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Attending physicians, residents, fellows, students, and providers using this handbook in the treatment of infants should recognize that this text is not meant to be a replacement for discourse or consultations with the attending and consulting staff. Management strategies and styles discussed within this text are neither binding nor definitive and should not be treated as a collection of protocols.

I would like to extend my gratitude to contributors to this first edition of the Handbook of Pediatric Surgical Critical Care.

Feedback regarding this edition as well as future editions is not only welcome, but also greatly appreciated.

Marjorie Arca, MD
April 2014
INTRODUCTION

To the Members of APSA:

Two years ago, a group of pediatric surgeons with interest and training in surgical critical care met to cultivate and enhance our collective experience within pediatric surgery. We felt that as pediatric surgeons, our voices remain unique, relevant and valuable in caring for our patients, in the training of our fellows, and in informing our colleagues. One of the first projects that we embarked upon is a Handbook of Pediatric Surgical Critical Care. We felt that this would create a uniform basis for our critical care and pediatric surgical curriculum. We also thought that this handbook would provide another dimension to the training for neonatology, pediatric critical care, and adult critical care fellows. Finally, we felt that this project may be helpful to our colleagues, who already in practice, as a point of reference in the care of the most complex surgical patients.

I personally would like to thank all the contributors to this seminal project. We also thank APSA Staff for helping us put this project together. We would also like to thank APSA for allowing the website to be the platform for dissemination of the handbook.

The authors of this handbook welcome any and all comments from the membership.

Marjorie J. Arca, MD
Editor
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I. Oxygen Consumption and Delivery

In a state of equilibrium, oxygen demand equals oxygen consumption, which is the amount of oxygen used for aerobic metabolism. Under normal aerobic conditions, O₂ delivery is 3 to 4 times what is consumed by the body and oxygen delivery does not dictate the amount of oxygen consumed. In a critically ill patient, delivery of oxygen must be closely considered.

Oxygen delivery is the product of cardiac output (CO) and arterial oxygen content. During the process of metabolism, oxygen is consumed as is expressed as volume of oxygen per minute (V₀₂) and is equal to 100-200 cc/m²/min. Oxygen delivery (DO₂) is equal to 500-600 cc/m²/min.

\[ O₂ \text{ Delivery} = CO \times [ (1.34 \times \text{Hgb} \times O₂ \text{ sat}) + (0.003 \times PaO₂)] \]

An analogy for oxygen delivery is as follows: Think of oxygen as beer that needs to be delivered from Milwaukee to Green Bay. The hemoglobin molecules are the trucks that need to be filled (low O₂ saturation) or if there are not enough trucks (low Hgb), then the amount of beer that gets to Green Bay is less. The cardiac output is the foreman that decides who many trucks per hour comes out of the beer factor’s garage.
In a patient, optimizing oxygen delivery has more options than manipulating oxygen demand. To optimize oxygen delivery, one should break down the components of the DO2 equation:

\[
DO2 = \text{Cardiac Output} \left[ 1.34 \times \text{Hgb} \times \text{O2 sat} + (\text{PO2} \times 0.003) \right]
\]

For practical purposes, one should ignore the contributions of "dissolved O2", since it is multiplied by a factor of 0.003. Increasing hemoglobin (transfusion) when one is anemic and optimizing oxygen saturation (oxygenation maneuvers) increase the number of “trucks” and the amount of beer in the trucks for delivery to Green Bay. Optimizing cardiac output CO requires manipulation of the components of cardiac output.

Stroke volume is affected by preload (volume status) afterload (systemic vascular resistance) and contractility (inotropic characteristics). Recall, however, that contractility of the heart is also dependent on the preload as depicted by the Frank Starling curve.
In the adult literature, increasing hemoglobin levels to normal has been shown to increase mortality in the ICU trauma setting.

Let us tease out the components of cardiac output in order to utilize each one to optimize O2 delivery. Preload is simply the volume that the heart sees. For the most part, the volume that the right heart sees is the same as that of the left heart. This value is often reported as CVP, which is normally 5-8 mm H2O. In the
past the left heart “preload’ has been reported as the “wedge pressure” in a patient who had pulmonary arterial monitoring (aka Swan Ganz catheter). This method of monitoring is not routinely used in the pediatric ICU setting. In the postoperative cardiac patient, the left heart preload is the left atrial pressure. Optimizing preload is giving volume-crystalloid or blood products depending on the clinical need. Afterload refers to the resistance of the vascular bed that receives flow from the heart. For the purposes of this discussion, afterload is the vascular resistance in the systemic vascular system. The most common instance where the vascular tone of the system is “loose” is sepsis. In septic shock, bacteria and host characteristics contribute to decreased vascular tone. Increasing afterload increases cardiac output and is accomplished by vasoactive medications such as neosynephrine. One must make certain that the patient has adequate preload before using medications to augment afterload.

Cardiac contractility refers to the force by which the heart ejects blood. As previously mentioned, preload, as dictated by the Frank Starling curve is responsible for part of cardiac contractility. Contractility can also be affected by inherent muscle weakness due to ischemia (MI), trauma (cardiac contusion), stun (postop state) or even electrolyte/hormonal dysfunction (hypocalcemia, hypothyroidism). Contractility can be augmented by myotropic agents such as dobutamine (B2 adrenergic), epinephrine (B1 and B2), milrinone(↑ cyclic AMP).

Decreasing oxygen consumption requires paying attention to the patient’s metabolic state. Normothermia should be achieved. Decreasing work of breathing,
ablating seizures and treating hyperdynamic states such as sepsis, thyrotoxicosis and helpful in modulating oxygen consumption.

II. Cardiorespiratory Interactions

When manipulating parameters of oxygen delivery, one should pay close attention to the respiratory oxygen. The heart and lungs interact so closely together that to only consider one system may prove detrimental to the patient as a whole.

Let us consider each ventricle separately. The right atrium (RA) fills from the superior vena cava and the inferior vena cava. Typically, the RA is passively filled by blood and the filling is augmented by negative intrathoracic pressure. Therefore, positive pressure ventilation decreases RV preload by decreasing the gradient between the SVC/IVC and the RA. Increases in the mean airway pressure (MAP) further decrease the pressure between systemic venous system and RA. In addition, increases in MAP, may translate to increase in pulmonary venous resistance (PVR) depending on the lung volume.

The left ventricle (LV) is also affected by positive pressure ventilation. (PPV) The effects of PPV on the LV preload are directly derived on the preload delivered to the right heart from the systemic vascular system. Therefore, PPV and higher MAP can decrease LV preload. Interestingly, however, PPV can decrease LV afterload. The positive intrathoracic pressure already present adds to total pressure that is needed to be generated by the LV to generate a certain systemic
blood pressure. In essence, in a spontaneously breathing patient with baseline P
\( P_{\text{thoracic}} = -10 \), the LV has to generate pressure of 110 to obtain systemic pressure of
100 (must overcome intrathoracic pressure of \(-10 + \text{MAP} \) 100). If there is MAP of
10 or intrathoracic \( P =+10 \), the heart has to generate \( P \) of 90 only to systemic
pressure of 100.

The dominant effect of PPV on lung and cardiac mechanics is through the
\( P_{\text{airway}} \). Effects due to phasic changes such as \( \Delta P \) are minor.

To some extent, pulmonary vascular resistance is modulated by lung
volume. When there is atelectasis, large pulmonary vessels are not straight,
increasing pulmonary vascular resistance. Smaller lung vessels are not taut so
resistance in these vessels is low. When lungs are over distended, resistance
through the straightened pulmonary vessels are low, but the large perialveolar
pulmonary vessels are impressed by the overly distended alveoli, increasing PVR.
Therefore when the lung is atelectatic or over distended, PVR can increase.
Hypoxia, respiratory alkalosis, metabolic alkalosis also decreases PVR. Note that it
is the change in pH and not the CO2 that modulates PVR.

**III. Consensus Statement on Oxygen Delivery in a Critically Ill Patient**

Hemodynamic stability must be maintained.
Normovolemia must be achieved.
Colloid and crystalloid resuscitation are equivalent.
Aggressive attempts for supranormal O2 delivery show no outcome advantage.
No vasopressor or combination of agents show decrease in mortality.

Achieving supraclinical indices of organ and tissue perfusion show no advantage

Ref: Tissue hypoxia how to detect, how to correct, how to prevent.
Consensus Conference, AJRCCM 1996.

**IV. Tissue Oxygenation**

Oxygen delivery at the tissues and cellular level remains difficult to measure.

At the cellular level, there are factors that we know favors the release of oxygen from hemoglobin molecules. These factors shift the $O_2$ dissociation curve to the right and include: ↑ HR, ↓pH, ↑2, 3 DPG, ↑CO$_2$, and hypoxia.
p50 for O₂ dissociation is partial pressure of 26-27mm Hg. In some NICU and PICUs, near infrared regional tissue oximetry to check trends in cerebral and somatic oxygen delivery. Although the absolute value is important the trend of the values provides invaluable dynamic information regarding the tissue perfusion of the child.
Chapter 2
THE PEDIATRIC AIRWAY

Marjorie J. Arca. M.D.

I. Anatomy and Physics

The pediatric airway has unique characteristics that must be considered to optimize delivery of gas.

1. The pediatric airway is small and short

   Hagen-Poiseuille’s Law describes the flow of gas through a cylinder.

   \[ R = \frac{8nL}{\pi r^4} \]
   
   where \( n \) = viscosity of gas
   
   \( L \) = length of tube
   
   \( R \) = radius of the tube

   Although children have a shorter airway, the small diameter of the airways (\( \downarrow r \)), is the more important determinate of flow. Consider for instance an infant with a 4 mm airway, that decreases by 2 mm. Diameter decreases by 50% but resistance to flow decreases by 16 \( (2^4) \). In comparison, an adult with an 8 mm airway that decreases by 2 mm, the diameter decreased by 25% but flow decreases by 3x.

2. Another factor that can influence flow of gas is the density of the gas defined by the Reynold’s number \( R \)

   \[ R = \frac{2Vrp}{n} \]
   
   \( n < 2,000 \) laminar flow
   
   \( n > 4,000 \) turbulent flow
For instance, helium is less dense than nitrogen and slightly more viscous, thereby increasing the chance of laminar flow. This accounts for why Heliox (helium and oxygen mix) being useful in upper airway problems such as croup, stridor where upper airway problems predominate. In contrast, Heliox does not work in status asthmaticus.

Venturi effect – flow of gas increases as it flows through a partially obstructed tube.
Bernoulli effect – increase on velocity associated with decrease in pressure.

3. Anatomic considerations:

Children have large tongues relative to their oral cavities and the tongues easily occlude the palate because it has less forward displacement. In addition, the larynx is cephalad (located at the region of C2-C3) compared to adults (larynx is at C4-C5). The airway in a child is funnel shaped, where the narrowed portion is the cricoid cartilage, which is circular-shaped. In comparison, adults have a trapezoid shaped laryngeal apex. Intubation in children should align oral opening, pharyngeal and laryngeal opening.

A child’s epiglottis is long and narrow compared to adults.

Practical points: Use Miller tubes versus MAC tubes. Children have large heads and bumping the shoulder may help in aligning the planes.

II. Controlling the Airway
Most infants and children who lose their spontaneously ability to breathe can have their breathing augmented by bag mask ventilation (BVM). Any obstruction (including salivary secretions, vomitus or foreign material) should be recognized. The tongue can also be obstructive especially when the child is sedated or non-responsive. A “jaw thrust” or a “sniffing” position creates the optimal alignment for BVM. Peripheral oxygen saturation should be monitored to assure the success of BVM. It is easy to distend the child’s stomach during this maneuver. Gastric distention can lead to bradycardia, and so it should be rectified.

When considering intubation, one should examine the airway carefully. This assessment should start with an external examination. In an awake child (e.g., prior to an elective intubation for a surgical procedure), this includes a mouth opening assessment to see whether the pharynx can be seen (Mallampati exam), measurement of hyomental distance (at least three fingerbreadths) and thyrohyoid distance (at least two fingerbreadths), and relative neck mobility.

When preparing to intubate, the child should be preoxygenated with a bag mask and ventilated with 100% oxygen. The HR and saturation should be monitored continuously. The suction, ETT, laryngoscope should be readily available. When needed, the Sellick maneuver (which refers to the gentle pressure on the cricoid cartilage to avoid aspiration of gastric contents) should be performed before the administration of induction agent which consists of sedative and a rapid acting neuromuscular blockade agent. NOTE: WHEN A PATIENT HAS A
SEVERELY COMPROMISED AIRWAY (e.g., trauma to the head and neck region), DO NOT GIVE NM BLOCKADE AGENT UNLESS A RELIABLE SURGICAL AIRWAY IS ON STANDBY. As a rule of thumb, use non-cuffed tubes for children < 8 years of age to avoid development of subglottic stenosis. To ensure a successful intubation, breath sounds should be checked on both lung fields and more importantly, CO2 should be noted on the exhaled breath either on the monitor or by color change. A CXR should confirm the placement of the ETT.

The formula most often used to determine the appropriate size ETT is

\[
\text{Age} + 4 - \frac{4}{4}
\]

However, approximating the size of the ETT to a child’s pinky finger or nare is also a well-known maneuver.
Chapter 3
MECHANICAL VENTILATION

Martin Wakeham, MD
Marjorie Arca, MD

I. Indications

The indications for using mechanical ventilation can be divided into primary respiratory, and non-respiratory (see below). The decision to place a patient on mechanical ventilation is usually based on the combination of clinical judgment, assessing the symptoms and signs of need for positive pressure ventilation and laboratory test (e.g. blood gases, measurements of pulmonary mechanics, etc.)

The goal of placing someone on mechanical ventilation is to achieve adequate/acceptable (not necessarily normal) gas exchange (oxygenation and/or removal of CO2) while minimizing the chance of developing ventilator associated lung injury (VALI).

Common indications for mechanical ventilation are:

Respiratory failure (hypoxemic and/or hypercarbic)
- Pump dysfunction (CNS or neuromuscular dysfunction)
- Primary lung disease (e.g. pneumonia, bronchiolitis, airway obstruction, etc.)
- Optimization of PaCO₂ (as needed in traumatic brain injury)
- Congestive heart failure (to decrease afterload, and work of breathing)
- Protection of airways (coma, altered mental status)

II. Ventilator Associated/Induced Lung Injury (VALI/VILI)

All forms of positive pressure ventilation (PPV) can cause ventilator associated/induced lung injury. VALI/VILI is the result of a combination of the following processes:

- Inactivation of surfactant
- Increase alveolar capillary permeability
- Activation of inflammatory cells and release of cytokines
Several animal studies have shown that mechanical ventilation with larger tidal volume (Vt). Volume-trauma rapidly results in pulmonary changes that mimic ARDS. These studies have also shown that alveolar over distention rather than peak or plateau pressure seems to be responsible for VALI/VILI.

Absolute trans-pulmonary pressure (alveolar-pleural), rather than peak and plateau pressure, is responsible for over distention and injury. Peak and plateau pressure could/are also influenced by the airway resistance and the chest wall component.

Repeated alveolar collapse and re-expansion (“atelectrauma”) also seems to play a significant role in the development of VILI/VALI.

III. Modes of mechanical ventilation

Conventional ventilation is by far the most often utilized mode of ventilation.

Other forms of mechanical ventilation include:

• High frequency oscillatory ventilation (HFOV)
• High frequency jet ventilation (HFJV)
• Liquid ventilation

A. Conventional Ventilation

During each breath on conventional ventilation, positive pressure is generated by the ventilator and airflow is delivered over time (amount of gas deliver in each breath = tidal volume) to the patient via the endotracheal tube; this is done at a certain frequency (respiratory rate). As simple as this sound there are several factors/available choices to consider when starting somebody on conventional mechanical ventilation:
1. Who (patient vs. ventilator), and what **triggers** (elapsed time vs. patient effort) the inspiration, and by what triggering mechanism?

2. What **limits/controls** (pressure or volume) the gas flow being delivered?

3. How does the inspiration end (**cycle**)?

---

**1. Triggering**

Based on who/what initiates the delivered breath, one can choose a mandatory mode, a support mode, or a combination of both. Below are the most common modes based on the triggering mechanism.

**Controlled mandatory ventilation (CMV):** The ventilator delivers the set mandatory breaths at equal intervals (based on a set respiratory rate) regardless of the patient effort. The patient is not able to breath above the set respiratory rate (RR).

**Intermittent mandatory breath (IMV):** Similar to CMV the ventilator delivers the set mandatory breaths at equal intervals regardless of the patient effort. The difference is that the patient is able to breath in between the mandatory breaths;
the size of these patient’s triggered breaths depend on the patient effort and they are not supported by the ventilator at all.

**Assist controlled (AC):** The ventilator delivers the set amount of breaths and will also deliver extra breaths (with the same level of support as the mandatory ones) if it detects a patient breathing effort above the set rate.

**Synchronized intermittent mandatory ventilation (SIMV) +/- pressure support (PS):** It is similar to IMV but the ventilator synchronizes the mandatory breaths with the patient effort. For example, if the RR is set at 12 breath/min, the ventilator would wait up to 5 seconds in order to detect a patient effort; if an effort is detected at any time during that period, a fully supported breath is delivered in ‘synchrony’ with that effort. If no effort is detected, a fully supported breath is delivered regardless of the lack of patient effort. Again similar to IMV, the patient is able to breath above the set RR. The level of ventilator support during these spontaneous breaths could be set from none to a level (by choosing the SIMV/PS mode) that equals the support received during the mandatory breaths.

**Continues positive airway pressure /Pressure support (CPAP/PS):** In this mode of ventilation, a constant airway pressure is set without a set RR (therefore no mandatory breaths are delivered to the patient). All breaths have to be triggered by the patient. The clinician can choose the level of support of these breaths from none to a very significant level depending on a set PS. Most ventilators have a backup RR option in case the patient is or becomes apneic while on this mode.

**Triggers:**

On modern ventilators ventilator circuits have constant gas flow going from the inspiratory limb of the circuit to the expiratory one; patient efforts are detected by
either a chance in the flow (more sensitive, less patient effort required) or drops of pressure in the ventilator circuit (less sensitive, more patient effort required).

2. **Limit/control:**

Based on what limits/controls the level of support of the set mandatory breath, the 2 traditional modes of conventional ventilations are:

**Volume controlled (VC):** level of support of mandatory breath is controlled/limited by a preset tidal volume (Vt)

**Pressure controlled (PC):** level of support of mandatory breath is controlled/limited by a preset peak inspiratory pressure (PIP).

If volume is set, pressure varies.....if pressure is set, volume varies..... according to the compliance.....

\[
\text{COMPLIANCE} = \frac{\Delta \text{Volume}}{\Delta \text{Pressure}}
\]

Flow patterns are also different. In pressure control ventilation, the flow pattern is decelerating; in volume control ventilation, the flow pattern is square (constant)
i. Pressure vs. Volume

Pressure advantages

The PIP is lower than on VC mode for the same Vt. The distribution of gas may be more even in a lung with heterogeneous mechanics (better gas exchange?). It is a useful mode in air leaks situations because the airway pressure will be maintained throughout inspiratory cycle. It is more comfortable for the patient (better patient-ventilator synchrony).

Pressure disadvantages

Changes in compliance will result in changes on minute volume ventilation.

Volume advantages

Clinician could have complete control of minute volume ventilation. Also because of the “fixed” Vt there is less chance of VALI.

Volume disadvantages

Because of the constant flow, it could be uncomfortable and therefore there is higher chance of patient-ventilator asynchrony. PIPs will be higher than in PC for the same Vt.

3. Cycle:

Pressure control: *Time cycled* – the expiration begins after preset inspiratory time (Ti) or according to preset I:E

Volume control: Volume cycled – expiration begins after certain Vt was delivered

PRVC (see below): Time cycled - the expiration begins after preset Ti

Pressure and volume support: Breath is flow (usually) cycled, when flow drops inspiration terminates and expiration starts
B. Advanced Modes

1. Pressure Regulated Volume Control (PRVC)
PRVC is a hybrid mode of mandatory ventilation that combines pressure and volume control/limited ventilation. A preset Vt and frequency (minute ventilation) is delivered with a pressure limit and at the lowest possible pressure by a changing (adapting) decelerating flow. The preset Vt is achieved with a different pressure by breath to breath regulation. This mode can be used in a controlled or SIMV mode.

2. Airway Pressure Release Ventilation (APRV)
This mode of ventilation can be thought of as giving a patient two different levels of CPAP. The clinician/operator sets “high” and “low” pressures with release time. The length of time at “high” pressure is generally greater than the length of time at “low” pressure. “Releasing” to the lower pressure, allows lung volume to decrease to FRC (and promotes ventilation). Spontaneous breathing is allowed on all phases of the cycle.

Biphase Ventilation (aka Bi-Vent, BiLevel, BiPhasic, and DuoPAP) ventilation is similar to APRV, except that T low is longer during biphase ventilation, allowing more spontaneous breaths to occur at P low.

3. Adaptive Support Ventilation
Based on respiratory mechanics, ventilator automatically adjusts respiratory rate and inspiratory pressure to achieve a desired minute ventilation. The Clinician sets desired minute ventilation and a patient weight (for estimating anatomic dead space). The ventilator calculates expiratory time constant from the flow volume loop and determines the respiratory rate that minimizes work of inspiration at a given
minute ventilation. Breaths are pressure-control, and there is pressure support for triggered breaths to achieve desired respiratory rate. As respiratory mechanics change, the frequency–tidal volume pattern is automatically adjusted to maintain this “optimal” pattern

4. **Volume Support (AKA Automatic Pressure Ventilation)**

Volume supoort is a pressure support mode that uses tidal volume as a feedback control for continuously adjusting the pressure support level. Clinicians select a target tidal volume, and ventilator makes automatic adjustments in inspiratory pressure within a clinician-prescribed range. There is potential for automatic support reduction by reducing PS as patient effort and mechanics improve.

5. **Inverse Ratio Ventilation**

Inversing I:E ratio (I>E) is used to potentially improve oxygenation in a patient with optimal PEEP and FiO2. It can be used with volume-limited or pressure-limited mechanical ventilation.

- In pressure: increase I:E ratio
- In volume ramp wave: decrease peak inspiratory flow rate until I exceeds E
- In volume square wave: add and increase end-inspiratory pause until I exceeds E

6. **Neurally Adjusted Ventilatory Assists (NAVA)**

NAVA is a new concept of mechanical ventilation. NAVA delivers assist to spontaneous breathing based on, and proportional to the detection of the electrical activity of the diaphragm. NAVA requires the insertion of a specialized naso-gastric tube that detects the diaphragmatic electrical activity, and transmits it to the ventilator. Theoretically this mode has the advantage of a much better patient-ventilator synchrony.
C. Choosing Initial Settings (for PC, VC and PRVC):

First choose a mode based on the desired triggering mechanism (mandatory breaths, support breaths or combination like e.g. SIMV), and the desired way of controlling/limiting for the delivered breath size (PC, VC, or PRVC).

Then the dealer’s choices are:

FiO2: start at 1.0 (100%) and decrease to the lowest level needed to accomplish adequate oxygenation. To avoid or minimize oxygen toxicity, the clinician/operator should manipulate other settings (see oxygenation below) in order to achieve adequate oxygenation with a FiO2 that is less or equal to 0.6 (60%).

RR: start with a RR that is somewhat normal for the child’s age (e.g. infants and small children 20-30, adolescent 15. Keep in mind that the higher the RR the less the exhalation time.

Inspiratory time (iT): Generally, also age dependent, shorter in infant-small children (0.4-0.7 seconds) than in adolescents (0.8-1). Increasing inspiratory time improves oxygenation, but causes a concomitant decrease in the expiratory phase which may be detrimental for CO2 elimination.

PEEP (positive end expiratory pressure): Setting the PEEP regulates the pressure at the end of the respiratory limb and this is a mechanism to control the patient’s functional residual capacity (FRC). The goal should be to maintain FRC > closing capacity (volume at which smallest start to collapse). PEEP should rarely be set below 4-5 (good starting point) and could be titrated up based on the oxygen
requirements. Other than increasing the FiO2, increasing the PEEP is the most effective way to increase oxygenation (see oxygenation below)

**On VC and PRVC:** The clinician/operator will set a desired Vt. Depending on the clinical situation, the initial desired Vt could range from 6 to 10 ml/kg (ideal body weight for height). The PIP becomes a dependent variable and will depend on the chosen Vt, iT (shorter iT result in higher PIP), PEEP, and respiratory system compliance.

**On PC:** The clinician/operator will set a pressure control (PC) above PEEP in order to achieve the desired/intended Vt. The PIP is then the sum of the set PC+ set PEEP. A range of 20-24 is a good starting point and should be titrated in order to achieve adequate chest rise and the desired Vt (6-10 ml/kg). On this mode, the Vt is the dependent variable and will depends on the set PC, iT (manipulating the iT will also affect the Vt, with longer iT generally resulting in larger Vt) and the respiratory system compliance.

### D. Adjustments:

**Oxygenation:**

Oxygenation is related primarily to the mean airway pressure (MAP) and % of inspired oxygen (FiO2). When you are having problems with oxygenation, you might need to increase the MAP; changes in arterial PaO2 are directly related to changes in MAP. The MAP is the average pressure of the airway throughout the respiratory cycle. On PC mode it depends on the PEEP, iT, PIP, and RR; on VC and PRVC, it depends on the PEEP, iT, Vt and RR. As stated above, the most effective way to increase the MAP (in any mode) is to increase the PEEP.
Ventilation

PaCO2 is inversely related to the minute volume ventilation (minute volume ventilation equals RR x Vt); therefore changes on the RR or on the Vt will affect the PaCO2 in the opposite direction.

Is it really that simple?

Increasing PEEP can increase dead space, and decrease cardiac output. Increasing the respiratory rate can lead to dynamic hyperinflation (aka auto-PEEP) because of not having enough exhalation time, resulting in worsening oxygenation and ventilation.

E. Troubleshooting

1. Is it working?

Look at the patient - Listen to the patient!!

Look at the data: Pulse Ox, ABG, ETCO2, Chest X ray

Look at the vent (PIP; expired Vt; alarms etc)

2. When in doubt

DISCONNECT THE PATIENT FROM THE VENTILATOR, and begin bag ventilation. Ensure you are bagging with 100% O2. This eliminates the ventilator circuit as the source of the problem. Bagging by hand can also help you gauge the patient’s compliance.

Airway first: is the tube still in? Is it patent? Is it in the right position?

Breathing next: is the chest rising? Breath sounds present and equal? Changes in

2. *Well, it isn’t working…*

   Are these the right settings? Is this the right mode? Does the ventilator need to do more work? Is the underlying process getting worse? (or new problem?) Is there air leaks? Does the patient need to be more sedated? Is the patient ready to be extubated?

Consider Patient - Ventilator Interaction problems

   Ventilator must recognize patient’s respiratory efforts (trigger)
   Ventilator must be able to meet patient’s demands (response)
   Ventilator must not interfere with patient’s efforts (synchrony)

You might have to: Lower your Expectations

   Permissive Hypercapnia: accept higher PaCO2s in exchange for limiting V₁ / PIP
   Permissive Hypoxemia: accept PaO2 of 55-65; SaO2 88-90% in exchange for limiting FiO2 (<.60) and PEEP?

F. NON-INVASIVE VENTILATION…

1. Continuous positive airway pressure ventilation.

   Although CPAP can be delivered while an endotracheal tube is in place, CPAP can be delivered using nasal prongs. Patient must initiate all breaths. It is
functionally similar to PEEP, but the positive pressure is delivered throughout the breath cycle.

2. Bilevel positive airway pressure (BPAP)

BPAP is another modaility of non-invasive ventilation. It delivers a set inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure. Tidal volume is determined by the difference between IPAP and EPAP. There is limited availability of FDA-approved interfaces in the infant and pediatric population.

3. Nasal Intermittent Mandatory Ventilation

Nsal IMV is an intermediate strategy for neonates weaned off from mechanical ventilation but require more than CPAP. The most common mode used is a time cycle, pressure control with our without preset constant flow. Unassisted breaths occur at present PEEP level. Pressure control breaths can be triggered by the patient or machine. Pressure support ventilation cannot be used for nasal AMV because because it cannot flow cyle breaths due to the airway weak.

The main challenge of noinvasive ventilation in children, expecially infants, is the limited availability of interfaces to deliver this type of ventilation. Current available interfaces for non invasive ventilation include face mask, short prong nasal cannula, intermediate size high flow nasal cannula •nasal cannula (Fisher Paykel, Auckland, New Zealand), or a RAM nasal cannula (NeoTech, Valencia, California). The RAM cannulae possess a larger-bore tubing than a standard oxygen or high-
flow nasal cannula, which reduces resistance so that more pressure can be transmitted to the nares without adding imposed work of breathing during spontaneous breathing

G. Ventilator Associated Pneumonias – (NEJM, 2004 Jan)

The daily hazard rate is highest at Day 5. Measures to decrease VAP include:

1) Semi-recurrent position
2) Non-invasive ventilation
3) Use antibiotics for 8 days (JAMA 2003) (just as good as 15 days)
4) Use of silver coated ETT (2008)
5) Selective GI decontamination.
## Commonly Used Terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCPAP</td>
<td>bubble continuous positive airway pressure</td>
</tr>
<tr>
<td>BPD</td>
<td>bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>CLD</td>
<td>chronic lung disease</td>
</tr>
<tr>
<td>CMV</td>
<td>conventional mechanical ventilation</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>$E_T$</td>
<td>expiratory time</td>
</tr>
<tr>
<td>ETCO2</td>
<td>end-tidal CO2</td>
</tr>
<tr>
<td>ETT</td>
<td>endotracheal tube</td>
</tr>
<tr>
<td>FIO2</td>
<td>fraction of inspired oxygen</td>
</tr>
<tr>
<td>HFNC</td>
<td>high-flow nasal cannula</td>
</tr>
<tr>
<td>HFOV</td>
<td>high-frequency oscillatory ventilation</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>$I_T$</td>
<td>inspiratory time</td>
</tr>
<tr>
<td>MAP</td>
<td>mean airway pressure</td>
</tr>
<tr>
<td>NAVA</td>
<td>neurally adjusted ventilatory assist</td>
</tr>
<tr>
<td>NCPAP</td>
<td>nasal continuous positive airway pressure</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
</tr>
<tr>
<td>PIP</td>
<td>peak inflation pressure</td>
</tr>
<tr>
<td>SIMV</td>
<td>synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>TcCO2</td>
<td>transcutaneous CO2</td>
</tr>
<tr>
<td>VALI</td>
<td>ventilator associated lung injury</td>
</tr>
<tr>
<td>$V_T$</td>
<td>tidal volume</td>
</tr>
<tr>
<td>$\Delta P$</td>
<td>power, amplitude</td>
</tr>
</tbody>
</table>
MECHANICAL VENTILATION (INVASIVE)

Three characteristics of mechanical ventilation to guide you through the thought process

- How is lung inflation initiated?
  - At a fixed rate independent of patient effort (a.k.a. control)
    - Controlled mandatory ventilation
      - Used in heavily sedated or paralyzed patients.
    - Triggered by patient’s inspiratory effort (a.k.a. assist)
      - Synchronized ventilation
      - Patient-triggered ventilation
      - Used in awake patients

- How is gas flow controlled during lung inflation?

<table>
<thead>
<tr>
<th>Pressure (pressure controlled, pressure-limited ventilation)</th>
<th>Tidal volume (volume-controlled ventilation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls inflation pressure</td>
<td>Controls delivered volume</td>
</tr>
<tr>
<td>Cycles when set time or flow is reached</td>
<td>Cycles when set volume is delivered</td>
</tr>
<tr>
<td>Volume depends on compliance</td>
<td>Pressure rises passively</td>
</tr>
</tbody>
</table>

- How is the inflation terminated?
  - A set inflation time has elapsed (time cycled)
  - Inflation flow has decelerated to a certain percent of peak flow (flow-cycled)
  - A set tidal volume has been delivered (volume-cycled)
MODES OF MECHANICAL VENTILATION

Conventional Ventilation vs. Non-Conventional Ventilation

*Conventional ventilation* is the primary mode of ventilation we think of when using a mechanical ventilator. Within conventional ventilation, there are two primary modes: *volume ventilation* and *pressure ventilation*.

*Non-conventional ventilation* incorporates the following types of ventilators:

- High frequency oscillatory ventilation (HFOV)
- High frequency jet ventilation (HFJV)
- Liquid ventilation

CONVENTIONAL MECHANICAL VENTILATION (VOLUME & PRESSURE)

VOLUME VENTILATION

*Volume control ventilation* operates under the precept of delivering a set tidal volume ($V_T$) of air with each breath, *regardless* of how much pressure it takes to get that breath in.

Operator sets the following parameters: $V_T$, PEEP, I-time, and rate.
**Where do you set the tidal volume?**

Normal VT for each breath in a newborn depends on their body weight in kg and type of ventilator used. In general, aim for 4-7cc/kg, but depending on ventilator, one may have to set the volume at 10 cc/kg.

This difference is due to where the different ventilators make their measurements of exhaled tidal volume. The measurement may take place at the endotracheal tube or at the ventilator. You may need to allow for dead space in the tubing.

Remember, in volume ventilation, the ventilator will use whatever pressure is necessary to deliver that set volume of air. That means the pressure will vary from breath to breath as the lung compliance changes, but the delivered volume of air will always stay the same. (ie, for one breath, it might take a PIP of 25 to deliver the set volume of air, and the next breath might only need a PIP of 20). If a large leak is present, may be very difficult to use this mode of ventilation.

This is actually a more physiologic way of ventilating the lung, and is used frequently outside the NICU. However, caution should be used in the premature, because their lung compliance changes rapidly. Ensuring that alarm limits are appropriate and monitoring of pressures is very important.
PRESSURE VENTILATION

Pressure control ventilation operates under the precept of delivering breaths with a set amount of pressure (PIP), regardless of how much air (tidal volume) accompanies that pressure.

Operator sets the following parameters: PIP, PEEP, I-time, and rate. On many ventilators, Pressure control above PEEP is set (not PIP) and one just needs to add the 2 settings to calculate the PIP.

Where do we set the PIP and PEEP?

Where we set the PIP depends on age, weight, and lung pathology.

PEEP is usually set between 4-6 cm H20

I-time is usually 0.25-0.45 seconds in younger/smaller infants and 0.4-0.6 seconds in larger/older infants

- Shorter I-times in infants with RDS
- Longer I-times for lung disease or decreased compliance

The tidal volume (VT) is now going to be what varies from breath to breath, but it is a value that is measured by the ventilator and this number can be followed to see how well we’re doing with volume delivery on a given PIP.
While in this mode we can control the amount pressure a newborn lung sees, accepting the fact that the necessary tidal volume may not always be achieved, BUT acceptance of lower tidal volumes may outweigh high pressures that will induce barotrauma. However, volutrauma is also a source of lung injury.

The VT may be followed as an indicator of improvement/worsening of the pulmonary status. When the tidal volumes start registering too high (based on what you would expect for that patient’s weight on that ventilator), it’s probably time to start weaning!

**CONVENTIONAL MECHANICAL VENTILATOR MODES**

**IMV: INTERMITTENT MANDATORY VENTILATION**

Ventilator delivers a preset number of mechanical breaths, independent of the patient’s effort. The ventilator is in complete control. Leads to significant asynchrony between spontaneous breaths of the patient and the mechanical breaths.

**SIMV: SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION**

Similar to IMV, but the ventilator is able to time its delivered breaths in conjunction with the inspiratory effort of the infant
**SIMV with Pressure Support**

Any breath the infant initiates beyond that which the ventilator is programmed to deliver will be supported with a given amount of pressure above PEEP but still less than PIP.

**AC: ASSIST CONTROL**

All patient breathing efforts result in a machine delivered breath. These modes (pressure control, volume control) do not compensate for the changes in pulmonary mechanics and are unable to deliver consistent tidal volume.

**(N)CPAP: (NASAL) CONTINUOUS POSITIVE AIRWAY PRESSURE**

This is simply PEEP. The infant breaths around a continuous flow of positive pressure. Helps to boost functional residual capacity (FRC) in neonates by stenting open otherwise floppy airways. Can be delivered either through ETT (CPAP) or through nasal prongs (NCPAP) or through a specialized cannula (RAM). If you are delivering NCPAP or RAM using some ventilators, you can add a rate, but one must also set a PIP for those breaths (often called nasal ventilation).

**PRVC: PRESSURE REGULATED VOLUME CONTROL/PRESSURE GUARANTEED VOLUME CONTROL**

Best of both worlds! Allows one to ventilate with volume, but within pressure limits that are pre-set. Operator sets VT, PEEP, I-time, and rate,
as well as maximum pressure limits the ventilator is allowed to deliver the set tidal volume within. The delivery of the breath is more gradual and allows for lower peak pressures. Because the pressure will now change with every breath based on the lung compliance at the time of that breath, (up to a limit you’ve set), one may actually find that they are able to ventilate an infant with even lower PIP’s than you would have otherwise chosen if in SIMV.

**MAKING CONVENTIONAL VENTILATOR ADJUSTMENTS**

**Increasing PEEP**

**Benefits:**
- Maintains Functional Residual Capacity (FRC)
- Prevents alveolar collapse
- Increases Mean Airway Pressure (MAP)
- Improves oxygenation
- Splints obstructed airways

**Risks:**
- Increased risk of air leak
- Decreases V₁ if no ↑ PIP
- Can cause CO₂retention
- Reduces venous return
- Less compliant lung

**Increasing PIP:**

**Benefits:**
- Increases MAP
- Improves oxygenation
- Prevents atelectasis

**Risks:**
- Reduces venous return
- Increased barotrauma, air leak, CLD
**Increasing Rate:**

**Benefits:**
- Improves ventilation

**Risks:**
- Inadvertent PEEP
- Inadequate emptying time
- Air trapping

---

**Increasing I-Time:**

**Benefits:**
- Increases MAP
- Improves oxygenation
- Increases Vt

**Risks:**
- Reduces venous return
- Inadequate emptying time
- Limited rate
- Increased barotrauma
NON-CONVENTIONAL VENTILATION

HIGH-FREQUENCY OSCILLATORY VENTILATION (HFOV)

HFOV is an alternative to conventional mechanical ventilation (CMV) and is used when ventilation cannot be adequately achieved on conventional modes. HFOV will often improve oxygenation under circumstances when CMV is failing or when CMV settings are excessive or air leaks are imminent.

Remember that during spontaneous breathing, and while breathing on CMV, exhalation is a passive process. On HFOV, however, exhalation becomes an active process, which obviously assists in CO2 management/ventilation.

HFOV is commonly utilized in infants with diaphragmatic hernia, pulmonary hypoplasia, respiratory failure resulting from air leak (pulmonary interstitial emphysema (PIE), and pneumothorax), meconium aspiration syndrome, and persistent pulmonary hypertension (PPHN). HFOV is actually deemed by some as a kinder, gentler way of ventilating already fragile lungs because it ventilates with Mean Airway Pressure, rather than PIP, so the lung is exposed to less repetitive barotrauma.

Infants receiving nitric oxide therapy often respond better when on HFOV due to improved alveolar recruitment.

HFOV Settings
**MAP: Mean Airway Pressure**
This is the pressure at which the alveoli constantly remain open. Remember, the ventilator can calculate this value for you on CMV, and what we will usually do is see what this measured value is on CMV and increase it by 1-2 when transitioning to HFOV. MAP is a major determinant of the infant’s oxygenation, until it compromises cardiac output and pulmonary blood flow. The general goal when starting an infant on HFOV is to achieve 9-10 rib expansion on chest x-ray, so you should always get a CXR within 30-60 minutes of putting someone on HFOV. Because the MAP is directly related to oxygenation, you can generally clinically correlate with your pulse oximeter readings.

**ΔP: Amplitude**
This is the degree of oscillation within the circuit around the MAP you’ve chosen. It is directly related to CO2 removal, and is the parameter you adjust when ventilation is a problem. This is also the setting that determines how much the baby’s chest is vibrating. Some people like to keep the MAP and ΔP in a 1:2 or 1:3 ratio, so after you’ve chosen your MAP, you can usually multiply that number by 2 or 3 to get a start point for your ΔP. Ultimately, though, you need to use whatever ΔP it takes to achieve good chest vibration.

**Hz: Hertz**
In physics, this is defined as cycles/second. This is the number of oscillations that occur around the MAP in any given second. A Hz of 10 equals 600 cycles/second. This value is rather fixed and isn’t changed much once HFOV is underway, except in circumstances
of worsening ventilation. Typically, we place premature babies on Hz of 12-15, and term babies on Hz of 8-10.

HFOV depends on achieving the optimal lung inflation with the optimal MAP. The aim is to obtain maximal alveolar recruitment without causing over distension. Consequences of inappropriate lung inflation are:

- Under-inflation results in elevated pulmonary vascular resistance and higher O2 requirements. Larger changes are needed in ΔP for chest vibration, and there is an increased risk of atelectasis, collapse and loss of lung recruitment.
- Over-inflation results in hemodynamic compromise, hypotension and hypoxia from decreased cardiac output. Higher amplitudes give rise to less chest vibration. This has grave clinical consequences and should be avoided under any circumstances.

HFOV: ADJUSTING THE SETTINGS

HFOV decouples ventilation from oxygenation. Thus, changing ΔP to alter ventilation has little effect on oxygenation. Likewise, changing the MAP to alter oxygenation has little effect on ventilation.

Oxygenation (MAP)

To improve oxygenation, increase the MAP and/or the FiO2.

- Be careful . . . sometimes if an infant is deteriorating, they may need less MAP rather than more as cardiac output is compromised by increasing pressure in the chest.
• Remember, you have no outward way of visualizing chest rise on HFOV, so without a CXR, you have no idea how over/under inflated you are.

**Ventilation (ΔP)**

Increasing the ΔP will increase the amplitude of the oscillator’s diaphragmatic movement, and thus increase tidal volume leading to better CO₂ removal. Because of the respiratory cycle in HFOV, a change in ΔP yields a geometric change in ventilation in the direction of the change.

You can think of it much as you do adjusting the rate on CMV.

- Increase in ΔP → geometric increase in ventilation (will ↓ CO₂)
- Decrease in ΔP → geometric decrease in ventilation (will ↑ CO₂)

**NOTE:** If MAP is decreased too rapidly, atelectasis may develop and lead to ↑ CO₂

**Ventilation (Hz)**

If efforts to alter ventilation with adjustments in the ΔP are unsuccessful, we will sometimes alter the Hz. Changes in the Hz actually alter the respiratory cycle itself. This change in the cycle of ventilation causes the relationship of Hz to ventilation to roughly be as follows:

- Increase in Hz → linear DECREASE in ventilation (will ↓ CO₂)
- Decrease in Hz → linear INCREASE in ventilation (will ↓ CO₂)

Think of adjusting the Hz in the direction you want the CO₂ to go.
HELPFUL TIPS:

- Use appropriate size ET tube to prevent (minimize) air leak
- Hemodynamic stability should be ensured before starting HFOV
- Infants may need to be sedated on HFOV
- CXR should be obtained within 30 minutes of starting HFOV for assessing lung volume
- Blood gas should be checked within one hour of starting HFOV to assess for

OTHER
Transcutaneous pCO2 monitoring

- A method of assessing pCO2 without drawing blood
- Where to apply probe?

<table>
<thead>
<tr>
<th>Patient &lt;1 month old</th>
<th>Patient &gt;1 month old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorax under clavicle</td>
<td>Earlobe</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Low on forehead</td>
</tr>
<tr>
<td>Back</td>
<td>Cheek</td>
</tr>
<tr>
<td>Low on forehead</td>
<td>Thorax under clavicle</td>
</tr>
<tr>
<td>Inner or anterior aspect of thig</td>
<td>Upper arm</td>
</tr>
<tr>
<td></td>
<td>Behind ear on mastoid process</td>
</tr>
</tbody>
</table>

- When Tc PCO2 doesn’t match blood gas pCO2, consider:
  - Site of probe is hypoperfused (e.g. shock, hypothermia, vasoactive drugs)
  - Condition of skin and subcutaneous tissue
  - Increased cell metabolism (e.g. fever)
  - Blood gas analyzer calibration
NONINVASIVE MODES OF RESPIRATORY SUPPORT

- **CPAP**
  - Initially delivered via endotracheal tube (now rarely used except as a pre-extubation trial).
  - Later delivered via a variety of devices including nasal prongs.
  - Essentially became PEEP with the introduction of infant ventilators.
  - Recent studies have shown early CPAP use leads to a 20% reduction rate in mechanical ventilation and is associated with lower rates of BPD.
  - Now delivered via nasal prongs connected to ventilators and flow drivers.

- **Bubble CPAP**
  - Uses an underwater seal to create distending pressure.
  - CPAP is regulated by submerging expiratory limb of gas circuit a set distance under water to create distending pressure.
  - Generates a variable distending pressure that is referred to the “noise” of BCPAP.
  - Distending pressure is flow dependent and intra-prong pressures may be higher than what is expected from depth of submersion in water (approximately 1.3 cm H2O higher).

- **High-Flow Nasal Cannula (HFNC)**
  - Flow rates greater than 2 L/min.
  - Advantages over low-flow or “regular” nasal cannula:
    - Washout of nasopharyngeal dead space leads to improved CO2 clearance and increased FIO2 in alveoli.
- Reduced inspiratory resistance.
- Better lung compliance with warm and humidified gas.

**RAM Cannula**
- Used with a ventilator
- Can apply PIP, PEEP, and rate in a noninvasive manner.
- Higher support pressures are needed compared to intubated patients.

**Neurally Adjusted Ventilator Assist (NAVA)**
- Can be invasive or non-invasive (when delivered via RAM cannula)
- Ventilator mode that uses the brain/phrenic nerve/diaphragm axis to trigger the ventilator and to determine ventilator support delivered to patient.
- The electrical activity of the diaphragm (Edi) triggers and controls the ventilator support.
  - When to initiate a breath
  - Size of breath to deliver
  - When to stop breath
- NAVA: Patient thinks of initiating breath and it is delivered.
- Conventional ventilation: Flow or pressure is needed to trigger a breath
- Benefits of NAVA:
  - Patient has more control of ventilator – better patient-ventilator synchrony.
  - Decreased risk of barotrauma and volutrauma.
  - Patient able to cough more effectively
  - Atrophy of diaphragm is reduced.
- Fewer sedation days.
- Fewer ventilation days.
- Aids in weaning to extubation.

- When not to use NAVA:
  - Patient is not spontaneously breathing (e.g. oversedation, neuromuscular abnormalities, no neural activity).
  - Patient does not have a working diaphragm.

- Equipment Needed:
  - Servo-I ventilator with NAVA software.
  - Edi catheter:
    - Special NG/OG tube, inserted with sterile water – no lubricants or gels.
    - 20-30 minute warmup time once placed.

- Signal

<table>
<thead>
<tr>
<th>Edi Peak</th>
<th>Edi Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures electrical of diaphragm</td>
<td>Diaphragm at rest</td>
</tr>
<tr>
<td>Normal level 1-10 microvolts</td>
<td>Normal level 0-2 microvolts</td>
</tr>
<tr>
<td>Higher the peak, harder the diaphragm is working</td>
<td>Increase peep to keep Edi minimum at 0-2 microvolts</td>
</tr>
<tr>
<td>Level is set by respiratory therapist (RT)</td>
<td></td>
</tr>
<tr>
<td>Higher the NAVA level set, the more patient’s work of breathing is off-loaded, resulting in lower peak value</td>
<td></td>
</tr>
</tbody>
</table>

- Starting NAVA level:
  - 1-2 cm H2O/microvolt
  - Use preview screen on ventilator
  - Optimal NAVA level is achieved when increase in NAVA level results in minimal changes in PIP, TV, and Edi peak.
    - TV of 4-6 mL/kg at lowest Edi peak.
• RT adjusts levels and follows trends to achieve optimal level.

• With NAVA, one may see:
  • Increase in PIP
  • Increase in respiratory rate (as breaths are initiated by patient)
  • Increase in PEEP

• Back-up modes that must be set:
  • Pressure support – this mode is activated when patient stops using diaphragm but is still able to trigger flow or pressure.
  • Pressure control volume ventilation is triggered when patient is apneic.

• Weaning NAVA

<table>
<thead>
<tr>
<th>Patient Controlled</th>
<th>Provider Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient will automatically self-wean</td>
<td>Go slow – allow time for diaphragm to adjust and strengthen</td>
</tr>
<tr>
<td>Will see decreasing Edi with unchanged tidal volume (diaphragm performance has improved)</td>
<td>Changes are made in 0.1 to 0.2 microvolt increments</td>
</tr>
<tr>
<td>PIPs will be lower</td>
<td></td>
</tr>
</tbody>
</table>

• If NAVA level too low, will see:
  • Widely fluctuating Edi signals and peak pressures
  • Increased need for sedation
  • Smaller tidal volumes
  • Increased oxygen requirement
  • Patient may appear air hungry

References:
Materials provided by Khris O'Brien, RRT-NPS, Clinical Program Coordinator, Respiratory Care, Children's Hospital of Wisconsin

I. Introduction

Extracorporeal life support (ECLS) denotes the use of prolonged cardiopulmonary bypass, usually via extra-thoracic cannulation, in patients with acute and reversible cardiac or respiratory failure, unresponsive to conventional management.[1] Although extracorporeal membrane oxygenation (ECMO) is the traditional term, ECLS is the current preferred mnemonic, since “life support” encompasses functions other than “oxygenation”, including cardiac and hemodynamic support, and carbon dioxide elimination.[2] ECLS is not a therapeutic intervention; instead, it simply provides cardiopulmonary support. The patient is spared the deleterious effects of high airway pressures, higher fraction of inspired oxygen (FiO2), and perfusion impairment, while pathophysiologic processes are allowed to heal, either spontaneously or through therapeutic interventions.[3] Therefore, ECLS should only be applied in settings where the pathophysiologic processes are considered “reversible”. Goals of ECLS are to improve oxygen delivery, remove carbon dioxide, and allow aerobic metabolism while the lungs rest. Simply put, deoxygenated blood is removed from the patient into an external membrane lung where oxygen is diffused into the blood and carbon dioxide is
removed. The blood is returned to the patient either via venous or arterial route. There are several “parts” to ECLS: the circuit through which the blood flows, the oxygenator where gas exchange occurs, the pump which controls the blood flow within the circuit, a heat exchanger which maintains normothermia of the blood, and several monitors placed throughout the device and on the patient (see Figure 1). Occasionally, a dialysis filter may also be incorporated into the circuit to address renal injury or failure. Finally, a bridge between the drainage and infusion tubing exists in most ECLS circuits to allow temporary dissociation of the patient from the extracorporeal circuit during emergencies and during trial periods off of ECLS.

