosis: USG reveals increased echogenicity of fetal lung due to fluid trapping. This may appear cystic on imaging.

b) Diagnosis at birth: Serial X-rays are required to demonstrate findings of classic CLE.The typical finding consists of a hyper inflated lobe compressing the normal lobe. Radiologically compressed lobe appears triangular and opaque at the base. This is associated with herniation of pleura to the opposite side with mediastinal shift.

CT chest will prove the above findings. In some situations if the classic findings are not present, ventilation perfusion scan can be done. This shows poor uptake and washout and little blood flow. The commonly involved lobes are left upper lobe, right middle lobe and right upper lobe. After a period of medical management which may include ventilator therapy, if regression of symptoms does not occur. surgical resection of the affected lobe is undertaken.

Bronchopulmonary sequestration

These are lesions which may be cystic or solid and are composed of non- functioning lung tissue that does not communicate with tracheo bronchial tree and have anomalous blood supply from systemic circulation.[8]

Etiopathology: Accessory lung buds develop apart from normal lung buds, deriving vascular supply from aorta.

Types: Extra pulmonary (95%) and Intrapulmonary (5%.). Left hemithorax is the commonest side.

Investigations: CT chest, MR angiography, aortography.

Treatment: Surgical resection.

Bronchogenic cysts

They are also called as bronchopulmonary foregut malformations. The cyst is most commonly found on midline chest structures of the body such as the esophagus, trachea, and lower lobes of the lung. Some of these cysts become symptomatic by becoming infected or enlarging in size to the point where they compromise on the function of the adjacent airways.

Etiopathology

Bronchogenic cysts occur due to abnormal budding from the tracheo bronchial tree. Two thirds of these cysts occur within lung parenchyma. They can also occur in remote locations such as tongue, neck, and back. Malignant transformations have been reported.

Clinical presentation of congenital lung cysts

Respiratory symptoms such as cough, fever, respiratory distress and cyanosis are present. Some of the lesions are associated with cardiac anomalies. Recurrent pneumonia, recurrent pneumothorax, chylothorax and hemothorax call for diligent search for these lesions. Significant amount of shunting of blood can occur within the bronchopulmonary sequestered lesion. This can precipitate congestive cardiac failure and hemoptysis.[9]

Long term outcome

Most studies suggest normal lung function in children for whom lobe resection was performed before four years of age, in view of the compensatory lung growth due to hyperplasia.[10] Resections done after four years of age show mild reduction in ventilatory function due to the lack of hyperplasia because compensatory hypertrophy does not fully restore lung function. Overall good lung function and good physical growth occur in children who have undergone pulmonary lobe resections.

Pneumonectomy patients develop kyphoscoliosis producing restrictive lung function. Following right pneumonectomy patients may develop post pneumonectomy syndrome where cor pulmonale can develop. Hence pneumonectomy should be done as a final resort in children.

Points to Remember

- ***Lung cysts are classified as congenital and acquired.***
- ***Congenital lung cysts are congenital pulmonary airway malformation, congenital lobar emphysema, bronchopulmonary sequestration and bronchogenic cysts***
- ***For congenital pulmonary airway malformation commonly described as "congenital cystic adenamatoid malformation", surgery is indicated even in an asymptomatic child.***
- ***For congenital lobar emphysema, after a trial of medical management, surgical resection of the affected lobe is undertaken.***

- ***For bronchopulmonary sequestration surgical resection is indicated.***
- ***For bronchogenic cysts over all good lung function and physical growth occur in children after pulmonary lobe resection.***

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CLIPPINGS

Steroids for acute sinusitis in adults and children

Acute sinusitis is a common reason for primary care visits; it is one of the 10 most common diagnoses in outpatient clinics, presenting with various symptoms and signs that include purulent nasal discharge and congestion and cough lasting beyond the typical seven to 10 days of a viral upper respiratory infection. There have been suggestions, based on studies of allergic rhinitis and chronic sinusitis, that intranasal corticosteroids (INCS) may relieve symptoms and hasten recovery in acute sinusitis due to their anti-inflammatory properties.