Figure 1. Simplified schematic of a patient on an ECLS circuit with its various parts followed by a picture of the various parts of the complete traveling circuit. A closeup of the monitoring devices is also provided.
II. Anatomy

A. Priming the circuit

Prior to cannulation (placing a patient on ECLS), the circuit must be primed with an isotonic solution with 4-5 mEq/L potassium purging all of the gas within the internal circuit and membrane lung. The circuit is also warmed to 37 degrees across the heat exchanger. For most adults, this “clear primed circuit” is adequate; however for most children, especially neonates, a “blood primed circuit” is preferable, bringing the hematocrit to 35-40%. [4] The volume of the neonatal circuit is approximately 400-500 mL which is 1-2 times the newborn blood volume. [3]

The circuit, therefore, must be primed carefully in order to perfuse the neonate at onset of bypass with blood containing appropriate pH, hematocrit, calcium, clotting factors, electrolytes, and temperature; however, ECLS may be instituted in those patients over 35 kg in weight without addition of blood to the prime. To prevent blood clots, heparin (1 unit/1mL prime) is added to the circuit prior to cannulation and is closely monitored during the course of ECLS. Calcium is added to replace that which is bound by the citrate in the bank blood. [4] Finally, the gas of the primed circuit should resemble the patient’s physiologic status (pH, carbon dioxide level) to avoid abrupt changes.

B. Cannulation techniques

Cannulation can be performed using cutdown or percutaneous techniques. In neonates, a transverse neck incision is commonly used to access
the jugular and carotid vessels. One possible method for cannulation is described [see Figure 2]:

The infant is positioned with the neck extended with a shoulder roll, facing the left side. A 2-3 cm transverse cervical incision is made one finger’s breadth above the clavicle over the right sternocleidomastoid muscle (SCM). Dissection between the heads of the SCM exposes the carotid sheath which is opened as the internal jugular vein, common carotid artery, and vagus nerves are identified. Gentle proximal and distal dissection of the vein should be performed; manipulation of the vein should be minimized to avoid induction of venospasm which may preclude placement of a large venous cannula. The common carotid artery lies medial and posterior and may be safely dissected since it has no branches at this level.

Ligatures of 2-0 silk are placed proximally and distally around the internal jugular vein and the carotid artery. Heparin (100 units/kg) is administered intravenously. During a 3 minute period, to allow heparin recirculation, papaverine may be instilled into the wound to enhance dilatation of the vein. The tips of the arterial and venous cannulas will be optimally located at the opening of the right brachiocephalic artery and the inferior aspect of the right atrium, respectively. The cannulas are marked with a suture at the intended extent of insertion (arterial = 2.5 cm and venous = 6 cm in the neonate).

An obturator is placed into the venous cannula to prevent bleeding via the cannula side holes during insertion. The common carotid artery is ligated distally and an angled ductus clamp is placed proximally. A transverse arteriotomy is made near to the distal ligature. 6-0 polypropylene stay sutures are placed on the edge of the artery to prevent subintimal dissection during cannula insertion. The cannula is anchored in place with two circumferential 2-0 silk ligatures with a small piece of plastic vessel loop inserted between the vein and ligature to prevent vessel injury during incision of the anchoring sutures at the time of decannulation. The marking ligature is tied to the most distal circumferential ligature for extra security and the cannula is debubbled. The vein is then ligated distally and occluded proximally by gently retracting the proximal suture. A venotomy is performed and the cannula is placed into the vein, secured, and debubbled.
The cannulas are secured with 2-0 silk sutures to the skin overlying the mastoid process. A chest x-ray is used to confirm position after placement of the cannulas; echocardiography may also be employed to identify the correct position of the cannulas within the great vessels. Care is taken to ensure that hemostasis is obtained and the skin is closed with a continuous 4-0 nylon suture.

Figure 2. A schematic of VA cannulation in a neonate; the vantage point is at the head of the bed.

Percutaneous access to the internal jugular and femoral vein is the preferred approach to cannulation in adults and children over 3 years of age.[3] Sequentially larger dilators are placed over a wire using a Seldinger technique. A variety of cannulas are available for percutaneous venous and arterial access to provide ECLS. The cannulas have varied abilities for gas exchange and flow
support (see Table 1), although the larger the cannula, the greater the flow that can be achieved.

In the percutaneous approach, an ultrasound is usually used to identify the vein. An introducer needle is used to access the vein under ultrasound guidance followed by placement of wire through the needle. The wire can be confirmed by fluoroscopy (the preferred approach at our institution) or echocardiography. Systemic heparin should be administered after placement and confirmation of the guidewire. After incising the skin next to wire, a series of dilators are placed gently over the wire under guidance (fluoro or echo). Generous lubrication is often necessary to place the dilators through the skin and subcutaneous tissues. Aggressive force, however, should not be used to advance the dilators. The ultimate cannula is then placed over the guidewire, with subsequent removal of the wire. An extension is used to connect to the ECLS circuit and de-bubbling of the circuit is performed prior to starting ECLS.

Transthoracic cannulation may be appropriate in the post-cardiac surgery patient with cardiac and/or pulmonary dysfunction, or a patient with septic shock to allow for increased blood flow with the larger cannulas that can be placed.[6] In general, however, access for ECLS is provided via extrathoracic cannulation. The first choice of venous access is the internal jugular vein since it is a large vein which provides easy access to the right atrium via a short cannula. The femoral vein is the second choice for venous drainage access during ECLS and the first for reinfusion during VV support. Drainage via the femoral vein is
relatively inefficient because of the high resistance associated with the long cannula required to reach the right atrium. A femoral cannula placed into the inferior vena cava does not usually provide adequate extracorporeal blood flow. In children under 5 years of age the femoral vein is too small to function as the primary drainage site; therefore, the iliac vein should be considered the second choice of access in young children.[7] Umbilical venous drainage may rarely be used to augment venous drainage, but the contribution of the umbilical vein flow is considered minimal.[8] A proximal venous drainage cannula (PVDC) may be placed into the proximal internal jugular vein to enhance venous drainage to the extracorporeal circuit, and may decrease intracranial pressure.[9]

The size of the reinfusion cannula is less critical than that of the venous cannula, although it must be large enough to tolerate the predicted blood flow rate at levels of total support without generating a pressure proximal to the membrane lung of > 350 mmHg.[4] Infusion cannulas typically have a single end hole while venous drainage cannulas have additional side holes. The first choice for placement of a cannula into the arterial circulation is the carotid artery in all age groups since it provides easy access to the aortic arch. Few complications have been associated with carotid artery cannulation and ligation in newborns, children and adults. The second choice for arterial access is the axillary or femoral artery in those patients over 5 years of age who require gas exchange support and the femoral artery in those with isolated cardiac dysfunction. Disadvantages associated with use of the axillary and femoral arterial access sites are that the femoral artery does not provide easy access to the aortic arch.
while the axillary artery is difficult to dissect and cannulate. In patients under 5 years of age, the femoral and axillary arteries are of insufficient size to provide arterial access: therefore, the iliac artery is the preferred site after the carotid artery. [5] Distal perfusion of the lower extremity arterial circulation is required when the femoral artery is cannulated, although distal perfusion is typically not required after cannulation and ligation of the iliac artery in young children.

In patients supported using venoarterial ECLS using the femoral artery, use of a distal reperfusion cannula has been described to improve limb perfusion. A percutaneous distal femoral artery cannula, placed distal to the arterial reinfusion cannula for ECLS, can be used in children.[10] A cutdown on the posterior tibial artery has also been successfully used to provide retrograde blood flow to the limb.[11] Limb reperfusion must be provided within 6 hours of the ischemic event (arterial cannulation) to prevent irreversible neuromuscular damage to the leg.

C. Monitoring

Once in place, the cannulas are connected to the ECLS circuit and cardiopulmonary bypass is initiated. Flow is increased over the ensuing 10-15 minutes. Once on extracorporeal support there typically is rapid cardiopulmonary stabilization. All paralyzing agents, vasoactive drugs, and other infusions are slowly discontinued during use of veno-arterial support, although some vasopressor support may still be necessary when veno-venous bypass is utilized.[12] Ventilator settings are adjusted to minimal levels in order to allow the lung to rest and seal any air leaks secondary to barotrauma. Application of
higher PEEP during the course on extracorporeal support has been demonstrated to decrease the duration of ECLS.[13] Since only partial bypass is utilized, oxygenation and carbon dioxide elimination are determined by a combination of native lung function as well as extracorporeal flow. The mixed venous oxygen saturation (SvO2) is frequently monitored allowing determination of the adequacy of oxygen delivery in relation to oxygen consumption. Pump flow is adjusted to maintain oxygen delivery such that the SvO2 is in the 60-75% range.

Heparin is administered to prevent thrombus formation throughout the ECLS course. The level of anticoagulation is monitored hourly by whole blood ACT, maintained between 170-230 seconds (normal is approximately 100 seconds).[14] In the setting of active hemorrhage, although circuit thrombosis is inevitable, temporary discontinuation of systemic heparin administration is not only feasible but a better alternative to withdrawal of ECLS. A primed circuit is kept available whenever the ACT is maintained less than 160 seconds. Heparin and other agents, including nitric-oxide, aprotinin, iloprost, and tranexamic acid, have been used to coat circuits to prevent thrombus formation and continue to be evaluated in laboratory and clinic settings.[5]

Depending on underlying physiology, transfusion of red blood cells, fresh frozen plasma, platelets, cryoprecipitate to maintain appropriate targets is frequently required. Therefore, laboratory values, specifically hemoglobin, INR, platelets, fibrinogen and other electrolytes, are routinely monitored and corrected as needed. Chest x-rays are routinely performed to check position of the
cannulas and the status of the pulmonary disease. An echocardiogram is used to
determine the cardiac physiology and identify any anatomic anomalies, though it
can be difficult to interpret while the patient is on ECLS. At our institution,
parameters on ECLS are assessed at least daily to allow for continued
adjustment in the absence of a physician. Finally, the sweep gas and flow
through the circuit are closely monitored, since increasing sweep gas decreases
the arterial carbon dioxide level, while increasing flow provides more oxygenation
and blood pressure support.
D. Oxygenator (see Figure 3)

Figure 3. A picture of the Maquet oxygenator in use within the ECLS circuit of a
neonate followed by a compilation of some of the available oxygenators today
Gas exchange devices (traditionally called oxygenators) are designed to oxygenate and ventilate the blood. “Rated flow” is the amount of desaturated (75%) venous blood with hemoglobin of 12 gm/dL that can be nearly fully saturated (95%) per minute.\[4\] The maximal oxygen delivery (typically 4-5 mL O2/dL), the amount of oxygen delivered per minute when running at rated flow, is calculated using the difference in oxygen content between the inlet and outlet blood. For example, a rated flow of 2 L/min reflects a maximum oxygen delivery of 100 mL O2/min.

The gas blown through the device, across the membrane, is called the sweep gas. The sweep gas is usually 100% oxygen, though occasionally carbon dioxide is added at small amounts (5%) due to the efficiency of carbon dioxide
transfer compared to oxygen through the membrane lung, creating a potential for hypocarbia. A gas flow rate equal to blood flow rate (1:1) is typically used to begin support, with tailoring further adjustments of the rate to the carbon dioxide level: increasing sweep gas decreases the level and vice versa. See Table 2 for specifications of different gas exchangers.

E. Pump (see Figure 4)

Figure 4. A picture of the CentriMag centrifugal pump in use within the ECLS circuit of a neonate.
Two basic pump types are available to provide the required blood flow for the patient: a modified roller pump and a centrifugal pump. Blood flow required for cardiac support is based on the size and age of the patient: 100 ml/kg/min for neonates, 80 ml/kg/min for pediatrics, and 60 ml/kg/min for adults. Single ventricle cardiac lesions and sepsis may require more with target SvO2 70% or greater. Normal oxygen delivery rates are also weight and age based: 6 ml/kg/min for neonates, 4-5 ml/kg/min for pediatrics, and 3 ml/kg/min for adults. The blood flow must be regulated to provide adequate oxygen delivery. Inlet pressure refers to the pressure generated in the venous drainage cannula by the pump. With any inlet occlusion, an extreme negative pressure is created that pulls dissolved gases out of the blood, creating a phenomenon called cavitation. To prevent cavitation, and subsequent local hemolysis, pressures are carefully regulated by decreasing the pump’s revolutions, manually or through a servo-regulator. Outlet pressure refers to the pressure exiting the pump head, and extremes can lead to loss of integrity between blood tubing connectors. Extreme positive pressure can also lead to heat generation and must be carefully dissipated within the pump.

Roller pumps create forward displacement of blood mechanically, and must be constantly monitored and servo-regulated to prevent excess negative inlet pressure. Centrifugal pumps use a series of spinning concentric cones to create centrifugal force to direct forward flow of blood, with a hole in the pumphead to reduce stagnant flow, which acts to decrease hemolysis and heat generation. Centrifugal pumps can be magnetically driven and suspended, and
must have outlet pressure carefully monitored. In neonates, centrifugal pumps may also create more hemolysis than traditional roller pumps and patients on these pumps should be carefully monitored for this finding.
III. Physiology

A. Indications/Contraindications

As with any support technique used in emergent settings, it is critical to continuously review the experience in order to identify those patients who predictably have a poor outcome and those who survive with solely conventional modalities. Many of the “absolute” exclusion criteria have been relaxed as experience with ECLS has allowed refinement and standardization of various aspects of the technique. Inclusion criteria are broadly defined to those who fail or are likely to fail conventional therapy for cardiac and pulmonary support.

To further define neonates that are likely to need ECLS for respiratory failure, an oxygen index and alveolar-arterial oxygen difference have been used. Oxygen index (OI), based on arterial oxygenation and mean airway pressure (MAP), is calculated thus: OI = (MAP x FiO₂ x 100)/PaO₂. An OI greater than 40 consistently on several blood gases is highly predictive of mortality; therefore, “early” initiation of ECLS based on an O.I. > 25 can be considered. The alveolar-arterial oxygen difference [(A-a)DO₂] value of ≥ 610 torr despite several hours of maximal medical management is associated with a very high mortality. Patients on high frequency jet or oscillatory ventilation and newborn patients with CDH are frequently placed on ECLS at lower criteria.

Criteria for high mortality risk among non-neonatal children with respiratory failure and for children of all ages with cardiac failure have been less well-defined. A combination of ventilation index (respiratory rate * PaCO₂ * peak inspiratory pressure / 1000) > 40 and an oxygen index > 40, or a combination of
peak inspiratory pressure $\geq 40$ cmH$_2$O and an A-aDO$_2$ $> 580$ mmHg have been used to predict mortality and a need for ECLS initiation.[17] In fact, the ELSO registry would suggest that the indication for ECLS is simply classified as “failure to respond” in $>90\%$ of pediatric respiratory failure patients. Similarly, criteria for initiation of ECLS in pediatric patients with cardiac insufficiency are poorly defined and include clinical signs such as decreased peripheral perfusion, oliguria (urine output $< 0.5$ ml/kg/hr), core hyperthermia, and hypotension despite administration of inotropic agents or volume resuscitation. [5] ECLS is applied in pediatric cardiac patients in the setting of cardiogenic shock, cardiac arrest, acute deterioration, and in the operating room due to inability to wean from heart lung bypass.

Previous contraindications to ECLS have been reevaluated and the criteria for inclusion broadened. ECLS may be successfully applied in the preterm newborn with EGA $> 30$ weeks and birth weight $> 1$ gram, although the incidence of ICH may be higher.[18] Development of ICH or extension of a previously present ICH was nonexistent when heparin administration was minimized and a proximal venous drainage cannula placed.[19] Reasonable outcomes have also been demonstrated when ECLS has been instituted in the setting of grade I ICH regardless of age group.[20] Mechanical ventilation pre-ECLS is no longer considered a contraindication to ECLS; although initiation of ECLS earlier in the course of respiratory insufficiency may reduce morbidity and mortality, survival in patients who have been managed with mechanical ventilation for up to 10 to 14 days may still be reasonable.[3] Cardiac arrest is
also not considered a contraindication but could be an indication for ECLS at many centers.\[21\] Finally, as an ethical consideration, those patients with profound neurologic impairment, multiple congenital anomalies, including severe CDH or other conditions not compatible with meaningful life are excluded as candidates for ECLS.

Additional relative exclusion criteria are the presence of irreversible multiorgan system failure, major burns, severe immunodeficiency, chronic lung disease, and the presence of an “incurable” disease process. It should be noted that preoperative cardiac anomalies in newborns also represent a relative contraindication to ECLS since they should be treated operatively, although they may be supported with extracorporeal support until surgical intervention may be accomplished.

B. Modes of ECLS

The basic configurations of ECLS are veno-arterial (VA) and veno-venous (VV). Additional variations include single site double lumen VV (DLVV) versus two sites. In the early experience, ECLS was almost always performed using VA support since it offered the potential to replace cardiac and lung function; however, significant disadvantages\[5\] include

1) major artery must be cannulated and at least temporarily, sacrificed
2) risk of dissemination of particulate or gaseous emboli into the systemic circulation
3) pulmonary perfusion may be markedly reduced
4) cardiac output may be compromised due to the presence of increased ECLS circuit-induced afterload resistance
5) coronary arteries are predominantly perfused by relatively hypoxic left ventricular blood
In contrast, both VV and DLVV support provide adequate gas exchange without these disadvantages, though a fraction of the infused blood recirculates back into the extracorporeal circuit. As a result, oxygenation levels are relatively reduced and extracorporeal blood flow rates must be increased approximately 20% to account for this effect. The VV and DLVV extracorporeal circuit configurations also do not provide cardiac support, though, patients who require pressor support prior to initiation of bypass improve once hypoxia and acidosis are resolved and high ventilator pressures reduced on ECLS.[12]

Since 1988, a double lumen cannula has been available for providing DLVV bypass via a single internal jugular access site, as opposed to a two site approach (using internal jugular vein for drainage and femoral vein for reinfusion). The DLVV configuration of bypass has now been used in newborns and older patients with an excellent survival rate, and minimal conversion from DLVV to VA ECLS. In older patients, however, the side needed for adequate drainage may preclude the use of DLVV cannulation, and two sites may be necessary.[5] In some settings, especially sepsis or cardiac dysfunction, an additional venous cannula may be needed for VA ECLS to provide increased drainage. This configuration, termed VAV ECLS, may be converted to traditional VV ECLS once cardiac support is no longer necessary.

C. Procedures on ECLS

Most operative procedures performed during ECLS are carried out in the intensive care unit. Either gas anesthesia administered via the oxygenator of the
ECLS circuit or intravenous anesthesia with narcotics, benzodiazepines and paralytics may be employed. Procedures on ELCS include recannulation or repositioning of the cannulas, tube thoracostomy, cardiac surgery or catheterization, repair of congenital diaphragmatic hernia, and thoracotomy for bleeding, effusion or lung biopsy.[22, 23] Hemorrhagic complications, which occurred in almost half the patients, were associated with a higher mortality; therefore, only procedures that are absolutely necessary should be performed while on ECLS and others delayed until ECLS can be discontinued. During all procedures on ECLS, electrocautery should be used generously, the ACT reduced to approximately 160-180 seconds, platelet count maintained well above 100,000/mm³, and the perioperative administration of aminocaproic acid should be highly considered.[5]

D. Weaning and Decannulation

Over the ensuing days on ECLS, as the cardiopulmonary pathology resolves, the inflammatory process subsides, the pulmonary radiographic appearance improves, and the elevated pulmonary vascular pressures normalize, gas exchange increases across the native lung.[5] The ECLS flow rate is weaned as gas exchange improves based on the SvO₂. Simultaneous increases in lung compliance are frequently observed.[24] Most practitioners transiently discontinue extracorporeal support in order to determine the true cardiopulmonary function; this “trial off” is performed during VA bypass by clamping the arterial and venous connectors between the bridge and the patient.
and allowing recirculation of extracorporeal blood flow through the bridge to prevent thrombosis in the circuit. Although, it is often clear during the initial 15-30 minutes whether ECLS may be discontinued, prolonged trials of up to 4 hours may occasionally be required. During VV bypass, the gas phase of the membrane lung may simply be capped indefinitely so that the patient remains on extracorporeal support but without contribution of the artificial lung to gas exchange. In patients with severe cardiac insufficiency, trials should be performed with optimal pressor support, frequently accompanied by echocardiographic evaluation to determine adjunct medications that may be needed to wean off ECLS.[5]

For decannulation, the incision is opened and the right carotid artery and/or internal jugular vein are ligated. Percutaneously placed cannulas may simply be removed and prolonged pressure applied. The long term follow-up of infants with right common carotid artery reconstruction demonstrated that nearly two-thirds of the anastomoses were occluded or stenotic.[25] Electroencephalography, neuroimaging, and neurodevelopmental follow up failed to demonstrate any differences during the first year of life between those newborns undergoing right common carotid artery reconstruction and historical controls where the right common carotid artery was ligated. Another study demonstrated that though the right internal carotid artery flow may be reduced following ligation and ECLS in newborns, cerebral blood flow is normal in the long term follow up.[5] Other theoretical risks of carotid artery reconstruction include those of acute thromboembolism and atherosclerotic plaque formation.
over a longer period of time, especially in view of the high incidence of stenosis. At our institution, we do not routine perform reconstruction of the carotid artery.

Considerations for discontinuing extracorporeal support at times other than when indicated by improvement of cardiopulmonary function include the presence of irreversible brain damage, other lethal organ failure, and uncontrollable bleeding. Those neonates with congenital diaphragmatic hernia or pneumonia and pediatric patients with cardiac or pulmonary failure may require substantially longer periods on ECLS before resolution of the cardiopulmonary process is observed. Judgment must be utilized regarding the reversible nature of the respiratory dysfunction, the presence of associated organ system failure, and the development of complications associated with ECLS in determining whether continuation of extracorporeal support is warranted after prolonged periods on ECLS.
III. Outcomes

As of July 2011, over 46,500 patients were placed on ECLS based on the ELSO registry (see Table 2), with over 34,250 (74%) surviving ECLS, and over 28,700 (62%) surviving to discharge. Neonatal respiratory failure, which includes persistent pulmonary hypertension (PPHN), meconium aspiration syndrome (MAS), and congenital diaphragmatic hernia (CDH), has 85% survival from ECLS and 75% survival to discharge (see Table 3). MAS has the best survival with ECLS use at 94% with CDH having one of the worst at 51%. ECLS use for cardiac failure in neonates has a survival off ECLS at 63% and survival to discharge at 39%. Overall, VV is the most commonly used mode of ECLS for respiratory failure. Though VA remains the most common support mode in neonates, the use of VV steadily increasing in this population.[4]

In the pediatric population, respiratory failure has a 65% survival from ECLS and 56% survived to discharge. Pneumonia secondary to various infectious etiologies is the most common diagnosis with a 61% survival. The use of VA is still more common in pediatric cases through cases started on VV are >45%. The use of DLVV is also increasing and is currently the predominant mode of VV access.[4]

Adult cases of ECLS have traditionally been small, though is the most rapidly growing segment coinciding with the use of ECLS for H1N1 infection, and publication of the CESAR trial. ARDS is the most common indication for ECLS in adults with survival rates around 51%. The highest survival of adults on ECLS is with viral pneumonia at 65%. VV is the predominant mode of support (88%) with
60% using DLVV. Intracranial complications were far less frequent in pediatric patients, though survival was much lower when they occurred. [4]

Overall, a second ECLS run was required in pediatric patients only 3% of the time. The rate was higher in patients on VA ECMO and for cardiac dysfunction. There were no differences in survival for a second run, however, among non-survivors, there was a higher rate of renal failure during the first run and there was higher rate of complications during the second run. About 5% of patients undergo a repeat ECLS run after an index run post cardiac surgery. The overall survival to discharge is about 25%, with non-survivors having a six-fold higher incidence of renal failure. Finally, in patients who underwent multiple runs, neurologic and infectious complications increased the most[4].

ECLS has been effective in other clinical situations such as in blunt trauma in children and adults where survival rates approximate 65%. Although thermal injury was previously considered a contraindication, ECLS has been applied in pediatric patients after significant body surface burns with excellent survival. ECLS has also been successfully applied to patients undergoing tracheal repair, to those with alveolar proteinosis who require lung lavage, and to those with lung hypoplasia due to in-utero renal insufficiency, asthma, sickle cell disease, and lung failure following lung transplantation[3]. Another growing application of ECLS has been in the form of extracorporeal cardiopulmonary resuscitation (ECPR) in adult or pediatric patients with cardiogenic shock, post traumatic hypotension, hypothermia, arrhythmias, and cardiac arrest. Favorable neurologic outcome was noted in about 80-90% of the survivors on short-term
follow-up[26]. In pediatric cardiac patients, ECPR has a survival to discharge of 71% in nonsurgical patients and 46% in postoperative patients[21]. In hospital cardiac arrest had the best neurologic outcomes and survival to discharge in all patients after ECPR.

IV. Complications

In general, the complications associated with ECLS are mechanical or patient related. Mechanical causes are the pathology of the anatomy of ECLS whereas patient related issues are the pathophysiology. The most common mechanical problems are clots in the circuit and cannula problems. The most common patient related complications are renal failure requiring dialysis, hemolysis and intracranial hemorrhage (ICH) or stroke. Mechanical issues are discovered through constant surveillance. Often, checklists are used to assess different aspects of the circuit: venous cannula, venous reservoir ("bladder"), pump, oxygenator, heat exchanger, arterial cannula, and environment.[4]

Patient complications include renal failure, hemolysis, ICH, bleeding/thrombocytopenia/coagulopathy, hypertension, myocardial stun, and sepsis. Oliguria and capillary leak resulting in decreased renal perfusion is common with ECLS. In the presence of elevated creatinine or lack of response to IV furosemide, anatomic anomalies in the kidney should be excluded with an ultrasound. A dialysis filter added to the circuit can facilitate removal of additional fluid to help pulmonary status and prevent further kidney injury. Hemolysis can occur due to red blood cell trauma during extracorporeal support, which is often
related to clot formation within the circuit, overocclusion of the roller pump, or use of a centrifugal pump. Hyperbilirubinemia is noted in 8% of patients and renal insufficiency in 10%[4]. If the serum free hemoglobin is noted to be elevated, a change in the circuit could be helpful to stifle this problem.

ICH can occur in about 13% of neonates, and at even higher rates in premature infants due to the immature germinal matrix. To decrease the rate of ICH, thrombocytopenia must be aggressively corrected, heparin infusion must be carefully monitored, adequate oxygenation maintained while avoiding abrupt changes to the pH and carbon dioxide levels. Management of ICH on ECLS varies based on extent of bleeding from treatment with aminocaproic acid to discontinuation of ECLS. Bleeding on ECLS can occur intracranial or at any other site including at a surgical or procedure site, gastrointestinal, and pulmonary so caution should be used with any procedure including IV placement, NG placement or bronchoscopy. Disseminated intravascular coagulation (DIC) can occur at any point during the course of an ECLS run and the most common causes should be addressed promptly: gram-negative sepsis, acidosis, hypoxia and hypotension. Finally, hypertension is seen most commonly with VA ECLS and increases the likelihood of ICH; therefore, management with hydralazine, nitroglycerin or captopril should be swiftly performed.[3]

In the early course of ECLS, myocardial depression can be common with decreased left ventricular shortening fraction (LVSF) seen after initiation, and improving slowly to normal after 48 hours. Impaired filling of the coronary arteries and persistent subendocardial ischemia during early high-flow phases is thought
to play a role in the lowered LVSF. Pneumothorax and pericardial tamponade are life threatening intrathoracic complications which demonstrate increasing PaO$_2$ with decreasing peripheral perfusion and SvO$_2$ followed by decreasing ECLS flow and progressive deterioration. The presentation can be similar to “myocardial stun” seen on initiation of ELCS, therefore, it is important to seek and identify these conditions quickly. Initial emergent placement of a pleural or pericardial drainage catheter followed by thoracotomy for definitive treatment of a pericardial tamponade may be lifesaving.

References:


I. INTRODUCTION

Continuous monitoring is one of the most identifiable features of the intensive care unit environment. Indeed, the original concept of such areas was to be ‘monitored’ environments where physiologic fluctuations may be tracked and analyzed in real time. Further, monitoring is essential to understand the impact of intensive care unit interventions and to characterize the nature and significance of derangements.

Monitoring strategies are designed to follow individual organ function and, to a lesser degree, the interaction between systems. Available devices can analyze physical parameters (pressure, temperature, flow, volume), electrical function (EEG, ECG, train-of-four), gas dynamics (saturation, partial pressure), concentrations (hemoglobin), and chemistries (microdialysis). However, monitors are limited in their ability to interrogate tissue health and cellular function. Most measurements are surrogates and should be interpreted carefully while considering population norms, baseline patient capability, demands of the physiologic circumstance, and tolerance of deviations from “optimal” or “normal” function. Furthermore, individual monitor values are often insufficient to draw conclusions about global physiology. For example, a normal
blood pressure may not be interpreted to signify adequate cardiac output or perfusion just as normal urine output may not equate with normal renal function.

II. Neurologic Monitoring

A. ICP Monitoring

Intracranial pressure (ICP) monitoring is indicated in patients at risk of or experiencing intracranial hypertension (ICH) from causes such as trauma, spontaneous intracranial hemorrhage, or hydrocephalus. Normal horizontal position ICP in healthy adults is 7-15mmHg and 5-10mmHg in children. An ICP >40 for 4 hours or more is considered unsurvivable. ICP is highly variable and a 30-minute average is utilized to follow Mean ICP. Measuring ICP allows the intensivist to calculate cerebral perfusion pressure (CPP=MAP-ICP). Goal CPP for an adult or teenage child is 60-70mmHg, for a school aged child is 40-65, and for children under two years old is ill-defined. Multiple modalities are available for ICP monitoring. The choice of modality weighs the risks (infection, hemorrhage, CSF overdrainage) vs. benefit (reliability of measurement and ability to therapeutically drain CSF).

A ventriculostomy is a catheter that is placed into the lateral ventricle and is considered the gold-standard for measuring ICP. In addition to monitoring, this modality has the benefit of therapeutic drainage of CSF to decrease ICP – although excess drainage can lead to emptying of the ventricular system and accumulation of subdural hematoma. The risk of infection (~5%) starts to increase after five days and is not improved with prophylactic antibiotics.
A catheter-tipped microtransducer (Camino ICP Bolt, or Codman MicroSensor) can be placed into the parenchyma, epidural space, subdural space, or ventricle. The technology makes use of the principle that increase pressure will place greater strain on the diaphragm at the distal tip which can be interpreted as pressure values using experimental norms. The main advantage of this modality is decreased risk of infection or hemorrhage. Downsides of this catheter include 1) inability to therapeutically drain and 2) measurement ‘drift’ over time (there is no way to externally re-zero the monitor once it is placed). This drift may begin as soon as 48 hours after catheter placement, though many intensivists argue that the vast majority of intracranial hypertensive issues occur early in patient courses.

While the monitor allows the intensivist to adjust systemic blood pressure to maintain CPP, this may not be indicative of stable cerebral blood flow. Indeed, in ICH cerebral autoregulation is unreliable. Therefore, additional monitors of cerebral oxygenation and metabolism are undergoing evaluation.

B. Monitors of Cerebral Perfusion

Jugular bulb saturation is a global marker of cerebral perfusion. It is insensitive to small regional abnormalities in brain oxygenation and has largely been abandoned in clinical use. Newer implantable tissue oxygen microsensors (Integra’s Licox Brain Oxygen Monitoring System) require a catheter be placed into the white matter. Normative values are being developed, with PbtO$_2$ < 10mmHg in adults being considered abnormal. Long-term outcome and
prognostic data are not yet available. The main limitation is the local measurement of oxygenation. If the catheter is not placed into the area of injury, the data may not correlate with metabolic activity in the zone of injury. Furthermore, it remains unclear whether such monitors should be placed in the area of injury, the penumbra (area around injury at risk for spread of damage), or in a distant site.

Cerebral microdialysis (CMA microdialysis catheter) is a new technology that measures brain tissue metabolites as a marker of perfusion allowing metabolic-directed therapy. Normative values are being developed and are not yet prognostic. A microcatheter placed into the brain parenchyma can measure cerebral glucose, lactate, pyruvate, glutamate, aspartate, and glycerol. Differing ratios in measured diasylate concentrations are thought to reflect altered substrate delivery and/or substrate utilization. This methodology again only measures the local effects in the tissue where the catheter is placed.

Near Infared Spectroscopy (NIRS) measures the difference in transmitted and measured light at specific wavelengths. The NIRS transducer emits/transmits light through the cerebral tissue and measures light as it exits tissue, allowing measurement of tissue oxygenation deeper than cutaneous pulse-oximetry. Similar to other technologies, NIRS is limited by its ability to interrogate individual locations, though in principle it may be applied to multiple sites simultaneously. Furthermore, the application of a flank sensor (measuring renal/somatic perfusion) allows comparison of cerebral and somatic perfusion.
Absolute normal values of NIRS saturation are not known, though following the trend can provide valuable information.

Surface tonometry can be used in the neonatal population with an open anterior fontanelle. This requires a pressure transducer to be placed on the neonate’s head directly over the open fontanelle. The measured pressure is influenced by the amount of external pressure, hence making the reported result less valuable than the trend. Because the sutures are not fused in the neonate, serial measurement of head circumference is also utilized as a measure of ICP.

C. Other Methodologies for Monitoring Brain Perfusion

Transcranial oxygen saturation monitors have been employed in adults to show hemispheric oxygen levels. While the absolute values may be less valuable, trends are potentially useful to evaluate hemispheric oxygenation. This may be particularly useful in circumstances where cerebrovascular event risk is elevated such as ECMO. However, significant decline in cerebral oxygen saturation may occur once tissue damage from intracranial hemorrhage or embolism/thrombosis is established and, therefore, less likely to be reversible.

D. Brain Activity Monitoring

Subclinical seizures in the ICU can be difficult to recognize and correlate with mortality. Excess excitatory activity may lead to neural injury or death (“excitotoxicity”) in as little as 30 minutes. Continuous EEG monitoring is utilized to detect subclinical seizures and to guide and evaluate interventions. Using 20
electrodes to be placed on the scalp for at least 12 continuous hours, one may detect subclinical seizures. In the absence of physical manifestations of epileptiform activity, the clinician may use the continuous EEG to evaluate the effectiveness of sequential therapies. Consideration should be given to prolonged EEG in patients at risk (status epilepticus, history of refractory seizures, head injury, cerebral ischemia). Skin breakdown with prolonged (>1-2 days) electrode placement has been reported.

Bispectral index (BIS, Covidien) monitoring has been developed to evaluate the state of wakefulness of patients under sedation and anesthesia. The device utilizes a single sensor placed on the patient’s forehead and employs complex algorithms to analyze the brain electrical activity to infer the level of consciousness (0=unconscious, 100=fully awake). In adults, values less than 20 are considered excessively ‘deep’ anesthesia while values greater than 70 may suggest inadequate anesthesia for noxious procedures. Routine use in adults has been shown to decrease intraoperative awareness, but this has not been validated in children. Nevertheless, there is growing interest in using this technology in ICU settings where patients may undergo prolonged sedation.

Special Considerations in infants versus older children

Many of the monitoring devices discussed above have either not been used in infants or have not been adequately validated to interpret absolute values. While reasonable norms exist for physiologic measures such as heart rate, blood pressure, temperature, arterial blood gas values, urine output, and others, equivalent reference points for ICP, CPP, local brain P0₂ and metabolic
activity have yet to be defined. Therefore, while the clinician may obtain an ever-expanding data set with regard to neurologic function in the neonate, enthusiasm must be matched with skepticism regarding the validity of any specific values.

III. Respiratory Monitoring

A. Pulse Oximetry

Prior to the development of modern continuous pulse oximetry, hypoxemia and its related complications were frequent events in the neonatal and pediatric ICU environments. Pulse oximetry makes use of the principle that hemoglobin saturated with oxygen (or other gases) will exhibit different absorbance and transmittance characteristics for specific wavelengths of light. By testing normal patients in the range of tolerable oxygen saturation (75-100%) and inferring the characteristics at lower saturations, manufacturers built algorithms to report continuous oxygen saturation that approximated arterial blood gas measurements to within 2-5 percent in the higher ranges and 10% at the lower ranges. However, early devices used single wavelengths of light and could only differentiate ‘saturated’ from unsaturated hemoglobin. Furthermore, they required pulsatile blood flow to differentiate arterial from venous signals and could not be used during ECLS. The addition of two more wavelengths has resulted in absolute values that reliably lie within 2% of blood gas measurements and can accurately report total hemoglobin, methemoglobin, and carboxyhemoglobin concentrations on a continuous basis.
Continuous hemoglobin oxygen saturation is a critical piece of data to assess the effectiveness of ICU interventions. The arterial partial pressure of oxygen (PaO\(_2\)) may be a more direct measure of the efficiency of gas exchange at the alveolar/capillary junction and is, therefore, an important tool to assess the degree of pulmonary dysfunction. However, it is a trivial contributor to overall oxygen content in the blood. Using the oxygen content equation (shown below), it becomes readily apparent that changes in SaO\(_2\) have substantially greater impact on oxygen content. While a decline in PO\(_2\) for a given inspired oxygen concentration and mean airway pressure may signal a decline in pulmonary function or anatomic shunt and may be useful for prognostic purposes, increased PO\(_2\) is not the primary goal of subsequent therapeutic manipulations to achieve improved patient oxygenation.

\[
O_2 \text{ content} = 1.36(SaO_2)(Hgb) + PO_2(0.003)
\]

Notably, the oxygen content equation also demonstrates the linear relationship between hemoglobin saturation and blood oxygen content. Therefore, there is no mathematical threshold of oxygen saturation that signals patient risk. Many intensivists empirically target 90% or greater as the desirable values though this is neither supported by available data nor by the mathematical principles of the equation. In circumstances such as respiratory failure, tolerance of lower arterial oxygen saturation may be an essential component of strategies to avoid ventilator-induced lung injury (VILI).

An important, but often overlooked additional value of pulse oximetry is the presence and quality of the waveform. An astute clinician recognizes that
this device also reports heart rate, may be a sensitive indicator of non-perfusing
dysrhythmias, and may indicate low cardiac output states. The waveform
visually demonstrates beat-to-beat perfusion and, though subject to artifact such
as patient movement and electrical interference, is a sensitive indicator of
perfusion.

There are special considerations for the use of pulse oximetry in
neonates. In children with patent ductus arteriosus and with structural congenital
heart disease, arterial oxygen saturation may vary by location. Pre-ductal
saturation (right arm, right ear) reflects blood ejected through the aortic route or
equivalent which, in turn, is a mixture of blood returning from the lungs and blood
traversing intracardiac defects such as ASD and VSD. Post-ductal saturation
(lower extremities) reflects a mixture of blood ejected from the left ventricle and
systemic venous blood from the pulmonary artery. Thus, pre-ductal saturation is
a better tool to assess pulmonary function though the absolute value may be
affected by changes in intracardiac shunt. In contrast, post-ductal saturations
are indicative of the significance of pulmonary hypertension and the oxygen
content delivered to abdominal viscera.

B. Apnea and bradycardia monitoring

Premature infants (<36 weeks gestation and total gestational age <60wks)
frequently experience apnea and may become bradycardic as a result. This may
occur spontaneously, but is also a well-recognized consequence of illness,
operation/anesthesia, and physiologic stress. A chest strap detects chest wall
motion while a simplified ECG tracks cardiac electrical activity. Thresholds for rate alarms may be set to notify care providers. When combined with continuous pulse oximetry, these tools are effective at notifying clinicians of impending compromise. Simple stimulation of the infant is often sufficient to address an apnea episode, though more definitive airway control may be required.

C. Capnography (Figure of normal capnogram)

Continuous monitoring of expired CO$_2$ has become the standard of care in anesthetic management and is rapidly proliferating in the ICU environment. In principle, the detected CO$_2$ levels at the end of respiration should reflect alveolar CO$_2$ concentration. In turn, this may be considered a surrogate for systemic arterial PCO$_2$ levels. In practice, ventilation/perfusion mismatch, timing of emptying of regions of lung, and lung disorders lower the detected values and limit the utility of the absolute value obtained in capnometry. However, trends in the capnometric measurement may be interpreted to reflect changes in endogenous CO$_2$ production, minute ventilation, expiratory restriction, and effective pulmonary perfusion as described in the examples below:

1. One of the earliest indicators of malignant hyperthermia (a hypermetabolic state) is rising end-tidal CO$_2$ (ETCO$_2$).

2. As lung compliance improves in states such as ARDS, increased tidal volumes may result in falling ETCO$_2$. 

3. In severe asthma, expiratory time may be inadequate to reach a stable ETCO$_2$ reflecting mixing of all lung units and may be significantly lower than arterial PCO$_2$.

4. In low cardiac output states, decreased delivery of CO$_2$ to the lung will result in diminished ETCO$_2$.

The graphical representation of expired CO$_2$, capnography, is also valuable in the interpretation of respiratory derangements. A normal waveform begins from a baseline value of zero (inspired gas washout), increasing towards an upper baseline, slowly rising towards the end-expiration value (gradual increase expiration of lung units), a rapid down-sloping line (initiation of inspiration), and rapid return to zero during the remainder of inspiration. Several important scenarios should be recognized:

1. Extubation, disconnection, or complete airway obstruction will result in the immediate disappearance of the waveform and reporting of a value of “zero”.

2. Cardiac arrest will also cause disappearance of the waveform and ETCO$_2$ will read as “zero”.

3. Asthma and other expiratory restrictive changes will manifest a slower upslope and either truncated or, more commonly, absent upper baseline. The waveform returns to the lower baseline.
D. Transcutaneous Monitoring

Surface monitoring devices may be used in neonates to track both tissue CO$_2$ and O$_2$ levels. Each may report values for gas partial pressure validated to track the trend of capillary gas concentrations, but do not report hemoglobin oxygen saturation. The devices are generally applied on the trunk and generally must be moved every two days or more frequently. Limitations of the technology include overestimation of systemic PCO$_2$, underestimation of arterial PO$_2$, and sensitivity to variations in cutaneous perfusion. These devices are generally used in neonates only.

IV. Cardiac Monitoring
Cardiac monitoring begins with rhythm and rate evaluation and surrogate measures of function such as blood pressure. As circumstances dictate, more detailed evaluation may require additional measures such as cardiac preload (central venous pressure, RV end diastolic pressure/volume, pulmonary arterial diastolic or wedge pressures), cardiac output, and the match between systemic oxygen delivery and consumption \((\text{SvO}_2=\text{mixed venous oxygen saturation})\). In recent years, many of the more invasive measures have been deemed unnecessary and surrogates have been increasingly used as indicators of cardiac function.

Standards of care dictate that all ICU patients should be monitored at a minimum with continuous ECG and non-invasive blood pressure cuff.

A. Blood Pressure Monitoring

Blood pressure can be monitored either invasively or non-invasively. Noninvasive blood pressure (NIBP) monitoring with a blood pressure cuff can be performed using a variety of methods. For all methods, the cuff bladder should cover at least 75% of the appendage circumference. The traditional auscultatory method (listening for Korotkoff sounds with a manual cuff over the brachial artery) is the most reliable noninvasive method, but requires the practitioner to repeat the measurement frequently. It is limited in low stroke-volume states or continuous flow (ECLS) in which circumstances doppler (see below) methods should be utilized. Automated oscillometric techniques measure the oscillometric waveform as the cuff deflates to determine a mean arterial pressure (MAP) and
systolic and diastolic pressures are back-calculated. Doppler measurement of blood pressure is highly reliable for ascertaining systolic blood pressure, although diastolic blood pressure is unreliable using this technique. In small neonates, the cuff method usually overestimates BP, while in larger babies the cuff method usually underestimates BP. If a baby is between cuff sizes, the larger size should generally be used.

Invasive blood pressure monitoring with an arterial line is indicated for patients with rapidly changing hemodynamics or if frequent labs or blood gas analyses will be required. Arterial lines can be placed peripherally (radial, dorsalis pedis, or posterior tibial) or more centrally (femoral, brachial, axillary or umbilical). Caution should be exercised in placing arterial lines in the feet of patients with anatomically impaired lower extremity circulation (diabetics or peripheral vascular disease) due to risk of infection and unreliable tracings. Furthermore, caution should be exercised in placing proximal/central arterial lines due to the significant risk of thrombosis leading to limb ischemia and potentially limb loss. Peripheral pulses should be documented frequently be the bedside nurse in patients with proximal arterial lines. Arterial waveform transduction and pressure measurement is dependent on the position of the catheter. Systolic pressures are greater and diastolic pressures are lower in more distal vessels due to pulse amplification of less elastic vessels. Pressures measured from femoral or brachial lines will have a decreased pulse pressure. The MAP, however, is constant across all points – peripheral or central. Arterial line waveforms are subject to dampening or amplification (‘whip’). The waveform
consists of three components: 1) systolic upstroke, 2) dicrotic notch signifying closure of the aortic valve and 3) diastolic runoff. Loss of the dicrotic notch is associated with a dampened waveform and excessive peaking of the upstroke is associated with pulse pressure amplification.

Arterial waveforms are subject to several operator errors. First, the device must have a zero point (reference zero) for purposes of transduction. In general this should be the interatrial axis of the heart the external analog of which is the mid-axillary line of the 4\textsuperscript{th} intercostal space. Changes in relative position of the patient or transducer may artificially alter the recorded values. Second, catheter malposition may result in dampened waveforms. Third, respiratory variation, which may be amplified in hypovolemic states, may cause relatively wide swings in arterial pressure recordings. Indeed, this finding forms the basis for many newer technologies that purport to analyze cardiac preload and effectiveness of volume administration.

At least one company has FDA approval for a device that calculates cardiac output using indicator dilution and arterial line sampling. The technology has been validated versus thermodilution technologies in adults but there is limited data in young children.

Operative arterial lines require additional considerations. Unlike percutaneous techniques, methods of open insertion often result in vessel ligation. Though in the majority of patients this may be done without sequelae, the clinician should consider the likelihood of disease chronicity and recurrence (congenital heart disease), duration (multisystem organ failure), vascular disease
that might compromise collateral blood flow (vasculopathies). When these or other future concerns are operant, consideration should be given to using “semi-open” technique wherein the vessel is isolated and cannulated using Seldinger technique without vessel ligation.

In newborns, either umbilical artery may be utilized for arterial access. The clinician should be familiar with the anatomy as the catheter will need to pass inferiorly and laterally to enter the internal iliac artery. The umbilical vessels are accessible for the first 24 to 48 hours of ex-utero life but rapidly thrombose. In the delayed circumstance, the risk of embolism rises.

**FIGURE 1:**

Volume Status and Cardiac Performance Monitoring
B. Central Venous Pressure Monitoring

Central venous pressure (CVP) is utilized as a surrogate of right atrial pressure (and correlating with left atrial filling pressure assuming a constant fluid column). Utilizing pressure as a marker of volume status is subject to multiple confounding variables (intrathoracic pressure, valvular abnormalities, pulmonary vascular disease), but is commonly utilized (at a minimum) for following a trend in volume status. CVP is ideally measured in the SVC but is often measured in the IVC although the pressures are often not equal. CVP is measured at the end of diastole (mean value of the a-wave) just prior to tricuspid valve closure and ventricular ejection) corresponding to RV end diastolic pressure.

![ECG Tracing]

**Figure 2 Fuhrman Figure 21-5**

C. Central Venous Pressure and Oxygen Saturation Monitoring

Central venous pressure (CVP) is a valuable surrogate measure of right heart preload. Ideally, the catheter should lie within the right atrium or equivalent structure and should be a semi-rigid device. Like arterial catheters, these devices require a zero point and a continuous water column to the transducer. In distinction from arterial catheters, intrathoracic vascular pressure monitoring devices are subject to the impact of oscillating thoracic pressure with respiration.
Therefore, whether the patient is spontaneously breathing or mechanically ventilated, measurements should be obtained at the end of inspiration when intrathoracic pressure is at baseline. Notably, two additional issues should be considered. First, positive intrathoracic pressures may artificially elevate recorded intravascular pressures. This can only be discerned through placement of an esophageal pressure monitor. Second, continuous pressure ventilators (oscillator, jet) do not have an expiratory phase. Again, intravascular pressure measurements may be artificially elevated and consideration should be given to placing an esophageal pressure probe to determine the contribution of intrathoracic pressure to values obtained.

Normal central venous pressure varies between 0-5 cm H₂O. However, certain pre-existing disease states such as pulmonary hypertension, right ventricular failure, tricuspid valvular disease, and others may result in elevated values and/or abnormal waveforms. In addition, acute disease states may require higher central venous pressures to facilitate cardiac output.

Central venous oxygen saturation monitoring (ScvO₂) is utilized as a marker of oxygen extraction when compared to arterial saturation. It does not include return from the coronary sinus and as such is often elevated as compared to true mixed venous oxygen saturation (SvO₂) as measured from the pulmonary artery. ScvO₂ should be measured from the SVC, as IVC measurements are highly variable with changes in mesenteric circulation and do not correlate with true SvO₂. ScvO₂ has been utilized to guide early goal-directed therapy for adult sepsis with good outcomes. Normal SvO₂ is 65-75%, with lower
values (<65%) signifying inadequate oxygen delivery (cardiogenic or hypovolemic shock) and higher values (>75%) signifying inadequate oxygen extraction (usually is vasodilatory shock).

D. Pulmonary Artery Catheters (Swan-Ganz Catheters)

Pulmonary artery catheter (PAC) placement has been the subject of great controversy over the past decade, with multiple adult studies demonstrating no improvement in mortality with PAC placement. Confounding these studies is a demonstrated lack of familiarity in interpreting PAC data – even among expert intensivists. PAC placement allows the measurement of multiple factors affecting cardiac performance: central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary artery capillary wedge pressure (PCWP), stroke volume (SV), mixed venous oxygen saturation (SvO2), and cardiac output/index (CO/CI). Systemic (SVR) and pulmonary vascular resistance (PVR) can then be calculated from these variables. Some systems will calculate LV end diastolic volume index (EDVI). The placement of a PAC is not without risk, with multiple reports of erosion through the PA or RV leading to cardiac tamponade or fatal hemorrhage. Additionally, each inflation of the balloon carries the risk of PA rupture. In many patients, the PA diastolic pressure correlates with PCWP and the balloon does not need to be regularly inflated. True indications for PAC use in children are controversial. Most patients can be managed without the use of a PAC, although discordant right and left ventricular dysfunction in an unstable patient may be an indication for use. PAC’s are being replaced by the increasing
use of bedside functional echocardiography for assessment of biventricular filling and function.

Placement of a PAC requires a large central venous sheath (7F for adult catheters, 5F for pediatric catheters). Advancing the catheter into the PA (following waveforms) is a skill that must be mastered and is easiest from the right IJ or left subclavian position. Placement via the left IJ or right subclavian is possible, but will often require multiple attempts due to the acute angles the catheter must traverse. Femoral insertion is possible, but often requires fluoroscopic guidance. In the pediatric population, PAC’s are often placed in the cardiac catheterization laboratory. PAC’s are not utilized in neonates due to size limitations.

Figure 3
E. Cardiac Output Monitoring

Cardiac output monitoring can be measured by two methodologies: the Fick method (calculated from oxygen consumption--$\text{VO}_2$--divided by arterial/venous oxygen content difference), or the thermodilution method (utilizes the injection of cold saline into the proximal port of a pulmonary arterial catheter and measurements from a thermistor at the end of the catheter and calculates the area under the curve as a function of decay over time). Optimal catheter position requires that the injection or energy coil lie within the right ventricle. As mentioned in the arterial catheter section, new dilution methods are being employed using systemic arterial sampling as well. In a study of outcomes of pediatric ICU patients stratified by severity of illness, patients with pulmonary artery catheters had higher mortality. Since then, the use of these devices has plummeted and most clinicians have turned to central venous catheters or non-invasive measures.

There are numerous other methods to measure cardiac output either intermittently or continuously, but none have been regularly employed in American ICUs. Echocardiography may calculate CO based upon aortic dimensions and Doppler. Impedance devices can calculate aortic flow via oscillatory changes in electrical impedance across the thorax.

F. Peripheral Stroke Volume and Cardiac Output Monitoring
In the last decade, technology to monitor stroke volume and cardiac output without a PAC has been implemented clinically. Utilizing a peripheral arterial line and a central venous line minimally invasive hemodynamic monitoring (Edwards Life Sciences Vigileo and LiDCO systems cardiac monitor) is possible. These monitors operate on the assumption that end systolic volume is fixed and that variability in stroke volume is due to variability in end diastolic volume. Using low-dose lithium ion infusion, the LiDCO monitor continuously measures cardiac output. These monitors are useful in measuring stroke volume, cardiac output, SVR, and indirectly calculating volume status. Studies in children at this point are lacking.

G. Further Notes on Umbilical Catheters

Critically ill neonates often require invasive monitoring. While peripheral arterial access or central venous access is possible, it can be challenging in small neonates. Umbilical vessel cannulation is common in these patients but, again, is not without risk. Umbilical artery catheter (UAC) placement is associated with mesenteric and renal arterial thrombosis. To decrease this risk, the catheter tip should always be in the chest between T6 and T10. Patients should be kept NPO while a UAC is in place. Umbilical venous catheterization is associated with portal vein thrombosis and hepatic hematoma formation. The tip of the catheter should be in the suprahepatic IVC. If the catheter falls back into the hepatic veins it should be removed. Catheters are never advanced after the initial placement due to the high risk of line infection. Most neonatologists advise
against UAC/UVC placement in patients with abdominal wall defects due to a high incidence of thromboses.

Summary:

Intensive care unit patient monitoring is a core component of critical care. As the degree of illness rises, so does the need to interrogate neurologic function, gas exchange, and cardiac performance. In the most severely ill, continuous monitoring devices must be employed though enthusiasm for these devices must be tempered by the knowledge of their limitations and complications. The data obtained from sophisticated devices is only as good as the individuals interpreting it. Numerous ICU studies document that even experienced clinicians frequently misinterpret data or fail to consider the full range of clinical data necessary to make accurate and timely clinical decisions. Values generated from invasive monitoring devices should be taken simply as adjuncts in overall patient care.
I. Introduction

Shock is a clinical syndrome of inadequate tissue perfusion, oxygen utilization and cellular energy production that ultimately leads to irreversible cellular damage. While shock manifests as an acute functional derangement of the macro- and microcirculatory systems, it is important to emphasize that it is not equivalent to hypotension. The diagnosis of shock is made clinically, and is based on assessments of volume status (e.g. urine output), cardiac function (e.g. heart rate, blood pressure), and vascular tone (e.g. capillary refill time).

Shock is classified in many different ways and its presentation may vary significantly over time. In general, shock is classified as (a) hypovolemic (lack of circulating intravascular volume), (b) distributive (loss of vascular tone primarily or secondarily related to neurologic or neurohormonal disturbances), and (c) cardiogenic/obstructive (cardiac pump failure). There is significant overlap between the different types. For example, “septic shock” has clinical characteristics of all three of the above.

A good understanding of the basics of myocardial function and oxygen delivery is vital for the timely diagnosis and management of patients with shock. (See Chapter 1)
II. Clinical Evaluation of Shock and Low Cardiac Output States

Any patient at risk of developing LCO or shock requires thorough and continuous monitoring of their hemodynamic status, responses to intervention, as well as an evaluation of new physiologic derangements as they arise. Various clinical, laboratory and physiologic variables are available to assess the adequacy of CO and DO$_2$. Systemic perfusion is often assessed indirectly by monitoring vital signs, signs of systemic perfusion as well as urine output. Specifically, these include tachycardia, narrow pulse pressures, hypotension, cold extremities, weak pulses, slow capillary refill, oliguria and/or anuria. In some centers use of non-invasive tissue perfusion are routinely used in the intensive care unit [1].

Vital Signs

Normative data is available for heart rate ranges based on age. Tachycardia, especially if > 180-220 beats per minute, will compromise ventricular filling and coronary artery filling time with a resultant decrease in SV, CO and myocardial contractility. Tachycardia can occur secondary to pain, agitation, acidosis, hypovolemia, anemia, hypoxemia, fever and low cardiac output. It is also a compensatory mechanism to maintain CO early in the development of cardiac tamponade. Tachyarrhythmias can also develop from a
variety of electrolyte and metabolic disturbances that require urgent investigation and intervention.

Blood pressure (BP) consists of two distinct phases. Systolic blood pressure is the pressure exerted within the arterial vasculature during ventricular contraction and is a reflection of the SV. Diastolic pressure reflects overall blood volume and vascular tone (capacity). It is important to note that children have such great physiologic reserves that they can sustain relatively normal systolic blood pressure in even in instances of moderate shock. BP is relatively insensitive since it drops only after all compensatory mechanisms to maintain CO have been exhausted. In hypovolemic shock, a decrease in pulse pressure (difference between systolic and diastolic blood pressures) is a more sensitive and earlier indicator of blood loss compared to a decrease in blood pressure. In certain congenital heart defects such as coarctation of the aorta, the BP may be normal despite compromised CO if the systemic vascular resistance is high. Normal to high systolic BP in conjunction with a low diastolic BP suggests systemic vasodilation with acceptable ventricular ejection whereas a low systolic BP with a high diastolic BP is indicative of poor ventricular ejection and systemic vasoconstriction. Despite some limitations, BP is still an important vital sign that can be monitored to trend responses to therapy. Normal ranges, based on age, are available. Therefore, a provider should not overly rely on blood pressure as indication of tissue perfusion.
Central venous pressure (CVP) is the pressure within in the great veins as blood returns to the heart and is an indicator of preload. It normally ranges from 8-10 mm Hg.

**Poor Systemic Perfusion**

Capillary refill time refers to the amount of time it takes for color to return after pressing on the skin or nail beds. It is normally measured at less than 3 seconds. A prolonged refill time may be the result of decreased intravascular volume or vasoconstriction and indicative of LCO or a shock state but may be confounded by fever, ambient temperature, or the use of vasoactive medications. Nonetheless, a capillary refill time >4 seconds does suggest reduced stroke volume and impaired peripheral perfusion.

Core-peripheral (toe) temperature gradients can be used as indicators of perfusion. While core temperature is best measured by an esophageal probe, rectal temperature measurements are also acceptable. The normal gradient should be less than 3°C. Low peripheral temperatures, especially if they approach ambient temperature, suggest impaired peripheral perfusion.

**Urine Output**
Infants and young children with normal CO should have a minimum of 1 mL/kg/hour of urine output. Older children and adults excrete 0.5 mL/kg/hr. Infants with LCO or shock lose the ability to maintain renal perfusion and glomerular filtration, which manifests as oliguria or anuria.

### Overview of Clinical Signs and Symptoms in Shock

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Hypovolemic</th>
<th>Distributive</th>
<th>Cardiogenic/Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway patency</td>
<td>Depends on state – may need intubation with fluid administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Breath sounds</td>
<td>Normal</td>
<td>Normal</td>
<td>Crackles, grunting</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>Compensated vs. uncompensated shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>Narrow</td>
<td>Variable</td>
<td>Narrow</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral pulses</td>
<td>Weak</td>
<td>Bounding or Weak</td>
<td>Weak</td>
</tr>
<tr>
<td>Skin</td>
<td>Pale, cool</td>
<td>Warm or Cool</td>
<td>Weak</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Delayed</td>
<td>Variable</td>
<td>Delayed</td>
</tr>
<tr>
<td>Urine output</td>
<td></td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Irritable at early stages or lethargic in late stages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td>Variable</td>
</tr>
</tbody>
</table>

(Adapted from PALS Provider Manual, 2011.)

### iii. Laboratory Evaluation of Shock and Low Cardiac Output States

It is important to remember that clinical signs and symptoms may be unreliable or late indicators of poor systemic perfusion. Supplemental laboratory testing is essential for the prompt recognition of LCO or shock and the implementation of appropriate management strategies. These include the
measurement of arterial-venous oxygenation gradients (A-V O₂), mixed venous saturations (SvO₂), acid base, and lactate.

A-V O₂ is the difference between arterial oxygen saturation and SvO₂, and is normally <30%. Changes in A-V O₂ are reflective of variations in CO when oxygen demands are stable in the absence of anemia or hypoxia. A high A-V O₂ in combination with elevated serum lactate could indicate an inability of the tissues to consume oxygen at the cellular level.

SvO₂ is the oxygen saturation within the pulmonary artery following the mixing of the systemic venous return (from the superior and inferior vena cavae) and the coronary venous circulation. It measures the overall balance of oxygen transport and consumption and thus provides the clinician with critical information pertaining to ability of the patient’s CO to meet metabolic demands. Ideally, these measurements are taken form a catheter in the pulmonary artery but if these are not present, samples may be taken from central venous or right atrial catheters. This measurement must be made using co-oximetry since this value cannot be determined solely using arterial oxygen tension values (i.e. PaO₂). Normal SvO₂ values range from 70-75%. Values <65% suggest increased oxygen extraction at the tissue level and is indicative of impaired tissue perfusion. Importantly, SvO₂ is affected by all 4 components that affect oxygen delivery (CO, Hgb, PaO₂, and SaO₂). Furthermore, an increase in oxygen consumption without a compensatory increase in oxygen delivery will also lead to low SvO₂ values.
The arterial blood gas is the most effective way to determine acid-base balance and oxygenation in the clinical setting. It can reveal the severity of hypoxemia and hypoperfusion. Normal pH values range from 7.34-7.45, with PaO₂ and PaCO₂ values ranging from 80-100 mm Hg and 35-40 mm Hg, respectively. The base deficit, which normally ranges from -2 to 2 mmol/L, reflects the degree of metabolic acidosis present at the peripheral tissue level. Values > -5 mmol/L correlate with impaired oxygenation and tissue perfusion, metabolic acidosis, and impaired end organ function. The serum lactate level is also a marker of tissue oxygenation, delivery and extraction. Lactate is produced when oxygen delivery is inadequate or the tissues are unable to extract it appropriately. In the latter situation, the cells turn to anaerobic respiration leading to the production of lactate. Normal lactate levels are generally less than 2.5 mmol/L. The liver and kidneys clear lactate and thus hepatic or renal insufficiency can contribute to elevated levels. A lactate >4 mmol/L or increasing levels on serial measurement are predictive of morbidity and mortality. Lactate levels will generally improve within 60 minutes of interventions used to improve tissue perfusion.

IV. Management of Shock and Low Cardiac Output States

Any patient suspected of developing LCO or shock needs to be placed in a monitored environment that allows for active clinical surveillance. Fluid resuscitation is always the first step of management in order to improve left ventricular preload and DO₂. Most children can tolerate up to 60 mL/kg of
intravenous fluid without developing pulmonary edema. Children with congenital heart disease may require more judicious use of intravascular volume expansion. The response to fluid administration must be carefully monitored and will usually demonstrate improvements in blood pressure, peripheral perfusion and urine output. CVP and arterial monitoring may also guide resuscitative efforts.

In the context of the child with severe shock, rapid, goal-directed therapy has been linked to improved outcomes. [2] This starts upon initial evaluation and continues for several hours thereafter. Once the “ABC’s” have been established and proper monitoring has been instituted, rapid volume expansion with 20 mL/kg of crystalloid should be administered over 5 minutes. Basic laboratory investigations including CBC, electrolytes, glucose, coagulation profile, blood cultures and blood gas should be procured. If septic shock is suspected, empiric broad-spectrum antibiotic therapy must also be initiated to cover all potential offending organisms once blood cultures have been obtained. Antibiotics can be tailored to the specific organism once culture results are received. Bolus intravenous fluids can be repeated up to 60 mL/kg within the ensuing 60 minutes. If the patient still demonstrates poor perfusion, the patient should be intubated. Invasive monitoring should be secured (central venous catheter and arterial catheter) concurrently. Inotropic support should also be initiated (see below). An urgent echocardiogram to evaluate cardiac function and rule out cardiac defects/obstruction should be considered in patients who do not respond to therapy in a timely fashion. The goals of therapy are to maintain a CVP > 10 mm Hg and mean arterial pressures at age-related norms. A conservative blood
transfusion strategy should be adopted and is generally indicated only in those patients with significant hypovolemia or anemia (i.e.) Hb < 7g/dL. SvO₂ and lactate measurements should be obtained with the goal to be >70% and <2 mmol/L, respectively (need reference).

VI Inotropic Agents

Pharmacotherapy using inotropic medications can be used effectively to improve cardiac function by increasing CO and contractility. Their effects are generally dose dependent. However, prolonged use or high doses can have deleterious effects on the heart that include: arrhythmogenesis, excessive chronotropy, increased myocardial oxygen consumption, down regulation of B-adrenergic receptors, increased afterload, and hypertension. Inotropic “resistance” may also be observed in the context of concurrent acidosis. Sodium bicarbonate may be helpful in this situation.

The initiation of inotropic support and the choice of medication are based on the clinical response to volume expansion and the correction of the metabolic acidosis. In patients with persistent low systolic blood pressures but peripheral vasodilation and SvO₂ > 70% (i.e. warm shock), consideration should be given to the use of norepinephrine and/or vasopressin. In patients with an SvO₂ <70%, normal blood pressures but poor peripheral perfusion, a blood transfusion (to get Hb > 10g/dL) and the use of milrinone, nitroprusside or dobutamine should be considered. In patients with an SvO₂ <70%, low blood pressure and poor peripheral perfusion (i.e.) cold shock, optimization of Hb > 10 g/dL and an
intravenous epinephrine infusion should be strongly considered. For patients with persistent shock despite fluid resuscitation and inotropic support, adrenal insufficiency should be suspected. In this situation, hydrocortisone (2 mg/kg) should be administered once baseline ACTH levels (any room for urine cortisol levels? have been obtained (need better dosing for hydrocortisone)

Specific Vasoactive Agents

Dopamine is a catecholamine that improves cardiac contractility but which can also improve splanchnic, cerebral and coronary blood flow. There remains controversy regarding dopamine’s ability to improve renal perfusion. In infants and children with hypotension, dopamine is a preferred initial inotropic choice due to its alpha-adrenergic effects at higher doses. Acceptable doses range from 2-20 µg/kg/minute.

Dobutamine, another catecholamine, has gained popularity due to its ability to improve cardiac performance at various levels, including chronotropy, contractility, and afterload reduction. Dobutamine reduces the degradation of cyclic AMP (cAMP). Thus, cAMP is more available to the myocardium. Dobutamine is thought to be less arrhythmogenic than other inotropic agents. Although dobutamine can reduce afterload, cardiac function may not be improved without a concomitant increase in blood pressure. In this circumstance, another medication may be required to increase blood pressure if hypotension occurs after the introduction of dobutamine. In cases of increased systemic and pulmonary vascular resistance, milrinone, in synergy with dobutamine, may be
an effective regimen as this combination can reduce afterload while also increasing myocardial contractility. Doses of dobutamine can range from 4-20 µg/kg/minute.

Epinephrine is a classic catecholaminergic medication that increases heart rate and blood pressure while also increasing stroke volume. Despite these beneficial effects, epinephrine increases metabolic rate, temperature, myocardial oxygen consumption, and systemic and pulmonary resistance. These effects could lead to end organ dysfunction and thus only low doses of epinephrine should be used, if at all possible. It may often be used in conjunction with other inotropic agents. Doses can range from 0.02-0.3 µg/kg/minute.

Norepinephrine is another classic catecholamine that possesses almost exclusive alpha-adrenergic activity that is normally secreted by the adrenal medulla. It is effective in “warm” shock as it raises systemic vascular resistance and diastolic blood pressure. It can also increase cardiac contractility without significantly increasing heart rate. Doses range from 0.1-3 µg/kg/minute.

Phenylephrine is a pure alpha-1 agonist that is used for sudden, severe hypotension (“Tet” spells, left ventricular outflow tract obstruction). It causes peripheral vasoconstriction that increases systolic blood pressure. However, in doing so, it causes a reflex bradycardia. Doses range from 0.1-0.5 ug/kg/minute.

Vasopressin (antidiuretic hormone) is a normally produced by the hypothalamus. It acts on V1 receptors on vascular smooth muscle cells to effect vasoconstriction. Since catecholamine effects on vascular smooth muscle can be inhibited by the activation of ATP-dependent potassium channels and nitric
oxide, vasopressin may be an effective alternative in catecholamine-resistant shock since it inhibits NO synthase. It also improves renal perfusion by vasodilating the afferent renal arterioles. However, large trials have failed to demonstrate improved outcomes with vasopressin when compared to norepinephrine (ref). Major complications with the use of vasopressin include cardiac arrest, as well as myocardial, mesenteric and digital ischemia. Dosing is extrapolated from adult experience but generally will not exceed 0.005 units/kg/minute.

Milrinone is a phosphodiesterase III inhibitor that combines inotropic activity with afterload reduction. It can improve left ventricular relaxation (i.e. lusitropy) and compliance, thereby improving stroke volume and CO. Indeed, milrinone is able to maintain a favorable myocardial oxygen supply to demand ratio. Milrinone also has vasodilatory effects that act to decrease systemic vascular resistance. Milrinone may be an ideal medication in the management of patients with LCOS and increased systemic vascular resistance (e.g. certain septic shock states). Doses generally range from 0.3-0.7 µg/kg/minute.

Vasodilatory agents can be used for afterload reduction. Sodium nitroprusside is a systemic arterial and venodilator that has a rapid onset of action (2 minutes) and a very short half-life (3 minutes). These factors make it an easy medication to administer and titrate to effect. Doses can range from 0.5 ug/kg/minute to 5 µg/kg/minute. However, toxicity, due to the accumulation of the metabolic by-product, thiocyanate, can occur with doses >10 µg/kg/minute or if it is used for >72 hours as a continuous infusion. Thiocyanate should therefore be
monitored with prolonged use. In addition to undesired hypotension, nitroprusside can also lead to pulmonary vasodilation and increased intrapulmonary shunting (i.e. reduced PaO₂), as well as cerebral vasodilation (i.e. increased intracranial pressure). Rarely, it can also affect platelet function.

Inhaled nitric oxide (NO) is an endothelium-derived vasodilator that is produced by the pulmonary capillary bed. Delivered through the airway, NO is able to diffuse through the airways into the smooth muscle of the surrounding pulmonary vasculature. NO is used primarily in the treatment of pulmonary hypertension or with LCO associated with high pulmonary vascular pressures. It selectively reduces pulmonary vascular resistance by dilating pulmonary arteries near areas that are better ventilated and thus is able to improve ventilation-perfusion matching within the lung. It has rare systemic effects since it is metabolized rapidly and then bound to Hgb. The administration of NO needs to include monitoring of methemoglobin levels, which can critically reduce oxygen carrying capacity if levels exceed >20% of the total circulating Hgb. Normal dose ranges for use are 1-40 parts per million (ppm).

Levosimindan is a newer agent that acts as a calcium sensitizer. It has both inotropic and lusitropic effects. It is a pyridazole dinitrate derivative with a short half-life but it has a longer acting metabolite (OR 1867; 70-80 hours) that explains its persisting effects. There are few studies utilizing this medication in pediatric patients. However, initial studies adult studies in heart failure suggest that it is equivalent to milrinone and provides an ability to reduce myocardial oxygen consumption as well as reducing concomitant catecholamine
requirements. Generally an intravenous bolus is given with a subsequent continuous infusion that ranges from 0.1-0.4 µg/kg/minute.

**Receptor Effects of Commonly Used Vasoactive Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>$D_1$</th>
<th>$D_2$</th>
<th>$\alpha_1$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$V_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>0.5-10</td>
<td>0.5-10</td>
<td>&gt;10</td>
<td>3-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.1-1.0+</td>
<td></td>
<td>0.05-0.1</td>
<td>0.05-0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

Dose ranges are presented in ug/kg/minute.

**VI. ECMO**

ECMO has been used in the neonatal and pediatric patients to treat pump failure or cardiogenic shock. This is most commonly seen in the post-operative setting. However, ECMO has also been used in patients with refractory septic shock. Some studies indicate that ECMO using central access has better results in this setting [8.9].

References:


I. Introduction and Basic Considerations

Sepsis remains a frequent cause of pediatric morbidity and mortality, despite significant advances in diagnosis and management of pediatric infections. While the outcomes are improving in the United States, the incidence of sepsis continues to rise, making it one of the most common admission diagnoses in the pediatric and neonatal ICUs. [1-6] Early recognition and initiation of goal-directed therapy remains the mainstay of care, whether caring for neonates or young children. In addition, timely source control, through appropriate antimicrobials and/or surgical intervention, is crucial in assuring recovery and best outcomes.

The principles of therapy, which have been applied in the adult population, carry over well into the management of pediatric sepsis, although modifications need to be made based on the child’s age and comorbidities. Neonates, in particular, represent a challenging population, as their source of sepsis varies, depending on the gestational age, congenital anomalies, and circumstances surrounding their delivery.[5] It should be stressed that regardless of the source, once sepsis is suspected, supportive care should not be delayed until
appropriate source has been identified. Therapy should be *initiated early* and continued throughout the diagnostic work-up. [7-8]

**II. Definition and Recognition of Sepsis Syndromes**

Sepsis encompasses a clinical continuum of established infection with physiologic evidence of systemic inflammatory response syndrome (SIRS), which may progress to severe sepsis, and ultimately septic shock. The goal of early therapy is to interrupt this progression, minimize end organ dysfunction, and provide supportive care, while treating the source of infection. Over the last 10 years, we have learned that genetic predisposition may play a role in the severity of host response to infection. Thus some individuals progress to septic shock much more rapidly than others, making the early diagnosis all the more important in those patients’ survival. [9]

The following outline the definitions of sepsis syndromes, as proposed by the International Consensus Conference on Pediatric Sepsis and the Surviving Sepsis Campaign. [7-8]

**1. Systemic Inflammatory Response Syndrome (SIRS)**
At last two of the following criteria, one being abnormal temperature or leukocyte count.

- **Hyper or hypothermia**, defined as core temperature of $> 38.3^\circ C$ or $< 36^\circ C$.

- **Tachycardia or bradycardia** (for children <1 year old). Tachycardia is defined as a mean heart rate $> 2$ SD above mean for age or otherwise unexplained persistent elevation over a 0.5-to 4-hr time period. Similarly, bradycardia is defined as a mean heart rate $< 10$th percentile for age in the absence of external vagal stimulus, $\beta$-antagonists, or congenital heart disease or otherwise unexplained persistent depression over a 0.5-hr time period.

- **Tachypnea**, defined as mean respiratory rate $> 2$ SD above normal for age or need for mechanical ventilation, except if secondary to recent general anesthesia administration and/or underlying neuromuscular disease.

- **Leukocytosis or leukopenia**, defined as elevated or depressed counts for age (excluding chemotherapy-induced leukopenia) or presence of $> 10\%$ immature neutrophils.
Laboratory reference values, in particular, may vary from one institution to another. However, the following may be a helpful guide in recognizing abnormal physiologic and laboratory ranges, by age. [8]

Table 1: Abnormal physiologic/laboratory findings by age:

<table>
<thead>
<tr>
<th>AGE</th>
<th>TACHYCAR DIA (beats/min)</th>
<th>BRADYCARD IA (beats/min)</th>
<th>TACHYPN EA (breaths/min)</th>
<th>LEUKOCYTOSIS/LEUKOPENIA (WBC x 10^3/mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7 days</td>
<td>&gt;180</td>
<td>&lt;100</td>
<td>&gt;50</td>
<td>&gt;34</td>
</tr>
<tr>
<td>8-30 days</td>
<td>&gt;180</td>
<td>&lt;100</td>
<td>&gt;40</td>
<td>&gt;19.5 or &lt;5</td>
</tr>
<tr>
<td>30 days -1 year</td>
<td>&gt;180</td>
<td>&lt;90</td>
<td>&gt;34</td>
<td>&gt;17.5 or &lt;5</td>
</tr>
<tr>
<td>2-5 years</td>
<td>&gt;140</td>
<td>n/a</td>
<td>&gt;22</td>
<td>&gt;15.5 or &lt;6</td>
</tr>
<tr>
<td>6-12 years</td>
<td>&gt;130</td>
<td>n/a</td>
<td>&gt;18</td>
<td>&gt;13.5 or &lt;4.5</td>
</tr>
<tr>
<td>13-18 years</td>
<td>&gt;110</td>
<td>n/a</td>
<td>&gt;14</td>
<td>&gt;11 or &lt;4.5</td>
</tr>
</tbody>
</table>
2. **Sepsis** is defined as SIRS secondary to suspected or proven infection. Diagnosis of infection itself is driven by clinical circumstances, positive cultures, notable findings on imaging, and physical exam. It should be stressed that suspicion of infection alone is sufficient to establish the diagnosis of sepsis and initiate timely therapy. Pediatric definition of infection includes any or all of the following: positive fluid or tissue cultures; presence of inflammatory cells in otherwise sterile fields, such as CSF, pleural or peritoneal space; radiographic evidence of pulmonary infiltrates, anastomotic complications, viscus perforation, or superficial and deep space abscesses; cellulitis, subcutaneous emphysema suggesting underlying necrotizing process, petechia, or purpura fulminans.

3. **Severe sepsis** includes all of the SIRS/sepsis criteria with evidence of single or multi-organ dysfunction. Pediatric guidelines require a presence of either cardiovascular or respiratory compromise, or presence of 2 or more other end organ dysfunction, as outlined in the table below.

4. **Septic shock** is the final progression of untreated sepsis or severe sepsis unresponsive to initial fluid resuscitation.
Table 2: Definition of Organ dysfunction

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Definition of Organ Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Need for vasoactive medications at any dose (dopamine &gt;5 mcg/kg/min)</td>
</tr>
<tr>
<td>(dysfunction despite volume</td>
<td>OR: Presence of at least 2: Oliguria, Lactic acidosis (&gt;1 mmol/L), Unexplained metabolic acidosis, Capillary refill &gt; 5 sec, Mottling, Core to peripheral temperature gap &gt;3°C</td>
</tr>
<tr>
<td>expansion with ≥ 40 ml/kg of</td>
<td></td>
</tr>
<tr>
<td>isotonic fluids in 1 hour)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong> (dysfunction</td>
<td>PaO₂/FiO₂ &lt;300 OR PaCO₂ &gt;65 OR PaCO₂ 20 mmHg &gt;baseline OR</td>
</tr>
<tr>
<td>unrelated to congenital heart</td>
<td>FiO₂ &gt;50% for O₂ saturation &gt;92% OR</td>
</tr>
<tr>
<td>disease or chronic lung disease</td>
<td>Need for invasive or noninvasive positive pressure ventilation</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td>GCS ≤ 11 or decrease by ≥ 3 from abnormal baseline</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td>Thrombocytopenia (&lt;100,00/mm³) or decrease by 50% over course of 3</td>
</tr>
<tr>
<td></td>
<td>OR Coagulopathy with INR &gt; 2</td>
</tr>
<tr>
<td></td>
<td>days, if already chronically low</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Acute Kidney Injury (AKI):</td>
</tr>
<tr>
<td></td>
<td>OR: ALT ≥ 2 times normal for age</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>Hyperbilirubinemia (&gt;4 mg/dl) *excluding newborns</td>
</tr>
</tbody>
</table>

### III. Treatment of Sepsis

Historically, goals of therapy in pediatric sepsis were adapted from the adult guidelines, which themselves were originally defined in the 2004 Surviving Sepsis Campaign. These guidelines have since been revised, both in 2007 and 2012, with the most recent publication defining more realistic goals for the pediatric population, particularly in severe sepsis and septic shock. The
overriding principles of sepsis therapy, however, remain constant regardless of age and focus on simultaneously restoring normal physiology via supportive measures, while identifying and treating the source of sepsis itself. Most importantly, supportive therapy is goal directed and time sensitive with ultimate goal of providing and escalating therapy within the hour of suspicion of sepsis. The latest guidelines incorporate evidence available through the fall of 2012 and are discussed in following section.[7]

Restoring Normal Physiology:

0-5 minutes: Have a high index of suspicion and recognize signs of hypoperfusion and changes in mental status. Establish vascular access and provide supplemental oxygen. Place either a peripheral or intraosseous IV. Central access, if not already present, can be established once resuscitation has already began, but attempts for a central line should not delay initiation of fluids, antibiotics, and other necessary intravenous therapies.

Supplemental O2 may be delivered via nasal cannula, high flow cannula, or other means of non-invasive ventilation such as CPAP.
Intubation and mechanical ventilation, although potentially necessary during the course of treatment, may initially impair venous return in an already hypovolemic child, worsening their hemodynamics. Non-invasive therapies, such as high flow nasal cannula or CPAP, have been shown to improve functional residual capacity, while allowing for initial resuscitation to start.[7,10] Mechanical ventilation may indeed be necessary early in the course of treatment. Proceed with intubation, if necessary, once the initial volume resuscitation and inotropes have been started.

**5-15 minutes: Initiate fluid resuscitation and start broad spectrum antibiotics.** Start with 20 ml/kg boluses, to at least 60 ml/kg, until perfusion has improved or signs of volume overload develop, limiting further aggressive fluid loading. Early signs of volume overload include hepatomegaly and rales and if present, further boluses should be limited. If more support is needed and another IV is present, add an inotrope, treat hypoglycemia and hypocalcemia.

Of note, if sepsis is suspected, fluid resuscitation should start even without signs of hypotension. Pediatric patients compensate for hypotension very well initially, using tachycardia and peripheral vasoconstriction as compensatory mechanisms. Once hypotension
develops, profound instability and cardiovascular collapse may soon ensue.

**15-45 minutes:** Assess for response to therapy and escalate if fluid refractory shock persists. Without presence of more invasive monitoring, initial therapy is titrated to normalization of blood pressure or distal perfusion, as manifested by improved capillary refill and peripherally pulses, resolution of oliguria, and improvement in mental status. If the response to fluid is poor, care needs to be escalated and inotropes started. Additional support, including placement of central access and intubation will likely be necessary at this stage.

Septic pediatric patients may present in one of three ways: Low cardiac output with high systemic vascular resistance (SVR) and normal blood pressure, often termed “cold shock;” Low cardiac output, high SVR, and hypotension, also considered “cold shock;” and low cardiac output with low SVR, or “warm shock.”[11] Choice of inotrope or other vasoactive drugs depends on the child’s state of shock:
Cold shock: Start with Dopamine up to 10 mcg/kg/min or Epinephrine 0.05 to 0.3 mcg/kg/min

Warm shock: Norepinephrine 0.05 to 0.3 mcg/kg/min

*Epinephrine and higher doses of dopamine should be given through central access only.

45-60 minutes: If catecholamine resistant shock persists, adjuncts to therapy and monitoring need to be considered. These include the following:

1. Treat absolute or relative adrenal insufficiency with Hydrocortisone at a dose of 50 mg/m^2/24 hr. Consideration of adrenal insufficiency should be timely, as septic shock in conjunction with absolute adrenal insufficiency carries a high risk of mortality, occurring within 8 hours of presentation. Close to 25% of children with sepsis may have absolute adrenal insufficiency. A baseline cortisol level may be obtained, but
treatment should not be withheld if steroids are felt necessary to improve reversal of shock.

2. Assure that hypovolemia has been adequately treated by checking a CVP. Children in sepsis may require significant ventilatory settings and an increased intrathoracic pressure may falsely elevate the CVP. Continuous monitoring for CVP trends may help better ascertain the true volume status.

3. Consider other causes for shock, including cardiogenic or obstructive etiology. Pneumothorax and pericardial effusion are generally ruled out early, both in the ATLS and PALS protocols. However, continued fluid resuscitation and mechanical ventilation may exacerbate cardiac function or cause barotrauma resulting in late pneumothoraces.

4. Recognize abdominal compartment syndrome (ACS), which has received more attention in the pediatric population lately. Healthcare providers have been shown to poorly recognize ACS with physical exam alone. Continuous monitoring with
bladder pressures can be helpful in early recognition of intra-abdominal hypertension, allowing for potential prevention of ACS development.[12-13]

>60 minutes: Treatment may be deescalated, based on the individual patient response, but in cases of severe sepsis and shock, prolonged therapy is generally necessary. Repeated examinations and close hands-on attention to a septic child require ICU setting. In modern ICUs, additional monitoring is helpful to guide goal directed therapy, avoid over-resuscitation with excessive fluid overload, and minimize risk of ischemia with use of vasoactive medications. In case of persistent shock, despite of all of the already discussed measures, additional measures may be necessary.

1. For cold shock with normotension: Titrate dopamine or epinephrine and fluids to an ScVO$_2$ >70%. Keep Hgb >10g/dl in the initial resuscitation. However, if stability is reached, Hct of >7 g/dl is acceptable and may limit unnecessary use of blood products. If cold shock persists, treatment of vasoconstriction may improve poor cardiac output and reversal of shock.[14-15]
Keep in mind that vasodilation may cause hypotension, and needs to be added in conjunction with volume loading and continued monitoring. Both phosphodiesterase inhibitors (mirlinone and imrinone), and calcium channel sensitizers such as levosimendan have been used, as well as nitrovasodilators.

2. For cold shock with hypotension, initial resuscitative targets are similar: Titrate fluids/inotropes to ScVO$_2$ >70% and Hgb >10g/dl. If shock persists, add norepinephrine and if ScVO$_2$ still remains <70%, consider adding dobutamine, or other vasodilators discussed above.

3. Warm shock with hypotension. Initial resuscitative targets are as above. If ScvO2 still remains low, adding vasopressin, terlipressin or angiotensin may be helpful, as well as low dose epinephrine.

If despite all of the above, patient remains unstable, hypotensive, and otherwise unresponsive to therapy, ECLS should be considered. Rationale for use of ECMO and other adjunct to pediatric sepsis therapy are further discussed in the next section.
Other principles of sepsis therapy and therapeutic adjuncts:

As previously discussed, successful management of sepsis includes early initiation of supportive therapy, while at the same time addressing the source of sepsis itself and minimizing secondary end-organ injury. In addition to the above guidelines, the following measures should be implemented:

1. **Source control:** Administer broad spectrum antibiotics early,[16-17] as part of the initial resuscitative efforts. The choice of antibiotics will vary from one institution to another, based on the local susceptibilities, microbiograms, and patient risk factors. For instance, resistant organisms and fungus should be considered in patients previously treated with antimicrobials. Therapy should not be delayed while awaiting collection of cultures. Antimicrobials should be administered within the hour once sepsis is suspected. Typical empiric therapy may include drugs, such as Ampicillin and Cefotaxime in infants and Vancomycin and Cefotaxime in children who are previously healthy. Zosyn and Vancomycin are also a
commonly used drug combination. Recent CCM literature suggests that this combination, however, may result in higher incidence of AKI. Again, therapeutic choice should be individualized to the institution and the patient, carefully weighing risks and benefits of each therapy.

Immunosuppressed patients may need possible double antibiotic coverage for Gram negative organisms, as well as antifungal agents and appropriate anti-MRSA therapy. If toxic shock syndromes are a possibility, addition of Clindamycin is strongly recommended by the ACCCM, particularly in the pediatric patients.

Once the organism data are available, therapy should be deescalated and tailored, based on susceptibilities, to minimize risk of resistant organisms.

As surgical septic patients often have infections that require an operation, source control involves early surgical intervention whenever appropriate. This may involve drainage of abscess, placement of peritoneal drain or laparotomy for NEC, damage control laparotomy for perforated viscus or intestinal ischemia,
colectomy or a diverting ileostomy for refractory cases of C-difficile colitis, and a number of other operations depending on the clinical scenario. Patients with Hirschsprung enterocolitis require not only IV antibiotics, but also colonic irrigations in order to decrease bacterial content and potential translocation.

2. **Prevent secondary injury to organs**: These measures include providing lung-protective mechanical ventilation, avoidance of nephrotoxic medications and/or dosing medications based on the degree of renal dysfunction, utilizing measures to decrease bloodstream infections in patients with central venous catheters. Consider early enteral feeding but only after an abdominal source has been ruled out and the patient is able to maintain an adequate blood pressure without major vasopressor support.

3. **Provide sedation/analgesia to minimize effects of stress and alleviate some of the inflammatory response**.[7,18] Choice of sedatives is often institution dependent, but continuous infusions are generally recommended to prevent drastic changes in
therapeutic drug levels and minimize periods of agitation. Propofol is discouraged for children <3 years of age and when used in older population, should be used briefly due to concerns for Propofol infusion syndrome.[19-20] Both Etomidate and Dexmedetomidine are felt to inhibit sympathetic system, therefore suppressing some of the native compensatory mechanisms in sepsis.[21] Regardless of the choice of drugs, sedation should be titrated to comfort, using standardly accepted sedation scores, as over sedation and particularly neuromuscular blockade actually correlate with more negative, long-term outcomes.

4. **Management of hyperglycemia:** Glucose targets in the pediatric population are similar to adults and are designed to avoid both hypo and overt hyperglycemia. Stress state and addition of corticosteroids, both induce hyperglycemia. Previous protocols for tight glycemic control have shown to worsen outcomes, due to induced hypoglycemic states. More moderate protocols are now recommended, with goal glucose <180 mg/dl.

5. **Use of blood products** has partly been discussed, particularly transfusion targets for PRBCs in unstable, septic children. Other products
particularly platelets and fresh frozen plasma can also be necessary, given particular clinical scenarios. In neonates, thrombocytopenia is commonly associated with sepsis and counts of $<50,000$ cells/mm$^3$ are associated with increased risk of intracranial bleeding. Therefore, transfusion is recommended to reach this target. In older children, platelet transfusion is indicated for counts $<10,000$/mm$^3$ in absence of bleeding and $<20,000$/mm$^3$ in presence of bleeding.

Fresh frozen plasma should not be given to correct laboratory values alone, as long as the patient responds to previously discussed sepsis therapy. However, DIC and thrombotic purpura are seen more frequently in pediatric population, and may progress to purpura fulminans. FFP is indicated in these cases, as is plasma exchange in centers that have such ability.

6. Consider adjuncts to conventional therapy

a) **ECLS:** Although heavily scrutinized in the adult population, both VV and VA ECMO have been used successfully in support of pediatric
patients with severe septic shock. Reported outcomes are center dependent and vary from 40 to 79%. Neonatal population has an excellent response, and recent data from Australia show a 74% survival to discharge with central, intracardiac cannulation. ECMO is therefore recommended for refractory pediatric septic shock. [22]

b) **Diuresis and CRRT:** Significant fluid overload (>20% of dry weight) is reported as having strong association with poor ICU outcomes. In treated septic patients, whose shock state has been reversed, gentle volume removal is recommended by the ACCCM. Diuretics and CRRT have both been used to manage fluid overload, allowing for ventilatory weaning and deescalation of other supportive therapies.

c) **IVIg:** is not recommended in patients with adult sepsis. However, it is still considered in pediatric population, particularly in neonates due to concerns of immature immune system, leading to consumptive deficit in native immunoglobulines.[23] The most recent review showed equivocal results, particularly in the
premature neonates. At this time, however, there is no clear consensus regarding IVIg and use is practitioner dependent. [24]

d) Activated protein C is no longer recommended in pediatric or adult sepsis, following results of the PROWESS SHOCK trial, published in 2011.[7]

IV. Neonatal Sepsis

Many of the principles of pediatric sepsis apply to the neonatal population, and the principles of therapy are essentially identical for the 2 groups. A proposed algorithm for management of neonatal sepsis is available at the end of this section.[25] Due to issues associated with their delivery, potential for prematurity, and possibility of undiagnosed congenital disorders, septic neonates comprise a unique population, which poses both diagnostic and therapeutic challenges. This is a
particularly fragile group of patients, making a timely diagnosis and therapy of sepsis, all the more important.

Surgical neonates with sepsis may be classified into 3 categories:

1) Those at risk for early onset infections, sustained via trans-placental or vaginal route, during gestation and delivery. This is often a consideration in infants who require urgent interventions within 72 hours of delivery, for example those with tracheo-esophageal fistula or imperforate anus, and who decompensate in the early post-operative period. Distinguishing early onset sepsis from post-operative complications, such as anastomotic leak, guides much of the diagnostic work-up in this population.

2) Those whose source is clearly “surgical,” such as neonates with complicated necrotizing enterocolitis or malrotation with volvulus, and who require immediate surgical intervention.

3) Those who are several days or even weeks into their post-operative period, at risk for post-operative complications, such as surgical site infections, or healthcare associated infections, such as line sepsis, ventilator associated pneumonia, or urinary tract infection.
Remember to consider undiagnosed congenital heart disease when faced with a decompensating neonate, whose presentation may be identical to a patient with sepsis. Many of the congenital cardiac anomalies will manifest in the first 24-48 hours of life, with clinical picture resembling early-onset sepsis. In the first week of life, as the ductus arteriosus closes, other duct dependent cardiac anomalies, such as aortic coarctation, may be confused for late-onset sepsis.[26] Having a high index of suspicion for any of these lesions expedites diagnosis and provides appropriate referral and care.

**Early-Onset Neonatal Sepsis:**

Infection may be both a cause of and a result of premature deliveries. This is specifically true in the case of early onset sepsis, which the AAP defines as sepsis affecting neonates within 72 hours of birth. These infections are contracted via trans-placental route prior to delivery or from the birth canal during vaginal birth. Risk factors for early onset sepsis include:[16]

a) Chorioamnionitis (as defined by maternal fever >38°C and at least one of the following: maternal leukocytosis, maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor from the amniotic fluid)

b) Prolonged rupture of the membranes (18-24 hours)

c) Premature rupture of membranes

d) Prematurity

e) Maternal colonization with gram negative organisms and GBS

The organisms most commonly responsible for early onset sepsis are:[17]
a) Group B *Streptococci*
b) *E. coli*
c) *Klebsiella*
d) *Enterococci*
e) *H. influenzae*
f) *Listeria*

Some also include the TORCH infections when discussing early neonatal infections, although these rarely present with a septic picture. When they do become symptomatic (in 5-10% of those infected), TORCH infections generally result in chronic co-morbidities, rather than acute, life threatening, organ dysfunction. For purposes of this chapter, common bacterial organisms resulting in early onset neonatal sepsis are discussed, as those are more commonly seen in the surgical neonate.

**Late-Onset Neonatal Sepsis:**
If an infection occurs beyond 5 days of age, late-onset sepsis needs to be considered. The principles of diagnosis and treatment remain the same. The organisms involved and the mechanisms by which they are contracted differ compared to the newborn patient. In additions to the organisms previously discussed, hospital acquired infections are more common in this group. These include organisms introduced by instrumentation, catheterization, mechanical ventilation, surgical incisions, and presence of congenital defects (i.e. myelomenigocele or ruptured omphalocele), all of breach natural skin and
mucosal barriers. Antibiotic resistant organisms, such as Methicillin Resistant Staphylococcus aureus (MRSA) and Vancomycin Resistant Enterococcus (VRE) become more prevalent.[27] Finally, fungal infections, can be seen in this population, particularly in premature infants or those on prolonged antibiotics. [28]

**Risk factors for neonatal sepsis**

Surgical neonates may have anatomic and physiologic problems that predispose them to certain infections. Gastrointestinal and genitourinary anomalies, which may promote bacterial stasis, overgrowth and possible translocation, are frequently seen in the neonates. Obstructive uropathy, intestinal atresias, post-NEC strictures, and biliary atresia, are only a few examples. Patients with abdominal wall defects or congenital diaphragmatic hernias, may have non-biologic implants that can become seeded and act as source of sepsis. Patients with GI dysmotility and GERD are at risk for aspiration, leading to respiratory infections. Many surgical neonates are dependent on parenteral nutrition and have long-standing central venous catheters, placing them at higher risk for bacteremia.

**Diagnosis of neonatal sepsis**
All of the previously discussed diagnostic principles of SIRS and sepsis may be applied to the neonatal population, but need to be supplemented by examination findings, particular to this group of patients.[29] Certain physical exam findings are subtle and may precede any of the physiologic derangements. These include temperature instability, apnea, bradycardia (<100 bpm), respiratory distress in a previously stable patient as manifested by grunting, retractions, tachypnea, and hypoxemia). Additional findings include feeding intolerance or poor feeding, irritability, decreased responsiveness, poor suck, decreased tone, weak cry, mottled and cool skin, and acute hypoglycemia or hyperglycemia. Certainly, any of these symptoms may be present in absence of an infection, whether as a result of prematurity or expected transition to post-natal environment. As such, they should be assessed in the context of each individual patient, along with their risk factors for infection. This will assure that the therapy is applied appropriately and responsibly, while avoiding a prolonged use of antimicrobials in otherwise healthy patients.

Figure 1: Treatment of Neonatal Sepsis

**Recognize warning signs of neonatal infection/sepsis:**
Temperature instability, increased work of breathing, RDS, apnea and bradycardia, feeding intolerance.

**Start infectious work-up and broad spectrum antibiotics**
within an hour of suspected infection. Provide supplemental O2 and appropriate IV access. Stop feeds, if initiated previously. Give IV bolus of 10-20 ml of crystalloid.
Infant stable

- Continue antibiotics and supportive care. If cultures are negative and suspicion of sepsis is low, discontinue antibiotics within 48 hours.

Infant Unstable

Escalate support
- Provide further hemodynamic and respiratory support, including positive pressure ventilation

Continue fluid resuscitation
- with isotonic crystalloid or colloid; up to **60-80 ml/kg** until hemodynamics improve.

Fluid resistant Shock

Start inotropic support
- Dopamine 10-15 mcg/kg/min and/or Epinephrine 0.05-0.3 mcg/kg/min
- Titrate to goal MAP based on age.

Catecholamine resistant shock

Assure source control and rule out obstructive shock (abdominal compartment syndrome, pericardial effusion with tamponade, pneumothorax)

Persistant Shock

- Continue and direct antibiotics toward most suspected source.
- Proceed with operative intervention, if indicated.

Consider undiagnosed congenital heart disease

ECHO and start prostaglandins, if indicated

Add stress dose steroids
- Hydrocortisone 1.5 mg/kg q 6 hours x 8, then 0.5 mg/kg q 6 hours as maintenance.

Refractory Shock

ECMO
V. Summary

Sepsis continues to be a diagnostic and a therapeutic challenge in infants and children. It remains a leading cause of morbidity, despite our recent advances in therapy. In those at risk for, or with an already established infection, early intervention provides the best chance of recovery. A high degree of suspicion and attention to initially subtle changes in physiology allows us to provide therapy before progression to physiologic instability. Timely therapy not only minimizes co-morbidities, but it significantly shortens the time in the ICU and allows for best long-term outcomes.

References:


I. Nutritional Physiology

Nutritional support for critically ill patients is an important element of care, especially for infants and children who have requirements for growth and development in addition to maintenance. Surgical patients have further supplementary needs due to the stress of trauma and surgery. Nutrition in all patients is best provided via the enteral route but many surgical patients require parenteral nutrition. Calories are delivered primarily from carbohydrates and lipids with protein provided to give essential amino acids for humoral and structural proteins. The caloric density of carbohydrates is 4 kcal/g (dextrose, 3.4 kcal/g), lipids 9 kcal/g and protein 4 kcal/g.

Adult caloric storage is mainly found in fat. The average adult male carries fat with the energy storage equivalent of 167,000 kcal. Muscle and visceral proteins contain approximately 24,000 kcals. Carbohydrates, which are stored in liver and muscle glycogen, contain a limited storage capacity of approximately 1,200 kcals, which is sufficient for approximately 18-24 hours of fasting. The brain and kidney have obligate glucose requirements of approximately 150-180 grams per day (600 to 720 kcal/day). Because fats cannot be converted to glucose, glycogenolysis is needed for the first 24 hours of
fasting followed shortly thereafter by gluconeogenesis. In the adult, gluconeogenesis converts approximately 75 grams of protein per day into amino acids (especially alanine), which then moves to the liver for gluconeogenesis. These early changes of starvation are accompanied by a decrease in insulin and increase in glucagon production. The respiratory quotient (C02/O2) is low at 0.85 indicating oxidation of both carbohydrates and fats.

The late phase of starvation (greater than 4 days) is characterized by adaptation of the brain to use ketone bodies from fat in place of glucose from protein. Indicative of the decrease in protein catabolism and increase in fat catabolism, the respiratory quotient decreases to 0.7 consistent with pure fat oxidation. Gluconeogenesis persists in the kidney with resultant decreased nitrogen in the urine to less than 5 grams per day.

Starvation in infants is a more precarious situation because of the minimal stores of fat and protein, which are further compromised in prematurity. Vital accretion of nutrients occurs during the last trimester of pregnancy. Decreased enteral intake and high metabolic demand also increase problems for infants with surgical, cardiac and chronic lung disease. The hazards of inappropriate nutrition for infants include bone demineralization, rickets, cholestatic jaundice, poor wound healing, impaired lung function and slow growth, which can affect both short and long term outcomes.
Nutritional assessment is based on clinical factors such as history of weight loss, vomiting, diarrhea or feeding intolerance. Physical examination may show signs of muscle wasting. Height, weight and head circumference normograms should be evaluated for signs of poor growth. Adequacy of nutrition may also be judged by evaluation of serum proteins. The half-lives of serum proteins aid interpretation of nutritional status: albumin, 18 days; transferrin, 8 days; pre-albumin, 3 days; and retinol binding protein, 12 hours. Understanding the half-lives of these proteins explains why patients with a low pre-albumin may be malnourished even if the albumin level is normal.