Objectives: To examine whether intranasal corticosteroids (INCS) are effective in relieving symptoms of acute sinusitis in adults and children.

Selection criteria: Randomised controlled trials (RCTs) comparing INCS treatment to placebo or no intervention in adults and children with acute sinusitis. Acute sinusitis was defined by clinical diagnosis and confirmed by radiological evidence or by nasal endoscopy. The primary outcome was the proportion of participants with either resolution or improvement of symptoms. Secondary outcomes were any adverse events that required discontinuation of treatment, drop-outs before the end of the study, rates of relapse, complications and return to school or work.

Authors' conclusions: Current evidence is limited for acute sinusitis confirmed by radiology or nasal endoscopy but supports the use of INCS as a monotherapy or as an adjuvant therapy to antibiotics. Clinicians should weigh the modest but clinically important benefits against possible minor adverse events when prescribing therapy.

Zalmanovici Trestioreanu A, Yaphe J. Intranasal steroids for acute sinusitis. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD005149. DOI: 10.1002/14651858.CD005149.pub4. Assessed as up to date: May 22, 2013.

RADIOLOGY

IMAGING OF THE UPPER AIRWAY

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****Natarajan B**
****Jeya Rajiah**
****Kasivisalakshi KP**
****Balan MP**

Acute upper airway inflammatory conditions are emergencies and radiology has no role in diagnosis, the emphasis being on immediate treatment. In this issue we will see a few conditions of the upper airway where imaging helps in diagnosis and delineation of pathology. The upper airway consists of the nose, nasopharynx, oropharynx, hypopharynx, larynx and trachea. We have seen nasal pathology in an earlier issue. One more important and rare condition is choanal atresia. If bilateral ,it is recognized at birth due to respiratory distress. Diagnosis is by inability to pass a nasogastric tube through the nose. If unilateral, it may be missed. The role of imaging is to show the extent and severity of the obstruction. In Fig.1, the choanal airspace is narrowed, the vomer is thick, the maxillary sinuses are medially placed. The obstruction itself can be membranous, bony or mixed.

A common nasopharyngeal condition is enlarged adenoids. Nasopharyngoscopy can be difficult in the child. The simple plain lateral x-ray of the neck is still an excellent tool for screening and identification of adenoids. Fig.2 shows the adenoids which are seen encroaching the air column. A useful point to remember is to look at the air column rather than the size of the adenoids. There are many ways of interpretation. Depending on the percentage of air column available- 25%, 50% or 75% reduction corresponds to mild , moderate or severe adenoid hypertrophy. Another method is by comparing air column with the thickness of the soft palate. The air column is normal if it is more than thickness of the soft palate. When the thickness is similar it is mild enlargement. When the air column is narrower than soft palate but wider than half the soft palate it is moderate hypertrophy and if further narrowed and less than half thickness of soft palate it is severe hypertrophy. However, x-rays can under estimate hypertrophy compared to nasopharyngoscopy. The palatine tonsil in the oropharynx cannot be assessed with x-ray.

The tissue behind the upper airway is rich with lymphatics and lymph nodes. Suppurating lymphadenitis and abscess formation is quite common in children. This widens the retropharyngeal space pushing the pharyngeal air column forward and narrowing it. A lateral x-ray of the neck can confirm a suspicion of retropharyngeal abscess which can then be drained. The space between the posterior border of the air column and the anterior border of C2-C3 interspace is compared with the width of the caudal edge of C2 vertebra. Up to one year their ratio is 1 (ie they are equal in width). Thereafter the retropharyngeal space decreases gradually till the ratio is 0.5 or half by the age of 6. Fig.3a shows widened retropharyngeal space due to abscess. Compare the retropharyngeal space in the same child after the abscess has been drained (Fig.3b). Spasm of the neck muscles can cause loss of cervical lordosis and mild subluxation of the atlanto-axial joint that will disappear on drainage. This is called Grisel syndrome.