Patients in the intensive care unit often have specific needs because of increased caloric requirements and negative protein balance. Caloric needs are altered by several factors such as surgical procedures, stress, cold, infection, and trauma. [1] Open wounds, such as the open abdomen or burn patients, have additional protein losses, which may be significant. Protein losses in body fluids can be measured but estimates range from 12-29 grams per liter. [2, 3]

II. Maintenance Fluids

Maintenance fluid requirements for children and adults are calculated based on the lean body weight or body surface area. Several issues can affect the suggested rate of fluid administration including environment, patient-related factors and disease-related factors. In addition, during the first week of life, infants are expected to lose 10-15% of body weight and an even greater
percentage for premature infants. Environmental factors that impact the amount of fluids needed may include ambient temperature and humidity, and specific treatments such as phototherapy. Patient related factors include skin maturity, birth weight, proportion of body fat, weight loss and urine output. Disease related factors might include large open wounds (such as patients with an open abdomen), burns, severe trauma or major surgery.

Suggested rates for initial fluid administration in neonates for each day of life (DOL) are listed in the table below.

<table>
<thead>
<tr>
<th>Birth Weight (gm)</th>
<th>DOL 1 (ml/kg/d)</th>
<th>DOL 2 (ml/kg/d)</th>
<th>DOL 3 (ml/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;700</td>
<td>100</td>
<td>120</td>
<td>120-140</td>
</tr>
<tr>
<td>700-2500</td>
<td>80</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>&gt;2500</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
</tbody>
</table>

Electrolytes are not added initially; D10W is used for maintenance fluid on DOL 1. On DOL 2, maintenance fluids are changed to D10W 0.2 NS with 20 mEq KCl/L. On DOL 2 and beyond, urine output and serum sodium are the most useful parameters to follow in determining the appropriate rate of fluid administration. Abnormal serum sodium levels are more responsive to changes in the rate of fluid administration rather than the amount of sodium supplementation.

Beyond the first week of life, children are given 4 ml/kg/hour for the first 10 kg, 2 ml/kg/hour for the next 10 kilograms and 1 mL ml/kg/hour for any weight over 20 kilograms. Added to maintenance fluid rates should be volume to
account for losses. Environmental losses are higher in radiant warmers compared to a humidified incubator. Infants with phototherapy should have a 50ml/kg/day increase in fluids while on phototherapy. Patients with gastroschisis, ruptured omphalocele, and bladder extrophy have greater evaporative losses requiring a bolus of 20 ml/kg of isotonic fluid at birth and an increase of the maintenance infusion by 20-25% until coverage of the exposed viscera is accomplished. Surgical patients often have gastrointestinal fluid losses that should be replaced with consideration of both the volume and electrolyte concentration of these losses. Gastric fluids are typically replaced with D5 0.45% NS with 20 mEq/liter of KCL, whereas biliary and intestinal losses are replaced with Lactated Ringers solution. Urine output should be monitored to ensure adequate perfusion.

### Gastrointestinal Fluid Losses

<table>
<thead>
<tr>
<th>Electrolyte Composition (mEq/L):</th>
<th>Na+</th>
<th>K+</th>
<th>Cl-</th>
<th>HCO3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>60-80</td>
<td>5-20</td>
<td>100-150</td>
<td>0</td>
</tr>
<tr>
<td>Biliary</td>
<td>120-140</td>
<td>5-15</td>
<td>80-120</td>
<td>30</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>120-140</td>
<td>5</td>
<td>30-50</td>
<td>80-100</td>
</tr>
<tr>
<td>Small bowel</td>
<td>100-140</td>
<td>5-15</td>
<td>90-130</td>
<td>30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10-90</td>
<td>10-80</td>
<td>10-110</td>
<td>10-75</td>
</tr>
</tbody>
</table>

### iii. Electrolytes
Electrolyte requirements are related to fluid metabolism and, consequently, are similar between adults and children, with allowances for weight differences.

Sodium is the primary extracellular cation, a major component of the serum osmolarity and is essential for growth as well as fluid homeostasis. Maintenance requirements for sodium are from 2-4 mEq/kg/day. Requirements may be greater for infants due to renal immaturity and the inability to maximally reabsorb sodium. Sodium requirements may also be affected by the administration of naturetic agents such as theophylline, caffeine, furosemide and dopamine. Hyponatremia is most frequently a result of water retention due to excess antidiuretic hormone secretion. Conversely, hypernatremia is most frequently due to dehydration.

Potassium is the primary intracellular cation and is essential for proper cardiac and neurologic function. Daily requirements are 1-2 mEq/kg/day to account for cellular proliferation and to replace obligatory renal losses. Consequently, for decreased renal function, careful adjustment and often cessation of potassium supplementation may be needed. Potassium is most safely administered by the enteral route; intravenous infusion should generally be 0.5 mEq/kg/hour with no greater than 1 mEq/kg/hr. Potassium is inflammatory to veins and therefore should be given at concentrations of no more than 60 mEq/L in peripheral lines and 120 mEq/L in central lines, but usually at lower
concentrations. Potassium requires careful monitoring for acute and chronic renal failure, abnormal acid base status, abnormal glucose status and during the use of certain drug therapies such as digoxin, amphotericin, high dose beta agonists, insulin drips and diuretics such as furosemide.

Chloride is an anion that is provided in parenteral solutions to balance the cations such as potassium and sodium. An overabundance of chloride can lower serum pH, causing a low anion gap metabolic acidosis.

IV. Enteral Nutrition

Enteral nutrition is the safest and most economical means of providing calories and nutrients, avoiding the complications of parenteral feeding such as the need for central catheter insertion, with all its complications such as mechanical malfunction, sepsis, and metabolic problems. Management of fluid and electrolytes as well as acquisition of all macronutrients (carbohydrates, lipids, proteins) and micronutrients are facilitated by the normal function of gastrointestinal absorption. Infectious complications are diminished by direct nutritional support of the intestinal mucosa. [4] Pediatric formulas can be given orally or by enteral feeding tube. A gastrostomy should be considered for any patient for whom it is anticipated that oral feeding is not possible or safe for a prolonged period of time.

Many special diets are available for patients with specific needs. For patients with inadequate digestive function due to intestinal loss, predigested or
elemental formulas are available. In addition, patients with compromised intestinal length may benefit from the addition of pectin, psyllium or loperamide. Special formulations are also available to assist patients with hepatic or renal failure.

Most pediatric formulas have a caloric density of 1 kcal/ml, but often have formulations in the 1.2 or 1.5 kcal/ml range. Pediasure is lactose free. Peptamen Jr is 100% hydrolyzed whey, 60% of fat provided as MCT oil (toddler equivalent of Pregestimil). Elecare is amino acid based, lactose free, has 33% MCT oil and has an oral formulation that is vanilla flavored. Neocate Jr. and Vivonex are also alternative elemental formulas. Nutritional supplementation can be accomplished by adding Duocal (fat and carbohydrates, 42 kcal/tbsp), vegetable oil, medium chain fat emulsions, Beneprotein or Benefiber as needed.

Newborns require 100-200 cal/kg/day for normal growth with an ideal weight gain goal of 15-20 g/kg/day in premies or 20-30 g/day in term babies. Ideally, infants should achieve a 1% increase in weight per day. When possible, breast milk is the preferred nutrition in the first six to twelve months of life. Donated expressed breast milk (EBM) can be used when the mother cannot produce sufficient volume. EBM confers immunologic protection and may decrease the risks for NEC. EBM is 20 kilocalories per ounce (30 ml). Infants who are exclusively breast milk fed require 1ml/day of liquid multivitamin.
The nutrient composition of most infant formulas simulates maternal milk: protein 8-12%; carbohydrates 41-43%; fat 41-49%. Docosahexaenoic acid (DHA) and arachidonic acid (ARA) are added for brain and retinal development. Iron is added to infant formulas to meet the 2-4 mg/kg/day requirements. Enfamil, Similac, and Good Start are made from bovine milk. Isomil and Prosobee, based on soy protein and corn syrup, can be used in infants with lactose or milk protein intolerance. Pregestimil and Alimentum are bovine milk based with hydrolyzed protein and are thought to benefit patients with suboptimal digestion and absorption such as short bowel syndrome, malabsorption, cystic fibrosis, and biliary atresia. Pregestimil and Portagen are formulas with the highest percentage of medium chain triglycerides and are used in children with lymph leak and some fatty acid disorders. Neocate and Elecare are elemental and are used in patients with severe milk protein allergies and those with other digestive problems whose nutrition has failed on Pregestimil and Alimentum.

Premature infant formulas are indicated for preterm infants with birth weights <1800 grams to account for their immature digestive tract. Similac Special Care and Enfamil Premature are only available in premixed 20, 24, and 30 kcal/ounce formulations. Preemies typically are fed with 22 kcal/oz formula.

Human Milk Fortifier (HMF) is a bovine milk based powder that can be added to EBM to increase caloric density. One packet adds 2 kcal/oz when added to 50 ml of EBM. Prolacta is a fortifier concentrated from donor human
milk available in four preparations to raise the caloric content of EBM by 4, 6, 8, and 10 calories per ounce.

Similac PM 60/40, used in renal failure patients, has the same amount of protein as term infant formula (whey:casein content of 60:40), the same mineral content as human milk, and less Na, K, and Phosphate than term infant formulas.

Carbohydrate-free formulas are indicated in patients who have disorders of carbohydrate absorptions such as disaccharidase deficiencies. Diet powder 3232A, which is free of monosaccharides and disaccharides, is a bovine milk protein hydrolysate with medium chain triglyceride (MCT) oil and minimal carbohydrate. RCF is a soy product with protein and fat but minimal carbohydrate and is used in infants who require a ketogenic diet. Both formulas require the addition of specific carbohydrates.

V. Parenteral Nutrition

Parenteral nutrition is a lifesaving modality in certain situations.[5] Premature infants require slow progression of feeding to allow tolerance and prevent necrotizing enterocolitis. Extra low birth weight infants can become deficient in essential fatty acids in as little as 3 days. Older children and adults may develop significant morbidity if starvation exceeds 5-7 days. This is especially true for patients with head injuries or burns who may be hypermetabolic. While it is reasonable to delay the initiation of parenteral
nutrition for older patients for up to 5-7 days, parenteral nutrition should be started early if it is anticipated that an illness will not allow feeding after 5-7 days. Infants should immediately be given parenteral nutrition because of the increased requirements for development and growth. Other indications for parenteral nutrition include short bowel syndrome, radiation enteritis, intractable vomiting and diarrhea, severe acute pancreatitis and high output enterocutaneous fistulae.

A. Composition of Parenteral Nutrition

Glucose is an essential fuel source especially for brain metabolism. At birth, the cord glucose is approximately two thirds that of the maternal blood glucose and falls to a low point at 1-2 hours of age. Sick infants should be monitored closely as their glucose levels may fall more rapidly and a glucose infusion should be initiated earlier. Infants who are preterm or growth restricted or who have experienced placental insufficiency often have low liver glycogen stores and may fail to maintain adequate serum glucose levels. Infants of diabetic mothers are also at risk for hypoglycemia because high levels of maternal blood glucose cross the placenta causing fetal hyperinsulinemia, which persists after birth. For any blood glucose less than 40 mg/dL, an infusion of dextrose should be initiated. Symptomatic hypoglycemia should be treated with a 2 ml/kg bolus of D10W followed by a continuous glucose infusion. Glucose levels should then be checked at 30-minute intervals with continued surveillance until stabilization. Insulin resistance and hyperglycemia may occur in septic patients or extremely premature infants.
Lipids are important both for caloric content but also to provide essential fatty acids. The two essential fatty acids are alpha-linolenic acid (ALA, omega 3 fatty acid) and linoleic acid (LA, omega 6 fatty acid). The appropriate balance of these two essential fatty acids is important for proper function of the multiple dependent physiologic processes including inflammation, cell signaling and cell wall structure. Omega 6 fatty acids (LA) are considered pro-inflammatory (prostaglandin and arachidonic acid precursor), while Omega 3 (ALA) are considered anti-inflammatory (docosahexaenoic acid precursor). The ratio of the fatty acids is important because of competition by these two fatty acids for the same enzymes in various physiologic processes. The omega 6 to omega 3 ratios found in the diet are usually very high with ratios of 10:1 or higher which is markedly different from the 1:1 ratio assumed to occur in the diet of our evolutionary ancestors. This presumed metabolic imbalance has been implicated as promoting inflammation, thrombosis and vascular constriction leading to a variety of chronic medical conditions. Intravenous lipid is frequently from soybean oil with a ratio of 7:1. An inverse ratio of 1:4, emphasizing omega 3 fatty acids, has been suggested as an optimal ratio. Cold-water oily fish including salmon, herring, mackerel and sardines have a ratio of 1:7. For this reason, fish oil is under investigation as an alternative to soybean oil.

The most commonly utilized intravenous solution for lipid administration in the USA is Intralipid®, which is made from soybean oil. Both the 10% and the
20% solutions of Intralipid® contain 1.2% egg yolk phospholipids and 2.25% glycerin. The 20% emulsion is preferred for infants because of the lower proportion of phospholipids relative to calories. The percentages of essential fatty acids are somewhat variable with linoleic ranging from 44-62% and linolenic 4-11%. Meaning that the omega 6 to omega 3 ratios can range from 15:1 to 4:1. Omegaven® 10% is a fish oil emulsion with an omega 6 to omega 3 ratio of 1:7, which has been used to treat parenteral nutrition associated liver disease.[6] This product is currently not available commercially in the US.

Fat is generally required for skin integrity but especially for brain growth, development and proper function. The balance of essential fatty acids appears to be the most important factor to providing healthy lipid nutrition, but patients can develop essential fatty acid deficiency syndromes. Neonates, especially premature infants, can develop this problem within a few days of life without the provision of fatty acids. The syndrome is characterized by dry skin, defective wound healing and respiratory distress. Provision of 5% - 8% of total calories as lipid is preventive. As a practical point, each ml of 20% Intralipid® provides 1.1 kcal of linoleic acid. EFA needs in an infant would be met with a dose of 1-2 ml/kg/day of 20% Intralipid®.

The third macronutrient is protein, which is required for anabolism, growth and proper immune function. Protein requirements in postoperative or stressed patients are increased due to accelerated visceral and somatic protein
catabolism and decreased extrahepatic protein synthesis. Evidence of this increased need is found by measurement of urinary nitrogen loses which may be 2-3 times higher than the usual 80 mg/kg/day. Protein anabolism requires 100 to 150 non-protein calories for each 1 gram of nitrogen. The nitrogen content of protein is approximated as protein grams divided by 6.25.

Two commercial preparations of crystalline amino acids are commonly available. TrophAmine® (10%) includes all essential amino acids except for L-Cysteine. It contains taurine, which is a conditionally essential amino acid in growing infants. When TrophAmine® is used, L-Cysteine is added as an additional component at a dose of 40 mg/gram of protein delivered. Typically, TrophAmine is used in newborns less than 3 months of age. Travasol® was designed for adults, but it will meet protein needs of children greater than 3 months. The table below compares the amino acid contents of TrophAmine® and Travasol®.

<table>
<thead>
<tr>
<th>ESSENTIAL AMINO ACIDS</th>
<th>TROPHAMINE® 1.6%</th>
<th>TRAVASOL® 1.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoleucine</td>
<td>131</td>
<td>76</td>
</tr>
<tr>
<td>Leucine</td>
<td>224</td>
<td>100</td>
</tr>
<tr>
<td>Valine</td>
<td>125</td>
<td>73</td>
</tr>
<tr>
<td>Threonine</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Methionine</td>
<td>53</td>
<td>93</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>77</td>
<td>100</td>
</tr>
<tr>
<td>Lysine</td>
<td>131</td>
<td>93</td>
</tr>
<tr>
<td><strong>SEMI-ESSENTIAL AMINO ACIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>Cysteine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Taurine</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>NON-ESSENTIAL AMINO ACIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>59</td>
<td>331</td>
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<tr>
<td>Alanine</td>
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<td>Proline</td>
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<td>Arganine</td>
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<tr>
<td>Aspartate</td>
<td>51</td>
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</tr>
<tr>
<td>Glutamine</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

Special situations require specific formulations of amino acids in parental nutrition. Branch chain amino acids (valine, leucine, isoleucine) are the main amino acids available in parenteral nutrition solutions. Aromatic amino acids (eg.
phenylalanine) should be avoided in liver disease. In renal failure, only essential amino acids are given, in order to avoid excessive production of urea, which requires renal excretion. Endogenous nitrogen sources are used to form the non-essential amino acids. Arginine supports immune function (T-cells) and also stimulates insulin production, which is anabolic.

Both calcium and phosphorus are essential for skeletal development and maintenance. Premature infants are deficient in calcium and phosphorus and have significant requirements. Potential precipitation of calcium with anions requires careful adjustments in parenteral nutrition. The calcium to phosphorus ratio should be optimized to provide for bone development and health. The ideal ratio is a 1:1 ratio of 2 mEq/1 kg/day of calcium to 2 mM/kg/day of phosphorus. Ratios can range from 2:1 to 0.5:1. A 10% calcium gluconate solution is typically used providing 1 mEq of calcium, which equals 200 mg of calcium gluconate. Calcium intake recommendations are 1 to 3 mEq/kg/day for maintenance and 3 to 5 mEq/kg/day for growth. Phosphorus intake recommendations are 1.3 mM/kg/day for maintenance and 2 mM/kg/day for growth. Ionized calcium concentrations should range from 4.5 to 5.3 mg/dL. Hypocalcemia is common in premature infants, asphyxiated infants, infants of diabetic mothers and infants of hypoparathyroid mothers. Symptoms include include irritability, jitteriness and seizures. Symptomatic or extremely low birth weight infants should have early supplementation. Central venous access is preferred because of soft tissue injuries that can occur with peripheral venous infiltration.
Magnesium is an essential component in maintaining calcium homeostasis. Magnesium infusions are often used for mothers with preterm labor or preeclampsia and these infants may have symptoms of hypermagnesemia. Magnesium levels should be monitored closely during the initiation of parenteral nutrition and daily doses of 0.5 to 1 mEq/kg/day should be administered.

Acetate is an anion that does not precipitate with calcium and therefore helps to balance the metabolic acidosis that may occur with chloride administration. Acetate is especially important in the preterm neonate who normally excretes excess bicarbonate. Any time that acetate is used to treat metabolic acidosis, the cause of the metabolic acidosis must be identified.

Trace elements are required for growth and metabolism in such small amounts that individual supplementation is not feasible. The trace elements solution is usually given as 0.15 mls/kg/day and consists of manganese 3.75 mcg, chromium 0.15 mcg, copper 15 mcg and selenium 2.25 mcg. Chromium and selenium undergo renal excretion and therefore should be used cautiously in patients with renal failure. Manganese and copper should be decreased in patients with liver compromise due to impaired biliary excretion. Ceruloplasmin levels should be checked two weeks after alterations of copper in parenteral nutrition.
Zinc is essential for growth and normal function of skin and intestine. Mature infants should receive 400 mcg/kg/day. Term infants under 3 months of age should receive 250 mcg/kg/day, and term infants over 3 months of age should receive 100 mcg/kg/day. In patients with high volume gastrointestinal losses from stomas or diarrhea, administration of more than 400 mcg/kg/day may be needed regardless of the patients’ age.

Trace elements are essential because lack of these nutrients leads to specific symptoms. Deficits of zinc cause acrodermatitis enteropathica, which is characterized by dermatitis, glossitis, alopecia, and diarrhea. Chromium deficits produce hyperglycemia. Copper deficits may present as an anemia that is not responsive to iron administration.

Carnitine is a co-factor for the transport of long chain fatty acids into mitochondria and some studies suggest that it is an essential co-factor in infancy. Premature infants can develop a deficiency of carnitine stores within one week. L-Carnitine at 5-10 mg/kg/day should be added to the parenteral nutrition of neonates.

Multivitamins should be provided on a daily basis by weight. Patients under 1000 grams should receive 1 mL, 1000-1500 grams should receive 2 mLs,
1500-2000 grams 3 mLs, 2000-2500 grams 4 mLs, greater than 2500 grams 5 mLs.

Additional medications may be provided as part of parenteral nutrition. Heparin may be added in small amounts to help maintain patency of central lines.

B. Ordering Total Parenteral Nutrition

Initiation of parenteral nutrition should begin with 25-30 kcal/kg/day with advancement over several days to reach goal calories. Adults and adolescents usually receive 35 kcal/kg/day. Term infants should receive 80-100 kcal/kg/day and preterm infants at least 90-110 kcal/kg/day. Goals for weight gain are 20 g/kg/day for infants less than 37 weeks gestational age and 30 g/kg/day patients for infants greater than 37 weeks gestational age.

The initial glucose infusion rate for infants should be 4-6mg/kg/minute advancing 2 mg/kg/minute each day as long as the serum glucose remains less than 150 mg/dL to the maximum of 12-14 mg/kg/minute. Exceeding the upper limit of 14 mg/kg/minute may result in overfeeding and fatty infiltration of the liver. [5] In addition, overreliance on glucose causes excessive CO2 production which theoretically could be detrimental to patients with compromised ventilatory function.
Initiation of Intralipid should begin slowly in infants with 1 g/kg/day for those less than 2 kg or 2 g/kg/day for patients who are over 2 kg. Advancement in lipids should be 0.5 to 1 g/kg/day while simultaneously monitoring serum triglyceride levels to keep levels below the 150 to 200 mg/dL range. The maximum dose in infants and children is 4 grams/kg/day and 2 grams/kg/day in adults. Higher doses may have deleterious effects on reticuloendothelial and pulmonary function. Lipids may provide up to 50% of total calories. Lipid administration can be given in peripheral veins. Intolerance to lipid may occur with overly rapid administration or in patients who are septic. Serum triglyceride levels should be obtained following any increase of parenteral lipid and at regular intervals during maintenance phase.

Protein should be started at 2.5 g/kg/day and advanced by 1 g/kg/day to a maximum of 4 g/kg/day for preterm infants, 3 g/kg/day for term infants and 1-2.5 g/kg/day for children and adults.

C. Guide to Daily Preparation of Parenteral Nutrition

1. Calculate maintenance fluid requirements using ideal body weight: 4ml/kg for the 1st 10 kg, 3ml/kg for 2nd 10 kg, then 1ml/kg for >20 kg

2. Calculate daily caloric needs: 100 kcal/kg for the first 10 kg, 50 kcal/kg for the 2nd 10 kg, and 20 kcal/kg for each kg>20 kg

3. Caloric distribution: 30-40% from fat, 50-60% from carbohydrates and 8-12% from protein.
a. Calculate daily protein calories
   
   Protein Calories = 2-4 g protein/kg x 4kcal/g protein

b. Calculate daily fat calories
   
   Fat Calories = 0.3 to 0.4 x total calories

   20% IL caloric density is 2.2 kcal/ml

   Fat calories/2 = ml of 20% IL

c. Calculate Carbohydrate calories
   
   CHO calories = Total Caloric Needs - [Fat Calories + Protein Calories]

   Caloric Density of IV dextrose is 3.4 kcal/gram

   CHO calories x 1 gram/3.4 kcal = grams Dextrose needed

   Usually start at D10 (infants) or D12.5 for older children

Glucose infusion rate (GIR) per minute is calculated by

   either of the following formulas

   \[
   \frac{\% \text{ glucose} \times \text{ml/kg/day}}{144} \quad \text{or} \quad \frac{\% \text{ glucose} \times \text{ml/hr}}{6 \times \text{body weight (kg)}}
   \]
d. Calculate the electrolytes, Ca, Mg, Phos based on needs and serum levels

e. Include carnitine, zinc, trace elements, vitamins, additional medications

D. Complications of Parenteral Nutrition

Enteral nutrition is preferred because it is more physiologic, but also because of complications associated with parenteral nutrition administration. Almost 5% of patients have catheter related problems including pneumothorax or hemothorax on insertion. Catheter migration may occur to an inappropriate site, such as within the heart or back into a more peripheral vein. Catheter erosion into the pericardial space also rarely occurs. The most frequent catheter related complication is infection, a problem that can be substantially mitigated with careful dressing changes following a specific protocol. Usual organisms are Staph. aureus and Staph epidermidis but also can include gram negative bacteria and fungi. Another parenteral nutrition associated problem is hyperglycemia. The sudden onset of hyperglycemia often indicates sepsis, but is rarely due to overfeeding. Chromium deficiency is another rare cause of hyperglycemia. Hyperchloremic metabolic acidosis can occur with parenteral nutrition and is treated by using acetate as a balancing anion rather than chloride.
Re-feeding syndrome is a specific problem that occurs after nutrition has been started for extremely malnourished patients. Carbohydrate is utilized along with phosphorus (PO4) to rebuild energy stores leading to hypophosphatemia. Providing adequate PO4 can prevent subsequent congestive heart failure and respiratory distress syndrome.

Liver dysfunction is seen as a complication of parenteral nutrition particularly in children after several months of therapy. The complication is multifactorial but recent studies suggest that this complication can be prevented or treated with restriction of soy based lipid formulations to 1gm/kg/day or replacement by a fish oil emulsion which has not been approved for use in the US. Another complication is acalculous cholecystitis, which some patients rarely develop while on parenteral nutrition.

VI. MONITORING ADEQUACY OF NUTRITION

Laboratory monitoring of parenteral nutrition should initially include daily electrolytes, Mg, PO4 and ionized Ca. Serum triglycerides should be checked with each increase in lipids. After a few days of stable values, these items are checked twice a week. Liver enzymes, bilirubin, alkaline phosphatase and CBC are checked every other week.
Adequacy of nutrition support is best estimated based on observed weight gain and serial observations on standard growth charts. Parenteral nutrition should be decreased as enteral nutrition is tolerated. The amino acid and lipid portions of parenteral nutrition can be stopped when the enteral route tolerates 50% of the total nutrition.

REFERENCES:

Physiology of the pediatric kidney

During the first days of life, the newborn is faced with the challenge of adapting to the extra-uterine environment and not depending on maternal regulatory mechanisms. This adaptation includes, in part, a tight homeostasis of water and electrolytes.

One of the early events in the newborn life is the “physiologic weight loss” by which a normal neonate loses approximately 10% of the body weight in the first week of life. This loss is the result of the elimination of excess total body water and sodium accumulated in-utero, and represents a loss primarily from the extravascular extracellular (EC) compartment through the kidney. As expected, a decrease in the EC water is undertaken without compromising the circulatory volume; homeostasis achieved by slow replenishment of the intravascular compartment from existing reservoirs of water in skin and muscle. This important phenomenon is believed to be regulated by prolactin.

Failure to recognize this normal process by replacing water and sodium losses would predispose to fluid overload leading to persistent ductus arteriosus (PDA), cardiac failure, necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD). [1, 2]

Neonates have a limited ability to manage loads or restriction of sodium because they have a decreased area of renal reabsorption (small and immature proximal tubules), ineffective interstitial reabsorptive capacity and immature sodium
transport mechanisms. Sodium is mainly reabsorbed in the proximal and distal tubules under the influence of aldosterone, which is produced by the adrenal cortex more effectively in term than pre-term infants. The kidney response to aldosterone is, similarly, better in term infants.

Physiologic mechanisms of sodium reabsorption in the proximal tubule include Na/H exchange transporters, Na-P and Na-glucose as well as Na-aminoacid co-transporters (at the apical side of cell) and by energy mediated Na-K-ATPase at the basolateral membrane. Fig 1.

Renal fluid and electrolyte balance is not only possible by a fully functional tubular system but by mature renal interstitium capable of concentrating urine. The renal interstitium regulates how much water needs to be kept or eliminated in the urine, therefore, the amount of water excreted in the urine will determine if the urine is concentrated or diluted. A normal urine osmolality of 300 mOsm/L to 400 mOsm/L is considered normal in the term baby but can range from 50 mOsm/L to 800 mOsm/L depending on specific circumstances. [23] The ability of the neonate to maintain a urine output in the range of 2-3 mL/kg/h reflects both a mature tubular system and a normal capacity of urine concentration.

The described physiologic changes are somewhat different in premature infants. Loss of water in the first week of life can approach 15-20% of the total body weight and sodium urinary losses are usually higher. Fluid management and electrolyte replacement in premature children should therefore be judicious and guided by clinical and laboratorial parameters.

Ultrafiltration of plasma occurs at the glomerular level. The _afferent arteriole_ brings blood to the glomerular capillaries where it is filtrated through the fenestrated glomerular endothelium and capsule of Bowman (podocytes). The filtrated blood exits the glomerulus by the _efferent arteriole_. To allow adequate filtration, there must be a difference in pressure across the Bowman’s capsule (transmembrane pressure). Thus, constriction of the efferent arteriole (partially closing the exit valve) elevates the pressure at the glomerular capillaries. In
conditions with decreased afferent pressure (renal artery stenosis, aortic valve stenosis, aortic coarctation, hypoperfusion states) a compensatory constriction of the efferent arteriole would provide enough pressure to allow ultrafiltration. The glomerular arterioles tone is mainly regulated by angiotensin.

The renal function of infants approaches adult state at the end of the second year of life. Useful parameters to assess the renal function in children are the glomerular filtration rate (GFR), urine output, urine concentrating capacity, sodium balance, acid/base balance and plasma renin activity.

**Glomerular Filtration rate**

Glomerular filtration rate (GFR) refers to the amount of serum filtrated across the glomerulus each minute. A GFR of 50 mL/min per 1.73m² is considered normal in the first week of life, increasing to 86 mL/min per 1.73m² at the end of the first year. Adult levels of GFR are reached around two years of age, as the lean body mass increases and steady creatinine production is achieved (90-140 mL/min). [25]

*Inulin clearance* is the gold standard method to determine the GFR because it is excreted 100% by the kidney after its administration. The test measures inulin concentration in plasma and urine after 90 minutes of IV infusion of inulin diluted in mannitol.

Clearance of inulin is calculated using the following formula:

\[ C = \frac{UV}{P} \]

*C=clearance, U=urinary concentration, V=volume, P=plasma concentration*

Values are corrected according to the surface body area applying the following formula:
Creatinine clearance is a simpler way to determine the GFR compared to inulin clearance but it is subjected to variations in both the daily production of creatinine and the ability of the diseased kidney to secrete creatinine.

Two formulas are generally applied to estimate the GFR:

**Cockcroft-Gault formula**, used mainly in adults

\[
(140 - \text{age})(\text{body weight in kg})/72 \times \text{PCr}
\]

\(\text{PCr} = \text{plasma creatinine}\)

**Schwartz formula**, used in children with renal failure

\[
K \times \text{height (cm)}/\text{PCr (mg/dL)}
\]

K factor (lean body mass) = 0.55 for children 2-12, 0.55 for girls 13-21, 0.70 for boys 13-21

In one study evaluating almost 200 children, the Schwartz formula overestimated the GRF by 25 to 30% in children. The Cockcroft-Gault formula was acceptable for children older than 12 years. No formula was accurate for infants and prepubertal children.

**Urine output**

Urine output (UO) is a clinical indicator of adequate renal function in children with normal circulatory volumes. UO of 1-2 mL/kg/h in infants and 0.5-1 mL/kg/h in children older than 1 year are considered within normal range.

**Definition of acute renal failure**

Acute renal failure (ARF) is defined as the inability of the kidney to maintain fluid,
electrolyte and acid-base homeostasis. In general terms, ARF is manifested clinically as a decline in urine output and a concomitant elevation of BUN and serum creatinine.

When using UO as a marker of acute renal failure (ARF), the clinician should keep in mind that a low UO does not always correlate with the severity of renal dysfunction. A classic example of normal diuresis during ARF is non-oliguric renal failure. Another example of ARF with normal or acceptable UO includes children receiving promoters of diuresis. Examples of these are diuretics and mannitol.

Renal failure criteria

Changes in urine output or serum markers of renal failure do not always reflect the severity of renal failure or indicate if the renal function is worsening or
improving. To address this issue, the Acute Dialysis Quality Initiative (ADQI) Group, (a multidisciplinary group working on developing evidence-based guidelines for the treatment of ARF), identified specific characteristics to help define and measure outcomes of renal failure. [18]

According to ADQI guidelines, the acute deterioration of kidney function follows a series of steps to finally reach a complete and permanent cessation of renal function. These are known as the RIFLE criteria for acute renal dysfunction and are represented by a progressive declining of the UO and GFR, and increasing plasma creatinine. (Fig. 2)

R= Risk of renal dysfunction
I= Injury to the kidney
F= Failure of kidney function
L= Loss of kidney function. Indicates persistent loss requiring RRT for more than 4 weeks
E= End stage kidney disease. Indicates need for RRT for more than 3 months.

The correlation of the RIFLE criteria with outcomes from renal failure has been investigated in depth. The initiation of RRT in early stages or “less severe” renal failure (RIFLE-R, RIFLE-I) has been associated with improved outcomes and decreased 30 day mortality. In contrary, when RRT was initiated in more severe stages (RIFLE-F, RIFLE-L), the 30 day mortality approached almost 50%. [27]

Unfortunately, a recent review demonstrated that the RIFLE criteria were inconsistent when used to determine the morbidity and mortality outcomes in children with renal failure. [28]
To estimate the stage renal function by RIFLE criteria one should know the baseline creatinine level. This may be difficult when baseline laboratory is not available. The creatinine level and GFR can be estimated using the “modification of diet in renal disease” (MDRD) formula which normalizes the GFR to the body surface area based on age, sex and race. Unfortunately, this formula can only estimate the baseline creatinine in children over 12 years of age. One should remember that estimations using the MDRD formula are not accurate when the patient is not in a steady state of creatinine balance such as the case of infants and patients with restricted creatinine secretion due to chemotherapy, cimetidine or AIDS therapy. [17]

**Causes of renal failure**

In developed countries, only 10% of cases of ARF are due to primary kidney disease. The majority are secondary to cardiac surgery for congenital heart disease, sepsis and nephrotoxic medications. [6] [14][15]

Years ago, hemolytic uremic syndrome was the main cause of ARF in children of developed countries. This is still the case in developing countries.

**a) Pre-renal failure**

In pre-renal failure, the kidney attempts to retain as much sodium and water as possible to increase the intravascular volume. Usually, this effect is mediated by the renin-angiotensin-aldosterone axis. Non-steroidal anti-inflammatory medications, which inhibit this physiologic response, cause renal insufficiency during states of hypoperfusion.

During renovascular disease and renal hypoperfusion states, the release of angiotensin causes vasoconstriction of the efferent arteriole, this way providing enough pressure for transglomerular filtration. The administration of ACE-inhibitors in patients with renovascular disease is
deleterious because it inhibits this compensatory mechanism by dilating the efferent arteriole (thus decreasing ultrafiltration pressure).

Mechanical ventilation and other conditions that increase the intrathoracic pressure, may lead to renal hypoperfusion and renal failure. This is particularly true during states of inadequate cardiac filling volumes.

<table>
<thead>
<tr>
<th>Causes of pre-renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypovolemia</strong></td>
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<tr>
<td>Hemorrhage</td>
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<tr>
<td>Extensive burns</td>
</tr>
<tr>
<td>Diarrhea</td>
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<tr>
<td><strong>Decreased pre-load</strong></td>
</tr>
<tr>
<td>Increased intrathoracic pressure with ventilation</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td><strong>Cardiac pump failure</strong></td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td><strong>Reno-vascular disease</strong></td>
</tr>
<tr>
<td><strong>Drugs that impair renal auto-regulation (ACE inhibitors, anti-inflammatory drugs)</strong></td>
</tr>
<tr>
<td><strong>Liver failure</strong></td>
</tr>
</tbody>
</table>

**b) Renal failure**

Parenchymal damage prevents the kidney from absorbing water and electrolytes while eliminating byproducts of catabolism (creatinine, urea).
Tubular casts precipitate and “plug” the fine tubular system causing acute tubular obstruction, back-leak into the interstitium, loss of epithelial integrity and epithelial damage. Direct toxicity of myoglobin occurs when the epithelial cells are exposed to free oxygen radicals originated from the oxidation of ferrous oxide to ferric oxide.

In acute interstitial nephritis (AIN), the inflammatory infiltration of extraglomerular structures (tubules and interstitium) and activation of proinflammatory cytokines lead to acute epithelial injury and renal dysfunction. This hypersensitivity process is usually secondary to the use of medications. AIN is, however, self-limited most of the times and rarely progresses to renal failure.

Radiocontrast dye imposes a high solute load to the tubular system which in turn imposes high energy demands to the renal medulla due to increased tubular activity. Since the renal medulla is an area of limited blood flow, the enormous metabolic demand easily leads to interstitial hypoxia and subsequent renal injury.[32]

<table>
<thead>
<tr>
<th>Causes of renal/parenchyma failure</th>
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</thead>
<tbody>
<tr>
<td><strong>Acute tubular necrosis</strong></td>
</tr>
<tr>
<td>Shock states</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Radiocontrast dye</td>
</tr>
<tr>
<td>Myoglobinuria</td>
</tr>
<tr>
<td>Acute tumor lysis syndrome</td>
</tr>
<tr>
<td><strong>Segmental glomerulosclerosis</strong></td>
</tr>
<tr>
<td><strong>Cardiac and aortic surgery</strong></td>
</tr>
<tr>
<td><strong>Acute interstitial nephritis (AIN)</strong></td>
</tr>
</tbody>
</table>

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Nephrotoxic drugs (Antibiotics, carbamazepine, NSAID’s, diuretics, ACE inhibitors)
Infectious (Bacterial, viral)
Glomerulonephritis
Systemic lupus
Acute transplant rejection

**a) Post-renal failure**

In post-renal failure, decreased ultrafiltration pressure and acute tubular injury result from obstruction of the urinary outflow. This obstruction leads to retrograde or “backflow” of urine causing tubular hypertension. Hydronephrosis or dilatation of the collecting system occurs with prolonged obstruction usually over days.

<table>
<thead>
<tr>
<th>Causes of post-renal failure</th>
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</thead>
<tbody>
<tr>
<td>Papillary necrosis</td>
</tr>
<tr>
<td>Posterior urethral valves</td>
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<tr>
<td>Urethral stricture</td>
</tr>
<tr>
<td>Retroperitoneal mass</td>
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<tr>
<td>Prostatic hypertrophy</td>
</tr>
</tbody>
</table>

**Causes of renal failure in young children**

Common causes of renal failure in young children include interstitial diseases such as renal dysplasia, hypoplasia and obstructive uropathy. Glomerular-based disease is more frequent in older children; this typically include glomerulonephritis.

**Clinical assessment of the child with acute renal failure**

The clinical evaluation of a child with suspected renal failure should include a
thorough investigation of previous medical and surgical conditions, presence of hypertension, recent infections and use of medications with potential nephrotoxic side effects. Examination of the child should be focused on the identification of hypovolemic states, generalized edema, measurement of the blood pressure and skin inspection to identify palpable (vasculitis) and non-palpable purpuric lesions (hemolytic-uremic syndrome).

Abdominal examination and auscultation often reveal renal artery stenosis and the presence of a pelvic mass responsible for obstructive renal failure.

**Laboratory findings**

- **Urinary osmolality**

  In pre-renal failure, the avid absorption of sodium to maximize water retention leads to a concentrated urine. Urine osmolality can reach very high levels.

  In renal/parenchymal failure, the inability to concentrate urine leads to diluted urine with osmolality levels of less than 300 mOsm/L.

- **Urinary sodium**

  Measurements of urinary sodium help differentiate if the failure is pre-renal or renal. In low flow states, the kidneys attempt to save sodium and water to expand the intravascular volume; therefore the urinary sodium is low (less than 20 mEq/L).

  In renal/parenchymal failure, the kidney has lost its absorptive ability and is unable to retain sodium; therefore the urinary sodium is high (greater than 30-40 mEq/L).

- **Fractional excretion of sodium**
Fractional excretion of sodium or $FE_{Na}$ refers to the fraction of filtrated sodium that is excreted by the kidney. In pre-renal failure, $FE_{Na}$ is less than 1% as the kidney is trying to conserve as much sodium as possible. In renal conditions, $FE_{Na}$ levels are above 2%.

Calculation of $FE_{Na}$:

$$ FE_{Na} = \frac{Urine\ [Na]}{Plasma\ [Na]} \times 100 $$

$$ \frac{Urine\ [Cr]}{Plasma\ [Cr]} $$

- **Urine microscopy**

A simple microscopic analysis of the urine will help identify several causes of intrarenal failure by revealing the presence of tubular casts, which are absent in the normal urine. Hematuria, pyuria and the presence of eosinophils in urine are indicative of specific conditions.

Epithelial casts are characteristic of ATN and are due to “shedding” of epithelial cells after tubular injury.

White blood cell and eosinophil casts are representative of AIN, pigmented casts are typical of myoglobinuria and red blood cell casts are characteristic of glomerunephritis.

- **Serum creatinine and BUN**

*Serum creatinine* is a valuable and consistent biochemical marker of renal function.

Serum creatinine levels are similar to those of the mother in the immediate neonatal period decreasing by 50% in the first week and reaching normal levels by the second month of life (0.40 mg/dL). [24] Normal adult levels are reached during adolescence (1- 1.5 mg/dL). [25]

Preterm infants do not show this pattern of creatinine production and an
increase, instead of a decrease, has been observed during the first week of life. It is not until an adjusted conceptional age of 34 weeks that the serum creatinine levels are comparable to those of term infants.[26]

**Initial management of renal failure**

1. *Determine the cause of renal dysfunction*

   Patients with oliguria and rising plasma creatinine levels should immediately be investigated. Urinary electrolytes and $F_{\text{E}}\text{Na}$, along with a microscopic analysis of the urine may give some clues as to whether the renal failure is pre-renal or renal. The physician should carefully review all medications and determine the recent use of intravenous contrast agents.

   Critically ill patients with severe sepsis often have ARF.

2. *Assess fluid deficit and correct hypovolemia*

   Hypotension, tachycardia and oliguria are clinical indicators of hypovolemia. Prolonged hypovolemia could inevitably lead to ischemic damage to the renal tubules with resultant injury. A central venous catheter (CVC) should be placed to guide fluid management in patients with ARF associated with oliguria. This important measure will prevent the development of pulmonary edema secondary to aggressive fluid resuscitation or commonly generalized edema. CVC allows the measurement of central venous pressure (CVP) and central venous oxyhemoglobin saturation ($\text{ScvO}_2$).

   Commonly, children with low circulatory volume and oliguria receive an initial fluid bolus challenge of 10-20 mL/kg over 30 min and repeated until there is a response. This measure is an acceptable step in the resuscitation process but should be conducted carefully in the critically ill children, in which, fluid
challenges are better guided by hemodynamic parameters obtained by CVC. In general, crystalloid solutions are preferred over colloid solutions.

3. Avoid and discontinue nephrotoxic drugs

All drugs with potential nephrotoxic side effects should be immediately discontinued. Radiologic tests should avoid the administration of contrast agents. High osmolality agents such as diatrizoate sodium (Hypaque) and iothalamate meglumine (Conray) have been associated more commonly with renal dysfunction. Low osmolality agents are associated with a decreased risk and are preferred in patients with renal dysfunction.

If needed, intravenous (IV) contrast agents should be used at least 5 days apart. Appropriate hydration with isotonic bicarbonate solution (3 ampules of Sodium Bicarbonate [50 meq/ampule] in 850 cc D5W) at a rate of 3 mL/kg IV one hour before the procedure and 1 mL/kg IV six hours after the procedure. Normal saline (0.9% NaCl) at 1 mL/kg/hr for 12 hours pre-procedure and 12 hours post-procedure is another commonly used protocol.[33]

Acetylcysteine (Mucomyst) have questionable benefits in preventing contrast-induced nephropathy. When used, give 600 mg PO twice daily in adults. There is no consensus on acetylcysteine dosing in children.

4. Adjust medication dosages according to GFR

Dosage of medications should be individually adjusted according to the patient’s GFR. Reducing drug doses and prolonging the dosing intervals are two recommended strategies in patients with established renal failure.

5. Low-dose Dopamine?

Low dose dopamine (<5µg/kg/min) was considered for a long time an adjuvant therapy in patients with compromised renal function due to its renal
vasodilator effects. There is little and inconsistent data supporting the use
dopamine in infants and children. [31] A recent meta-analysis including 17
randomized clinical trials indicated that low dose dopamine did not prevent
mortality, onset of ARF or need for dialysis. [29]

Holmes et al demonstrated that the effects of low dopamine in the critically ill
patient have deleterious effects in the GI, endocrine, immunologic and respiratory
systems and its use is no longer justified in ARF. [32]

6. Adequate oxygenation

Adequate oxygen supplementation helps minimize the effects of organ
hypoperfusion, including the kidney. High metabolic demands of the renal
medulla, which is by nature a poorly perfused zone, are only met with high
oxygen supply to prevent hypoxic injury (oxygen extraction of renal medulla
approaches 90%).

7. Correction of hyperkalemia

Hyperkalemia (K >4.7 mEq/L in children) is the result of decreased
excretion of potassium in the distal and collecting cortical tubules, mostly
under the influence of aldosterone and kinases.

Elevation of K leads to muscle weakness, respiratory failure, and cardiac
conduction abnormalities such as bradycardia, ventricular fibrillation and
asystole. Classic electrocardiographic signs include peaked T waves, ST
depression, loss of P wave and widening of the QRS.

Once identified, parenteral potassium must be stopped and extracellular
potassium should be forced into the intracellular compartment with glucose
and insulin infusions. Glucose loading at a rate of 0.5 g/kg/h in children is
enough since these have an increased endogenous insulin production in
response to glucose. Insulin at a rate 0.05 u/kg/h should be added if blood
glucose levels reach 10 mmol/l. [35]
Cardiac excitability secondary to hyperkalemia with evidence of EKG abnormalities should be treated with IV calcium gluconate at a dose of 0.5 ml/kg over 5–10 minutes. [34]

**Renal replacement therapy (RRT)**

Failure of improvement and/or progression of renal dysfunction despite supportive therapy require more aggressive interventions such as renal replacement therapy (RRT).

RRT refers to a form of therapy in which full support replaces most of the kidney’s metabolic functions.

**Classification of RRT**

1. **Acute RRT**
   Include intermittent and acute hemodialysis.

2. **Chronic RRT**
   Include intermittent hemodialysis, peritoneal dialysis and renal transplantation

**Indications for renal replacement therapy**

The following are well recognized indications for RRT:

1. Metabolic/electrolyte imbalance,

2. Uremia with bleeding and/or encephalopathy,

3. Hypervolemia with pulmonary edema/respiratory failure,

4. Intoxications,

5. Inborn errors of metabolism (IEM), and

6. Nutritional support (removal of fluid to make space for nutrition)
Hemodialysis

Hemodialysis (HD) is a form of RRT that involves the removal of undesired solutes from the blood after it is passed through an “artificial kidney” or dialyzer. To understand how HD works, let’s define some basic terms:

1. Hemofiltration

   Hemofiltration is the process of clearing blood of metabolic waste by the passage of blood through a semi permeable filter or membrane.

2. Convection

   During convection, hydrostatic pressure “forces” water and solutes to pass through a filtration membrane (hemofilter), including small and large molecules. The hemofilter is impermeable to proteins and cells due to the small size of its pores.

3. Diffusion

   Is the mechanism by which, solutes are transported across the filtration membrane in direction to a concentration gradient. Solutes move or “diffuse” to the side of the membrane that has lower concentration of that solute. Diffusion is effective in clearing small molecules such as potassium and urea but ineffective for larger solutes or albumin (LMW proteins).

4. Adsorption

   It is the mechanism by which non-desired molecules are adhered to the dialyzer membrane.

5. Molecule size

   a. Small molecules. <500 Daltons. Most electrolytes, creatinine and urea
fall in this category.

b. Medium size molecules. 500-5000 Daltons

c. Large molecules. 5000-50000 Daltons. Include proteins and cytokines

6. **Sieving coefficient.**

Is the ability of a molecule to pass through the membrane. A Sieving coefficient of 1 indicates that 100% of the solute will move across the membrane (K, Na, Creatinine, etc). Proteins have a Sieving coefficient of zero as they are unable to pass across the membrane due to their large size.

**Continuous vs. intermittent renal replacement therapy [5]**

Continuous renal replacement therapy, has the advantage of providing clearance of nitrogenous waste products, correction of electrolytes/acid-base abnormalities and management of fluid overload with a much gentler and effective mechanisms than intermittent hemodialysis.

Due to the small blood volumes in small children, intermittent HD is difficult. The frequent episodes of hypotension could compromise even more the perfusion of end organs in the critically ill child.

When used, the utilization of volume-controlled dialysis machines is extremely important in children. Frequent hematocrit measurements during dialysis help prevent sudden changes in intravascular volume

Continuous RRT uses convection or hemofiltration by which, water and solutes are eliminated without causing volume shifts or hypotension. Hemofiltration is the preferred method of RRT in critically ill and small children due to their small blood volumes.
These are the most commonly used forms of CRRT: (indicate what conditions use what)

1. CUF (continuous ultrafiltration), removes only water. Used in patients with fluid overload or severe electrolyte abnormalities.

2. CVVH (continuous veno-venous hemofiltration). Uses convection and requires a replacement solution. It helps remove medium to large molecules. Replacement solutions are electrolyte and bicarbonate-based solutions. Indicated in patients with severe kidney injury, uremia or severe pH/electrolyte imbalance with or without fluid overload that require removal of solutes (large molecules) maintaining a near normal volume. Some hypothesize that it helps remove mediators in inflammatory states (i.e cytokines, lipopolysaccharide) and successfully used in conditions such as SIRS, ARDS, septic shock or critically ill burn patients.

3. CVVHD (continuous veno-venous hemodialysis). Uses diffusion and requires a dialysate solution to create a concentration gradient across the filter (semipermeable membrane). It helps remove small molecules. No replacement solution is required. The dialysate solution uses buffering agents, electrolytes and glucose at normal plasma values with concentrations that can be changed according to the indications for RRT. Used in critically ill patients with hemodinamyc unstability or in children with inborn errors of metabolism.[53]

4. CVVHDF (continuous veno-venous hemodiafiltration) – uses both convection and diffusion providing clearance of a wide range of solutes at very low flow rates. Requires both dialysate and replacement solution. Commonly used in critically ill patients with multiple organ dysfunction syndrome.
**CRRT Circuit (Fig 3)**

1. Central double-lumen veno-venous hemodialysis catheter

2. Extracorporeal circuit and filter (dialyzer)

3. Blood pump

4. Dialysate pumps

5. *Replacement fluid pump*

---

**Dialyzer**

The dialyzer is the main constituent of the circuit. It allows blood flow in opposite direction to the dialysate solution (countercurrent), both separated by a dialyzer membrane.

**Dialyzer membranes**

Membranes are made of synthetic and biocompatible materials designed to filter unwanted molecules from the blood during dialysis. They are semi permeable as they allow the selective clearance of small, medium or large molecules size according to the size of its pores. A commonly used membrane is the AN-69 is associated with hypotension due to bradykinin release. Some propose the use of synthetic membranes such as polyarylethersulfone (PAES) membranes to avoid this reaction. Other biosynthetic membranes are made of polysulfone, polyamida, polyacrylonitrile.

**Dialysate pump**

The dialysate pump regulates the pressure of the dialysate solution. Although low pressures are preferred in the dialysate side of the system
(to promote ultrafiltration), increasing the dialysate pressure could reduce the filtration rate in desired circumstances

- **Blood priming**

Blood priming refers to filling the circuit volume with blood prior to its connection to the patient circulation. It is particularly needed when the circuit volume exceeds 10-15% of the estimated blood volume of the child. [5]

- **Anticoagulant**

Anticoagulation is needed to keep the circuit patent.

  a. Heparin. It is delivered in the pre-filter area of the circuit and titrated to achieve a post-filter PTT of 1.5 times normal or an ACT of 180 s. Heparin is given continuously at a rate of 10-20 units/kg/h after a bolus of 20-30 units/kg. Bleeding complications are more common with heparin [9]

  b. Citrate based anticoagulation. It is better tolerated in children and has lower complication rates. Citrate binds free calcium ions thus preventing coagulation. Sodium citrate is delivered to the initial part of the circuit providing a local anticoagulation effect. Calcium chloride is added to the blood before it is returned to the patient.

  Citrate is converted to bicarbonate in the liver which could cause metabolic alkalosis. Be careful in patients with hepatic insufficiency because citrate overload could cause metabolic acidosis.

**Buffering agents.**

Bicarbonate and lactate based dialysate solutions are the two main buffering agents used during CVVHD and CVVHDF. Conversion of lactate to bicarbonate in the liver limits the use of lactate based solutions in
patients with associated liver impairment. Furthermore, due to its vasodilator properties and non-physiologic pH, lactate could cause hypotension and worsen acidosis due to accumulation of lactate.

**CRRT solutions for dialysate and replacement fluid**

Dialysates are iso-osmotic solutions with physiologic concentrations of electrolytes and glucose. The lack of urea and other non-desired metabolic byproducts in the dialysate solution creates a concentration gradient by which these solutes are cleared from the blood. High concentrations of urea, potassium and phosphorus in blood of patients with renal failure are easily eliminated through the membrane both by convection (ultrafiltrate) and diffusion (low or physiologic concentrations in the dialysate solution).

Bicarbonate-based fluid is preferred over lactate-based due to the risk of metabolic acidosis leading to cardiac dysfunction, vasodilatation, and hypotension.[8]

Solutions without calcium are utilized when citrate anticoagulation is used.

Albumin can be added to the dialysate fluid to help eliminate protein bound drugs.

Dialysate solutions are warmed to a temperature of 35 to 37° to avoid hypothermia.

**Circuit flow rate**

Blood flow (Qb) should be started below the goal rate and advanced to maximum rate over 30 min. Flow rates vary from to 10-12 mL/kg/min in neonates and 2-4 mL/kg/min in older children and adolescents .[7] Usually the dialysate flow (Qd) is matched to the Qb to allow maximal exposure time.
Circuit pressure

Pressure detectors are placed in both the arterial and venous side of the circuit to regulate transmembrane pressures and allow adequate ultrafiltration. Low arterial pressures may be due to hypotension, kinks in the tubing system, catheter malfunction or stenosis of the arterial inflow. Venous hypertension may be due to clotting of the dialyzer/membrane, kinks in the tubing system or stenosis of the venous outflow.

Vascular access for RRT

- **Catheter location**

  Hemodialysis catheters should be preferentially placed in the IJ vein. Femoral vein and SC vein are alternatives to IJ vein but are associated with vein thrombosis and vein stenosis respectively. SC vein stenosis, a common complication of dialysis catheters, is of concern because some children will eventually require permanent vascular access for chronic hemodialysis.

- **Catheter size**

  According to Poiseuille’s Law, the greater the diameter of the catheter, the less resistance to flow. Long catheter should be avoided for this same reason.

  Catheter sizes vary from 7 to 12 F according to the weight of the child. Neonates and children up to 6 kg usually require 7 Fr, 6 to 15 kg require 8 Fr, 15 to 30 kg require 9 Fr and >30 kg 10 Fr catheters. [3]

- **Catheter insertion**

  In neonates and small children, use cut down techniques similar to ECMO
cannulation. In older children and adolescents, US guided catheter insertion is acceptable.

Pre-insertion preparation should include evaluation of hematologic parameters; platelet count of at least 50,000 and INR of no greater than 1.5 times normal.

In children with previous multiple access catheters, US study to evaluate the patency of the veins to be used should be done.

Cutdown technique involves the use of general anesthesia in children. Tunneled dialysis catheters can be used in children who will require prolonged HD and in those waiting for renal transplantation.

**Complications of RRT**

- Hypotension
- Bleeding
- Electrolyte an acid/base imbalance
  
  Metabolic alkalosis is seen in circuits using citrate as an anticoagulant, citrate is metabolized to bicarbonate in the liver.
- Air embolism
- Catheter malfunction
- Catheter infection
  
  Signs of infection should prompt blood cultures and the initiation of empiric antibiotics.
Adequate dialysis

Adequacy of dialysis is usually determined by the fractional clearance of urea (Kt/V$_{urea}$) which is also used to guide dosage of dialysis. Determinations of daily urea clearance are derived by the following formula:

\[
\text{Daily total Kt/V}_{urea} = \text{peritoneal Kt/V}_{urea} + \text{renal Kt/V}_{urea}
\]

Where: K=clearance of urea, t=time (min), V=volume of distribution

*Adequate dialysis* is a term employed to describe the effects of a dialysis dose by returning the patient with renal failure to almost physiologic parameters of kidney function and keeping him/her asymptomatic. *Optimal dialysis* is used to describe the reduction in morbidity and/or mortality with a determined dose of dialysis keeping in mind the financial burden or excessive workload if the dose is increased. [52] Both terms are commonly employed in patients with ESRD.

### Outcomes of CRRT in children [12]

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Number of patients</th>
<th>Number of survivors</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>81</td>
<td>48</td>
<td>59%</td>
</tr>
<tr>
<td>Stem cell transplant</td>
<td>55</td>
<td>25</td>
<td>45%</td>
</tr>
<tr>
<td>Cardiac disease/transplant</td>
<td>41</td>
<td>21</td>
<td>51%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>32</td>
<td>27</td>
<td>84%</td>
</tr>
<tr>
<td>Liver disease/transplant</td>
<td>29</td>
<td>9</td>
<td>31%</td>
</tr>
<tr>
<td>Malignancy (w/o tumor lysis)</td>
<td>29</td>
<td>14</td>
<td>48%</td>
</tr>
<tr>
<td>Ischemia/shock</td>
<td>19</td>
<td>13</td>
<td>68%</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>15</td>
<td>11</td>
<td>73%</td>
</tr>
<tr>
<td>Drug intoxication</td>
<td>13</td>
<td>13</td>
<td>100%</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>12</td>
<td>10</td>
<td>83%</td>
</tr>
<tr>
<td>Pulmonary disease/transplant</td>
<td>11</td>
<td>5</td>
<td>45%</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>5</td>
<td>71%</td>
</tr>
</tbody>
</table>
The outcomes of children receiving CRRT is proportional to the underlying condition of the child. Patients with fluid overload at initiation of therapy, multi-organ failure, hemodynamic instability and younger age are factors influencing the outcomes of kidney injury and not necessarily CRRT therapy. [12] [13] [14] [16]

**Chronic Kidney Disease and End Stage Renal Disease in children**

*Chronic Kidney Disease* (CKD) occurs when the function of the kidney is affected for a period of at least three months, usually accompanied by structural damage of the kidney and a decreased GFR. According to KDOQI guidelines, a GFR <60 mL/min/1.73m$^2$ for at least three months is considered CKD. However, patients with a subnormal GFR of >60 to 89 mL/min/1.73m$^2$ are at risk for further kidney function loss and cardiovascular disease.

*Indicators* or *markers* of CKD include:

1. Proteinuria (more specifically albuminuria), which is determined by the ratio of the concentration of albumin to creatinine in spot urine. Protein content in urine varies at different times of the day and proteinuria has been reported as high as in 10% of normal children but only less than 1% of these have persistent proteinuria. [36]

2. Decreased GFR. GFR is the best marker of kidney function and varies according to age, gender and body size as mentioned before. Adult GFR levels are reached by 2 years of age. [37] Normally, the GFR is adjusted to standard body surface area of 1.73 m$^2$. The average GFR in a week old neonate is 40-50 mL/min/1.73 m$^2$, increasing to 65 mL/min/1.73 m$^2$ at 1 month of age, 95 mL/min/1.73 m$^2$ by 2 months of age, and reaches 130 mL/min/1.73 m$^2$ in the age group of 2 to 12. [37, 38]
CKD is classified in 5 stages (adults):

**Stage 1.** Kidney damage with normal or elevated GFR (GFR >90 mL/min/1.73m²)

**Stage 2.** Kidney damage with mild decrease of GFR (GFR 60-89 mL/min/1.73m²)

**Stage 3.** Moderate decrease of GFR (GFR 30-59 mL/min/1.73m²)

**Stage 4.** Severe decrease of GFR (GFR 15-29 mL/min/1.73m²)

**Stage 5.** Kidney failure (<15 mL/min/1.73m² or dialysis)

As mentioned before, the *Schwartz* and *Cockcroft-Gault* formulas are used in children to calculate the GFR.

*End Stage Renal Disease* (ESRD) refers to those patients with kidney failure that require long term dialysis or transplantation.

Indications for RRT in children with CKD are based on the level of renal function, uremic syndrome, availability of therapy and patient’s preference. [36]

**Peritoneal dialysis**

Peritoneal dialysis (PD) is a form of RRT that uses the peritoneum as a membrane for interchange of solutes and water. PD is easy to apply to small children and in those requiring chronic RRT. PD is performed on a daily basis at home, therefore, family involvement and continuous commitment is important if chosen as a preferred therapy.

The peritoneum provides a surface of approximately 40 m² in the adult. This extensive absorptive surface allows for an effective exchange of water and solutes and transfer of proteins and cells in normal circumstances. Its large surface is mainly due to the existence of microvilli which, along with tight
intercellular junctions of the mesothelial cells are in charge of most transport mechanisms. Aquaporin channels have been identified and believed to be responsible for at least 50% of the water transport through the peritoneum. [40] However, convection and osmotic gradient seem to play the most important roles in water movement across the membrane since small increases of the intraabdominal pressure during PD and small solute concentration differences effectively move water across the peritoneum. [39]

Transport or diffusion of solutes and small proteins through the peritoneal surface is facilitated by electric differences across the membrane and mechanisms that may involve active transport.

Indications and contraindications of PD

PD is preferable over hemodialysis in children less than 5 kg; lack of vascular access and contraindications to anticoagulation. [20] Contraindications to PD include congenital defects of the abdominal wall such as gastroschisis and omphalocele, CDH, bladder extrophy, obliterated peritoneal cavity and peritoneal membrane failure. [20]

Termination of PD is common after peritonitis, ultrafiltration failure, peritoneal adhesions and renal transplantation.

Technique

1. Types of PD catheters

PD catheters are made of silicone or polyurethane and have intraperitoneal and extraperitoneal segments connected by an intramural segment which is tunneled in the muscular layer of the abdomen. The tunneled portion of the PD catheter has two polyester cuffs of 1 cm in length to secure the catheter in place and help reduce bacterial contamination of the tunnel and the peritoneal cavity.

The intraperitoneal catheter segment may be straight or coiled with
multiple side holes of about 500 microns in diameter. Coiled catheters tend to migrate less and cause less pain with dialysate infusion.

Catheters such as the Toronto Western have two silicone discs (placed in the intraperitoneal portion) which limit the free movement of the tip keeping the intraperitoneal portion in the pelvis thus reducing migration, a common problem with straight and coiled PD catheters.

The extraperitoneal segment of the PD catheter may be straight or bent (swan-neck). Because of their configuration, bent catheters are associated with fewer occurrences of cuff extrusion and leaks. [41, 42]

2. Catheter placement

PD catheters are usually inserted surgically and occasionally percutaneously with radiologic guidance. Peritoneoscopic and laparoscopic techniques of catheter insertion are well described and are associated with decreased rates of site infections, leaks and prolonged catheter survival. [45]

The tip of the catheter or coiled part of the intraperitoneal segment should be placed in the pouch of Douglas between the visceral and parietal peritoneum.

The internal cuff is placed in the musculature of the abdomen and the external cuff in the subcutaneous tissue. The catheter should exit facing downward and laterally and the exit site should not be placed near the midline, belt line or near any prior scars.

For children with ostomies, fecal incontinence or obesity, the presternal exit site is preferred.
3. Dialysate solutions

Dialysate solutions for PD have physiologic concentrations of electrolytes such as sodium, chloride, magnesium and calcium. Hypertonic dextrose (2.5%) have been traditionally used in the dialysate solutions as an osmotic agent but was associated with peritoneal neoangiogenesis and fibrosis due to nonenzymatic glycosilation of proteins.[19] Recently, hypertonic glucose has been replaced by glucose polymers such as icodextrin which provide a more stable osmotic pressure and avoid the mentioned side effects.

The preferred buffer for PD is lactate. Bicarbonate and acetate are rarely used as they commonly produce calcium precipitation and changes in the structure of the peritoneum, respectively.

Protein losses during PD lead to common malnutrition and hypoalbuminemia. The addition of amino acids to the dialysate solution, proved to be beneficial to improve the nutritional status of the malnourished child on PD. [50] Furthermore, amino acids can be used as an alternative osmotic agent with comparable results.[49]

4. Dialysis is usually started 2 weeks after catheter placement to allow for adequate healing, incorporation of the cuffs and avoid leaks. For children with no other access, low volume dialysis in the supine position may be started in the first 24 hours without a significant risk of leak or subsequent infection and survival of the catheter.[43]

5. Exchange volume

The exchange or “fill” volume is approximately 600-800 mL/m2 in children <2 years and 100-1200 mL/m2 in children >2 years old.
6. Types of PD [51]

a) *Intermittent PD*

Intermittent PD is not routinely performed because the patient needs to be hospitalized every 3 days.

b) *Continuous Ambulatory Peritoneal Dialysis (CAPD)*

With CAPD, the patient performs 3-5 dialysate exchanges a day using the double-bag technique. With this technique, one empty bag is used to drain the peritoneal cavity and the other contains the dialysate solution (1.5 to 3L), both connected with a Y connector. First, the peritoneal cavity is allowed to drain from the previous dwell keeping the dialysate channel closed, then, the draining tube is flushed with dialysate solution keeping the PD catheter closed. Finally the dialysate solution is allowed in the peritoneum, keeping the draining tube closed (Fig…)

c) *Automated Peritoneal Dialysis (APD)*

APD is a technology that allows for a more convenient “automated” dialysis performed by newly developed PD machines. Advantages of APD are higher dialysate volumes and greater number of cycles with decreased dwell times.

A variations of APD includes “tidal dialysis”, in which, after the dialysate is infused, it is allowed to drain only partially in between exchanges and replaced by new “fresh” dialysate solution. The peritoneum is completely drained at the end of the day. It seems to reduce the pain associated with rapid exchanges of dialysate fluid.
Complications of PD

Complications of PD include peritonitis and catheter tunnel infections. Peritonitis is more common in younger children compared to adolescents. Both Gram-negative and Gram-positive organisms are responsible for the majority of episodes of peritonitis. Fungal infections are responsible for less 5% of the total infections. Approximately 50% of children had an episode of peritonitis in the first two years of initiation of PD. [21]

Abdominal pain, cloudy fluid or elevated counts of neutrophils in the peritoneal fluid are suggestive of peritonitis. Intraperitoneal antibiotics should be started immediately. Typically, vancomycin and a third generation cephalosporin are the antibiotics of choice. Peritoneal fluid cultures should be obtained prior to initiation of antibiotics.

Catheter site infections are prevented with appropriate handling of the catheter and the use of local mupirocin in some series.[22] Confirmed infections should be treated with oral antibiotics and removal of the catheter done when there is no improvement or complicated with peritonitis.

Wrapping of omentum around the intraperitoneal segment of the PD catheter is common. In a retrospective review of 121 PD catheters, concomitant omentectomy seemed to significantly reduce the rate of early failure. [47] Others have proposed a more aggressive approach to catheter migration by performing omentectomy and suturing the tip to the pelvic peritoneum. [48]

Migration of the PD catheter tip has been reported in up to 15%. [44] The catheter should be repositioned if symptomatic or when the dialysate drainage is compromised.

Leaks occur in up to 10% of PD catheters and tend to be less significant with swan-neck catheters.

Other complications include bowel perforation, usually when PD catheters are
placed blindly by radiologic techniques (fluoroscopic or ultrasound guided), cuff extrusions, fibrin clot obstructions and pain with infusion. Bleeding due to erosion of mesenteric vessels by the catheter is rare complication.

References


[25] Nelson's


[28] Slater MB, Anand V, Uleryk EM, Parshuram CS. A systematic review of


[39] Flessner M.F., Schwab A.: Pressure threshold for fluid loss from the


[51] Taal: Brenner and Rector’s The Kidney, 9th ed


Chapter 11
Transfusion and Anticoagulation

Robert L. Ricca, MD
Marjorie J. Arca, MD

I. Introduction

The oxygen carrying capacity of hemoglobin and its role in oxygen delivery is well understood. Transfusion of packed red blood cells has, therefore, become an important tool in the armamentarium of intensivists, and surgeons alike, in an attempt to reduce the oxygen debt associated with an underlying disease process. This topic remains relevant as up to 50% of children receive a blood transfusion during their stay in the pediatric intensive care unit (PICU) and almost 80% of extremely low birth weight (ELBW) infants receive a transfusion [1,2].

Currently no absolute value of hemoglobin concentration below which transfusion is mandated exists. There are multiple physiologic variables that dictate the necessity of transfusion. These include the rapidity of drop in hemoglobin or hematocrit, associated cardio-respiratory collapse or compromise, infection, injury to the CNS or physiologic anemia as seen in premature infants. Defining this transfusion level has been the centerpiece of most recent literature on transfusion medicine. The impetus for these studies was the complication profile seen after transfusions including transmission of infectious disease, fluid overload and acute lung injury seen in patients post-transfusion. The underlying immunosuppression seen in many of our pediatric patients due to malignancy or
prematurity may complicate therapy with an increased risk of graft-versus-host
disease in this population.

The Transfusion Requirements in Critical Care (TRICC) study has become
a landmark article in adult critical care that supports institution of restrictive
transfusion policies [3]. This study showed a decreased in-hospital mortality rate
and no difference in 30-day mortality in critically ill patients who had a more
restrictive transfusion threshold (7g/dL). Guidelines, therefore, have been
proposed and instituted at many centers to standardize transfusion medicine.
These guidelines vary from institution to institution and rely upon critical review of
the current literature as well as local transfusion policies and expert opinion.
Clinical judgment remains an integral part of the decision making process [4].

ii. RBC Transfusion Products And Volumes

There are different types of blood products. As a rule of thumb, use the
following table for specific patients in the ICU.

<table>
<thead>
<tr>
<th>Blood Product Type</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV negative</td>
<td>Severely immunodeficient patients who are CMV negative. CMV negative transplant patients</td>
</tr>
<tr>
<td>Irradiated (prevents GVHD)</td>
<td>Infants, congenital immunodeficiency, cancer, HSC</td>
</tr>
<tr>
<td>Pharesed/leukofiltered</td>
<td>Everyone</td>
</tr>
<tr>
<td>Washed PRBC</td>
<td>Patients known to have exposed antigen-causing hemolytic reaction</td>
</tr>
</tbody>
</table>
As with all pharmacotherapy in children, weight based volumes are used to determine the appropriate amount of component therapy to provide. The following are guidelines to be used for transfusion therapy:

Estimated Blood Volume:
- Newborn: 90ml/kg
- Child: 80ml/kg
- Adult: 70ml/kg

Replacement Volumes.\(^5\)
- 10ml/kg of packed RBC’s – Increase HCT approximately 3%
- 1 unit/10kg of platelets – Raise platelet count by 25,000
- 10ml/kg of FFP for coagulopathy
- 1 unit/5kg of Cryoprecipitate to replace Fibrinogen

iii. Neonatal Transfusion

Premature infants are among the most commonly transfused patients in the hospital setting. Nearly 50% of infants will receive their first blood transfusion within two weeks after birth, and almost 80% of infants will receive at least one blood transfusion during their hospital stay [2,6]. Anemia in the preterm infant is most commonly due to either acute blood loss from multiple laboratory draws or due to inadequate marrow production – anemia of prematurity. Defining which patients will benefit from transfusion of blood components is difficult as the
symptoms of poor oxygen delivery or increased oxygen demand are vague and
nondescript consisting of poor weight gain, tachycardia, apnea, persistent
oxygen requirement or prolonged mechanical ventilation and lactic acidosis.

Common practice in the 1970’s and 1980’s were to maintain a hematocrit
of 40% in premature infants [6]. A trend towards more restrictive policies has
been seen over the last several decades. Neonates are subject to the same
complications from transfusion found in adults. Additionally, more severe
consequences of transfusion of packed red blood cells have been described
including the development of bronchopulmonary dysplasia [7,8], retinopathy of
prematurity [9] and necrotizing enterocolitis [10]. It is felt that these outcomes
may be due to the inflammatory modulators that are found from presence of
leukocytes in non-irradiated red blood cells.

The largest study to date evaluating a transfusion threshold in
premature infants is the Premature Infants in Need of Transfusion (PINT). This
study randomized 451 infants to a low or high hemoglobin threshold. There was
no difference in the associated mortality, presence of retinopathy of prematurity
or bronchopulmonary dysplasia between the two groups. Additionally, there was
no statistically significant difference in the rates of intracranial hemorrhage or
brain injury (18.5% vs. 21.1%) between the low and high threshold groups [11].
This study supported previous thoughts that a high transfusion threshold subjects
the infant to more risks of transfusion but does not confer any physiologic
benefits.
Multiple transfusion guidelines have been included in the recent literature and can be easily implemented clinically [2,3,5]. Most of these continue to use a tiered approach to transfusion depending upon the requirement for cardiopulmonary support. None of these guidelines have been compared in a prospective trial and many rely upon clinical expertise. Currently, no national consensus exists. A sample guideline is listed below:

**Transfuse with PRBC’s if:**

- HCT < 35% and intubated (or on CPAP > 8 cm H2O) with FiO2 > 0.35
- HCT < 30% and intubated (or on CPAP) with FiO2 < 0.35
  - Undergoing surgery
  - Poor weight gain for one week (< 10 gm/day)
  - Significant apnea or bradycardia requiring intervention
- HCT < 20% if asymptomatic with low reticulocyte count

All units will be single donor, CMV negative

Irradiated blood products will be used in the following circumstances:

- Birthweight less than 1500 grams
- Exchange transfusion
- Directed donor of relative’s blood
- Transfusions to neonates who have received intrauterine transfusions

**Erythropoietin in the Neonate**
The anemia of prematurity is a normocytic, normochromic anemia that is characterized by inadequate production of erythropoietin. Recombinant erythropoietin has been used to stimulate marrow and reduce the need for transfusion of autologous blood cells. One study showed a statistically significant reduction in number and volume of transfusions in preterm infants treated with erythropoietin. Additionally reticulocyte counts were higher with a higher hematocrit value at the end of the study in treated patients [12]. A recent phase I/II trial of high-dose erythropoietin without iron supplementation showed no difference in rates of intracranial hemorrhage or periventricular leukoplacia, necrotizing enterocolitis or retinopathy of prematurity [13]. Erythropoietin appears to be a safe and important part of a conservative transfusion practice in neonates. Sample criteria and dosing guidelines are listed below [14].

Criteria for Use
- Gestational age at birth of 30 weeks or less
- Birth weight of 1250 grams or less
- Hematocrit of < 35% at start of treatment

Dosing
- 300 units/kg/dose, subcutaneously, 3 times per week
- Alternatively, 300 units/kg/day for 5-10 days may be used
- Supplemental oral iron doses of 4-6 mg/kg/day should be given

Therapy Duration (one criteria must be met)
- Corrected gestational age of 34 weeks is met
- 6 weeks of EPO therapy have been completed
IV. Transfusion in the PICU

A study of over 1000 admissions to the PICU showed that the four significant determinants for red blood cell transfusion during an ICU stay were: a hemoglobin level < 9.5 during the PICU stay, an admission diagnosis of cardiac disease, an admission Pediatric Risk of Mortality score > 10 and the presence of multi-organ dysfunction syndrome during the stay. Only the latter of these were concerning for increased oxygen demand and oxygen debt that would be treated by increasing the hemoglobin level [15]. Bateman et al, looked prospectively at 977 children admitted to an intensive care unit. Children who did receive a transfusion had longer days of mechanical ventilation, increased nosocomial infection and increased mortality. Interestingly, the most common reason for transfusion was low hemoglobin and the average pre-transfusion hemoglobin was 9.7 g/dl [16].

In 2007, members of the Canadian Critical Care Trials group along with Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI) reported their use of a restrictive transfusion guideline in children. 637 children were enrolled and randomized to receive transfusion for hemoglobin levels of 7 g/dl or 9.5 g/dl. Hemoglobin levels were significantly lower in children in the restrictive arm during the study (8.7 g/dl vs. 10.8 g/dl). Patients in the restrictive arm also received 44% fewer transfusions. There was no difference in the rate of new or progressive multiple organ dysfunction between the two groups (12% in each
arm). This study added support to the theory that children will tolerate a more restrictive transfusion threshold without an increase in adverse events, similar to the results seen in adults [1].

Overall, children appear to have better outcomes with a more restrictive transfusion protocol. Set transfusion thresholds of 7 g/dl similar to adult trials appear to be tolerated well in the pediatric population although the diverse patient population seen in pediatric intensive care units prevents one from making a single threshold that is all inclusive. Certain subsets of patients, such as sickle cell patients who have better postoperative outcomes when transfused to a hemoglobin of 10 g/dl, require the surgeon to treat each patient individually and consider the underlying pathophysiology that is treated when deciding upon an appropriate transfusion threshold [17].

V. Transfusion of Platelets

Transfusion of platelets and other factors typically follow the recommended guidelines from adult surgical practice. The normal platelet count of neonates and older children is similar to that seen in adults. Replacement of depleted or congenitally absent factors, as seen in hemophilia, is done with specific factors such as factor VIII or IX. These factors should be replaced prior to surgical intervention and routinely monitored after surgery to ensure hemostasis. Consultation with a hematologist to guide therapy should be performed.
Premature infants are at an increased risk of intraventricular hemorrhage. Underdeveloped subependymal matrix and diminished coagulation cascade lead to subsequent rupture at the capillary level. Platelet levels should be kept at 100 x 10^9 in sick premature infants and at 50 x 10^9 in more stable patients [23]. A second area where children may benefit from increased platelet levels greater than 100 x 10^9 is during ECMO. No standard guidelines exist and there is some institutional variability in protocols. However, one should consider transfusion to this level and possibly higher in the face of active bleeding [23]. Other clinical scenarios should follow guidelines and practical application that is seen in adult patients.

**Platelet Transfusion Guidelines**:^24^

Transfuse if:

- Stable premature infant with platelets < 50 x 10^9
- Sick Premature infant with platelets < 100 x 10^9
- Term infant < 4 months old with platelets < 20 x 10^9
- Term infants > 4 months old with platelets > 10 x 10^9
- Child scheduled for invasive procedure with platelet count < 50 x 10^9
- Active bleeding in patient with platelet count < 50 x 10^9
- Child on ECMO with platelet count < 100 x 10^9
- Bleeding in patient with qualitative platelet defect (i.e., ASA therapy), regardless of the platelet count
VI. Transfusion Reactions

There are several types of transfusion reactions (see Table 2). When a transfusion reaction is suspected, the transfusion should be stopped. The blood bank should be notified. The transfused blood must be cultured. A new type and crossmatch of the patient should be performed. CBC, Bilirubin, LDH, and Coomb’s test should be sent.

Transfusion reactions can take several forms and occur from exposure to proteins, red blood cells, white blood cells, platelets or their breakdown products. A study evaluating 2509 transfusions in 305 pediatric intensive care unit patients revealed 40 acute transfusion reactions (1.6%). The majority of these reactions were febrile nonhemolytic reaction [18]. Febrile nonhemolytic reactions occur in children who have previous exposure from transfusion or pregnancy. This reaction is due to acquired antibodies to proteinacious material in the blood. Pretreatment with antipyretic agents, anti-inflammatory agents or antihistamines may alleviate the symptoms. Hemolytic reactions are rare and when they occur the infusion should be stopped. Typical symptoms may include fever, pain, tachycardia, hypotension, renal failure or hemoglobinuria.

Currently screening for HIV and other infectious agents has made these rare events. Transmission of HIV occurs in 1 in 2.3 million units of blood transferred [19]. Hepatitis B and C are transmitted in 1 in 280,000 units and 1 in 1.8 million units transfused respectively. CMV transmission is also minimized by using leukocyte-reduced RBC’s as CMV is carried in leukocytes [19,20]. Given the reduction in transmission of infectious agents seen, transfusion related acute
lung injury (TRALI) has now become the leading cause of transfusion-related morbidity and mortality worldwide. Defined criteria for diagnosis of TRALI have been adopted. Mortality increases for critically ill patients. Treatment centers on supportive therapy and limiting further transfusions.\(^{21}\)

Graft-versus-host disease is a transfusion related condition that is seen in immunocompromised patients. This is especially important to pediatric surgeons in that many of their patients either are immunocompromised due to age and underdeveloped immune systems (neonates) or have acquired immunodeficiency due to chemotherapeutic regimens (oncologic patients). This disease can present up to 28 days following transfusion. Associated mortality is extremely high, up to 90%, with most deaths occurring within one month. Irradiation of all blood products transfused in immunodeficient patients readily decreases this risk [22]. Patients who should receive irradiated components include:

- Infants < 6 months of age
- All pediatric oncology patients
- Patients undergoing myelosuppressive therapy
- Patients with congenital immunodeficiency syndromes
## TABLE: TYPES OF TRANSFUSION REACTIONS

<table>
<thead>
<tr>
<th>TYPE OF TRANSFUSION REACTION</th>
<th>CAUSE</th>
<th>SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic, immediate</td>
<td>ABO incompatibility</td>
<td>Fevers, chills, back pain, hemolysis, red urine</td>
<td>Measures to reduce risk of renal failure such as hydration with crystalloid solution and osmotic diuresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At risk for renal failure</td>
<td></td>
</tr>
<tr>
<td>Hemolytic, delayed</td>
<td>SCD patients</td>
<td>Fever, hemolysis 5-14 days after transfusion</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Hepatitis B, C, HIV, CMV, bacteria</td>
<td></td>
<td>Appropriate antimicrobial treatment, as needed</td>
</tr>
<tr>
<td>Febrile</td>
<td>Donor WBC’s produce cytokines. Older blood products more likely to cause reaction</td>
<td>Fever</td>
<td>Pre-treatment with acetaminophen and washing blood products are helpful. Otherwise, supportive measures once it develops</td>
</tr>
<tr>
<td>Allergic</td>
<td>Recipient is allergic to donor blood; usually seen in IgA deficient recipients. These patients need to be transfused with blood from IgA deficient donors or washed cells</td>
<td>Can be as mild as skin rash or anaphylaxis</td>
<td>Diphenhydramine and/or support for allergic reaction (i.e., epinephrine) if needed</td>
</tr>
<tr>
<td>GVHD</td>
<td>Donor leukocytes attacking immuno-compromised host</td>
<td>Skin rash, diarrhea, liver dysfunction. Can be life threatening</td>
<td>Supportive care. Treat as GVH</td>
</tr>
<tr>
<td>TRALI</td>
<td>Complement activated WBC</td>
<td>Occurs 4 hrs after transfusion.</td>
<td>Supportive care and steroids</td>
</tr>
</tbody>
</table>
migrates to recipient's lungs. Donor antibodies reacting with recipient antigen on granulocytes. Sicker patients tend to be more susceptible

Pulmonary failure

| migrates to recipient's lungs. Donor antibodies reacting with recipient antigen on granulocytes. Sicker patients tend to be more susceptible | Pulmonary failure |

VII. Anticoagulation

The American College of Chest Physicians recently published their updated recommendations on antithrombotic therapy in neonates in children [25]. This reference that provides updated recommendations and guidelines for management of thrombosis and neonates. One cannot stress enough their conclusion that there is a paucity of prospective randomized literature evaluating this condition in children and that the evidence supporting the majority of recommendations remains weak. Additionally, consideration of consultation with a hematologist experienced in the management of VTE in children is strongly supported [25].

Venous thromboembolic (VTE) disease in children is an uncommon occurrence when compared to the adult population. Overall the incidence has been found to be about 10 fold lower in the pediatric population [26]. Evaluation of all pediatric discharges (<18 years of age and excluding routine newborn hospitalizations) revealed an overall incidence of 0.14% over the period from 1994 to 2009 [27]. The rates were highest in children less than one year of age and over the time period study increased from 18.1 per 100,000 admissions to 49.6 per 100,000 admissions. The presence of VTE was associated with the use
of venous catheter devices, mechanical ventilation, malignancy, prolonged stay in the hospital (> 5 days). Additionally, increased awareness of VTE as a condition in children and improved diagnostic imaging most likely contributed to the increasing prevalence of VTE that has been seen [27].

The neonate has an increased risk of venous thromboembolism due to its inherent prothrombotic hemostasis system. Levels of Protein C, Protein S, antithrombin are low compared to normal adult ranges. Despite the lower level of Vitamin K dependent clotting factors this does not translate to a lower risk of VTE. Fibrinolysis also is less active during the neonatal period [28]. In addition to an immature hemostasis system, newborn infants can have inherited and acquired thrombophilic traits similar to adults. The most common association with VTE in neonates, however, is an indwelling central venous catheter. One study suggests up to 80% of VTE in neonates and infants were related to central venous catheters [29]. While the incidence and prevalence of VTE has increased in the neonate, there still is a paucity of randomized controlled trials with which to derive an evidence based therapeutic approach.

Management of thrombus utilizing unfractionated heparin remains the most common therapy. Heparin binds to antithrombin III, causing a conformational change in ATIII, making it a much better inhibitor of factor II and X. Initial loading dose of 75 units/kg followed by a continuous infusion of 28 units/kg is a safe starting point. It should be adjusted to a aPTT level that is two to three times the baseline level or a heparin level that is 0.2-0.4 u/ml. [30]. If
needed, heparin reversal can be reversed with protamine (1 mg protamine for 100 units of heparin).

Low molecular weight heparin (LMWH) may also be utilized and has recently garnered more interest by neonatologists. LMWH binds to and activates ATIII. ATIII inhibits Xa. Factor Xa is needed to convert protamine to thrombin. LMWH is too small to directly inhibit thrombin formation. Initial dosing should be 1.5mg/kg every twelve hours. Factor Xa levels should be measured every 4 hours to obtain a level of 0.5 to 1.0 units per ml. [30] If needed, LMWH can be reversed with protamine (1 mg protamine for 1 mg LMWH). Vitamin K levels are not commonly used in the neonatal period.

Heparin Induced Thrombocytopenia is a procoagulant state that occurs when heparin binds to PF4 on the platelet surface, activating platelets. Activated platelets are cleared by the RES, causing decreased platelet counts at 5-14 days. Diagnosis can be made by platelet aggregation test and serotonin release (more specific, less sensitive) or an ELISA for PF4 antibodies (more sensitive, less specific). To treat this entity, Heparin should be discontinued, and anticoagulation with other agents such as lepirudin and argatroban should be done.

References


I. Introduction

The alleviation of pain and anxiety is an important component of caring for the critically ill infant and child. Children in the intensive care unit require sedation and analgesia as adjuncts to procedures, facilitate mechanical ventilation, and assist with post-operative management and care. The goals of sedation are to ensure the patient’s safety, minimize physical discomfort and pain, control anxiety, minimize psychological trauma, and control behavior and movement [1]. Adequate sedation and analgesia also have benefits of reducing the stress response and catabolism associated with surgery [2]. The approach to sedation and analgesia management has implications for a child’s overall hospital course in the intensive care unit. Specifically, ventilator days, ICU length of stay, risk of nosocomial infections, unplanned extubation, and risk of withdrawal are all morbidities that are increased with prolonged or ineffective sedation regimens [3,4]. The following chapter outlines the impact of sedation regimens on morbidity in neonatal and pediatric ICUs and highlights the various pharmacologic agents commonly used for sedation and analgesia in the intensive care unit.

II. Impact of Sedation in the ICU

There are 4 levels of sedation as defined by the American Academy of Pediatrics. Minimal sedation (anxiolysis) is a drug-induced state whereby patients are sedate but able to respond normally to verbal commands. There is no significant change in cardiovascular or respiratory function. Moderate
sedation (conscious sedation/sedation/analgesia), is a drug-induced depression of consciousness during which patients are able to respond purposefully to verbal commands or light touch. Monitoring of respiratory status is important, as there is a potential risk of airway compromise. Deep sedation/analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated verbal or painful stimulation. Patients lose the ability to protect their airway and require assistance for airway protection. Lastly, general anesthesia is a drug induced loss of consciousness during which patients are not arousable and are unable to protect their airway. Impairment of cardiovascular or respiratory function is also common [5,6].

Adult critical care literature highlights the importance of implementing a standard sedation/analgesia algorithm in order to reduce total sedative use and ICU morbidity. Sedation protocols may decrease morbidity, ICU length of stay, duration of mechanical ventilation, decreased duration of opioid and benzodiazepine infusion and total duration of sedative exposure [4] Several pediatric studies have also demonstrated the impact of sedation on a child’s ICU course. The RESTORE trial was a prospective evaluation of sedation related adverse events among 22 PICUs. Inadequate pain or sedation management comprised 70% of reported adverse events in mechanically ventilated patients [7]. Gupta examined interrupted versus continuous sedative infusions in a randomized control trial and found days on ventilator, duration of ICU stay, total dose of midazolam was significantly increased in the continuous infusion group. Additionally the percentage of awake days was significantly less in continuous infusion [8].

The relationship between sedation regimens and mechanical ventilation has been examined in several studies. In the randomized control trial by Randolph et al, sedative use in the first 24 hours of weaning was found to strongly influence length of time on the ventilator and extubation failure in
infants and children [9]. Payen et al also found continuous intravenous sedation was an independent risk factor for prolonged mechanical ventilation after multivariate analysis [10]. Sedation regimens can also impact unplanned extubations. Another review highlighted prospective studies that demonstrated a significant reduction in rates of unplanned extubation following institution of a sedation algorithm [11]. The best practice recommendations included establishment of a sedation protocol and regular assessment of level of sedation to help reduce the rates of unplanned extubations, however a specific algorithm or sedation assessment tool was not identified [11]. Hartman, et al published a systematic review of pediatric sedation regimens in the intensive care unit in Pediatric Critical Care Medicine. The primary objective was to identify and evaluate the quality of evidence supporting sedatives and sedation regimens commonly used in the PICU to facilitate mechanical ventilation. Thirty-nine studies were included in the review, representing 39 sedation algorithms and 20 scoring systems used to evaluate level of sedation. Although sedation regimens have been used extensively across neonatal and pediatric intensive care units, the data are lacking as to the appropriate dosing, safety and protocols for use [12].

III. Common Analgesics

A. Opioids

The CNS has 4 primary opioid receptors: μ, κ, δ, σ. μ agonists are most commonly used in pain management regimens. Opioids exert their clinical effects as a sedative and analgesic. Side effects include respiratory depression, nausea, vomiting, delayed gastric emptying, delayed intestinal motility, pruritus, constipation, miosis, tolerance, and physical dependence.
Elimination half life is prolonged in neonates due to reduced hepatic activity and blood flow [2,13,14](Table 1)

1. Morphine [5,13,14]
   - Clinical characteristics: most commonly used opioid for management of pain
   - Dosing: IV 0.1mg/kg; Oral route: 1:3 conversion IV to oral (due to high first pass effect)
   - Onset and elimination: peak effect 20 minutes; duration of action 2-7 hours; Half life 2-3 hours in infants, 9 hours in preterm neonates, 6.5 hours in term neonates
   - Precautions:
     o renal failure patients or neonates with decreased GFR can have accumulation of morphine 6-glucuronide (active metabolite), which can cause respiratory depression.
     o Cirrhosis, septic shock, and renal failure decrease the clearance of morphine and metabolites.
     o Can produce venodilation, histamine release, hypotension

2. Fentanyl [13]
Clinical characteristics: 100 times more potent than morphine. Most hemodynamically stable opioid

Dosing: 1 mcg/kg

- sufentanil: fentanyl derivative that is 10x more potent than fentanyl. Used commonly in cardiac anesthesia.
  - Doses of 15-30mcg/kg
- remifentanil: extremely short half life. Used as continuous infusion only. 10x as potent as fentanyl

Onset and elimination: rapid onset: <1 minute; brief duration 30-45 minutes. Half life 8 hours

Precautions:

- glottis and chest wall rigidity following rapid infusion of > 5mcg/kg
- bradycardia


- Clinical indications: used to treat or wean opioid addicted or dependent patients. Post op pain relief
- Clinical effects: high oral bioavailability (90%). Full analgesic effect 3-5 days after initiating dosing.
- Dosing: load dose: 0.1-0.2 mg/kg IV; titrate in 0.05mg increments every 4-12 hours
  - conversion morphine to methadone - 1: 0.25
Onset & elimination: slow elimination, long duration of action; half life 19 hours

Metabolism: hepatic metabolism. metabolite is morphine

Precautions:
  o prolonged QT syndrome, torsades de pointes
  o Respiratory depressant effects occur after analgesic effects

  - Clinical effects: inactive until metabolized in liver by cytochrome P450 2D6 into morphine. It has unpredictable effects in patients with liver failure.
  - Dosing 0.5-1mg/kg q3-4 hours
  - Current FDA warning in children after tonsillectomy and adenoidectomy. Children with ultra-rapid metabolism for this drug can have higher than normal doses of converted morphine in their system
  - 10% of children are poor metabolizers and will experience less analgesia

5. Hydromorphone [6]
  - No active metabolites. Five times more potent than morphine.
  - Dosing 0.01-0.03mg/kg q2 hours
   - Metabolized into normeperidine, which is toxic metabolite that can accumulate in patients with liver disease and cause seizures.
   - Dosing 1mg/kg q 2-3 hours

B. Non opioids

1. Acetaminophen [2,13]
   - Clinical indications: treatment of mild to moderate pain, antipyretic
   - Clinical effects: Effects centrally by inhibiting COX 3. Has additive effect to opioids. No tolerance or respiratory depression.
   - Safe for use in neonates. Has same analgesic efficacy as 0.5-1mg/kg codeine.
   - Dosing:
     - rectal doses 20-25mg/kg
     - PO dose 10-15mg/kg q4-6 hours
       - Max daily doses
         - preterm 60mg/kg
         - term 80mg/kg
• child 90mg/kg

• >60kg – 4000mg

  o IV dose 15mg/kg q6 hours ages 2-12 years; age >12 years 1g q6 hours
    ▪ max daily dose
    ▪ ages 2-12 years or <50kg: 75mg/kg/day
    ▪ >12 years and >50kg: 4g/day

• Onset: 30 minutes

• Precautions: hepatotoxicity at high doses

2. Etomidate [23,24]

Carboxylated imidazole, IV general anesthetic, diluted in propylene glycol


• Clinical effects: ultra-short acting non-barbiturate hypnotic
  o Minimal cardiovascular effects – often used in patients with impaired cardiovascular function
  o Dose dependent depressant respiratory effects
  o Decreases cerebral metabolic rate, causing decreased cerebral blood flow and decreased ICP - used in patients with elevated ICP and closed head injury
- May cause hiccups, nausea, vomiting on emergence. Myoclonus and uncontrolled eye movements also reported.

- Dosing: 0.2 – 0.3 mg/kg bolus over 30-60 seconds.
  - Maintenance: 10-20 mcg/kg/min
  - Procedural sedation: 0.1-0.3 mg/kg

- Onset & elimination: onset 30-60 seconds. Maximum effect 1 minute.
  - Dose dependent duration of action 2-10 minutes
  - Rapid redistribution resulting in rapid recovery
  - Elimination half-life 2 -3 hours; prolonged in patients with renal failure or hepatic failure.

- Precautions:
  - Single dose of etomidate blocks normal stress induced increase in cortisol production by inhibiting 11-B – hydroxylase, which is necessary for the production of cortisol.
    - Avoid in patients in septic shock due to the adverse consequences of adrenal suppression
  - Prolonged infusions not recommended due to risk of propylene glycol toxicity.
  - Use with caution in patients with seizure disorders. May cause EEG burst suppression at high doses.
2. NSAIDS [13]

- Clinical effects: Pain relief by blocking peripheral and central prostaglandin production by inhibiting cyclooxygenase (COX) type 1, 2, and 3.
- Advantages: low rate of adverse reactions; no respiratory depression; no sedative effect; long duration of action; no tolerance
- Dosing: 5-10mg/kg q6 hours
- Onset: 30 minutes
- Precautions:
  - GI bleeding
  - hepatotoxicity
  - interferes with platelet function
  - hematuria

IV. Common Sedatives (See Table 2)
A. Benzodiazepines

Benzodiazepines have anxiolytic and amnestic properties. They do not have analgesic effects. Benzodiazepines act by augmenting GABA (gamma amino butyric acid) transmission, which is an inhibitory neurotransmitter in the brain. Clinical effects include decreased cerebral metabolism and blood flow, sedation, hypnosis, anxiolysis, anticonvulsant activity, anterograde amnesia, muscle relaxation, dose dependent depression of breathing, and decreased tidal volume. Use of benzodiazepines without opioid in presence of painful stimulus can cause hyperalgesia and agitation [13].

1. Midazolam [2,13]
   - water soluble, short acting, rapidly crosses BBB
   - Dosing:
     - Loading dose: 0.2mg/kg
     - continuous infusion 0.4mg/kg/minute
     - invasive procedures: 0.05-0.2mg/kg bolus dose
     - long term sedation with intubation: 0.025-0.05mg/kg/hour
   - Onset & elimination: 30 minutes. Half life 6 hours
   - Side effects: respiratory depression and hypotension, tolerance.
   - Precautions: Withdrawal symptoms after prolonged IV use, which include agitation, poor visual tracking, constant choreoathetoid
and dyskinetic movements of face, tongue, and limbs, depression of consciousness.

- Precautions in neonates: midazolam and fentanyl given by rapid infusion can cause severe, life threatening hypotension and cardiorespiratory arrest in neonates

2. Lorazepam [2,13]

- Insoluble

- Clinical effects: Prolonged effects on mental status and respiratory drive.

- Dosing: 0.05-0.1mg/kg

- Elimination: Half life 10-20 hours

- Precautions: Contains polyethylene glycol 400 in propylene glycol, which causes elevated osmolar gap, metabolic acidosis, and is nephrotoxic in high doses.

- Avoid use in infants under 6 months of age.
  - Infusions can lead to significant metabolic acidosis and acute renal failure in infants
B. Barbiturates [2,13]

Barbiturates globally depress the central nervous system. They do not have anxiolytic or analgesic properties.

1. Phenobarbital
   - Clinical indications: anticonvulsant. Routine use for sedation discouraged
   - Clinical effects: Hyperalgesic effects – may increase requirement for analgesia. Rapid tolerance.
   - Advantages: increased bilirubin metabolism, mild cardiovascular and respiratory depression
   - Dosing: Loading dose: 5-20mg/kg. Maintenance dose: 2.5mg/kg q12 hours PO or IV for sedation
   - Onset & elimination: very slow onset. Prolonged elimination half life in infants (5-6 days)
   - Precautions: May increase risk of intraventricular hemorrhage in premature neonates

2. Pentobarbital
   - Clinical indications: Adjunct for sedation of intubated child when tolerance to benzodiazepines and opioids has occurred
   - Dosing: Intermittent doses: 0.5 - 2 mg/kg q4 hours
• Onset & elimination: 10-15 minute onset. Elimination 20-45 hours.

• Precautions:
  o Associated with tolerance and withdrawal.
  o Can cause hypotension – infuse slowly over 15-30 minutes.
  o Mixed in propylene glycol – avoid continuous infusion that may cause metabolic acidosis and nephrotoxicity.

C. Chloral hydrate [2]

Sedative. Mechanism unknown, however likely causes global neuronal depression, without side effects of respiratory depression, emesis, or hemodynamic alterations.

• Dosing: 25-50mg/kg for sedation PO or PR. 50-100mg/kg for hypnotic doses for procedures
• Onset of action: 30 minutes, duration 2-4 hours. half life 4-6 hours
• Precautions: risk of laryngeal edema, cardiac arrhythmias, pneumatosis intestinalis

D. Ketamine [2]
Dissociative anesthetic, used for induction agent for anesthesia, analgesic for conscious sedation, premedication before induction of anesthesia, sedative in critically ill.

- Clinical effects: Increase catecholamine release & cholinergic stimulation, causing bronchodilation, increased SVR, HR and cardiac output. Tolerance with chronic administration
- Dosing: 0.5-1 mg/kg. Infusions 1-2 mg/kg/hour
- Onset & elimination: 1-2 minutes, duration of action 15 minutes. Elimination 3-6 hours
- Precautions: can cause hallucinations, myotic jerking, hypersalivation, increased cerebral blood flow.
  - Avoid in patients with elevated ICP
  - Can cause apnea in infants

E. α-2 Agonists

These analgesics are used for the management of acute and chronic pain. They are also used to treat opioid-related withdrawal. They typically do not cause respiratory depression and associated with few withdrawal symptoms [2,13]

1. Clonidine [2,13]
Clinical indications: analgesic. Most effective via epidural route. Oral or transdermal use as adjunct for sedation/analgesia in critically ill.

Dosing: 5mcg/kg/day; transdermal patches -100-300mcg

Onset & elimination: 1-3 hours. Half life 12-24 hours.

Precautions: May develop rebound hypertension with abrupt discontinuation. Can stop without weaning if given for 3-4 days. If weaning transdermal patch, titrate off over 2-3 weeks.

2. Dexmedetomidine [13,15,17]

Clinical indications: sedative and analgesic for mechanically ventilated patients in an intensive care settings and non intubated adult patients prior to or during surgical or other procedures. Only FDA approved for adult use, but is used widely in children.

Safety in children described in literature with low rate of adverse effects, which include hypotension, bradycardia, and hypertension. Majority of adverse events resolved without treatment or by decreasing dose of infusion The incidence of adverse effects did not increase with increased duration of therapy.\(^{16}\)

Clinical effects: Highly lipid soluble – crosses the blood brain barrier quickly.
Effects on CNS to decrease sympathetic tone, stimulates central parasympathetic outflow, decreases sympathetic outflow.