Fig.4 is another case of retropharyngeal abscess but it is a cold abscess. Note the destruction of the vertebral body in Fig.5. TB of the spine rarely occurs in the cervical spine. The tuberculous focus starts near the disc with destruction of the adjacent vertebral bodies. The destruction can also be on the anterior aspect of the vertebral body extending up or down behind the anterior longitudinal ligament or can be limited to a vertebral body with collapse. Involvement of vertebrae along with the interspace is a hallmark of caries of the spine. The accompanying cold abscess can also be behind the prevertebral fascia, track to the anterior border of the sterncleidomastoid, supraclavicular area or down into the mediastinum. Clinical presentation is not acute as in pyogenic retropharyngeal abscess.

Fig.6 shows a cyst just posterior to the hyoid bone. This is a vallecular cyst which is a rare cause for stridor and respiratory distress in neonates and can cause sudden

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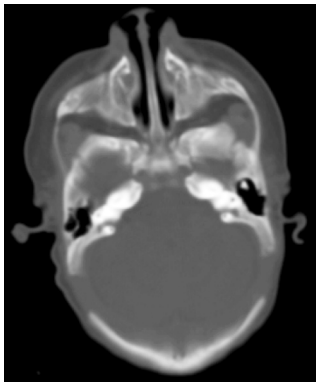

Fig.1. Choanal atresia

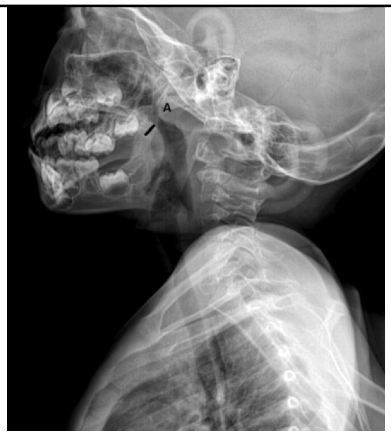

Fig.2. Mildly enlarged adenoids. (A). The line is the thickness of soft palate

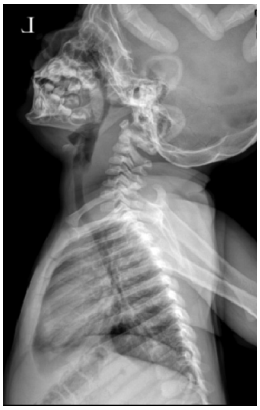

Fig.3a. Retropharyngeal abscess

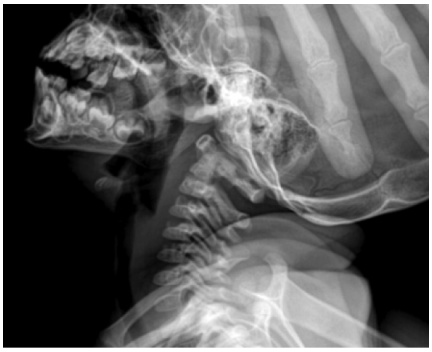

Fig.3b. After drainage of retropharyngeal abscess

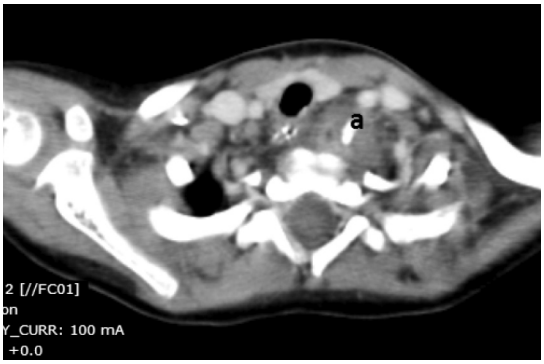

Fig.4. Note the cold abscess (a) to the left of midline

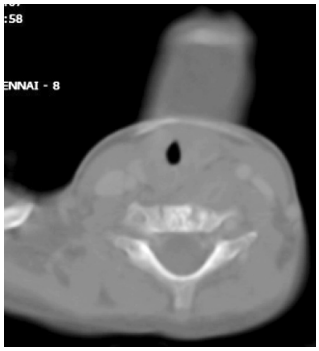

Fig.5. Same patients as fig.4 showing destructive foci in the body of the vertebra