Induces natural REM sleep and is associated with rapid and easy arousal.

- Dosing: 0.2-0.7mcg/kg/hour. Bolus 0.3-1 mcg/kg
- Elimination: Half life 1.5 – 3 hours
- Precautions: Bolus dosing can cause rapid, transient decrease in heart rates and increased blood pressure. At lower doses reduction in blood pressure.
- Adverse effects: bradycardia, sinus arrhythmias, heart block, nausea and vomiting
- Relative contraindications: hemodynamically unstable patients; moyo moyo disease or patients who have had a stroke; concomitant use of clonidine

V. Common Anesthetics

A. Systemic Anesthesia
1. Propofol [13,17]

2,6 di-isopropylphenol, an alkylphenol IV general anesthetic

- **Clinical indications:** Use as sedative to facilitate short term mechanical ventilation and procedures
- **Clinical effects:** Dose-proportional sedative/anesthetic effects
  - Clinical effects dissipate quickly with discontinuation of infusion
  - Negative ionotropic effects
  - Potent vasodilator
- **Dosing:** initial bolus 1-2 mg/kg. Infusion 75-250 mcg/kg/minute
- **Onset & elimination:** Rapid onset – within a minute of injection.
  - 3 compartment pharmacokinetics – blood, rapidly equilibrating tissue (i.e. brain), slowly equilibrating tissue. Rapid distribution in blood & rapid clearance, which is responsible for short duration of action. Short distribution half life, long elimination half life.
- **Precautions:** Avoid use >12 hours in critically ill children
  - Risk of propofol infusion syndrome with prolonged use causes lactic acidosis, hyperlipidemia, bradyarrhythmias, myocardial failure & potential risk of death
B. Local Anesthesia [13]

These agents reversibly block the conduction of neural impulses along central and peripheral nerve pathways. Their use produce analgesia with minimal physiologic changes, therefore making them desirable for children undergoing procedures and post traumatic pain management.

- Dosing: maximum local anesthetic dosing guidelines (Table 3)
- Absorption from highest to lowest:
  intercostal, intrapleural, intratracheal > caudal/epidural > brachial plexus > distal peripheral > subcutaneous > fat
- Precautions:
  - systemic toxicity is determined by total dose, protein binding, absorption into blood and site of injection
  - bupivacaine toxicity: occurs with inadvertent injection of bupivacaine intravenously. It presents as asystole refractory to treatment causing death. Treatment is IV intralipid

C. Regional anesthesia [13]

1. Nerve block

- Injection of local anesthetic to provide regional anesthetic for procedure or treat regional pain
2. Spinal
   - Injection of local anesthetic into subarachnoid space.
   - Side effects: dural puncture headaches, hemodynamic compromise

3. Caudal/epidural
   - Injection of local anesthetic into potential space between the dura mater and ligamentum flavum.
   - Advantage over spinal for long term or continuous administration
   - Clonidine effective as adjunct to local anesthetic infusion
   - Complications: toxicity from infusion into epidural space or intravascular space, urinary retention, site infection, chemical meningitis, inadvertent spinal anesthesia, respiratory depression
   - Contraindications: coagulopathy, infection or open wound at insertion site

VI. Neuromuscular Blockade

A. Depolarizing [13]
Noncompetitive binding of acetylcholine receptor at motor end plate causing interruption of nerve impulse transmission. No sedative or analgesic effects.

1. Succinylcholine
   - fast onset (<1 minute), 3-5 minute duration of action
   - Depolarization causes fasciculations which causes increase in intragastric, intraocular, and intracranial pressures
   - Can have prolonged neuromuscular blockade if have pseudocholinesterase deficiency, pregnancy, liver dysfunction, or hypermagnesia
   - Side effects: lethal hyperkalemia, severe bradycardia, myalgia, increased intracranial pressure
   - Not recommended for routine use

B. Non-depolarizing [13]

  Competitive binding of post-synaptic nicotinic acetylcholine receptors produces neuromuscular blockade. No sedative or analgesic effects. Occupation of 60% of receptors does not result in any weakness or paralysis. Occupation of 95% of receptors will result in inability to swallow, cough or protect airway, however can still take normal tidal volume
• Choice of muscle relaxant dependent on duration, route of metabolism, hemodynamic side effects (table 4).

1. Monitoring: train-of-four (TOF) [13,25,26]

It is recommended that the degree of neuromuscular blockade should be monitored during administration of a continuous infusion. There is a lack of data in the literature to support a standardized method, however the adult critical care practice guidelines recommends both clinical assessment and TOF monitoring for all patients on continuous infusions of neuromuscular blockade, with the goal of adjusting the degree of neuromuscular blockade to obtain 1 or 2 twitches on TOF [25]. There are no specific practice guidelines in the United States for children, however consensus guidelines published in the United Kingdom for neuromuscular blockade in children recommended TOF monitoring at least once every 24 hours in children receiving continuous infusions [26].

• Peripheral nerve stimulator placed over ulnar nerve and impulse is generated

• Twitch response of adductor pollicis and flexor digitorum correlates to presence or absence of neuromuscular blockade
Dimunition of fourth twitch response compared with first twitch response following four 2-Hz stimuli

Abolition of single twitch corresponds to 95% receptor blockade

VII. Tolerance and Withdrawal

A. Tolerance [3,18] receptor desensitization causing decreasing clinical effects after prolonged exposure. This is thought to be due to upregulation of cAMP pathway and desensitization of opioid receptors.

Factors that affect development of tolerance

- duration of therapy
  - develops 10-21 days of morphine use
- infants in early developmental stages develop long term tolerance to developing brain
- greater tolerance with shorter acting opioids

Approaches to address tolerance

- dose escalation
- use longer acting opioids
- add non opioid analgesics
- add drugs that prevent or delay tolerance
B. **Tachyphylaxis** [13]: rapid loss of drug effects caused by compensatory neurophysiologic mechanisms due to exhaustion of synaptic neurotransmitters.

C. **Dependence** [13]: physiologic and biochemical adaptation of neurons, such that removing a drug precipitates withdrawal, which generally occurs after 2-3 weeks of continuous use.

D. **Withdrawal** [13] clinical syndrome that develops after stopping or reversing a drug after prolonged exposure to that drug.

- Symptoms are evident within 24 hours of drug cessation and peak within 72 hours.
- Symptoms of opioid withdrawal include cramping, vomiting, diarrhea, tachycardia, hypertension, diaphoresis, restlessness, insomnia, movement disorders, reversible neurologic abnormalities, and seizures.
- Opioid withdrawal occurs over 50% of PICU patients and in 60% of all PICUs. Risk of withdrawal is over 50% after 5 days of continuous infusion or around the clock administration of an analgesic or sedative. Withdrawal can complicate medical treatment, increase morbidity, as well as prolong hospitalization.
- There is no gold standard tool to measure withdrawal symptoms, however one tool that has been validated in children is Withdrawal assessment tool (WAT-1) (Table 5).
Strategies for treatment of withdrawal

- gradual wean
- conversion to long acting enteral medications (i.e. methadone, clonidine, lorazepam),
- addition of dexmedetomidine infusion as an adjunctive medication

VIII. Pain and Sedation Assessment Tools

A. WAT-1 [18]
Withdrawal Assessment Tool, which is an 11-item symptom assessment of opioid and benzodiazepine withdrawal focusing on motor, behavioral state, autonomic disturbances, and gastrointestinal symptoms. WAT-1 has been studied and validated in a multicenter prospective trial by Franck and Curley. (Table 5)

- 12 point scale. Score 0-12
- Start scoring on first day of weaning, perform twice daily
- Score of 3 or higher had best sensitivity and specificity of clinically significant withdrawal

B. SBS [19]
State Behavioral Scale is a sedation assessment instrument for infants and children on mechanical ventilation, which is a description of sedation-agitation continuum as measured by response to voice, gentle touch, and noxious stimuli. (Table 6)

- Range from -3 to +2

C. FLACC [20,21]
Face, Legs, Activity, Cry, Consolability behavior and pain assessment scale validated for infants >34 weeks (table 7)

- Pain scores 0-10
  - mild 0-3; moderate 4-6; severe 7-10

D. PIPP [21,22]
Premature Infant Pain Profile pain assessment tool validated for premature infants <34 weeks. (Table 8)

- Pain score 0-21.
  - None to minimal pain 0-6; slight to moderate 7-12; severe >12

IX. Weaning [3,13]
A. Strategies for weaning

- May stop infusions administered for <5 days
  - Start WAT-1 scoring to monitor for withdrawal
- Wean any infusion administered for > 5 days
- Weaning for extubation
  - Continuous infusions for 5-10 days
    - If SBS less than target, then reduce morphine and midazolam infusions by 50% and start WAT -1 scoring
  - Continuous infusions for > 10 days
    - If SBS less than target, reduce morphine and midazolam by 25% and begin WAT -1 scoring
  - Unable to wean due to safety or comfort issues
    - Consider transitioning through extubation with propofol or dexmedetomidine infusion
    - After starting dexmedetomidine or propofol, wean opioid and benzodiazepine by 25-50%
- Post extubation weaning
  - SBS goal 0, max acceptable WAT-1 usually 4
  - Opioid/benzodiazepine infusion:
    - Wean infusion by 10-20% every 8 hours until off, assuring WAT-1 <5
- If WAT-1 >5 and unable to wean: give rescue doses, consider adding clonidine patch and/or transitioning to intermittent methadone and/or lorazepam

- Long term wean
  - Conversion to intermittent dosing: give dose for 24-48 hours before any subsequent wean is made
  - Goal to decrease drug by 10-20% of the original total dose per day
  - If withdrawal symptoms develop, then stop weaning for 24 hours
  - If withdrawal symptoms don’t improve or worsen, then increase opioid/benzodiazepine to previous dose or consider adding clonidine patch

X. Sample Sedation Algorithms

The literature supports sedation and analgesia algorithms in neonatal and pediatric intensive care units, however there is no consensus as to the agents or protocol to implement. The figures at the end of this chapter are examples of sedation and analgesia algorithms used at a high volume tertiary care center. They are meant for general suggestions for algorithms to follow, not absolute recommendations, as they have not been validated scientifically.
• Figure 1: NICU sedation & analgesia algorithm
• Figure 2: PICU short term extubation algorithm for anticipated intubation <3 days
• Figure 3: PICU long term extubation algorithm for anticipated intubation >3 days and/or chemically paralyzed
• Figure 4: NICU/PICU titration algorithm

XI. Summary

This chapter highlighted the common sedative and analgesics used in neonatal and pediatric intensive care units. Although sedation and analgesia algorithms have been used in neonatal and pediatric intensive care units, there is no consensus as to the specific agents or protocol to implement. It is important, however, to be mindful of the impact of sedation on morbidity and mortality. Prolonged sedation is associated with increased procedures, acquired neuromuscular disorders, length of mechanical ventilation, ICU length of stay and adverse events. Additionally, it is unclear of the effects of prolonged sedation on developing brains. Therefore, it is recommended to establish and follow a sedation and analgesia algorithm for children in the intensive care unit. The information contained in this chapter is meant as a guideline for use. The following algorithms outlined are general frameworks to assist in sedation and analgesia management, however may be individualized for each patient or
institutional protocols. In difficult cases, further assistance from pain treatment services may be helpful in guiding sedation and analgesia regimens.

REFERENCES


### Table 1. Initiation Doses for Common Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Load/prn</th>
<th>Infusion Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>1mcg/kg</td>
<td>1 - 5mcg/kg/hr</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.05 - 0.1mg/kg</td>
<td>0.05 - 0.1mg/kg/hr</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.015mg/kg</td>
<td>10 - 15mcg/kg/hr</td>
</tr>
</tbody>
</table>

### Table 2. Initiation Doses for Common Sedatives/Anesthetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Load/prn</th>
<th>Infusion Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.05 - 0.1 mg/kg</td>
<td>0.05 - 0.1 mg/kg/hr</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.05 - 0.1 mg/kg</td>
<td>----</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>0.5 - 1 mg/kg</td>
<td>1 - 2 mg/kg/hr</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>25 - 100 mg/kg</td>
<td>----</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.5 – 1 mg/kg</td>
<td>1 - 2 mg/kg/hr</td>
</tr>
<tr>
<td>Clonidine</td>
<td>2 – 5 mcg/kg/day (transdermal patch 100 – 300 mcg, change q 7 days)</td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.3 - 1 mcg/kg</td>
<td>0.2 - 0.7 mcg/kg/hr</td>
</tr>
<tr>
<td>Propofol</td>
<td>2 - 3 mg/kg</td>
<td>75 - 250mcg/kg/min</td>
</tr>
</tbody>
</table>
Table 3. Maximum Local Anesthetic Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose without epinephrine (mg/kg)</th>
<th>Dose with epinephrine (mg/kg)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>2*</td>
<td>3*</td>
<td>3 - 6</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>5</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>2</td>
<td>3</td>
<td>3 - 6</td>
</tr>
</tbody>
</table>

* Reduce dose by 50% in neonates


Table 4. Neuromuscular Blocking Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intubating dose</th>
<th>Continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>0.1 mg/kg</td>
<td>NA</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1 mg/kg</td>
<td>1 mcg/kg/min</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6 - 1.2 mg/kg</td>
<td>3 - 10 mcg/kg/min</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.1 mg/kg</td>
<td>0.4 - 4 mcg/kg/min</td>
</tr>
</tbody>
</table>

### Table 5. Withdrawal Assessment Tool Version 1 (WAT-1)

<table>
<thead>
<tr>
<th>Information from patient record in previous 12 hours</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any loose/watery stools</td>
<td>(No= 0; Yes = 1)</td>
</tr>
<tr>
<td>Any vomiting/wretching/gagging</td>
<td>(No= 0; Yes = 1)</td>
</tr>
<tr>
<td>Temperature &gt;37.8 °C</td>
<td>(No= 0; Yes = 1)</td>
</tr>
<tr>
<td><strong>2 minute pre-stimulus observation</strong></td>
<td></td>
</tr>
<tr>
<td>State</td>
<td>SBS≤/ = 0 or asleep/awake/calm = 0</td>
</tr>
<tr>
<td></td>
<td>SBS≥/ = +1 or awake/distressed = 1</td>
</tr>
<tr>
<td>Tremor</td>
<td>none/mild = 0; moderate/severe = 1</td>
</tr>
<tr>
<td>Any sweating</td>
<td>(No= 0; Yes = 1)</td>
</tr>
<tr>
<td>Uncoordinated/repetitive movement</td>
<td>none/mild = 0</td>
</tr>
<tr>
<td></td>
<td>moderate/severe = 1</td>
</tr>
<tr>
<td>Yawning or sneezing</td>
<td>none or 1 = 0</td>
</tr>
<tr>
<td></td>
<td>≥/ = 2 = 1</td>
</tr>
<tr>
<td><strong>1 minute stimulus observation</strong></td>
<td></td>
</tr>
<tr>
<td>Startle to touch</td>
<td>none/mild = 0</td>
</tr>
<tr>
<td></td>
<td>moderate/severe = 1</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>normal = 0</td>
</tr>
<tr>
<td></td>
<td>Increased =1</td>
</tr>
<tr>
<td><strong>Post – stimulus recovery</strong></td>
<td></td>
</tr>
<tr>
<td>Time to gain calm state (SBS ≤/ = 0)</td>
<td>&lt;2 min = 0</td>
</tr>
<tr>
<td></td>
<td>2-5 min = 1</td>
</tr>
<tr>
<td></td>
<td>&gt;5 min = 2</td>
</tr>
<tr>
<td><strong>Total score (0-12)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. State Behavioral Score (SBS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
</table>
| -3    | Unresponsive | No spontaneous respiratory effort  
|       |             | No cough or coughs only with suctioning  
|       |             | No response to noxious stimuli  
|       |             | Does not move |
| -2    | Responsive to noxious stimuli | Spontaneous yet supported breathing  
|       |             | Coughs with suctioning  
|       |             | Responds to noxious stimuli  
|       |             | Occasional movement of extremities or shifting of position |
| -1    | Responsive to gentle touch or voice | Spontaneous but ineffective non supported breaths  
|       |             | Coughs with suctioning/repositioning  
|       |             | Responds to touch/voice  
|       |             | Able to pay attention but drifts off after stimulation  
|       |             | Distresses with procedures  
|       |             | Able to calm with comforting touch or voice when stimulus is removed |
| 0     | Awake and able to calm | Spontaneous and effective breathing  
|       |             | Coughs when repositioned/occasional spontaneous cough  
|       |             | Responds to voice/no external stimulus is required to elicit response  
|       |             | Spontaneously pays attention to care provider  
|       |             | Able to calm with comforting touch or voice when stimulus removed |
| +1    | Restless and difficult to calm | Spontaneous effective breathing/having difficulty breathing with ventilator  
|       |             | Responds to voice/no external stimulus is required to elicit response  
|       |             | Intermittently unsafe  
|       |             | Does not consistently calm despite 5 minute attempt  
|       |             | Restless, squirming |
| +2    | Agitated | May have difficulty breathing with ventilator  
|       |             | Coughing spontaneously  
|       |             | No external stimulus required to elicit response  
|       |             | Spontaneously pays attention to care provider  
|       |             | Unsafe (biting ETT, pulling at lines)  
|       |             | Unable to console  
|       |             | Increased movement (restless, squirming, or thrashing side to side, kicking legs) |

Table 7. FLACC Behavioral Pain Assessment Tool

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Score (0-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>0 - no particular expression or smile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 - occasional grimace/frown, withdrawn or disinterested</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 - frequent/constant quivering chin, clenched jaw</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td>0 - Normal position or relaxed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 – uneasy, restless, tense</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 – kicking or legs drawn up</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>0 – lying quietly, normal position, moves easily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 – squirming, shifting back and forth, tense</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 – arched, rigid or jerking</td>
<td></td>
</tr>
<tr>
<td>Cry</td>
<td>0 – no cry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 – moans or whimpers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 – crying steadily, screams or sobs</td>
<td></td>
</tr>
<tr>
<td>Consolability</td>
<td>0 – content and relaxed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 – reassured by occasional touching, being talked to, distractible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 – difficult to console or comfort</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Process</th>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
</table>
| Chart   | Gestational age | 0 – 36 weeks or more  
1 – 32-35 weeks  
2 – 28-31 weeks  
3 – less than 28 weeks |       |
| Observe infant for 15 seconds | Behavioral state | 0 – active, awake, eyes open, facial movement  
1 – quiet awake, eyes open, no facial movements  
2 – active sleep, eyes closed, facial movements  
3 – quiet sleep, eyes closed, no facial movements |       |
| Observe baseline HR & oxygen sat for 30 seconds | Heart rate maximum | 0 – 0 beats per minute increase  
1 – 5-15 beats per minute increase  
2 – 15-24 beats per minute increase  
3 – 25 beats per minute increase |       |
| Observe infant’s facial actions for 30 seconds | Oxygen sat maximum | 0 – 92-100%  
1 – 89-91%  
2 – 85-88%  
3 – <85% |       |
| Observe infant’s facial actions for 30 seconds | Brow bulge | 0 – none  
1 – minimum  
2 – moderate  
3 – maximum |       |
| Observe infant’s facial actions for 30 seconds | Eye squeeze | 0 – none  
1 – minimum  
2 – moderate  
3 – maximum |       |
| Observe infant’s facial actions for 30 seconds | Naso-labial furrow | 0 – none  
1 – minimum  
2 – moderate  
3 – maximum |       |

Total Score: 0-6 minimal to no pain; 7-12 slight to moderate pain; >12 severe pain

Figure 1. NICU ANALGESIA AND SEDATION ALGORITHM

Pain

PLUS

Fentanyl 2mcg/kg dose IV or morphine 0.02mg/kg/dose IV q 15 minutes until pain controlled

Exhibiting signs of discomfort despite multiple bolus dosing (as assessed by FLACC or PIPP scale)

fentanyl infusion 2-5mcg/kg hr IV or Morphine 0.02-0.1 mg/kg/hr IV

Exhibiting signs of discomfort requiring rescue prn bolus dose equal to total of 1 hour infusion dose

>3 nonprocedural boluses in 8 hours or >1 bolus dose in 1 hour

Increase infusion and bolus doses by 10%

Acetaminophen 15 mg/kg PR for 72 hours

>44 weeks q4h
33-44 weeks q8h
28-32 weeks q12h

Agitation

Midazolam 0.03-0.1mg/kg/dose IV q1h prn

Exhibiting signs of agitation despite bolus dosing

Midazolam infusion 0.03-0.1 mg/kg IV

>3 nonprocedural boluses in 8 hours or >1 bolus dose in 1 hour

Increase infusion and bolus doses by 10%
Figure 2. PICU SHORT TERM EXTUBATION ALGORITHM (<3 days)

Pain

Morphine 0.05-0.1 mg/kg/dose IV q2h prn

Exhibiting signs of discomfort requiring rescue boluses

Morphine 0.05 mg/kg/dose IV q2h prn

>3 non procedural boluses in 8hrs

Increase bolus dose to Morphine 0.15-0.2 mg/kg/dose IV q2h

Unable to capture despite increase in sedation boluses, Consider additional agent to avoid further escalation:

Dexmedetomidine gtt 0.2-0.7 mg/kg/h

OR

Propofol gtt 12.5-25 mcg/kg/min

Agitation

Midazolam 0.05-0.1 mg/kg/dose IV q1h prn

Exhibiting signs of agitation requiring rescue boluses

Midazolam 0.05 mg/kg/dose IV q1h prn

>3 non procedural boluses in 8hrs

Increase bolus dose to midazolam 0.15-0.2 mg/kg IV q1h
Figure 3. PICU LONG TERM EXTUBATION ALGORITHM (>3 days or chemically paralyzed)

Morphine 0.05 mg/kg/hr IV to maintain comfort

Exhibiting signs of discomfort requiring rescue boluses

Morphine 0.05 mg/kg/dose IV q1h prn

Midsazolam 0.05 mg/kg/hr IV to reduce physiologic stress and anxiety

Exhibiting signs of agitation requiring rescue boluses

Midazolam 0.05 mg/kg/dose IV q1h prn

>3 non procedural boluses in 8hrs or SBS greater than target

Increase infusion of narcotic or benzodiazipine by 10%

>3 non procedural boluses or SBS > target

Increase other infusion by 10%

Repeat if >3 non procedural boluses in 8hrs or SBS > target

Consider clonidine patch or ketamine infusion (15-40mcg/kg/min) if continuing to escalate on infusions
Figure 4. NICU/PICU Titration Algorithm

- No longer actively resuscitating, weaning ventilator or plateaued
  - Titrate narcotic and benzodiazepine infusions for minimum effective dose
    - <3 non procedural boluses in 8hrs
      - Decrease infusion of narcotic by 10%
        - SBS goal maintained
          - Decrease benzodiazepine infusion by 10%

  - No procedural boluses within 8 hrs
  - 3 or more non procedural boluses in 8 hrs

- Transition midazolam to intermittent lorazepam
- Start methadone (1/4 of hourly morphine infusion as methadone dose q4h)
Chapter 13
PEDIATRIC NEUROTRAUMA

Alessandra Gasior, DO
David Juang, MD

I. Introduction

Traumatic brain injuries (TBI) are a leading cause of morbidity and mortality in the pediatric population and account for more than half of all injuries sustained [1]. Approximately 37,000 children ages 14 years old or less are admitted to hospitals every year for TBI. Annually nearly 3000 children will die from TBI [2]. Head trauma commonly occurs due to falls, motor vehicle accidents, sports accidents, as well as non-accidental trauma (NAT). In the United States, children account for 30% of the TBI patients each year [3]. There is a bimodal age distribution: 0-4 years old and 15-19 years old. Moreover, the highest mortality rates occur in children younger than 2 years old and older than 15 years old. Males are twice as likely as females to be affected by TBI [4]. Infants and toddlers are more likely to suffer from falls, motor vehicle accidents, accidental blows to the head and child abuse, in order of frequency. These three mechanisms are also the highest contributors to brain injury in regards to total billed charges and account for more than $1 billion in total charges over a 5 year period [5]. Unlike adults, children have structural limitations that cause them to be more susceptible to changes in head inertia. The infant brain doubles its size during the first 6 months of life. By the age of
2, toddler brains are 80% of their full grown size. There is less buoyancy and therefore less protection than the mature brain with a smaller subarachnoid space. Children, therefore, are subject to a higher rate of diffuse cerebral edema and parenchymal injuries [6]. Guidelines were revised and released in January of 2012 for the acute medical management of severe TBI in infants, children, and adolescents [7,8]. The guidelines provide a means for decreasing variability in the care provided across centers but there is very little data from well designed randomized controlled trials and therefore much of the recommendations come from expert advice and retrospective data.

The vast majority of TBI in the United States is blunt or non-penetrating trauma frequently due to a motor vehicle collision or fall. This type of injury typically results in focal damage to the underlying brain (coup), and, in some instances, contrecoup damage occurs from the rebound movement of the brain within the skull. This is commonly seen with subdural hemorrhages with associated cortical contusion. Blunt trauma will often lead to axonal injury or shearing and is often coupled with vascular injury. This injury is classically observed as petechial hemorrhages in white matter and commonly referred to as diffuse axonal injury (DAI). The neurologic impact due to axonal shearing can present as a transient loss of consciousness or as profound and persistent neurologic deficits, even leading to death.

Concussions deserve mention but the management and treatment of this disease is beyond the scope of this chapter. Concussions are described as mild to moderate TBI without a hematoma or intracranial process. Classically
these patients will have headaches, nausea, difficulty concentrating, personality changes and retrograde and/or anterograde amnesia. Long term implications of concussions have long been known but it has only been recently that concussion recognition, treatment, management and prevention have gained increasing notoriety due to professional athletes and media.

Intracranial hemorrhages are classified as epidural, subdural and subarachnoid hemorrhages. Epidural hematomas are typically associated with middle meningeal artery injuries and is classically seen on CT as a lenticular hematoma (Figure 1). The classic presentation in adults is described as a lucid interval followed by rapid deterioration; however this is rare in children. Children with large clots > 40mL may require evacuation.

Figure 1: Epidural hematoma: Lens shaped convexity. Most often from skull fractures causing laceration to the middle meningeal artery

<table>
<thead>
<tr>
<th>Subdural</th>
<th>Age of injury (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Subacute</td>
<td>3-10</td>
</tr>
<tr>
<td>Chronic</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>
Table 1: Subdural hemorrhage grading

Subdural hemorrhages are associated with the age of the injury (Table 1). Both acute and subacute hemorrhages may occur from birth injury or abuse in infants. Crescent-shaped lesions at the surface of the brain are often associated with mass effect and cortical edema (Figure 2). Operative intervention is indicated when neurologic decompensation occurs with both subdural hemorrhage and parenchymal injury. Acute subdural hematomas have a worse prognosis than epidural hematomas due to the underlying brain damage. Patients with a midline shift greater than 5 mm should be promptly taken to the operating room for neurosurgery evacuation.

Figure 2: Subdural hematoma: Note the concave or crescent-shaped appearance associated with mass effect and loss of ventricles.

Subarachnoid hemorrhages are also common in children. Subarachnoid bleeding in acutely traumatized children is common and rarely the result of aneurysmal bleeding (Figure 3). If associated with minor trauma, surgical intervention may not be warranted. However, hydrocephaly may occur in subarachnoid hemorrhages requiring ventricular shunting to decrease the
elevated ICP. A subarachnoid hemorrhage is associated with a poor outcome in severe TBI as there is associated cerebral vasospasm. Techniques such as angiography and transcranial Doppler imaging can be utilized to identify vasospasm. Calcium channel blockers and neurointerventional techniques are not well studied in children and not commonly used.

Figure 3: Subarachnoid hemorrhage

Skull fractures are commonly associated with head trauma in 2-21% of children.\textsuperscript{9} CT is the diagnostic study of choice for skull fractures, which will allow concomitant diagnosis of underlying brain parenchymal injury. The four major types of skull fractures are linear, depressed, diastatic and those at the skull base. Linear skull fractures are the most common and should be followed for epidural hematoma. Skull fractures depressed deeper than surrounding inner table (> 1cm) may require operative management. Deeper depressions are associated with greater risk of dural tear as well as cortical laceration and therefore worse prognosis [10]. Skull base fractures are uncommon in children. Clinical signs of skull base fractures include raccoon’s eyes (periorbital ecchymosis) and battle’s sign (mastoid ecchymosis) [11]. (Figure 4)
Figure 4: Raccoon’s eyes (periorbital ecchymosis) and mastoid ecchymosis (Battle’s sign)

Hemotympanum may also be a sign of basilar skull fracture. If otorrhea is noted, a cerebrospinal fluid (CSF) leak can be detected by the presence of β-2 Transferrin. Despite the risk of meningitis with basilar skull fractures (2 – 9%), the routine use of prophylactic antibiotics is not recommended as increased use tends to select out for resistant organisms [12-15]. On the other hand, patients with a basilar skull fracture and a CSF leak should be considered for vaccination against Streptococcus pneumonia due to the increased risk of pneumococcal-associated meningitis [16].

II. Evaluation and Management

The management after TBI relies on an understanding of the Monro-Kellie doctrine and the avoidance of secondary brain injury. The Monro-Kellie doctrine states that given that the cranium is a rigid, nonexpansile container, the total volume of the intracranial contents must remain constant and any increase in the volume of one component must be at the expense of the others, assuming the intracranial volume remains constant (Figure 5). Despite the
complexity and variability between the relationship of ICP and cerebral blood flow, the Monro-Kellie doctrine provides a reasonable basic explanation of intracranial dynamics.

Figure 5: ICP and volume relationship: Initially the ICP remains unchanged with increasing volumes due to compensation mechanisms, however at elevated ICP's, small volume increases cause a significant change in pressure.

Interventions are therefore tailored to decrease CSF and/or hyperemia, while ensuring adequate oxygenation and blood flow and preventing secondary brain injury. Secondary damage includes both the evolution of damage within the brain leading to edema, ischemia, and necrosis and secondary insults such as hypotension and hypoxia which further exacerbate damage, elevate ICP or decreased CPP.

Figure 6 and Figure 7 published in the first edition of the guidelines for pediatric TBI provides an algorithm for the management of pediatric TBI. Initial trauma management in the emergency department begins with the ATLS (Advanced Trauma Life Support) protocol of Airway, Breathing, Circulation, Disability and Exposure. Physical exam with Glasgow Coma Score (GCS)
assessment remains essential (Table 2; Figure 8). This exam should be performed, preferably before the administration of sedation and neuromuscular blockade. Clinical symptoms suggestive of intracranial injury or elevated ICP (Intracranial pressure) include coma, irritability, lethargy, emesis or seizures. Physical exam findings associated with elevated ICP include frontal bossing, enlarged heads, dilated scalp veins, sun-setting eyes, papilledema, and bulging fontanelles. Attention should be paid to scalp lacerations, which may be the source of shock in pediatric patients. Isotonic fluid should be given early during the child’s assessment. Dextrose containing fluid should be avoided in the early stages of resuscitation. Although pediatric patients are prone to hypoglycemia, this is rare in the first phases of trauma. As hypoxia and hypotension can cause secondary brain injury, this should be avoided in the suspected head trauma. CT scan remains the gold standard diagnostic study. Cervical spine images should also be obtained. There is an approximately 10% association of cervical spine fractures associated with intracranial injuries [18].

TBI can predispose the pediatric patient to coagulopathy. In patients with a GCS of 8 or less, 81% are coagulopathic and carry a worse prognosis [19]. Additionally, hyperglycemia after TBI is associated with a higher mortality. Glucose levels ≥ 300mg/dL upon admission were associated with death [20]. Moreover, patients with hyperglycemia in the first 48 hrs after admission are also associated with a worse prognosis [21]. Serial CT scans may be necessary to monitor the progression of the injury, particularly to monitor cerebral edema. ICP increases drastically with small increases in intracranial
volume after the compensatory mechanisms of the infant brain have been used. Cerebral edema peaks at 72-96 hours after injury and will slowly resorb over a 7 day time period.

III. Intracranial Monitoring

“Treating TBI without knowing the ICP is like treating diabetes without knowing the serum glucose” ~ PM Kochanek

Although prospective, randomized clinical trials are lacking, there is robust evidence to support improved outcomes and decreased morbidity with patients who undergo aggressive management and treatment for increased ICP. ICP monitoring should be considered for any child with a GCS less than 8 [22]. Additionally, infants with open fontanelles should still be considered for ICP monitoring. Cerebral perfusion pressure (CPP) is the difference between the arterial inflow and venous outflow and is considered the transmural pressure gradient that is ultimately the driving force required for supplying cerebral metabolic needs. CPP is easily measured from ICP with the mathematical difference between the mean arterial pressure and ICP. At a CPP of 10 mm Hg, blood vessels collapse and blood flow ceases. Studies have shown a good correlation between CPP and cerebral blood flow (CBF) in patients with intact cerebral autoregulation [23]. CBF is defined as the velocity of blood through the cerebral circulation. In normal adults, CBF is 50 to 55 mL/100 g of brain tissue/min. In children, CBF may be much higher depending on their age. At 1 year of age, it approximates adult levels, but at 5 years of age, normal CBF is
approximately 90 mL/100 g/min and then gradually declines to adult levels by the mid to late teens. However, cerebral auto-regulation is often disrupted after severe TBI thereby making CBF difficult to interpret and utilize consistently in the management of TBI. Further details regarding monitoring can be found in chapter detailing ICU monitoring.

In the past, treatments were directed towards decreasing ICP. Both fluid restriction and hyperventilation were key strategies. However, current methods include optimizing the CPP and decreasing ICP. Pediatric TBI guidelines involve maintaining CPP between 40 and 65 mm Hg. Most guidelines recommend a minimum CPP of 40 mmHG. ICP elevations above 20 mmHg are not tolerated well by the injured brain and are likely to have poor morbidity and mortality. Sustained increased ICP may result in decreased cerebral perfusion and lead to subsequent herniation. Therefore patients with ICP greater than 20 mmHg should undergo treatment for ICP. Intraventricular devices effectively allow drainage of CSF in order to decrease ICP.

IV. Intensive Care Management

The patient should be positioned with the head of the bed elevated to 15-30 degrees. This position facilitates venous drainage from the head. Ventilation should maintain a PaCO2 of 35-40 mmHg as hypercapnia may cause significant increases in cerebral blood volume and flow. Hyperventilation can temporarily assist in reduction of ICP by causing cerebral vasoconstriction and thereby reducing cerebral blood flow. However, hyperventilation is
reserved for patients with brain stem herniation and current evidence, though severely limited, supports that prophylactic severe hyperventilation to PaCO2 <30 mmHg should be avoided in the initial 48 hours after injury given the reduction in CBF with resultant ischemia [8]. The clinical diagnosis of herniation is often hallmarked by the development of nonreactive, dilated pupils and Cushing’s triad (abnormal respiration, hypertension, and bradycardia).

Studies have shown that noxious stimuli can increase ICP by increasing sympathetic tone with resulting hypertension [24,25]. Sedation and analgesia should therefore be implemented when clinically possible and safely at the discretion of the treating physician. Adult studies have shown these medications to assist in maintaining or decreasing ICP. These medications must be used with caution as they can also exacerbate hypotension leading to decreased CBF. In addition to sedation and analgesia, neuromuscular blockade may be necessary. Importantly, these medications should be reserved for the patient with increased ICP who are unresponsive to sedation and analgesia. Overuse of these medications have been associated with prolonged ICU stays and increased risk of nosocomial infections.

The usage of hyperosmolar treatments for the management of ICP has been used since the 1960’s [26]. Current recommendations are to begin therapy in patients with documented intracranial hypertension and/or impending signs of herniation. Prophylactic use of these solutions is no longer recommended. Mannitol usage has fallen out of favor due to several side effects including the rebound effect of secondary cerebral ischemia, serum
electrolyte imbalance and hypovolemia. Recent data suggests that 3% hypertonic saline should be used as the mainstay therapy to maintain serum Na concentrations of 150-170 mEq/L and serum osmolarity of 360 mOsm/L. Serum osmolarity of 360 mOsm/L has been reported to be well tolerated in the pediatric patient with a head injury [27]. Hypertonic saline has also been reported to have several other potentially beneficial effects which include vasoregulatory, hemodynamic, neurochemical, and immunologic properties. Initial therapy should be 3-5 mL/kg or continuous infusion of 0.1 – 1.0 mL/kg/hr titrated to decreased ICP. Myelinolysis is more likely to occur with a rapid transition from hyponatremia to hypernatremia.

Early posttraumatic seizures (EPTS) occur in 19% of children [28]. EPTS occur within the first 7 days of injury. Children suffer from EPTS much more often than adults and this may lead to secondary brain injury with increased ICP and metabolic demands. Recommendations for monitoring include EEG. EPTS are associated with late posttraumatic (greater than 7 days after injury) seizures. Young age and non-accidental trauma are independent predictors for the development of seizures. Treatment includes a loading dose of phenobarbital 15-20 mg/kg as a single dose with maintenance dose given 12-24 hours later at 5 mg/kg/day divided every 12 hrs and subsequently titrated for therapeutic levels at 15-40 mcg/mL. Class II evidence exists supporting the use of prophylactic anticonvulsants in adults but no compelling data exists in the pediatric literature to show these medications improves long-term outcome or reduces PTS [8].
Steroids are routinely used and supported in the management of non-traumatic neurologic conditions. However, in the management of pediatric TBI, current data indicates that treatment with steroids is not associated with improved functional outcome, decreased mortality or reduced ICP [29, 31]. These studies have also noted trends of increased pneumonia and suppression of endogenous cortisol levels. Given the lack of beneficial evidence and the potential harm from these medications, corticosteroids are not recommended in the management of pediatric TBI.

It is estimated that 21% to 42% of children with severe TBI will develop refractory intracranial hypertension despite aggressive medical management.\(^8\) Decompressive craniectomy, high-dose barbiturate therapy, hyperventilation, lumbar drain placement, and the use of moderate hypothermia should be considered in these patients. Early decompressive craniectomies has been shown to provide improved outcomes in several small single-center studies [32-33]. High doses of barbiturates are known to reduce ICP and have been used in the management of increased ICP for decades. Their side effects limit their current use to those patients with injuries refractory to first-line therapies as evidence has been limited to several small case series [34, 35]. Their use is associated with hemodynamic instability therefore close monitoring is imperative. Finally, therapeutic hypothermia may be considered as a second line therapy as the benefits seen in animal models remains unproven in humans. Data extrapolated from the adult literature indicate that hyperthermia adversely affects TBI outcomes, and it may be advisable to consider passive
Rewarming of the mild to moderately hypothermic trauma patient with isolated head injury [36]. Unfortunately, current large randomized clinical studies in both adults and children have been unable to prove the effectiveness of hypothermia on improved outcome after TBI [37-41].

References


I. INTRODUCTION

Trauma is the leading cause of death in children between the ages of 1 and 14 years in the United States. In 2012, according to the National Trauma Database Registry, 12% of pediatric trauma patients suffered injury to the chest. Although chest trauma is less common in children, it remains an area of concern because it is associated with increased mortality. In fact, chest trauma accounts for up to 14% of trauma-related deaths in the pediatric population, making it second only to blunt head injuries. Children with isolated chest injuries have a mortality of approximately 5%. However, in cases where there is multi-system involvement concomitant with thoracic injuries, such as abdominal or brain injury, mortality drastically increases to nearly 40% to 70%.

Blunt force injury is the most common cause of thoracic trauma in children. Among these cases, 77% are due to motor vehicle accidents. This makes motor vehicle crashes the number one mechanism of traumatic chest injury in the pediatric population overall. Children are either passengers in traffic accidents or pedestrians struck by motor vehicles. The next most common cause of blunt thoracic injury is falls. Other less frequent causes include child abuse, high-risk sporting activities, violence, or suicide.
Penetrating chest injury is even rarer. It occurs 6 times less frequently than blunt trauma and almost exclusively during the teenage years. The most common mechanisms for penetrating injury are gunshot wounds. Penetrating thoracic trauma usually occurs in isolation and is less frequently associated with other injuries.

When dealing with a pediatric trauma patient, childhood thoracic injury should be considered separately from adult chest trauma. In general, thoracic injury patterns are different in children due to anatomic and physiologic differences between children and adults. The pediatric chest wall has increased compliance and ligamentous flexibility, and the mediastinum is more mobile. Ribs and skeletal structures tend to deform and bend, rather than fracture, even when significant compressive force is applied. This pliability allows the transfer of energy to underlying soft-tissues and organs, and may result in intra-thoracic injury without obvious outward signs of damage. In addition, mediastinal blunt injury is less likely in children due to the increased mobility of the mediastinal structures. This increases, however, susceptibility to tension physiology secondary to mechanical displacement of the trachea, superior vena cava, and heart. Thus, pediatric chest trauma should be approached with diligent evaluation and with a high degree of suspicion for life-threatening injuries, even in the absence of substantial physical exam findings.

II. EVALUATION
A. Physical Exam

1. Primary Survey

   The initial evaluation of a child sustaining thoracic trauma begins with a primary survey, prioritizing airway, breathing, and circulation. A child who has the capacity to cry or speak demonstrates an intact airway. In cases where the airway is questionable or the patient has altered mental status, maintenance of a patent airway can be achieved by repositioning the head with a chin lift and jaw thrust to move the mandible anteriorly. Suction and oral airways are also useful adjuncts to ensure airway clearance. Ventilation can then be achieved by bag-valve masking the patient. In patients with severe head injury, unresponsiveness, or hemodynamic instability, endotracheal intubation with in-line cervical spine stabilization is indicated. Once the airway is secure, breath sounds should be evaluated bilaterally to ensure adequate air movement and ventilation. Intravenous access, hemodynamic monitoring, and resuscitation occur simultaneously as the patient is evaluated for life-threatening injuries that may require immediate intervention.

B. Examination for chest injury

   The chest examination in blunt injury should be approached systematically to ensure injuries are adequately identified. An efficient physical exam begins with a quick visual inspection of the neck and chest in the cephalad to caudad direction. The trachea is checked for midline position and the internal jugular veins are inspected for distention. Any abrasions,
contusions, or lacerations are noted as visual surveillance is carried down the chest for obvious signs of external injury. In addition, the chest wall motion is observed for asymmetric chest rise or paradoxical movement with respirations. The exam should then proceed with auscultation of the chest for symmetrical, bilateral breath sounds. Absent or decreased breath sounds are suggestive of a hemothorax or pneumothorax and immediate drainage with tube thoracostomy is indicated if the patient has cardiopulmonary instability. Auscultation is followed by palpation of the neck, clavicles, sternum, and chest wall to assess for any tenderness, skeletal instability, or crepitance. Finally, percussion of the chest for dullness or hyperresonance completes the chest examination. Abnormalities in the chest exam should prompt further investigation with radiological studies for intrathoracic injuries.

For penetrating injuries, particular attention should be directed to Zone I of the neck, which is bordered by the cricoid cartilage superiorly and the clavicles inferiorly. This location is the thoracic outlet and is densely occupied by significant structures that may be potentially injured, including the carotid artery, internal jugular vein, trachea, and esophagus. As visual inspection descends down the chest, the number, location, and character of open wounds should be noted. Sucking chest wounds should be addressed immediately with a three-sided dressing to prevent precipitation of a tension pneumothorax. In cases of missile injury, the wounds should be marked with a radiopaque marker, prior to chest X-ray. The chest is then auscultated bilaterally to assess for symmetric breath sounds. Lastly, the neck and chest are palpated for
tenderness and subcutaneous emphysema. There is increased risk of intrathoracic damage with penetrating injuries, particularly hemothorax and pneumothorax. There should be a low threshold to perform chest tube thoracostomy, if the clinical situation warrants.

The heart, esophagus, and tracheobronchial tree reside in the anterior “cardiac box” and penetrating wounds over the precordium or traversing missiles through this area should prompt concern for cardiac injury. The boundaries of the box are the clavicles superiorly, the nipples laterally, and the costal margin inferiorly. As part of the physical exam, the patient should be examined for signs of cardiac tamponade. Three classical signs, known as Beck’s triad, include hypotension, distended neck veins, and muffled heart sounds. Additionally, pulsus paradoxus, or a drop in 10mm Hg of arterial pressure with inspiration, may be seen. Sonographic examination should also be done at the bedside to assess for pericardial effusion. Confirmation of cardiac injury or hemodynamic instability warrants emergent thoracotomy. In cases of severe tamponade, pericardiocentesis may be done as a temporizing measure prior to the operating room.

The posterior “cardiac box” is occupied by the tracheobronchial tree, esophagus, and aorta. Physical exam findings may be non-specific for injuries in this area of the cardiac box. Patients may present with hoarseness, chest wall crepitance, or substernal tenderness. However, the location of the penetration wound and knowledge of the cardiac box may be the only clue to
intrathoracic injury. Concern for injuries in this area, regardless of physical exam findings, merits further endoscopic or radiographic evaluation.

C. Chest Radiography

Patients who sustain chest trauma should be evaluated with a screening anterior-posterior chest x-ray. Portable chest radiographs can be quickly obtained in a supine immobilized patient. Films should be interpreted methodically to ensure life-threatening injuries are efficiently identified. The airway is examined for midline position and for any aspirated foreign bodies. Lungs fields are then evaluated for pneumothoraces, pleural effusions or intrathoracic radiopacities for hemothoraces, and lung parenchymal consolidation for pulmonary contusions. The mediastinum is assessed for pneumomediastinum and abnormal widening. Air in the mediastinal region suggests esophageal or tracheobronchial injury, while a widened mediastinum is suspicious for aortic injury. Skeletal structures are then examined for fracture and dislocation, and soft tissues are assessed for subcutaneous emphysema. Supportive lines and tubes should be evaluated for location and positioning.

D. Ultrasonography

Ultrasonography of the chest may be indicated in hemodynamically stable patients when chest x-ray findings are inconclusive for pleural injury or pleural effusions. Resuscitation should not be delayed in a hemodynamically
unstable patient for chest US, unless there concern is for cardiac tamponade. Bedside ultrasound (US) is typically performed as a focused assessment with sonography for trauma (FAST), which evaluates the abdomen for free fluid and heart for pericardial effusion. Sonographic examination in the trauma setting may also be extended to include the thorax. The sensitivity and specificity of ultrasound for the detection of pneumothoraces are 86%-98% and 97%-100%, respectively. Hemothoraces can be identified with similar accuracy when a minimum of 20 mL of pleural fluid is present for a supine patient. To evaluate for a pneumothorax, a high frequency probe is usually placed on the anterior chest at the 3rd and 4th intercostal space, mid-clavicular line. Diagnosis is established with the absence of pleural sliding and comet tail artifacts. Hemothorax is diagnosed with an anterior or lateral approach by the presence of an anechoic dependent effusion with inspiratory movement.

D. Computed Tomography

The use of thoracic computed tomography (CT) scans has increased tremendously in the pediatric trauma setting. This imaging modality is more sensitive than plain film chest x-ray for injury detection and can provide immediate high resolution images of the soft tissue, skeletal, and visceral components of the chest. Furthermore, a CT angiography scan with intravenous contrast is particularly useful when there is concern for mediastinal
vascular injury and can rule out life-threatening aortic or major vessel injury with a negative predictive value approaching 100%.

Although immediate data may be obtained from a CT scan, this imaging modality should be used selectively as there may be a 100-fold increase in radiation dose when compared with a plain chest radiograph. Additionally, imaging protocols used in the adult population do not necessarily apply to the pediatric trauma patient. This is primarily because traumatic thoracic injury patterns are different in children due to their compliant and flexible chest wall. Major life-threatening thoracic injuries are rare in children and recent retrospective reviews have demonstrated that routine screening CT scans of the chest in the pediatric population, while more sensitive for injury detection in the trauma setting, rarely alter patient management.

CT scan of the chest should be considered a supplemental study in blunt thoracic trauma based on mechanism of injury, clinical exam, initial chest x-ray findings, and hemodynamic stability. Patients who suffer high impact blunt injury suggested by fractures to the spine, sternum, and shoulder girdle should be evaluated by CT angiography to rule out associated major vascular injuries or unstable spine fractures. In addition, children with radiographic findings of an abnormal or widened mediastinum should prompt further investigation with a CT aortogram. Rarely, significant blunt injury may be associated with pneumomediastinum on chest x-ray, and CT scan of the chest may help delineate the presence of esophageal rupture versus tracheobronchial tree disruption. In the absence of significant clinical examination and chest x-ray
findings, CT scan of the chest may be considered in patients with severe thoracoabdominal trauma who are unable to communicate, are unconscious, or require mechanical ventilation. Hemodynamically instability is a contraindication to CT scan and warrants prompt resuscitation and intervention.

Hemodynamically stable patients with penetrating thoracic trauma should undergo CT scan of the chest because of the high risk of internal damage to mediastinal structures. Missile penetration injury in particular may result in multiple organ injuries. A contrasted CT scan of the chest can also characterize the trajectory of the penetrating agent and efficiently inventory intrathoracic injuries to guide endoscopic interventions or operative management.

E. Angiography

Catheter-directed angiography has traditionally been the gold standard for evaluating thoracic aortic injury. However, this study has now largely been replaced by thoracic CT angiography. Not only does thoracic CT have a high negative predictive value for vascular injuries, but it is also non-invasive and provides immediate high resolution images of the chest and intrathoracic structures. An angiographic examination is considered in rare cases where CT scan results are equivocal and suspicion for aortic injury remains high.

The use of angiography for endovascular stent repair of the thoracic aorta is described in the adult literature. However, limited knowledge is available regarding the safety and efficacy of thoracic endovascular aortic
repair (TEVAR) in the management of traumatic aortic injuries in children. Between 1999 and 2012, at least 12 patients younger than the age of 18 years underwent TEVAR for traumatic aortic injuries. The youngest patient that underwent stent placement was 11 years old. Three deaths occurred in these cases, but they were not attributed to TEVAR-related causes. Delayed endoleak was identified in only one patient.

Although endovascular stents may be successfully placed in children, long-term data is still lacking. Currently, there are no stents approved for the use in pediatric traumatic aortic injury and off-label use is largely investigational. Selected pediatric patients considered for TEVAR include those with an absolute contraindication to anticoagulation, such as traumatic intracranial hemorrhage, and patients with multiply injuries making open aortic repair prohibitively risky. Further studies are required in the pediatric population to determine the effects of endovascular stents on the growth of the aorta, effects of the growing aorta on stent collapse and migration, and long-term durability of the stent material. The role of endovascular stents in pediatric thoracic trauma, though promising, has yet to be determined.

III. SPECIFIC INJURIES

A. Pulmonary Contusion

A pulmonary contusion is lung parenchymal injury that involves alveolar destruction, alveolar hemorrhage, and interstitial edema. It is the most common
injury after major blunt chest trauma, occurring in up to 48% of all pediatric thoracic trauma patients. The most common causes of pulmonary contusions are motor vehicle accidents, pedestrian accidents, and falls. Due to the compressibility of the pediatric chest wall, external signs of chest injury may be completely absent on physical exam. Patients may, however, present with clinical signs of respiratory insufficiency including tachypnea, increased work of breathing, or acute oxygen desaturation. Clinical history, mechanism of injury, and a high degree of suspicious should prompt a screening chest radiograph.

Chest x-ray findings include the presence of non-anatomic areas of consolidation or opacification in the area of the lung fields. Pulmonary contusions may have delayed clinical and radiographic presentation, as injured parenchyma, edema, and atelectasis blossoms over a 6 hour period. Thus, an initial normal chest x-ray does not completely exclude pulmonary contusion. Patients who have concern for this injury should be continually reassessed and a repeat chest x-ray should be done 6 hours from the initial study for interval change. CT scan of the chest is rarely necessary to diagnose isolated pulmonary contusions. With significant chest trauma, however, a CT scan may be performed to assess for other thoracic injuries and pulmonary contusions may be coincidentally identified with the exam. Pulmonary contusions on CT scan appear as areas of air-space consolidation without air bronchograms. Severe pulmonary contusions on CT scan involving at least one-third of the lung parenchyma has been shown to correlate with the need for intubation and mechanical ventilatory support.
Pulmonary contusions result in respiratory compromise due to ventilation-perfusion mismatch, impaired pulmonary compliance, hypoxemia, or hypercarbia. Management of minor pulmonary contusions consists of cautious balanced fluid administration, supplemental oxygen, and aggressive pulmonary toilet. Strict fluid management may limit alveolar edema. Incentive spirometry and early mobilization are essential to prevent progressive atelectasis. In cases of severe pulmonary contusions, additional oxygen therapy and respiratory support may be indicated. Alert patients with marginal respiratory status may be trialed with non-invasive positive pressure mask ventilation. Respiratory failure warrants intubation and mechanical ventilatory support.

Sequelae from pulmonary contusions are frequent. The most common secondary complication is pneumonia, occurring in 20% of affected children. Less frequently, acute respiratory distress syndrome develops.

B. Pleural Injuries

Pneumothorax and hemothorax together are the second most common intrathoracic injuries in pediatric chest trauma with an overall incidence of 41% to 51%. Blunt injury from motor vehicle accidents, pedestrian accidents, and falls are the most common causes. Pneumothorax in the setting of blunt trauma occurs secondary to (1) pleural laceration or lung puncture due to penetrating rib fractures; (2) increased intrathoracic pressure with rupture of alveoli; (3) or air leak into the pleural space from tracheobronchial disruption.
Hemothoraces develop from bleeding into the pleural space, which may originate from intercostal vessels, lung parenchymal injury, or pulmonary vasculature.

On physical exam, diminished breath sounds may be noted on the affected side during auscultation or subcutaneous emphysema may be felt on palpation of the chest wall. With percussion of the chest, hyperresonance is suggestive of a pneumothorax, while dullness is associated with a hemothorax. A pneumothorax is seen on screening chest radiograph as a collapsed lung with a visceral pleural line outlined by free pleural air. If an associated hemothorax is present, it presents as a pleural effusion. Thoracic CT is highly sensitive for pneumothorax and illustrates air in the pleural space. Pneumothorax not apparent on plain chest x-ray, but diagnosed incidentally by CT scan is termed an occult pneumothorax.

Management for a traumatic pneumothorax in a stable patient requires the placement of a tube in the pleural space, in order to remove trapped air and allow lung reexpansion. Early intervention is necessary because the pediatric mediastinum is at increased risk of tension physiology, due to its increased mobility. Chest tube size should be determined by patient size and if there is an associated hemothorax present (Table). Small chest tubes are sufficient for isolated pneumothoraces, while larger tubes should be used to evacuate both air and blood in the case of a hemopneumothorax.

To place a chest tube, the affected chest is prepped and draped in sterile fashion allowing exposure of the nipple, which serves as a landmark for
the 4th rib. After the administration of local anesthesia, a small transverse incision is then made below the 4th or 5th intercostal space, anterior to the mid-axillary line. Sharp dissection is carried through the subcutaneous tissues above the rib into the pleural cavity. A rush of air or bloody drainage may be noted upon entry into the intrathoracic space. A chest tube is then inserted into the pleural space directed cephalad towards the thoracic apex for a pneumothorax, or caudad and posteriorly for a hemothorax to optimize drainage. The chest tube is connected to a drainage device and evaluated for initial output. Non-absorbable suture is used to secure the tube in place and an occlusive dressing is applied. A chest x-ray is obtained to verify tube position and evacuation of the pneumothorax or hemothorax.

In cases of small or occult pneumothoraces, supportive care with oxygen supplementation and close monitoring with serial chest x-rays may be pursued. However, in children who require mechanical ventilation, tube thoracostomy is recommended because positive pressure ventilation can convert a simple pneumothorax into a tension pneumothorax.

Tension pneumothorax occurs with progressive accumulation of air in the pleural space, resulting in severe ipsilateral lung compression and mediastinal shift to the contralateral hemithorax. This is an acute life-threatening condition and mandates immediate intervention. Diagnosis is established clinically by diminished breath sounds on the affected side, tracheal deviation to the contralateral side, jugular venous distention, and hypotension. Management should not be delayed for radiographic confirmation, and prompt
evacuation of the pleural air should be performed with a 14 gauge needle thoracostomy at the second intercostal space, mid-clavicular line. Subsequently, definitive treatment requires a tube thoracostomy.

Hemothorax secondary to thoracic trauma typically only requires evacuation with tube thoracostomy and surgery is rarely indicated. In order to adequately drain hemothoraces and avoid tube obstruction from clots, large chest tubes are preferred. Chest tubes should be placed in the dependent position to permit adequate drainage in a supine patient. Inadequately drained blood can lead to the development of fibrothorax and lung entrapment.

Initial output of blood at chest tube placement should be monitored closely. Massive hemothorax is characterized as hemorrhage exceeding 20% to 30% of the child’s blood volume at initial tube insertion, or persistent bloody drainage at a rate more than 3 cc per kilogram per hour. In these cases of severe hemorrhage, emergent thoracotomy should be considered to achieve hemostasis.

C. Rib Fractures

Rib fractures are less common in the children when compared to adults, secondary to the greater flexibility of the pediatric chest wall. It occurs in only 1% to 2% of pediatric trauma victims and most commonly is the result of blunt trauma from motor vehicle accidents, pedestrian accidents, or child abuse. Physical exam rarely identifies substantial clinical findings and diagnosis is established most frequently by a screening chest radiograph performed at the
initial presentation. Although rib fractures alone are usually of minimal clinical significance, 70% of patients with multiple rib fractures have associated injuries in other organ systems. Consequently, the presence of rib fractures in blunt trauma necessitates thorough evaluation for other concomitant injuries. CT scan and angiography are useful adjunctive diagnostic tools to delineate other injuries associated with broken ribs in selected cases.

In patients less than 3 years of age, child abuse should be strongly considered in the absence of a plausible mechanism for major trauma or underlying metabolic condition predisposing to fractures, such as rickets or osteogenesis imperfecta. When reasonable causes are excluded, the positive predictive value of rib fractures for child abuse in children younger than 3 years of age is 95% to 100%. In cases suspicious for abuse as the primary etiology, further imaging with a skeletal survey and bone scintigraphy should be pursued and social work involvement should be initiated.

The location of rib fractures may prompt further examination for associated organ injuries. First rib fractures indicate a high-energy impact and may be associated with multisystem injury, including shoulder girdle injury, clavicle fracture, pulmonary contusion, hemopneumothorax, vertebral spine injury, or intra-abdominal trauma. However, fractures in the first and second rib are no longer considered to be markers for major vascular injury, nor are they indicators for further angiographic examination. Fractures of the lower ribs, depending on laterality, are associated with hepatic or splenic injuries.
Children with rib fractures are managed with supportive care, pain control, and aggressive pulmonary toilet. Non-steroidal anti-inflammatory medications, intravenous or oral narcotics, and epidural anesthesia are effective options for analgesia and should be used judiciously.

D. Flail Chest

Flail chest occurs in less than 1% of pediatric trauma patients. It manifests when three or more ribs are fractured at more than two points. This results in an unstable chest wall and is clinically diagnosed as paradoxical chest wall motion with respiration. Two main factors associated with the morbidity of flail chest are paradoxical wall motion and underlying pulmonary contusion.

Management is similar to simple rib fractures and is essentially non-operative. The primary goal in treating flail chest is supportive respiratory measures and adequate analgesia. However, in cases of severe respiratory compromise, such as hypoxia or hypercarbia, intubation and mechanical ventilatory support may be necessary.

Rib fixation for the treatment of flail chest has been described in the adult literature with promising results. Open reduction and internal fixation of flail rib segments stabilizes the chest wall and improves pulmonary mechanics. Morbidity is consequently reduced because there is an appreciable reduction in time on the mechanical ventilator, as well as length of stay in the intensive care
Available prosthesis includes stainless steel wires, metal plates or struts, and absorbable plates and screws.

Reports of rib fixation in children are sparse in the pediatric literature and it is still largely uninvestigated. Although it has been shown to be beneficial in adults and short-term results may potentially be reproducible in children, there are concerns regarding rib fixation with metal plates or struts in children. One primary concern is that hardware implanted on a developing child’s rib cage may inhibit future chest wall growth or result in chest wall deformity. Other concerns include the long-term risk of infection of embedded hardware and need for subsequent surgeries to modify or remove hardware. The utility of rib fixation in pediatric thoracic trauma is yet to be determined. Additional studies are required to define the appropriate indications in the pediatric population and assess long-term outcomes in children.

E. Sternal and Scapular Fractures

Sternal fractures are rare in children. Direct blunt impact is the most common mechanism of injury. On physical exam, a chest wall contusion may be visualized and pain may be elicited with palpation of the sternum. Diagnosis is made by AP and lateral chest x-ray or CT scan. The most common location of fracture occurs at the sternomanubrial junction of the sternum. Although the majority of sternal fractures are usually isolated injuries, they are associated with cardiac dysrhythmias. Electrocardiogram (EKG) evaluation should be done
in the emergency room. A normal EKG requires no further cardiac evaluation or monitoring and the patient may be discharged home with pain medication. An abnormal EKG, on the other hand, warrants an admission for 24-hour cardiac monitoring and pain control.

Fracture of the scapula is also uncommon in children. Blunt force trauma is the most common mechanism injury. A significant amount of energy transfer is required in order to fracture the scapula and associated injuries are seen in 90% of patients with this injury. The most common related injury is pulmonary contusion. Scapular fractures that are non-displaced can be managed non-operatively with a sling, while surgical intervention may be required for deformed or significantly displaced fractures.

F. Tracheobronchial Injuries

Tracheobronchial injuries in children are rare, occurring in less than 1% of pediatric traumas. Although rare, these injuries have a 30% mortality and half of the deaths occur within the first hour of injury. Disruption of the trachea or bronchi may result from a direct penetration injury or from high energy blunt chest trauma. The most common causes of tracheobronchial injuries are motor vehicle accidents, pedestrian accidents, and falls. Mechanisms for airway rupture in blunt trauma include abrupt increase in intraluminal pressures from chest compression with a closed glottis, violent acceleration-deceleration of the tracheobronchial tree and lungs, or anterio-posterior compression of the sternum against the spine causing sudden displacement of lungs laterally. Up
to 80% of injuries occur within 2 cm of the carina, most commonly the proximal right main stem bronchus.

Physical findings suggestive of an airway injury include hoarseness, cervical crepitus, substernal tenderness, or hemoptysis. However, outwards signs of injury may be completely absent on exam. On chest x-ray, the common radiographic findings are subcutaneous emphysema, pneumomediastinum, or pneumothorax. In rare cases where there is complete transection of a distal mainstem bronchus, a “fallen lung” sign may be seen on chest x-ray. This highly suggestive finding refers to the collapsed lung in a dependent position, hanging only by its vascular attachments. In the absence of clear physical or radiographic findings, clinical suspicion should be raised when there is a large, persistent air leak after chest tube placement for pneumothorax.

Tracheobronchial disruption is potentially fatal and requires early diagnosis and intervention. Fiberoptic bronchoscopy can be used to confirm and measure the extent of airway injury. In addition, interventional maneuvers may be done at the time of bronchoscopic diagnosis, such as occlusion of the defect with an endobronchial blocker or selective bronchial intubation of the unaffected side.

Once tracheobronchial injury is diagnosed, surgical intervention is indicated. Delay in surgery may result in respiratory failure in the acute setting or eventual stenosis in the future. The disrupted tracheobronchial tree may be repaired through a standard posterolateral thoracotomy. The right thoracic
approach allows access to the trachea and right-sided bronchial injuries, while
the left approach permits access to left bronchial injuries. Hilar exposure is
achieved with anterior retraction of the lung. Primary repair is completed with
interrupted simple absorbable sutures. Tenuous repairs may be reinforced with
a well-vascularized tissue buttress from an intercostal muscle pedicle flap.

G. Esophageal Injuries

Traumatic esophageal injuries are extremely rare in pediatric trauma. This is primarily because it is a mobile mediastinal structure in children and it is
well-protected in the posterior mediastinum of the thoracic cavity. Although it is
an uncommon injury, it remains clinically significant because esophageal
perforation with mediastinal contamination is associated with high morbidity and
mortality.

Perforation or rupture of the esophagus can rarely occur with rapid
intraluminal pressure elevation following high-impact blunt force trauma. More
commonly esophageal injuries are the result of penetrating injury to the neck or
chest. Esophageal injuries tend to have an occult presentation, therefore
suspicion should be raised in patients with the appropriate mechanism to
prevent delay in diagnosis. On clinical exam, fever, chest tenderness, or
crepitus may be appreciated. A chest x-ray may reveal pneumomediastinum
and subcutaneous air. Depending on the location of the esophageal injury and
degree of esophageal leakage, a pleural effusion may also be present.
Concern for esophageal perforation should be further evaluated with a water-soluble esophagram. Up to 15% of perforations may be missed with water-soluble contrast, so a negative study should be followed by a barium contrasted esophagram. Endoscopic evaluation is used selectively in inconclusive swallow studies.

Once an esophageal injury is identified, prompt intervention is necessary to prevent mediastinitis. Operative repair is directed to the site of injury with goals to debride areas of contamination, primarily close the perforation with autologous tissue reinforcement, and control for esophageal leak with tube thoracostomy drainage. Non-operative management may be considered in select cases where there is a contained perforation without evidence of mediastinitis.

H. Diaphragm Injuries

Diaphragmatic injuries occur in 1% to 2% of pediatric chest traumas. Traumatic injuries are more commonly caused by lacerating penetrating agents; however, blunt diaphragmatic rupture is possible in high energy acceleration-deceleration traumas where a sudden elevation in intra-abdominal pressure results in diaphragm avulsion. The most common mechanisms of blunt diaphragm injury are motor vehicle accidents and falls. Thoracoabdominal penetrating injuries may also result in diaphragmatic injuries. Injuries to the diaphragm most commonly occur on the left side, because the right hemi-diaphragm is well-protected by the liver, which can
absorb a significant amount of kinetic energy. A common sequelae of diaphragm injury is herniated abdominal viscera into the thoracic cavity through the diaphragmatic defect. Abdominal contents in the pleural space can subsequently compromise lung expansion, impair cardiac function, or volvulize and strangulate.

Patients with traumatic diaphragmatic injuries may present with dyspnea, abdominal pain, or vomiting. Physical examination may identify non-specific findings such as abdominal tenderness or unilateral decreased breath sounds. Unfortunately, diagnosis of diaphragmatic injury based solely on history and physical exam is extremely challenging. Delay in diagnosis occurs in 15% to 77% of patients.

A surveillance chest x-ray usually provides the first clue to a diaphragmatic injury with gastrointestinal contents seen in the thoracic cavity. With a left sided injury, a nasogastric tube can be placed in the stomach and the tip will be seen in the thoracic cavity confirming the diagnosis. Right sided injuries are more difficult to identify and may be seen as an elevated right hemidiaphragm. Hemodynamically stable patients may undergo CT scan, which has an 82% specificity and 87% sensitivity, and herniated liver or gastrointestinal contents in the chest are more easily visualized. Up to one-third of diaphragmatic injuries are not diagnosed after thorough evaluation with imaging studies. In cases where there is significant concern for diaphragmatic injury, such as penetrating injury traversing across the level of the diaphragm, diagnostic laparoscopy should be considered.
Once diaphragmatic injury is identified, operative repair is indicated. Primary repair can be achieved through a laparotomy incision and the abdominal approach is preferred in the acute setting to rule out associated injuries to other abdominal organs. The defect is closed with non-absorbable sutures in horizontal mattress fashion. Large defects with significant tension may require repair with a synthetic mesh patch or muscle flap. In cases where there is a delay in diagnosis, a thoracic or combined thoracoabdominal approach is preferred to reduce a mature diaphragmatic hernia sac.

I. Blunt Cardiac Injuries

Blunt cardiac injury in children occurs in less than 3% of pediatric trauma patients. Majority of children who suffer blunt cardiac trauma are involved in a motor vehicle crash. Cardiac contusions account for over 95% of blunt cardiac injuries, while ventricular rupture and valvular disruption occur less frequently.

Suggestive physical findings for blunt cardiac injury include anterior chest wall tenderness, visible chest wall contusion, anterior ribs fractures, or sternal fracture. In addition, patients may present with dysrhythmias or unexplained hypotension. Concern for blunt cardiac injury should be initially evaluated with an EKG to rule out arrhythmias. Cardiac specific enzyme levels, including CPK, CPK-MB, and troponin-I, may be elevated with blunt thoracic trauma; however, their utility in identifying clinically significant blunt cardiac injury is negligible. Echocardiography is only indicated in cases with an
abnormal EKG and hemodynamically instability to look for structural cardiac pathology, such as impaired wall motion or valvular dysfunction.

Management of blunt cardiac injury is essentially supportive care. Hemodynamically stable patients with a normal EKG require no further evaluation or intervention and may safely be discharged home. An abnormal EKG, on the other hand, merits admission for cardiac telemetry and observation for 24-hours. Hemodynamic compromise not associated with other injuries necessitates further evaluation with echocardiogram and transfer to an intensive care setting.

Commotio cordis, which means “agitation of the heart” in Latin, refers to sudden cardiac death from a non-penetrating precordial chest wall blow in the absence of an identifiable structural injury to the chest wall or heart. This is the second leading cause of young athletes and has been reported in sports such as baseball, basketball, hockey, football, and lacrosse. This devastating condition occurs most frequently between 7 and 16 years of age. Although the mechanism is not clearly understood, it is postulated that a blunt impact in the precordial region of the chest wall during a vulnerable period of cardiac repolarization can trigger ventricular fibrillation and, consequently, sudden death. According to the National Commotio Cordis Registry, survival rates from commotio cordis between 1970 to 1993 were a dismal 10% to 15%. However, with increasing awareness, early activation of emergency medical services, and increased availability of automated external defibrillators (AED), survival rates have improved between 2006 and 2012 to 58%.
Once sudden cardiac arrest is identified, management should follow the advanced cardiac life support algorithm. Chest compressions should be initiated immediately and early utilization of automatic external defibrillators can be lifesaving.

J. Aortic Injury

Traumatic thoracic aortic occurs in 0.05% to 0.1% of children with major chest injuries. The mean age of children with blunt aortic injury is 12 years old, and less than 10% occurs in children younger than 10 years of age. Motor vehicle crashes are the most common cause of aortic injury and up to 85% of patients die at the scene. The mechanism of thoracic aortic injury is thought to be secondary to sudden deceleration of the mobile aortic arch against the fixed descending aorta at the level of the ligamentum arteriosum, resulting in a sheer injury distal to the left subclavian artery. Patients who survive to present to the hospital often have multi-system injuries.

On physical exam, there are no specific signs of aortic injury. Thus, high energy blunt trauma with rapid deceleration or multi-system injury should be approached with a high degree of suspicion. A screening chest x-ray for thoracic trauma may identify radiographic findings suggestive of aortic injury, including a widened mediastinum, obscured aortic knob, "apical capping" or pleural blood above the apex of the lungs, and depression of the left mainstem bronchus. Concern for aortic injury should be further assessed with CT angiography. Pseudoaneurysm is the most common CT finding, although
aortic contour abnormalities, peri-aortic hematoma, focal aortic dissection, endoluminal thrombus, or active contrast extravasation may also be seen. In cases where results are equivocal, catheter-directed angiography may be necessary.

Aortic injuries require urgent operative repair. Since these patients often have other associated injuries, prioritization in management is essential. Life-threatening issues involving airway, breathing, and circulation are addressed first. In the face of intra-abdominal hemorrhage and hemodynamic instability, laparotomy should be performed before any other procedure, including aortography or aortic repair. Stable patients are otherwise admitted to the intensive care unit for further resuscitation and strict heart rate and blood pressure control until definitive care is appropriate. Short acting b-blockers, such as esmolol, are preferred to reduce shear stress on the aortic wall and risk of free rupture.

In the pediatric population, open repair for aortic injury is the standard management. The operative procedure of choice for traumatic aortic injury repair is the “clamp and sew” technique. This procedure is performed by occluding the proximal aorta and repairing the aorta without establishing a bypass for distal perfusion. This procedure avoids the need for distal vascular cannulation and, more importantly, anti-coagulation, which would increase the risk of bleeding in a multiply injured patient. Although this procedure is the simplest and fastest technique for aortic repair, it has a higher risk of paraplegia and renal failure.
With increasing experience with endovascular techniques in the adult population, selected cases of thoracic aortic injury in children have been successfully treated with endovascular stents. Thoracic endovascular aortic repair (TEVAR) is currently investigational and has been performed in cases where severe concomitant injuries preclude open repair. Concerns regarding the use of TEVAR in the pediatric population include complications associated with growth of the aorta around a fixed sized stent and long-term durability of the stent in young children with a long life expectancy. Although TEVAR is an attractive alternative and less invasive procedure for aortic repair, little is known about the long-term outcomes in children. Thus, surgery is the mainstay of therapy unless otherwise contraindicated.

K. Traumatic Chylothorax

Non-iatrogenic traumatic chylothorax is extremely rare in children with only sporadic case reports of chylothorax occurring in children after blunt trauma. The thoracic duct is the main vessel of the lymphatic system that originates from the cisterna chili in the abdominal cavity at the level of the second lumbar vertebrae. It travels on the right anterior surface of the vertebral column in the cephalad direction to enter the posterior mediastinum through the aortic hiatus of the diaphragm. The duct then crosses to the left side of the vertebral column between the fourth and sixth thoracic vertebrae. The duct then terminates at the junction of the left subclavian and internal jugular vein. Due to its proximity to the vertebral column, it is susceptible to traumatic disruption.
from compressive or acceleration-deceleration forces. Although traumatic chylothorax in children has been described after motor vehicle crashes, it is also seen after child abuse.

Traumatic chylothorax usually has a cryptogenic and sometimes delayed presentation, because the development of a clinically significant chyloous effusion may take up to 24 hours to accumulate. In the acute setting of trauma, clinical examination may be similar to pleural injury or hemothorax, with findings of respiratory distress or diminished breath sounds on auscultation. Regardless, evaluation remains unchanged, as these findings should prompt further evaluation with a chest x-ray.

The identification of a pleural effusion in the acute setting of trauma is a hemothorax, until proven otherwise. Consequently, a tube thoracostomy should be placed to drain the affected side. Diagnosis of a chylothorax is established with the evacuation of milky-white pleural fluid. Fluid analysis demonstrating triglycerides levels > 110 mg/dL, lymphocytes > 1000 cells/mL, presences of chylomicrons, and low cholesterol levels is confirmatory. Due to its association with non-accidental trauma, further evaluation of the child is necessary for concomitant injuries.

Chylothorax can result in respiratory, nutritional, and immunologic compromise, due to losses in the pleural space. Management includes chest tube decompression, dietary modification, and nutritional support. The primary goal of therapy is to decrease chyle flow to allow closure of the disrupted thoracic duct. The patient may be trialed on a low-fat diet consisting of only
medium-chain triglycerides, which is absorbed directly into the portal system, rather than the lymphatics. While on a diet, the chest tube output should be monitored closely. If drainage persists or increases, the patient should be made nothing by mouth and total parental nutrition should be initiated.

Octreotide is a long-acting somatostatin analog, which acts directly on vascular somatostatin receptors, may also be considered for adjunctive therapy to decrease lymph fluid excretion. Traumatic chylothorax typically resolves with non-operative management within 10 to 14 days. However, when conservative measures fail, operative ligation of the thoracic duct through thoracotomy or video-assisted thoracic surgery may be necessary.

L. Penetrating Lung Injuries

Penetrating wounds occur almost exclusively in teenagers in the pediatric population and account for 10% to 15% of pediatric trauma cases. Injuries are usually the result of stab wounds or gunshots. In comparison to blunt chest trauma, penetrating chest injuries are associated with higher rates of operative intervention and mortality.

Stab wounds to the chest should be evaluated for penetration into the thoracic cavity. Suggestive physical exam findings include crepitus in the subcutaneous tissue or active air movement through the wound itself. Open “sucking” chest wounds require immediate attention. Placement of a three-sided occlusive dressing over the wound can be a life-saving maneuver and prevents the precipitation of a tension pneumothorax.
Stab wounds or projectiles that violate the thoracic cavity can potentially lead to lung, heart, major vessel, or mediastinal injury. Fortunately, the majority of stab wounds to the chest in children do not go beyond the muscle wall.

Thoracic bullet penetration injuries can result in significant tissue damage from direct missile penetration or secondary missiles from bone fragments. Furthermore, bullets may travel in an unpredictable trajectory, necessitating complete evaluation of intrathoracic structures, including the mediastinum.

A chest X-ray is obtained to assess for pneumothorax, hemopneumothorax, or mediastinal air. It can also verify the location of the projectile and its potential trajectory. Tube thoracostomy should be placed for pneumothorax or hemothorax, and a persistent air leak should prompt further evaluation for tracheobronchial tree injury. Cardiac injury should be evaluated with a FAST exam or echocardiogram. If the patient is hemodynamically stable, a CT angiogram of the chest may be considered to efficiently inventory all the intrathoracic injuries.

Bleeding from bullet penetrating lung injury may require operative intervention. Operative criteria for bleeding include > 20 mL/kg blood loss on initial tube placement or persistent bleeding at a rate of 3cc/kg per hour. In cases where significant bleeding occurs from a missile tract through the lung parenchyma, a pulmonary tractotomy should be performed. The entry and exit wounds on the lung are first identified, and a penrose drain is subsequently placed through the tract to assist with retraction. A gastrointestinal anastomosis stapler is then placed into the tract and fired to complete the tractotomy. This
allows exposure of the injured lung and hemostasis can be achieved with selective suture ligation of bleeding vessels or tissues. The lung parenchyma is then reapproximated with a running interlocking suture. The entry and exit wounds should be left open to allow drainage and the suture line should be tested for leak at the end of procedure.

**Penetrating Injuries to the heart**

Penetrating injuries to the heart in children are rare. In a recent retrospective review of 4569 pediatric trauma patients, only 0.7% sustained a cardiac injury. The most common mechanisms of injury are stab wounds and gunshot wounds. The right ventricle is the most often injured cardiac chamber, followed by the left ventricle, because of their anterior location in the chest. Penetrating cardiac injuries are fatal in 70% to 80% of cases.

Patients with penetrating cardiac injury may develop pericardial tamponade. Clinical manifestations of tamponade physiology include tachycardia, hypotension, distended neck veins, muffled heart sounds, and pulsus paradoxus. Penetrating thoracic trauma concerning for heart injury should quickly undergo FAST evaluation to look for pericardial fluid. In unstable patients with hemodynamic compromise, bedside pericardiocentesis or subxiphoid pericardial window can be life-saving, temporizing maneuvers.

Regardless of hemodynamic stability, definitive surgical repair for penetrating cardiac injury is necessary. The chest is entered through a left
anterolateral thoracotomy or sternotomy, and the pericardium is opened sharply with scissors taking care not to injure the phrenic nerve. Depending on the size of the cardiac wound, a finger may be used to occlude the laceration. Repair is then performed with nonabsorbable mattress sutures over Teflon pledgets. For larger wounds, occlusion of laceration can be achieved by inserting a balloon catheter into the wound and inflating the balloon with saline. Traction on the catheter will stem bleeding temporarily to allow suture repair of the wound.

IV. PEDIATRIC THORACIC TRAUMA MANAGEMENT ALGORITHM

A. Hemodynamically Stable Thoracic Trauma

Pediatric trauma resuscitation begins with a primary survey to assess for life-threatening conditions that demand immediate intervention. Establishing a secure airway is the first priority in trauma resuscitation, followed by breathing and circulation. Although there are levels of prioritization for the primary survey, the patient assessment and execution of care are performed simultaneously in a systematic and expeditious manner. Breath sounds are assessed for symmetry and air movement, and cardiopulmonary monitoring is established as peripheral intravenous access is established. As the patient is quickly surveyed, life-threatening injuries should be identified and addressed accordingly.

In a hemodynamically stable patient, once the primary survey is determined to be intact, the exam should then proceed to the secondary survey to sufficiently assess the patient from head to toe for external signs of injury.
For thoracic trauma, particular attention should be directed to the neck and chest. Physical examination should include auscultation, visual inspection, manual palpation, and percussion of the chest wall. Depending on the mechanism of injury, particularly blunt trauma, the physical exam may not demonstrate outward signs of injury. Therefore, a chest x-ray is indicated if there is a clinical history of a high-risk mechanism for trauma, or if there is any clinical signs of chest injury present on the child.

A surveillance anterio-posterior chest X-ray can be obtained without significant difficulty in a supine, immobilized patient. The x-ray should be examined systematically to evaluate for pleural injury, pulmonary contusions, mediastinal abnormalities, and rib fractures. If findings on chest x-ray are inconclusive for hemothorax or pneumothorax, the study can be supplemented with a bedside ultrasound of the chest. Positive findings for pleural injury or effusion warrants management with chest tube thoracostomy. Other chest x-ray findings for thoracic injury, including rib fractures and pulmonary contusions, should prompt admission for pain control and pulmonary hygiene. If rib fractures present or the patient history is not congruent with the patient’s presentation, social work involvement may be necessary to assess for possible child abuse.

Mediastinal abnormalities on chest x-ray or clinical history of high speed acceleration-deceleration traumas warrant further imaging in a hemodynamically stable patient. Computed tomography angiography should be performed in these select cases to efficiently evaluate for aortic,
esophageal, or tracheobronchial tree injury. Aortic injuries require admission to
the intensive care unit for strict heart rate and blood pressure control.
Esophageal and tracheobronchial tree injuries require further endoscopic
examination and immediate surgical intervention.

An EKG should be done in children with physical or radiographic signs of
anterior chest trauma or an abnormal heart rhythm on the cardiopulmonary
monitor. A normal EKG in an asymptomatic patient requires no further
investigation. An abnormal EKG, on the other hand, requires an admission for
24 hour telemetry monitoring.

Hemodynamically stable patients, who are asymptomatic, without
significant mechanism of injury, and negative radiographic findings of
intrathoracic injury may safely be discharged. Otherwise, an injured child
should be admitted for cardiopulmonary monitoring, pain management, and
radiographic reassessment as indicated.

B. Hemodynamically Unstable Thoracic Trauma

In a hemodynamically unstable patient with altered mental status or
unresponsiveness, the airway should be secured immediately with
endotracheal intubation. Verification of proper tracheal intubation may be
established with the appreciation of symmetric bilateral breath sounds and
appropriate change in the end-tidal carbon dioxide detector. Fluid resuscitation
should be initiated with a 20 mL/kg bolus of isotonic crystalloid fluid such as
Lactated Ringers or normal saline. Access in hypotensive children less than 6
years of age may be difficult. If access is not obtained in 2 attempts or 90 seconds, intraosseous access should be obtained without delay. During resuscitation the mechanism of injury and external signs of thoracic injury should be assessed to determine the etiology of cardiovascular collapse. Life-threatening conditions associated with thoracic injuries include tension pneumothorax, massive hemothorax, cardiac tamponade, and cardiac arrest.

A patient that has suffered blunt or penetrating chest injury to the chest presenting with hypotension and unilateral diminished breath sounds should be quickly assessed for tension pneumothorax. The trachea is evaluated for midline position and the internal jugular veins are examined for distention. Tension pneumothorax is a clinical diagnosis and treatment should not be delayed for radiographic imaging. If the constellation of signs and symptoms are present and clinical suspicion is high, needle thoracostomy should be performed immediately. Introduction of a large bore angiocatheter in the 2nd intercostal space, mid-clavicular line to the affected side will evacuate the pleural space of air and alleviate tension physiology. Chest tube thoracostomy is subsequently performed to definitively address the pneumothorax.

If the patient is hemodynamically unstable with unilateral diminished breath sounds and does not clinically appear to be demonstrating tension physiology, hemorrhage into the chest may potentially be the cause of shock. If the patient responds to fluid resuscitation, a prompt chest x-ray should be performed to evaluate for a large hemopneumothorax. A FAST exam could also be performed to rule out intra-abdominal free fluid and pericardial effusion.
In the absence of an intra-abdominal source of hemorrhage or cardiac tamponade, a chest tube should be placed in the affected side of the chest to directly assess for hemothorax. With initial placement of the chest tube blood will immediately evacuate and the initial output should be noted. Initial volume out of a chest tube that is greater than 20 ml/kg of bleeding, especially if the bleeding persists, may warrant emergent thoracotomy in the operating room to control the bleeding.

If tension pneumothorax and massive hemothorax are absent and the patient remains hemodynamically unstable despite appropriate fluid resuscitation, the patient should be evaluated for cardiac tamponade. This is particularly important in a patient who has suffered a penetrating injury in the region of the “cardiac box.” A FAST exam or echocardiogram (ECHO) should be performed to evaluate for pericardial effusion. Confirmation of fluid in the pericardial sac demands emergent exploration in the operating room. In the event that the patient is too unstable to transfer, a temporizing pericardiocentesis may be performed at the bedside in the ED.

Rarely, a child with severe thoracic trauma may lose vital signs upon arrival to the ED or during resuscitation. If the patient has suffered a penetrating injury to the chest, emergent ED thoracotomy may be indicated. In blunt trauma, however, emergent thoracotomy should be avoided as it is almost uniformly futile.

C. Emergency Room Thoracotomy
The role of emergent thoracotomy in the pediatric population remains unclear. Prior to 1990, the survival of pediatric trauma patients after an emergent thoracotomy ranged from 0% to 4%. Over the past two decades, only two retrospective studies have since examined the role of emergency room thoracotomy in children. A total of 34 patients were reviewed and only 3 patients (10%) suffering penetration injuries survived. No children who suffered blunt injury and underwent emergent thoracotomy survived in these studies. Despite significant improvements in pre-hospital trauma care by emergency medical response teams and the development of specialized pediatric trauma centers, pediatric survival rates after emergent thoracotomy remain concerningly low.

Unfortunately, the infrequency of this procedure in children limits sufficient data to draw definitive conclusions. The paucity of information regarding emergent thoracotomy in children is likely due to the fact that children rarely have cardiac arrest after trauma. Penetration injury in children, in particular, is extremely rare. Furthermore, when patients do present with sufficient indications for thoracotomy, the procedure may not be performed due to either lack of evidenced based data regarding utility of the procedure in children, or providers may lack appropriate surgical experience to perform the procedure.

Although the pediatric literature demonstrates low survival rates after emergent pediatric thoracotomy, it should still be considered as there are no other alternative to death in these patients with critical injuries. Currently,
management algorithms are extrapolated from the adult literature and follow the Advanced Trauma Life Support guidelines. Based on adult data, emergency thoracotomy in the ED is indicated in children with cardiac arrest after a penetrating injury and signs of life were previously present at either the scene or on arrival.

The procedure is performed by first prepping and draping the left chest in the usual sterile fashion. An incision is made at the 5th intercostal space from the sternum to the mid-axillary line. Sharp dissection is carried through the intercostal muscles into the thoracic cavity. A rib spreader is used to open the wound for further exposure. The left lung is retracted anteriorly and superior, and the pericardium is examined for pericardial tamponade. The pericardium is incised with scissors anterior and parallel to the phrenic nerve. Manual cardiac compression may be initiated directly on the heart. In the face of severe hemorrhage, the aorta is identified just above the diaphragm. Placement of a nasogastric tube may assist in identification of the esophagus. The aorta is then cross-clamped with a large vascular clamp to stem ongoing bleeding during resuscitation. If necessary, the left sided thoracotomy incision may be extended through the sternum into the right chest to fully expose the heart and allow evaluation for right thoracic injuries.

IV. SUMMARY
Pediatric thoracic trauma is associated with significant morbidity and mortality. Additionally, thoracic injuries are often associated with multi-system involvement. Optimal treatment includes a systematic approach to resuscitation and thorough evaluation for life-threatening injuries.

REFERENCES


Chapter 15
Pediatric Abdominal Trauma

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I. INTRODUCTION

The highest mortality associated with trauma in the pediatric population is caused by severe head injury. However, abdominal injuries occur in 10-15% of injured children and continue to lead to significant morbidity and mortality [1]. The most common mechanism leading to abdominal solid organ injury in this population is motor vehicle related accidents. The most likely injured organ is the spleen, followed by the liver. Regardless of the mechanism or organ injured, the pattern of injury does differ in the pediatric population when compared to the adult population. This is due to the differences in anatomic and physiologic characteristics of children when compared to adults.

Compared to adults, children have a more compliant abdominal wall and rib cage, as well as less body fat. These factors all contribute to an increased risk for abdominal injury due external forces. Physiologically, children manifest the effects of blood loss much differently than adults, because of their ability to compensate by increasing heart rate and systemic vascular resistance to compensate for blood loss. In children, hypotension is an ominous sign that suggests impending cardiovascular collapse.

II. EVALUATION
It is important to obtain as much of the prehospital information as possible. Aside from the vital signs and patient’s condition, facts about the scene of the trauma and mechanism of injury should be elicited. For instance, in a motor vehicle crash, the use of restraining devices (seat belts, car seats), the patient’s location within the vehicle, damage to the vehicle, extraction methods utilized, and any fatalities in the scene give the clinician a sense of the severity of the MVC. In cases of falls, knowledge regarding the height from which the child has fallen and the surface where he landed lends a sense of the force of impact that he may have sustained. A quick summary of the child’s past medical history, allergies, medications, and last meal should be elicited from pre-hospital medical personnel.

The evaluation of the abdomen during trauma can occur during the primary or secondary survey, depending on the mechanism of injury and the known injuries sustained. Once in the trauma bay, findings on physical exam may give clues as to potential intra-abdominal injuries. Findings such as abdominal contusions or abrasions, tenderness, distention, or a “seat belt sign” or “handle bar mark” may indicate the presence of abdominal injuries.

In a patient with suspected abdominal injuries, a complete blood count and a metabolic panel are typically obtained. In a stable patient, elevation of AST or ALT beyond 250 mg/dL may prompt a CT scan to look for occult hepatic injury (Oldham). Amylase and lipase are often sent, but some investigators argue that they are reliable or cost effective screening tools [10]. In children with suspected non-accidental trauma, elevations in AST or ALT, or abnormal
physical exam findings (such as bruising, distention, or tenderness), may indicate the need for further abdominal imaging looking for occult injury [11].

Computed tomography (CT) is the preferred diagnostic modality for children with a potential abdominal injury. A CT scan with intravenous contrast is the most sensitive and specific imaging modality with regard to evaluating the abdomen and retroperitoneum. In fact, CT scan is very sensitive and has led some to suggest that a negative CT scan after blunt abdominal trauma may obviate the need for in-patient observation [2]. A child with hemodynamic instability should not be sent for CT evaluation.

CT scan is limited in evaluating acute diaphragmatic, mesenteric, intestinal injuries. A typical diagnostic uncertainly in a trauma patient is the presence of free fluid without solid organ injury. Fluid in the abdomen may be a normal finding or may suggest bowel injury or may be an incidental finding. In these circumstances, laparoscopy may be utilized common diagnostic adjunct, depending on the clinical scenario. In two relatively large reviews, laparoscopy was found to be safe; by avoiding laparotomy, length of hospital stay is potentially shortened in patients undergoing laparoscopy [8-9]. A number of injuries can be approached using laparoscopic techniques. CT and laparoscopy may provide complementary information: CT evaluates areas that are cumbersome to access laparoscopically such as the retroperitoneum, kidneys, and pancreas, while laparoscopy allows for direct visualization of the regions not well assessed by CT such as bowel, mesentery, and diaphragm surfaces.
Ultrasound can be very useful for a rapid evaluation in the initial resuscitation, and in cases where the child in unstable. There has been an increase in the use of ultrasound in the trauma bay in the form of FAST (Focused Assessment with Sonography in Trauma) exams. The goal of the FAST scan is to identify fluid in four specific places: the pericardium, the pelvis, the pouch of Douglas, and the left upper quadrant. The FAST scan can be performed by surgeons or emergency medicine physicians in an expeditious fashion within the trauma bay. The FAST scan cannot identify the source of the fluid found. It is not designed to evaluate the individual organs in the peritoneal cavity and the retroperitoneum. In multiple studies, the traditional FAST exam has been found to have a low sensitivity and specificity for the diagnosis of injuries in children [3-8]. A recently published large series directly comparing FAST exam in children to CT or laparotomy for the presence of free fluid concluded that a positive FAST suggested hemoperitoneum and associated abdominal injury, but a negative FAST adds little in decision making. [7] Since the majority of pediatric solid organ injuries, even those with significant free fluid (hemoperitoneum), can be managed non-operatively, experts argue that a positive FAST exam may not be very helpful in directing clinical care in the pediatric population. In a practical sense, pediatric trauma surgeons utilize the FAST scan to evaluate pericardial fluid or to give a quick assessment of the peritoneal cavity if a child has to have an emergent non-abdominal procedure (e.g., evacuation of epidural hematoma).
III. MANAGEMENT

A. Liver and Spleen

The contemporary approach for managing blunt spleen and liver injuries is primarily non-operative; more than 95% of all spleen and liver are managed with expectant observation. In order to be a candidate for non-operative management, the child must have normal hemodynamic parameters, and be in a facility where there is close monitoring for signs of on-going hemorrhage. The recommended period of observation was initially proposed by the APSA Committee on Trauma, and is based on the American Association for the Surgery of Trauma (AAST) grade of injury as determined by CT [12-15]. A recent paper has challenged these recommendations, finding that abbreviated periods of bedrest (a single night for injuries with Grades 1&2 and two nights for Grades 3-5) do not result in delayed bleeding, return to the hospital. With this approach, the authors found a decrease the length of hospitalization by two days when compared to the APSA recommendations [16]. Routine repeat imagin is not recommened regardless of the grade. Patients should be allowed to return to contact sports 4-6 weeks after the injury.

Nearly all children with spleen or liver injuries experience complete recovery and excellent long-erm outcomes without the need for operative intervention. However, a few patients may still require operative intervention for ongoing hemorrhage. Tachycardia, not responsive to fluid resuscitation, decreased end-organ perfusion (low urine output, changes in mental status),
and continued need for blood products warrant consideration for operative intervention. The operative approach in these cases should be though a generous laparotomy. If possible, a cell saver should be set up. Appropriate exploration should be undertaken with four-quadrant packing followed by a systematic exploration to identify the major source(s) of hemorrhage. In the trauma bay or the ED, rapid transfusion protocols are being increasingly implemented in children. Rapid transfusion protocols are utilized with the goal of 1:1:1 transfusion of packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelets. In infants and children, this translates to 20cc/kg of PRBC, FFP and platelets [17].

If the spleen is identified as the source, a splenectomy can be rapidly performed and will allow for the resuscitation of an unstable patient. Splenectomy confers to the patient a future risk for post-splenectomy sepsis, an overwhelming infection caused by encapsulated organisms. For this reason, vaccination with the 23-valent pneumococcal vaccine, as well as vaccinations against H. influenzae type B and meningococcus, should be administered after splenectomy, prior to the patient’s discharge from the hospital. In patients with splenic injuries, but are not in shock per se, are potential candidates for splenic salvage operations. Partial splenectomy and mesh splenorrhaphy are techniques that can save splenic parenchyma. These approaches are time consuming, and may not appropriate in the unstable patient [18].

A major hepatic injury can be one of the most challenging injuries that a pediatric surgeon may encounter. Numerous descriptions for the management
of these injuries have been reported. Successful management requires an understanding of the segmental anatomy of the liver. Peitzman and Marsh published an excellent review of the operative management of complex liver injuries in 2012 [19]. Their report highlights the components of operative control of hepatic parenchymal injury, which includes adequate exposure, an experienced co-surgeon, good anesthesia support, and supradiaphragmatic intravenous access. They recommend initial management of deep parenchymal fractures with compression, followed by suture ligation of bleeding vessels, and the avoidance of deep liver sutures. The Pringle maneuver can help differentiate between hepatic arterial bleeding (bleeding decreases when the clamp is engaged) and hepatic venous bleeding. Ideally, intermittent clamping of the porta hepatis (<30 minutes at a time) should be performed to decrease the degree of hepatic ischemia. When large fractures are present and not able to be controlled with finger fracture and tying of vessels, an anatomic resection should be considered. The definitive operation should control bleeding and any potential bile leak, debride non-viable tissue, and adequately drain the resected margin if the patient is stable. However, in cases where there is uncontrolled hemorrhage, coagulopathy, and coldness, a massive liver resection should not be undertaken. Control of the hemorrhage by packing and placement of a temporary abdominal closure can buy valuable time for ongoing resuscitation and stabilization of the patient. Definitive treatment may be deferred until the patient is stable.
A complication that is uniquely associated with severe hepatic injuries is the development of a bile leak from disrupted liver parenchyma or a disrupted bile duct. At the time of operation, closed suction drains should be placed around the liver, particularly if a non-anatomic resection was performed. In cases of non-operative management, a significant bile leak may manifest by feeding intolerance, abdominal pain, elevations in hepatic enzymes, and fever [20]. CT or ultrasound will reveal a fluid collection. Initial management involves the insertion of catheters to drain the bile collection usually performed percutaneously with image guidance. If the bile leak persists after drainage, endoscopic retrograde cholangiopancreatography (ERCP) can be used to identify the location of the leak, as well as the ability to perform a sphincterotomy to decrease biliary pressure and promote internal drainage [21,22]. If necessary, placement of biliary stents can also be performed, both to improve drainage and to treat the ductal injury.

Hemobilia presents with symptoms of an upper GI bleed, such as hematemesis or melena. Though uncommon, this symptom signifies a fistula between a branch of the hepatic artery and the biliary tree. Angioembolization is the treatment of choice.

**B. Renal Injuries**

Fortunately, the kidney is less frequently injured than the liver or spleen with a reported incidence of approximately 10% of all abdominal traumas [23]. However, major renal injuries are more common in children than adults for the reasons noted at the beginning of this chapter. A staging system for renal
injuries has been developed by the AAST, which is important for discussing the injuries as well as validating treatment strategies. Also similar to spleen and liver injuries, the vast majority of renal injuries are blunt in nature, and can be managed non-operatively with several studies have documented renal preservation in over 95% of children [25-27]. Unfortunately, no evidence-based guidelines regarding length of activity restriction in these patients exist. A multi-institutional prospective study allowing for immediate ambulation and discharge based on standard criteria, rather than resolution of gross hematuria, is currently underway to address possible guidelines. Indications for operative intervention include hemodynamic instability, penetrating injuries, and, in some centers, urinary extravasation and urinoma [26-28]. Selective angioembolization of renal artery branches has been successful in nearly 80% of cases with delayed hemorrhage [29].

C. Pancreatic Injury

Pediatric pancreatic injuries are rare, but occur more commonly than in adults with a reported incidence of approximately 5%. The most common mechanism of injury is blunt trauma, often a handlebar or seatbelt injury. Patients usually present with epigastric pain and bilious emesis, particularly in the case of injuries that have a delayed presentation. CT scan with IV contrast is the preferred imaging study, although definitive identification ductal injuries may require ERCP (endoscopic retrograde cholangiopancreatogram). Recently, magnetic retrograde cholangiopancreatography (MRCP) has been shown to be useful.
Regarding specific injuries, isolated contusions can be managed non-operatively with gut rest until the abdominal pain has resolved. An oral diet can then be re-introduced while monitoring for signs of pancreatitis. Trends in serum amylase and lipase may be helpful, although the absolute value of these tests does not correlate with outcome [30]. When a ductal injury is encountered, surgical intervention is generally required. Management of ductal transection is currently controversial. The standard approach for a distal ductal transaction is a laparoscopic or open spleen preserving distal pancreatectomy [31-32]. Although this procedure is well tolerated, concerns regarding late morbidity, particularly endocrine insufficiency, have led to other treatment approaches including Roux-en-Y distal pancreaticojejunostomy using a retrocolic jejunal limb to drain the distal pancreas, while some have advocated a non-operative approach to pancreatic ductal injuries, with percutaneous or endoscopic drainage of subsequent pseudocysts [33-35]. A recent APSA Trauma Committee retrospective review compared operative and non-operative management for blunt pancreatic injury. Although they found a similar length of hospitalization, a higher rate of pseudocyst formation and days on total parenteral nutritional (TPN) was seen in the nonoperative group [36]. Additionally, patients who underwent non-operative management often requires ERCP to define the ductal anatomy, perform sphincterotomy, and potentially stent the pancreatic duct, as well as percutaneous or endoscopic drainage of pseudocysts. A multiinstitutional review was conducted involving patients with blunt pancreatic transection in twelve pediatric trauma centers reviewed non-
operative approach and operative approach. Patients undergoing the operative approach were divided into pancreatic resection or drain placement only. The patients who underwent distal pancreatectomy were quicker to attain goal feeds and discharge to home. Those who underwent a drain placement alone had similar outcomes to the non-operative group with regard to having prolonged ileus and protracted lengths of stay. These two groups had similar morbidities with regard to pseudocyst formation and requirement for intervention such as percutaneous or endoscopic drainage. Presently, no data exists regarding long term pancreatic function of these patients.