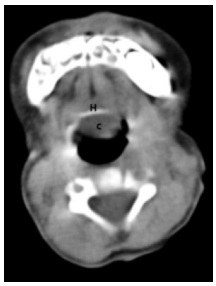

Fig.6. Vallecular cyst(C). H is hyoid bone

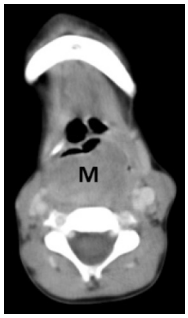

Fig.7. Pharyngeal mass(M) - synovial sarcoma

death. At endoscopy there is a cyst arising from and distorting the lingual surface of the epiglottis. It can be diagnosed antenatally.

Coming to malignancies, the commonest head and neck malignancy in children is rhabdomyosarcoma. Fig.7 shows a large mass apparently arising from the wall of the pharynx, displacing and obliterating the air space. The biopsy revealed synovial cell sarcoma. It is a tumor of adolescents and young adults occurring mostly in the extremities near joints. Very few are seen in the pharynx.

Pathology around the upper airway is often occult and imaging plays a vital role in patient evaluation. While cross sectional imaging is important,the plain x-ray also has a definite, though limited role in the child.

CLIPPINGS

Antibiotics for preterm rupture of membranes

Certain antibiotics given to women whose waters have broken early will improve babies' health. Babies born too soon are more likely to suffer ill health in the early days and sometimes throughout life. Early labour and birth (before 37 weeks) may be due to undetected infection as well as the waters breaking early.

Objectives was to evaluate the immediate and long-term effects of administering antibiotics to women with PROM before 37 weeks, on maternal infectious morbidity, neonatal morbidity and mortality, and longer-term childhood development.

Selection criteria: Randomised controlled trials comparing antibiotic administration with placebo that reported clinically relevant outcomes were included as were trials of different antibiotics. Trials in which no placebo was used were included for the outcome of perinatal death alone.

Authors' conclusions: Routine prescription of antibiotics for women with preterm rupture of the membranes is associated with prolongation of pregnancy and improvements in a number of short-term neonatal morbidities, but no significant reduction in perinatal mortality. Despite lack of evidence of longer-term benefit in childhood, the advantages on short-term morbidities are such that it is recommended that antibiotics are routinely prescribed. The antibiotic of choice is not clear but co-amoxiclav should be avoided in women due to increased risk of neonatal necrotising enterocolitis.

Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD001058. DOI: 10.1002/14651858.CD001058.pub3. Assessed as up to date: November 26, 2013.

NEWS AND NOTES

PEDGASTROCHENNAI CME UPDATE - 2014

Department of Pediatric Gastroenterology, KKCTH - CTMRF, IAP - TNSC & CCB

Date: 19th January 2014 Venue: Hotel GRT Convention Centre, T Nagar, Chennai.

Postgraduate Rs. 500/- Delegates Rs. 800/- Spot Registration Rs. 1000/-

Registrations: Pls Contact Ms.Kalaivani Mob: 9655544537 and Mrs.Pechiammal, KKCTH, Ph: 42001800 Ext 159 (10am-4pm except Sundays)

Cheques / Draft to be drawn in favour of The CHILDS Trust Medical Research Foundation payable at Chennai, addressed to Dr. Srinivas S, Kanchi Kamakoti CHILDS Trust Hospital, 12-A, Nageswara Road, Nungambakkam, Chennai-600034.

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For further information, please contact **Dr David Inwald,** Clinical Director of Intensive Care on **D.Inwald@imperial.ac.uk**

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