D. Intestinal Injury

Most intestinal injuries in children are related to a high force blunt injury such as a direct blow from a fall, handlebar, non-accidental trauma or seat belt. Distended hollow viscera are more prone to rupture with blunt trauma due to the increased intra-luminal pressure [37]. Areas at risk to injury include sites of mesenteric fixation such as the proximal jejunum near the ligament of Treitz, the distal ileum near the ileocecal valve, and the rectosigmoid junction. Seat belt signs may be markers of severe deceleration injury to the abdomen with associated intra-abdominal blunt hollow viscus injuries, as well as lumbar spine injuries in approximately 10% of cases; the fractures associated with this constellation of injuries has the eponym of “Chance” fracture [38]. These injuries are more prone to occur in young children who are secured in appropriately, such as adult seat belts without booster seats or using lap belts
without shoulder straps. Therefore, use of age-appropriate child restraints in cars may decrease the risk of some of these injuries [39].

Traumatic intestinal injuries associated with perforation typically present with signs of peritonitis due to the contamination of the peritoneal cavity. In a neurologically intact patient, serial examinations with the development of abdominal tenderness, guarding, and rebound have been shown to be more specific for hollow viscus injury than abdominal US or CT findings for intestinal injuries [40-42]. Hemodynamically unstable patients with signs and symptoms of hollow viscus injury should undergo emergent exploration. Although CT scans have a lower sensitivity in detecting intestinal injuries, findings suggestive of intestinal injury include bowel wall thickening and enhancement, mesenteric stranding, and free intraperitoneal fluid in the absence of solid organ injury [43]. Current imaging modalities may miss partial thickness intestinal injuries, hematomas, or mesenteric injuries. Over time, these injuries may evolve or cause full thickness intestinal wall ischemia and perforation with leakage of intestinal contents. Some mesenteric injuries may result in intestinal strictures or internal hernia diagnosed at a time remote from after the acute injury. A recent multi-institutional retrospective review by the APSA Trauma Committee determined that delay in operative treatment for up to 24 hours after injury did not significantly affect outcome [44].

Laparoscopy should be considered an extension of the diagnostic armamentarium in patients with equivocal imaging findings. In hemodynamically stable patients with evidence of bowel injury, a laparoscopic
approach for repair is a reasonable alternative to a traditional midline laparotomy. In penetrating traumas, initial local wound exploration to identify penetration of the anterior abdominal fascia is recommended. If local exploration shows that peritoneum has been violated or if the exploration has equivocal finding, then laparoscopy can be performed to determine peritoneal penetration. [9, 45, 46]. Regardless of the approach, principles of management of hollow viscus injury include prompt resuscitation, complete removal of devitalized tissue, reconstruction or diversion of the intestinal tract, and perioperative antibiotic coverage.

When the small intestine is the portion of the intestine that has been injured, it can nearly always be resected with subsequent primary anastomosis performed even in the presence of significant contamination. For colonic injuries, a primary repair should be performed in all cases of minimal contamination, and even in most cases with significant contamination. However, in the setting of significant devitalizing colonic injury in a patient in shock, initial damage control laparotomy is recommended with delayed colonic anastomosis at the time of abdominal wall closure. In this scenario, a higher complication rate has been found with delayed anastomosis if fascial closure occurs greater than 5 days after injury and in the case of a left colonic injury [47]. A diverting colostomy rather than a delayed anastomosis should be performed at the time of abdominal wall closure in patients with recurrent intra-abdominal abscesses, severe bowel wall edema and inflammation, or persistent metabolic acidosis [48].
Initial management for rectal injuries include proctoscopy to definite extent of the trauma and diversion colostomy. Stool should be evacuated from the distal rectum at the time of operation. Patients with significant rectal injuries should be monitored for local and systemic infections. Wound management of these patients may be complex.

Injuries to the duodenum merit special discussion. The most common mechanism of injury resulting in duodenal injury is blunt abdominal trauma [49,50]. In younger patients, the finding of a duodenal injury is often the result of non-accidental trauma and should raise suspicion if the history or mechanism is inconsistent with the injury [51,52]. Due to its anatomic relationship to many other vital structures, associated injuries may be seen. Abdominal CT is the imaging modality that best evaluates duodenal injuries. Duodenal injuries are graded by the AAST and range from grade 1 (hematoma) to grade 5 (devascularization of the duodenum or massive disruption of the duodenopancreatic complex) [53].

The spectrum of duodenal injuries include mild duodenal hematomas with transmural thickening, moderate partial thickness injuries with partial to total obstruction to transmural injuries. If no clinical or radiologic evidence of perforation, exist duodenal injuries should be managed nonoperatively with nasogastric decompression and TPN [54]. Though rare, operative evacuation of the hematoma may be required if obstructive signs and symptoms do not resolve. Duodenal perforation is often a delayed diagnosis due to a delay in
presentation or the paucity of findings on initial imaging [55, 57]. When present, CT scan findings of full thickness injury include extravasation of air or contrast into the paraduodenal, pararenal, or retroperitoneal space [54].

Complications are more common after repair of duodenal injuries than following operative repair for any other area of the gastrointestinal tract. Operative repair of duodenal injuries are tailored to the extent of the injuries. Approaches may include a serosal patch, transverse primary repair, duodenal diverticularization, pyloric exclusion, and gastrojejunostomy [54,57]. Full-thickness injuries not involving the biliary or pancreatic ductal system with healthy surrounding tissue can be repaired primarily [51]. In patients with a complex duodenal injury, diversion and drainage should be considered. In these cases, a duodenostomy tube and gastrostomy may be helpful for decompression. A feeding jejunostomy is recommended for early enteral nutrition, and drains should be placed near the repair. Earlier diagnosis of duodenal injuries may make the injury more amenable to primary repair. Proximal drainage via a gastrojejunostomy and pyloric exclusion may be warranted when there is a significant delay in diagnosis (>24 hrs), or those with a grade III or greater injury [50].

Compartment Syndrome

Compartment syndrome occurs when the pressure within an anatomic compartment increases to the point where tissue perfusion and celluar oxygenation are compromised. High intercomparmental pressure initiates
venous obstruction and may lead to arterial compression. Tissue swelling initiates progressive cellular injury, edema formation, inadequate oxygen delivery, anaerobic metabolism, and cell death.

There are three types of compartment syndrome (CS): primary, secondary, and recurrent. Primary CS occurs when there is direct traumatic or ischemic insult resulting in physical tissue destruction (crush injury) or vascular injury. Secondary CS is thought to result from cytokine release and systemic inflammatory response. Recurrent CS is due to a “second hit” phenomenon following initial injury from primary or secondary CS.

Factors that modulate effects of elevated compartment pressures include rapidity of onset, duration on intracompartmental hypertension, compartmental perfusion pressure and rapidity of decompression.

Abdominal compartment syndrome (ACS) occurs when the pressure in the abdominal cavity increases significantly to result in adverse physiologic consequences and possible organ system failure. Normal intraabdominal pressure is usually subatmospheric. Postoperatively, the pressure may increase to 3-15mm Hg. Organ system dysfunction may be seen at 10-30 mm Hg. At abdominal pressures greater than 30 mm Hg, there may be organ dysfunction. At these pressures, anuria and ventilatory compromise may be seen.

End organ manifestations may occur at pressures as low as 15 mm Hg. In fact, some authors define ACS as intraabdominal pressure greater than 15 mmHg and one or more of the following problems: metabolic acidosis despite
resuscitation, oliguria despite volume repletion, elevated peak airway pressures, hypercarbia refractory to increased mechanical ventilation, and hypoxemia refractory to increased FiO2 and PEEP, and intracranial hypertension.

Abdominal compartment syndrome can be seen in several pediatric situations including severe penetrating and blunt abdominal trauma with prolonged operative intervention, prolonged shock, and burns with high volume resuscitation. Other causes of ACS include pancreatitis, ischemic bowel, pelvic fracture, ascites, and tumor.

Bladder pressure is the most common method of measuring IAP. A foley catheter is placed to drain the urine, then 1 ml.kg body weight of sterile saline is instilled into the bladder. The end of the Foley is connected to a pressure transducer or a manometer via a 3-way stopcock. The transducer is placed at the height of the public symphysis as the “zero point”. Since water is used, the value obtained is converted to mm Hg by dividing the value by 1.36 (1 mm Hg=1.36 cm H2O).

Abdominal Perfusion Pressure is the difference between Mean Arterial Pressure and IAP. Normal abdominal perfusion pressure should be greater than 50 mm Hg. Some authors feel that abdominal perfusion pressure is a better predictor of end organ injury than lactate, pH, urine output, or base deficit.

Treatment of ACS is dictated by the physiologic effects. If IAP is 10-25 mm Hg, maintaining normovolemia and sometimes hypervolemia may be adequate.
If fluid is present, paracentesis may be therapeutic. However, with any physiologic compromise or IAP of 30 or greater, a decompressive laparotomy should be considered.

REFERENCES


I. Introduction

Burn injuries affect approximately 2 million people in the United States on an annual basis, approximately half of these occur in children. Although most tend to be minor burns, fifty thousand injuries will be considered moderate to severe requiring hospitalization. Approximately 5.6% of affected patients will succumb to their injury; burn injuries are responsible for approximately 2500 deaths in the pediatric population annually.

Scald burns are the main culprit in children younger than 5 years of age. Flame burns are commonly seen in older children, especially in adolescents, who tend to experiment with fire and volatile agents.

Child abuse accounts for a significant cause of burns in the pediatric population. The following burn injuries should prompt suspicion of child abuse: injuries with bilateral symmetric distribution and/or a stocking glove distribution, injuries to the dorsum of the hands, or burns in patients whose medical care has been delayed.

II. Pathophysiology

Thermal injury produces coagulation necrosis of the epidermis and a varying depth of injury to the underlying tissue. Although the extent of burn
injury depends on the temperature, duration of exposure, skin thickness, tissue conductance and specific heat of the causative agent; a burn-induced inflammatory response that is not limited to the local burn wound is elicited. This can lead to a massive systemic release of inflammatory mediators inducing a significant burden on the respiratory, renal and gastrointestinal systems.

Infants and children have a relatively large body surface area (BSA) per unit of body weight than adults. This body surface area: body weight relationship is maintained until the child reaches approximately 15 years of age. The disproportionately thin skin in young children (<2 years old) accounts for full thickness injuries following heat exposure that would otherwise produce partial-thickness burns in older patients. For example, exposure to temperatures of 130°F (54°C) produces severe tissue destruction in just ten seconds in children whereas exposure to this temperature in adults requires 20 seconds to produce burn injury. Temperatures of 140°F (60°C), a common setting for home water heaters, can cause tissue destruction in 5 seconds or less. Full thickness burns are almost instantaneous with temperatures exceeding 170°F (77°C).

II. Initial Evaluation

All patients should be treated as trauma patients, following ATLS protocol. Patients must be removed from the thermal source of injury; those suffering
from chemical burns should be removed quickly from the causative chemical agent and the burns should be irrigated with copious amounts of water.

IV. Immediate Resuscitative Measures

A. Airway

Securing a patient’s airway should be a priority in any injured patient. Patients suspected of having inhalation injury should be admitted for close monitoring such as those trapped in a house fire with excessive smokes and fumes or those with facial burns, singed hairs and carbonaceous sputum. Inhalation injury, implicated in approximately 50% of all deaths from burn injury, has become one of the more frequent causes of death in this population. The pathophysiology of inhalation injuries arises from the thermal and chemical injury to the supraglottic region as well as tracheobronchial and parenchymal damage caused by the chemical and particulate constituents of smoke. This damage usually leads to sloughing of the airway mucosa, resulting in bleeding and formation of obstructing clots and casts. Suspect inhalation injury in patients presenting with evidence of respiratory distress (shortness of breath, hoarseness, wheezing, or carbonaceous sputum), abnormal mental status, or evidence of facial burns accompanied by signed nasal hairs/eyebrows or the presence of soot. These patients, more often than not, require intubation. The gold standard for diagnosing inhalation injury is fiberoptic bronchoscopy. Bedside bronchoscopic examination of the airway allows direct visualization of
the airway, identifying edema and inflammatory changes to the tracheal mucosa, such as hyperemia, mucosal ulceration and sloughing. It can also serve as an adjunct to intubation in situations where a difficult airway may be encountered such as patients with postburn facial and airway edema. In these cases, intubation with a transnasally inserted endotracheal tube is preferable. Please remember that the full extent of injury may not be evident until 12-24 hours after the initial insult. Another definitive method of diagnosing inhalation injury is Xenon 133 ($^{133}\text{Xe}$) scanning in which the radioactive tracer, $^{133}\text{Xe}$ is injected intravenously and exhaled from the lungs. Failure to clear the tracer in 90 seconds, or the segmental retention of it, is diagnostic of inhalation injury. However, this technique requires transport to the nuclear medicine suite in a patient who is already critically ill. Both of these techniques are more than ninety percent accurate in determining the presence of inhalation injury.

Carbon monoxide (CO) is a component of smoke that results from partial combustion of carbon-containing compounds such as cellulosics (wood, paper, coal, charcoal), natural gases (methane, butane, propane) and petroleum products. Carbon monoxide intoxication is a particularly serious consequence of smoke inhalation and has been implicated in up to 80% of fatalities. Any patient trapped in an enclosed space, or exhibiting neurologic symptoms, should have carbon monoxide levels measured in addition to concurrently receiving 100% oxygen with a tight-fitting mask for at least 4 hours. Symptoms of CO intoxication appear when the levels of carboxyhemoglobin exceed 15%; levels of 40-50% may be reached after only
two to three minutes of exposure. On the cellular level, CO impairs mitochondrial function and causes brain injury as the result of oxidative stress. The rationale for supplemental oxygen is to decrease the half-life of CO from 90 minutes on room air to 20-30 minutes with high flow oxygen. Although hyperbaric oxygen therapy (HBOT) clears CO beyond the clearance achieved using 100% oxygen, proponents primarily advocate its use for prevention of delayed neurocognitive syndrome. A Cochrane review performed on six randomized controlled trials exploring the effects of HBOT on CO poisoning suggested no benefit. Factors associated with an increased mortality in patients exhibiting CO poisoning are decreased level of consciousness of presentation, fire as a source of carbon monoxide, and elevated carboxyhemoglobin level on presentation.

B. Resuscitation

The first forty-eight hours of treating pediatric burn patients are the most critical due to the burn-induced hypovolemic shock these patients exhibit. The primary goal of fluid resuscitation in burn patients is to achieve adequate organ and tissue perfusion while trying to minimize soft tissue edema as a result of diffuse capillary leak. The Parkland formula (4mL x kg x %TBSA) is the resuscitation guideline most commonly used in the United States. However, many institutions utilize the Parkland formula for the first 24 hours then vary their resuscitation strategies in the second 24 hours. There is currently no consensus regarding the type of fluid, or formula to be used in pediatric burn
resuscitation. However, all would agree that prompt resuscitation is of utmost importance. Evidence shows that pediatric burn patients demonstrate a significant higher incidence of sepsis, renal failure, and mortality if fluid resuscitation is initiated ≥ 2 hours after the injury. The addition of maintenance fluids should not be neglected during the initial phase of resuscitation. In addition, patients with inhalation injury combined with cutaneous burns, have a greatly increased fluid resuscitation requirement during the first 48 hours. Resuscitation should be guided by endpoints, such as urine output. Patients weighing less than 30 kg, should make between 1-1.5 ml/kg/hr. Close monitoring of the urine output during the first several hours is extremely important. Proper attention to endpoint titration rather than adhering to rigid parameters will lead to better resuscitation. Ultimately, the response to fluid therapy will determine the rate and volume of fluid administration. Children have a greater BSA relative to their body weight. Weight-based formulas often under resuscitate children with minor burns and grossly over resuscitate children with extensive burns. Monitoring the trend of serum base deficit and lactic acid can also provide useful information regarding the generalized state of burn shock. The use of invasive monitoring is reserved for severe or refractory cases of resuscitation, where hemodynamic monitoring will provide further guidance. Most guidelines for the use of inotropic and hemodynamic support are based on the general sepsis and shock literature. Norepinephine or dobutamine are the preferred vasopressors for refractory hypotension. Dobutamine can provide inotropic support when the cardiac output remains low
despite fluid resuscitation. It is particularly useful in younger children who can develop a relative state of right-sided heart failure after receiving large volumes of fluid resuscitation.

The benefit of using colloids during the critical phase of burn resuscitation still remains unanswered. Although several trials have been performed, none have demonstrated superior long-term outcome with the use of colloids.

Over the past two decades, there has been an increasing tendency of using higher resuscitation volumes than those calculated which has the potential to lead to serious consequences such as abdominal compartment syndrome (ACS). ACS is defined as impairment in organ function due to increased abdominal pressures. Approximately, one percent of the general burn population, will develop ACS, this prevalence increase in patients with a TBSA > 70%. Although not thoroughly discussed in the pediatric literature, case reports suggest it happen at any point during resuscitation. Studies have shown that patients who receive excessive amounts of fluids (250-300 ml/kg) during the first 24 hours of injury are susceptible to increased abdominal compartment pressures. One should suspect ACS in patients with unexplained drops in urine output despite adequate resuscitation or patient with unexplained increases in peak inspiratory pressures (PIP). The patient can develop a distended abdomen, hypercarbia, and decreased cardiac output. A simple way to estimate intra-abdominal compartment pressure is by attaching a pressure monitor to the patient’s Foley catheter. Many agree that bladder
pressures ≥ than 25 mmHg should prompt consideration of aggressive intervention as elevated abdominal pressures can quickly lead to mortality if not promptly addressed. Two modalities that have been described to treat ACS is paracentesis or decompressive laparotomy. Mortality rates have been reported to be in the 50-60 percent range.

V. Wound Care

Appropriate wound care is generally determined by thoroughly assessing the burn depth and size. Superficial partial thickness burns can be treated with daily dressing changes with topical antimicrobial agents or application of petroleum gauze to facilitate rapid reepithelialization. These burns will usually heal within three weeks of injury without the need of surgical intervention. Several topical antimicrobial agents are available for the management of these burns. The most commonly used are silver sulfadiazine (Silvadene), mafenide acetate (Sulfamylon) and bacitracin/neomycin/ polymyxin B. Silvadene is known to have activity against a variety of organisms such as S. aureus, E. Coli, Klebsiella species, P. aeruginosa, Proteus species and C. albicans. Some of the reported side effects of its use are maculopapular rash, evident in 5% of patients and transient leukopenia, evident several days after initiating therapy, occurring in 5-15% of treated patients. This transient leukopenia has not led to an increase incidence of infection in these patients. Sulfamylon has antimicrobial activity against gram positive species, including Clostridium, and gram negatives organisms. However, it has limited activity against some
Staphylococci species and has minimal antifungal coverage. Unlike, Silvadene, mafenide acetate has excellent eschar coverage. However, because it is a potent carbonic anhydrase inhibitor, it can cause hyperchloremic metabolic acidosis with continuous use. This systemic toxicity as well as the pain it elicits on application has limited its use. Mafenide can penetrate cartilage.

Deeper partial thickness burns are unlikely to heal in less than 3 weeks without becoming hypertrophic and pruritic. Patients with deep partial or full thickness burns benefit from early excision and grafting usually defined as 1-7 days after injury. Early excision decreases the risk of local infection and subsequent systemic inflammation as well as decreasing the resting energy expenditure. Following a thermal insult, the affected skin becomes colonized with Gram positive organisms gradually followed by gram negative organisms. However, the mere presence of these organisms does not define an invasive burn wound infection. A quantitative culture yielding $> 10^5$ bacteria per gram of affected tissue and the histological verification of bacterial invasion into viable tissue constitute a localized burn wound infection. The decision to perform a split versus full thickness skin graft is mostly influenced by the size, depth and location of the burn. Split thickness skin grafts (STSG) function well in patients with moderate to large affected areas. The donor sites reepithelialize in ten to fourteen days allowing it to be used for additional grafting, if needed. However, STSG tend to contract significantly more than full-thickness skin grafts (FTSG)
making the latter optimal for smaller burns where functionality and cosmesis take precedence.

Patients suffering from large TBSA burns, usually ≥ 20%, also benefit from an aggressive surgical approach. These children tend to require serial trips to the operating room given the extent of injury. Although autograft is the substitute of choice in any thermal injury, patients with large burns will often require skin substitutes given the limited availability of non-burned skin. Skin substitutes can accelerate healing by allowing spontaneous reepithelialization. These can be biological or synthetic substitutes. Alloderm, an acellular dermal matrix derived from donated human skin, is an example of a biological dressing. Its dermal template allows it to become incorporated into the existing tissue, however, it requires the use of a thin skin graft. Proponents of Alloderm have observed a decreased length of stay and decreased donor site healing time.

Escharotomy

Burn patients may require escharatomies to relieve vascular compromise or ventilatory impairment. Full thickness circumferential burns to the extremities can produce constricting eschar that leads to edema, followed by vascular compromise (venous congestion and arterial insufficiency) prompting an escharotomy +/- fasciotomy. This compromise can produce pain, paresthesia, pallor and/or pulselessness, although these signs frequently are
late appearing. Circumferential, deep burns of the chest can lead to impaired respiratory function regardless of the presence of inhalation injury. The progressive edema that develops under the tightly affected skin impedes proper respiratory function leading to poor compliance, poor ventilation and an increase in peak inspiratory pressures. An chest wall escharotomy can be useful in these circumstances.

VI. Nutrition

Patients affected by thermal injury exhibit a hypermetabolic, hypercatabolic state that can result in severe loss of lean body mass. Children are more vulnerable to protein-calorie malnutrition, given their proportionally less body fat and smaller muscle mass. Patients affected by large burns experience an increase in energy expenditure and protein metabolism just a few days following the injury. This results in a negative nitrogen balance that can last as long as 9 months after the insult. Significant weight loss, muscle wasting, impaired immunity and delayed wound healing is evident. Prompt initiation of nutrition (within the first 24-48 hours) to counteract this catabolic state cannot be overemphasized. The enteral route is the preferred route when possible. Most children can tolerate continuous feeds with subsequent transition to bolus feeds. Patients who are intolerant of enteral feeds, will require total parenteral nutrition (TPN). Tight control of serum glucose is required given the predisposition of a hyperglycemic state after the injury. Most
affected children will have a protein requirement of approximately 2.5g/kg/day with caloric needs close to 1.5 times the calculated basal metabolic rate.

Children suffering from major burns should receiving vitamin supplementation in the form of a multivitamin, in addition to vitamin C, vitamin A and zinc sulfate to ensure adequate wound healing. In select patients, provision of adequate calories and nitrogen fails to arrest the hypermetabolism prompting the use of pharmacologic adjuncts to aid in halting this hypercatabolic state. One such adjunct is oxandrolone, a synthetic derivative of testosterone, which has shown to increase protein synthesis and decrease loss of lean body mass. Its use has been shown to be beneficial in expediting recovery in children in both the acute and recovery burn phases.

Another useful agent in pediatric burns is propanolol, a nonselective beta blocking agent. Beta blockade in severely burned children diminishes supraphysiologic thermogenesis, tachycardia, myocardial oxygen demand and resting energy expenditure. This decrease in the hypermetabolic response lessens the deleterious effect of muscle catabolism.

VII. Cold Injuries

Exposure to cold temperatures can also lead to tissue injury, particularly in the extremities. The extent of injury is dependent on the temperature and duration of exposure. Management consists of rapid rewarming and aggressive wound care with debridement of nonviable tissue to minimize systemic effects. Debridement should not be done with the same immediacy
as burn wounds. The surgeon should allow the wounds to be definitely necrotic and non-salvageable.

VIII. Chemical burns

Children usually suffer chemical burn injuries when coming into contact with strong acids or alkalis such as household solvents. Alkaline agents cause liquefactive necrosis making them more harmful than acids due to deeper tissue penetration. Initial management consists of copious irrigation with water, for approximately 20 minutes, to dilute the agent. Certain agents containing calcium oxide (lime) should be dusted off the patient prior to irrigating with water to prevent further damage caused by the resultant calcium hydroxide. Chemical burns tend to appear superficial immediately after the injury, however, are more likely to be deep partial or full thickness injuries.

A highly corrosive agent with a specific antidote is hydrofluoric acid. It causes tissue destruction by the combination of its fluoride ions with calcium and magnesium inhibiting cellular metabolism. Treatment consists of application of calcium gluconate gel to the affected area, direct injection of calcium gluconate to the burn or-intra-arterial infusion of calcium ions into vessels perfusing the injured area. Pain cessation is a good indicator of successful treatment. Patients with extensive damage caused by hydrofluoric acid should be closely monitored in the ICU given the potential of severe
hypocalcemia; at times these patients require urgent surgical excision of the affected area to decrease systemic toxicity.

IX. Transfer Criteria

Certain patients will require extensive multidisciplinary burn support and are better served at a designated Pediatric Burn Center. These patients are usually infants and children with third degree burns, patients with burns to the face, feet, genitalia or perineum, children with inhalation, electric or chemical injuries and those with > 10% TBSA burns.

References:


I. NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis ( NEC ) is bacterial infection of the intestine in a neonate, its involvement vary from a limited segment of intestine to “ NEC totalis”, including all of the midgut and colon. It is a major cause of morbidity & mortality among premature infants, especially those with a birth weight ≤ 1500 grams. It is seen in infants who have received enteral feeds. Major risk factors include prematurity, use of indomethacin, presence of UAC, UVC, enteral feeds, intrapartum cocaine exposure.

Symptoms may occur suddenly or insidiously. Early symptoms may include delayed gastric emptying (gastric residuals, bilious residuals). Other symptoms include abdominal distention. Signs on examination include abdominal tenderness, abdominal discoloration. Lab data may include thrombocytopenia, acidosis, glucose instability.

NEC Stages
(Walsh & Kliegman’s modification of Bell’s Criteria)

Stage I (suspect NEC)
Suggestive clinical signs & symptoms but radiographs non-diagnostic

Stage II (definite NEC)
Abdominal X-ray findings of pneumatosis, plus
Stage IIA: mildly ill, or
Stage IIB: moderately ill with systemic toxicity including acidosis, thrombocytopenia, or ascites

Stage III (advanced NEC)
Critically ill with
Stage IIIA: impending intestinal perforation
Stage IIIB: proven intestinal perforation

When evaluating a patient with NEC, look for these conditions

1. History: EGA, history of enteral feeds, PDA, UVC, UAC, indomethacin administration.

2. Exam: VS (tachycardia, bradycardia, hypotension), abdominal tenderness, abdominal discoloration. Note that abdominal discoloration may be an ominous sign for intestinal necrosis.

3. Lab work: Platelet count, ABG

4. KUB: 2 views of abdomen are necessary to thoroughly evaluate abdomen for free air.
Findings may include:

   Fixed, dilated loop of bowel

   Pneumatosis intestinalis
   Sub-mucosal: bubbly
   Sub-serosal: linear

   Portal venous gas

   Free air in abdomen
   Classically above liver on LLD view
   May see round lucency over mid-abdomen on KUB ("football sign")
   Outlined falciform ligament on Xray indicates free air
Recommendations for management may include:

- NPO for 7-14d
- Ampicillin, Gentamicin, and Flagyl for 7-14d
- Considere prophylactic antifungal (Fluconazole)
- Repogle to low intermittent suction to decompress the abdomen
- Q 6-8 hr 2-view abdominal X-rays (esp. during 1st 24 hrs of diagnosis).
- Monitor CV status and blood gases IVF/volume expanders
- Consider NIRS

Operative intervention is necessary if there is free air on Xray, (maybe) abdominal discoloration, fixed loop of intestine on several X-rays, clinical deterioration/non-improvement.

To drain or not to drain? The type of operation performed for perforated necrotizing enterocolitis does not influence survival or other clinically important early outcomes in preterm infants. (ClinicalTrials.gov, NCT00252681.), Moss et al NEJM
II. GI HEMORRHAGE

GI hemorrhage is relatively rare in the NICU population. An essential part of the initial work-up is to send the blood from the GI tract for an Apt test to determine the presence/absence of maternal blood.

When consulted, differentiate between upper and lower GI hemorrhage. Blood per rectum can definitely be from upper GI source. Upper GI causes include gastritis, swallowed maternal blood, iatrogenic cause (OG tube, suctioning trauma). Lower GI bleed etiologies include NEC, anorectal fissures.

Management recommendations include: OG tube, CBC, abdominal Xrays, PPI. Mostly supportive therapy, APT test.

III. ABDOMINAL MASSES

Nearly 50% of neonatal abdominal masses are of renal origin. Other masses in the newborn include neuroblastoma, hepatoblastoma, proximal intestinal atresia, intrauterine intestinal perforation. In addition to physical exam, check BP, UA, BUN, creatinine, ultrasound. Then proceed as dictated by these tests to CT, MRI and/or appropriate consultation.
### Diffuse
- Multicystic kidney
- Hydroureter
- Mesoblastic nephroma
- Neuroblastoma

### Midabdominal
- Mesenteric cyst
- Duplication of intestine

### Upper abdominal
- Liver tumor
- Choledochal cyst
- Subcapsular hematoma of liver

### Lower abdominal
- Bladder
- Sacrococcygeal teratoma
- Anterior meningocele

### IV. CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Congenital diaphragmatic hernia is one of the most complex neonatal conditions encountered in contemporary neonatal and pediatric surgical practice. Each hemidiaphragm has four leaflets that come together embryologically to create a whole. The left hemidiaphragm is most commonly involved with the posterolateral aspect being the area of deficiency.
Posterolateral diaphragmatic defects are called Bochdalek hernias. Anteromedial defects, which are less common, are eponomously called Morgagni hernias. Posterolateral hernias are usually associated with the more physiologic challenges.

During fetal development, both hollow and solid organ compression on the developing lung can result in anatomic changes. First, there is less segmental bronchi and alveolar units in the contralateral lung. The media of the pulmonary arteries are much thicker compared to “normal” pulmonary arteries. There is usually mediastinal shift. In a baby with CDH, the uninvolved lung still has these changes compared to the "normal" baby.

Currently, babies with CDH are prenatally diagnosed. Babies are recommended to be delivered in a facility that has capability to provide full cardiorespiratory support including ECMO. In the delivery room, there is a variable respiratory distress. The abdomen may be scaphoid. Other signs include bowel sounds are in the chest, with decreased or absent breath sounds on the affected side.

In the delivery room, the baby may require small amount of oxygen by nasal cannula or, more often, intubated. An orogastric tube should be placed to decompress the air collected in the stomach.
Physical findings may include decreased or absent breath sounds on the affected side, a scaphoid or flat abdomen, shift of the cardia PMI.

Recent literature have described prenatal anatomic parameters that predict a baby who may have difficulty with pulmonary hypertension. These include having an intrathoracic stomach and/or liver. In a left sided CDH baby, having a lung/head ratio (taken at EGA 24-26 weeks) predicts usually associated with a larger diaphragmatic defect and a smaller lung (sicker baby).

Babies with CDH vary from those who do not require O2 to those who require significant help with regard to oxygenation, ventilation, and even cardiac support. The main reason for the physiologic problems of a baby with CDH stem from increased pulmonary vascular resistance and pulmonary hypertension. The media layer of the pulmonary arteries in a baby with CDH contain more smooth muscle cells that are comparatively larger in size than those of a baby without CDH. These cells are also more sensitive than normal to factors that cause vasoconstriction, namely, hypoxia, academia, and hypercarbia. As previously mentioned, the lungs of babies with CDH has a decreased cross sectional arterial surface area due to the smaller number of branching seen with lung units. Cardiac dysfunction from hypoxia, ventricular hypoplasia, or right heart dysfuction may increase pulmonary venous pressure and PVR.
Poor oxygenation results from a combination of alveolar hypoventilation, pulmonary hypoperfusion and potential lack of surfactant.

Management

Early recognition followed by aggressive proactive management is crucial to outcome.

Antenatal management: Diagnosis by prenatal ultrasound educates the parents when planning for delivery at an experienced center. In general, the earlier in gestation CDH is diagnosed, the worse the prognosis. Also right-sided lesions tend to be worse than left sided lesions.

Several attempts have been made to correlate prenatal imaging with postnatal outcome. The lung-to-head ratio (LHR) was first described in 1996 correlates a two dimensional lung size in a fetus in relation to a growth standard such as the head circumference. The LHR is measured at 24-26 weeks in a left sided CDH baby.

The lung area contralateral to the CDH was originally obtained by taking the product of the longest two perpendicular linear measurements of the lung measured at the level of the 4-chamber view of the heart on a transverse scan of the fetal thorax. The product is divided by the head circumference (HC) to obtain the LHR.

- If the LHR is 1 or less, the prognosis is poor. The prognosis is poorer still if the liver is in the thorax. Such patients may be candidates for prenatal intervention. (The University of California, San Francisco, http://fetus.ucsfmedicalcenter.org/cdh/)
- If the LHR is between 1.0 to 1.4, ECMO is often needed.
• If the LHR is greater than 1.4, the prognosis is better

More recently, MRI and three dimensional ultrasound has been used to calculate three dimensional volumes in fetal CDH.

Liver position (intrathoracic vs intraabdominal has also been described as a measure of severity. Polyhydramnios has been variably predictable of poor outcome.

Delivery room management: Adequate oxygenation and ventilation must be established quickly and efficiently while preventing large volumes of air from entering the stomach & bowel. Bag and mask resuscitation must be avoided unless in respiratory distress; and therefore prompt intubation is indicated. Placement of OG tube to decompress the bowel needs to be done during the resuscitation period.

NICU Management of CDH

• Placement of umbilical arterial and venous lines for continuous BP monitoring and access for possible vasopressor therapy

• Urine output should be closely monitored as an index of organ perfusion

• Adequate sedation; paralysis if necessary

• Echocardiogram: R/O congenital heart disease, assess for ventricular function and PPHN; also a pre-ECMO evaluation

• Head U/S: R/O intracranial hemorrhage is a “pre-ECMO” criteria
• Pre and postductal O2 saturation monitoring
• QUIET ENVIROMENT
• If patient has hypoxia, consider increasing FiO2, adjusting PEEP.
• Consider starting inhaled nitric oxide to decrease pulmonary vascular resistance.
• HFOV can be used for both hypercarbia and hypoxia.
• If all therapy fails, consider ECMO.

NOTE: As these infants are at significant risk for PFC/PPHN, please refer to PFC/PPHN section for further management details.

Postnatal physiologic measurements were validated to correlate with outcome. The CDH Study Group developed an equation for predicting survival based on birth weight and a 5-minute APGAR score. The Canadian Neonatal Network validated the SNAP-II score as predictive mortality in CDH

Surgical Correction

Operative repair is generally undertaken when infant is physiologically stable (NEAR extubatable vent settings) However, there are instances when this cannot be achieved. Some patients may actually have to be repaired on ECMO. Surgical correction does NOT generally change the physiology of PPHN.

In patients that are physiologically well, a minimally invasive approach (thoracoscopic or laparoscopic) can be attempted. In these patients, expect a high
pCO2 in the immediate post-operative period. This is due to the CO2 insufflation that is required for a minimally invasive approach. Slight hyperventilation (increased rate and TV) will rectify this within a few hours postoperatively.

In some patients, reduction of the viscera from the chest to the abdomen may cause abdominal compartment syndrome. These patients would require the viscera to be temporarily placed in a silo or for a silastic patch to be placed on the fascia. Abdominal closure can be achieved a few days later (usually after diuresis has been achieved).

Post-Operative

On return from the OR, obtain a chest X-ray to check ETT placement. An ABG to assess oxygenation and ventilation should be performed. Utilize the parameters. Maintain appropriate oxygenation and ventilation, as outlined in the PPHN section. Note that maintenance of ventricular filling pressures may result in increased fluid requirements. Inotropic support may be needed to maintain appropriate mean arterial blood pressure.

Potential Long Term Complications

Chronic lung disease

Feeding difficulties

Bowel obstruction

Recurrent herniation
Post Discharge Considerations

Developmental assessment in neonatal follow-up clinic

Chest X-ray q3 months during 1st year of life

Chest X-ray q6 months during 2nd year of life

Yearly chest X-ray thereafter until adult height reached &/or 18 years old

PRN chest X-ray/KUB for sudden respiratory distress or small bowel obstruction symptoms
V. ESOPHAGEAL ATRESIA (EA) WITH OR WITHOUT TRACHEOESOPHAGEAL FISTULA (TEF)

Esophageal atresia with or without tracheoesophageal fistula occurs in about 1 in 4500 births. EA/TEF can occur in associated with other anomalies, therefore in a child with EA/TEF these anomalies must be sought out. The cluster of anomalies often found with EA is termed VACTERL (acronym for the systems affected). In a baby with EA/TEF, Vertebral anomalies (baby gram), Anus, Imperforate (physical exam), Cardiac (ECHO), Tracheo-Esophageal, Renal anomalies (ultrasound), Limb anomalies (radial dysplasia) can be found. In addition, up to 7% of babies can have a tethered cord. No genetic association has been found.

EA/TEF is usually occurs sporadically, although familial cases have been reported.

Babies with EA/TEF may have antenatal history of maternal polyhydramnios. After birth, there are copious secretions, often w/coughing and choking. Intermittent cyanosis can be seen, as the baby may aspirate their oral secretions. If the baby was bagged during delivery, abdominal distention may be seen if a distal fistula is present. A definitive bedside test is the inability to pass an orogastric tube in the stomach.

Several anatomic types of EA and TEF occur. The most common is EA with distal TEF (85-87%). Isolated EA (aka “long gap” EA) occurs in 7% of cases. A fistula can occur connecting an intact trachea and esophagus (“H-type fistula”) occurs 4% of
the time. Because there is an intact esophagus, these children typically present days to weeks later after birth with symptoms of intermittent aspiration. The least common types are EA with a proximal fistula (1%) and EA with proximal & distal TEF (1%).

In a child with pure EA or EA with proximal fistula only, NO air is seen in the stomach on a babygram. In a patient EA with distal TEF or a proximal and distal (double) fistula, inhaled air goes through the fistula and gets into the GI tract; there is presence of air in stomach. In a patient with H-type fistula, there is usually a delay in diagnosis, since the baby is often able to tolerate some feeds. The clinical scenario is a baby with episodic aspirations sometimes associated with apnea. To rule out an H type fistula a CAREFUL esophragram with an experienced pediatric radiologist is usually needed. Alternatively or in addition, a bronchoscopy would also show the fistula.

Preoperative Management

Position upright at 30-45 degree angle
Intubation, if necessary

Replogle suction to esophageal pouch
Evaluate for other anomalies

Respiratory support
VATER/VACTERL

Suction airway as needed

A Replogle tube is different from a regular Salem sump tube. A Replogle only has holes in the distal 1-2 cm, accommodating the length of the esophageal pouch in a newborn. A regular Salem sump has holes along a longer length. If a Salem sump were to be
used instead of a Replogle in a baby with EA, the suction can potentially entrain air and/or oxygen that the baby has in the pharynx.

Work-Up

- Chest X-ray and KUB
- Cardiac ECHO -- visualize cardiac anomalies and the side of the aortic arch & descending aorta. This determines the side of the thoracotomy for surgical repair.
- Renal ultrasound
- Spine ultrasound or Spine MRI at 3-6 months (modality depends on the institution)

The overall prognosis is function of preoperative weight and presence of anomalies. In a full term and no anomalies, there is nearly 100% survival. If the birthweight < 1.5 kg and anomalies, there is about 50% survival.

Surgical Repair of Esophageal Atresia with Distal TEF

A primary repair of the TEF is considered if the child weighs greater than 1.5 kg, with minimal respiratory compromise and no life threatening anomalies. Consideration for a delay in fistula ligation and esophageal repair is given until the child reaches a weight of at least 1.8-2 kg. In patients where delayed repair is considered, a gastrostomy tube may help decompress the stomach, drain gastric secretions and decrease aspiration of gastric contents into the lung. While waiting for weight gain, the child would require suction of the esophageal pouch and parenteral nutrition. Some
literature exists on the advantages of ligating. If the fistula is not ligated initially, attention must be paid to how much of positive pressure breaths are transmitted into the G tube. The tube may need to be placed under water pressure to force the positive pressure breath into the lungs.

There are some case series that advocate a staged approach to EA/TEF repair in very low birth weight infants <1.5 kg (CHLA). These infants would get their tracheoesophageal fistulas ligated prior to the definitive esophagoesophagostomy. Fistula ligation would decrease the contamination of the respiratory tract from the stomach. These patients can be enterally fed into their stomach if a G tube is placed.

The typical repair consists of a posterolateral thoracotomy on side opposite aortic arch. The fistula is identified, divided and repaired on the trachea side. The proximal esophagus is identified and an esophagoesophagostomy

Surgical Repair/Management of Isolated EA

Typically isolated EA has very long gap (defined as > 2 vertebral body gap between the proximal and distal pouches. We wait 6-12 weeks to attempt to repair these babies in order to achieve primary esophageal anastomosis. While waiting a G tube is placed in these babies to feed them enterally. Bolus feeds are given to the babies in temporal synchrony with oral stimulation, to train them into associating feeding with feelings of satiety. Bolus feedings also enlarge the stomach, and potentially distends and elongates the distal esophageal remnant.

The repair
Esophago-esophagostomy is preferred (may be tight).

If unable to do so, consider gastric or colonic transposition.

If unable to achieve primary esophageal continuity and reluctant to do primary esophageal replacement, cervical esophagostomy can be performed. The proximal esophageal pouch brought out on left neck allowing salivary secretions to drain and not be aspirated into the lungs. An esophagostomy automatically buys an eventual esophageal replacement with stomach or colon.

Surgical Repair of H-Type TEF

H type TEF’s are usually higher than those associated with esophageal atresia. These are not repaired through a thoracotomy. The operation starts with a rigid bronchoscopy to identify the fistula. A Fogarty balloon catheter is inserted into fistula and passed into the esophagus. The balloon is inflated. An esophagoscopy usually is done to confirm catheter placement. The fistula ligation is usually done via a low right cervical approach

Postoperative care

A CXR is done post-operatively to assess the lung fields and document the placement of the chest drain, epidural catheter, and endotracheal tube when applicable. The ETT tube should have the tip well above the carina. Manipulation of he ETT is kept at a minimum.

The post operative care is usually straightforward. If needed, assisted ventilation is provided. Reintubation and ETT manipulation must be done with extreme care, after
discussion with attending SURGEON AND NEONATOLOGIST. The most experienced person should intubate these babies since repeated intubations can damage either the tracheal or esophageal repair.

When suctioning of salivary secretions is needed, the tip of the catheter should only reach the posterior pharynx proximal to esophageal anastamosis (shallow suctioning). Similarly, tracheal suctioning should not go beyond the end of the ETT.

The head of bed is at 45 degree angle to promote drainage of salivary secretions. Some surgeons prefer the patient’s neck to be slightly flexed to decrease the tension on the anastomosis. Other maneuvers to decrease the tension on the anastomosis include mechanical ventilation for 3-5 days, with chin-to-chest position. Notably, there are no data to support that these actually promote anastomotic healing.

A chest tube or chest drain is typically left during the procedure. There is usually no injury to the lung and, therefore, no “air leak” is seen. The tip of the drain is placed adjacent to the esophageal anastomosis. The drain is left in place until there is fluoroscopic confirmation that the anastomosis is intact and there is no leak.

Prophylactic antibiotics (24 hrs) are given.

Parenteral nutrition is administered. Alternatively, a small orogastric feeding tube can be passed at the time of the operation, and low volume feedings into the stomach. can be initiated prior to the contrast esophagram

Contrast esophagram at 7-10d post-op to rule out leak. If no leak is seen, the baby is started on oral feeding. The chest drain is removed. If a leak is seen, feeds are held until another contrast esophagram documents an intact anastomosis (usually 7 days
later). If the baby shows discoordinated oral motor skills, he or she may need evaluation by speech therapy

Evaluation for other anomalies should be completed.

Complications

Anastomotic leaks are usually seen in 30-70% of esophageal repairs. The wider the gap between the upper and lower esophagus portends higher leak rates. Leaks are documented during esophagrams scheduled at a predetermined time after repair. Majority are small, sub-clinical, and resolve with time. In contrast, anastomotic disruptions are symptomatic and present with pneumothorax and/or hydrothorax. The leak from the anastomosis is large enough that the thoracic drain cannot handle the salivary secretions and swallowed air. It requires surgery to make certain that the area is adequately drained, and the lung is able to inflate fully. An attempt at re-doing the repair is usually not done, since the tissues are often friable and contaminated. Any leaks associated with esophageal anastomosis increases the likelihood of a stricture.

Esophageal strictures are usually seen 2-6 weeks post-operatively and present with inability to handle secretions, apnea/bradycardia episodes (from oropharyngeal aspirations). The causes of strictures are multifactorial and may include anastomotic tension, local vascular insufficiency, and tissue fragility leading to leak. Gastroesophageal reflux which is commonly seen in babies who have TEF/EA can also contrite to stricture. Balloon dilation is the current standard of care and may be required several times.
Recurrent TEF occur seldomly. Surgeons attempt to put intervening tissue or graft(Surgisys) between the tracheal repair and the esophageal anastomosis to prevent this complication.

Children with TEF can have varying degrees of airway compromise due to tracheomalacia or laryngomalacia. Tracheomalacia is one of the differential diagnoses in children with apnea and bradycardia episodes after definitive surgery. (Other etiologies include sever GER with reflux and bronchospasm, recurrent TEF, laryngotracheal clefts, undiagnosed cardiac anomalies. A rigid bronchoscopy in a spontaneously breathing child is required to make the diagnosis of tracheomalacia; the posterior trachea coapts with the anterior trachea during expiration. If tracheomalacia is severe, an aortopexy (aorta is pexed to the underside of the sternum) may be necessary.

Gastroesophageal reflux is seen in most TEF/EA patients. It is hypothesized that the distal esophageal dissection added to the cephalad pull on the distal esophagus straightens out the gastroesophageal junction, leading to increased reflux in this population. If reflux leads to recurrent aspiration pneumonias, significant apnea, emesis leading to failure to thrive, repeated episodes of anastomotic stricture, a fundoplictaion may be necessary.
VI. GASTROSCHISIS

Gastroshisis is congenital defect of the anterior abdominal wall characterized by herniation of a variable amount of uncovered intestine. The liver is normally positioned. The defect is usually on to the right of the umbilical cord. It is thought that this may be due to the natural disappearance of the right umbilical vein during the course of fetal development.

Incidence of gastroschisis is about 1 in 3,000-8,000 live births. Associated anomalies are rare except for intestinal atresia (10-15%) of cases

Risk factors include maternal use of tobacco, salicylates, pseudoephedrine, or phenylpropanolamines during the first trimester. Maternal young age is also a risk factor.

Gastroschisis is NOT a contraindication to vaginal delivery.

Management in the Delivery Room

In the delivery room, an airway if infant in respiratory distress. The intestines should be handled gently making sure that the mesentery is straight. The bowel is placed on top of abdomen without tension to avoid impediment to venous drainage and to avoid inducing bowel edema and injury. Consider putting the baby on the side. The baby should be have his legs placed in a plastic bag (bowel bag) or if this is not
available, the bowel should be carefully wrapped in warm saline-soaked gauze. An OG tube for gastric decompression should be placed.

Management in the NICU

If the baby is transferred to the NICU and not directly to the OR, vascular access should be established. Gastrochisis babies tend to lose a lot of fluid. Therefore, a 20 cc/kg NS bolus; 1.5 maintenance D10W. Intravenous antibiotics such as ampicillin and gentamicin are given. The baby’s position should be optimize position of baby (see above)

Operative Decision Making

In some institutions, the decision whether a primary fascial closure versus a silo closure is performed is determined in the operating room. In this case, the baby should be brought to the OR ASAP: the longer the bowel is out, the more edematous it gets and more difficult to achieve primary abdominal wall closure.

In the OR, the baby is anesthetized. The intestines are cleaned and slowly replaced in the peritoneal cavity. The decision whether the abdominal wall is closed or a silo is placed depends upon the physiologic ramifications of having the intestines inside. In the OR, the intestines are placed in the abdominal cavity. Anesthesia and surgery look at the ventilating pressures, BP, somatic NIRS, lower extremity pulses to assess whether there is a prohibitive increase in the abdominal pressure. If the baby cannot be oxygenated or ventilated (too much “push” on the diaphragm), BP decreases
(decreased preload due to caval compression), dampened pulse tracings of the lower extremities, decreased somatic NIRS, the baby is re-eviscerated and a silo is placed.

In other institutions, all babies with gastroschisis get a silo placed over the intestines while in the NICU. This practice commits all babies with gastroschisis to a staged closure. It makes operative closure an elective procedure.

Post-operative Management:

Primary Abdominal Closure: The baby is extubated as soon as possible. A PICC line is placed so TPN can be started. It takes several weeks (mean 21 days) for GI tract to work. Enteral feeds are slowly started, since up to 30% of gastroschisis babies can develop NEC.

Silo Closure: The baby remains intubated usually. Serial reduction of abdominal contents occur over several days (start on POD 2). The baby requires sedation and pain medication about 15 minutes before the reduction. The baby’s ventilator settings may need to be temporarily increased during the reduction due to the sedation and increased abdominal pressure. The reduction is done under sterile conditions. Apply gentle pressure on the intestines, pushing the intestines about 2-3 cm during each reduction. Tie with an umbilical tape. Keep the silo vertical by securing the bag with another umbilical tape to the top of the bed. Apply iodine ointment along the base and wrap with sterile Kerlix.

The nurses weigh the dressings. If there is significant fluid loss, it is replaced.
A PICC line is placed. TPN is started. Ampicillin and Gentamycin continue while a silo is in place. Final closure is usually achieved 7-10 days after the silo is initially placed.

VII. OMPHALOCELE

An omphalocele is a congenital defect of the anterior abdominal wall characterized by herniation of varying amounts of uncovered viscera (including liver) into an avascular sac consisting of fused amnion and peritoneum. If a “giant” omphalocoele (>5 cm), C-section is warranted.

Incidence of omphalocoele is ~ 1 in 6,000-10,000 live births

Like gastroschisis, omphalocoeles are now most commonly diagnosed prenatally. Unlike gastroschisis, the defect is contained within umbilical cord, unless ruptured. Even in small sized omphalocoeles, the bowel is nonrotated. In the large omphalocoeles, there usually is a globular liver within the sac.

Associated anomalies seen in at least 50% of cases: These include

Cardiac
Tetralogy of Fallot, VSD
PS, coarctation, AV canal

Neurological
Genitourinary
Imperforate anus
Management in the Delivery Room

Establish an airway if infant in respiratory distress. Place an orogastric tube for gastric decompression. If the sac is not ruptured, carefully wrap herniated viscera in warm saline-soaked Kerlix. BE CAREFUL NOT TO DISRUPT AN INTACT SAC.

If a ruptured omphalocele is present, the initial management is similar to gastroschisis. Place the baby feet first into a “bowel bag” and tie the bag loosely around the axilla. BE VERY CAREFUL NOT TO INJURE THE LIVER, since this can cause significant and potentially fatal (in preemies) bleeding.

Management in the NICU

In the NICU, vascular access is established. The baby’s fluid status should be monitored. A sepsis work-up should be considered, especially in ruptured omphalocele patients. Administration of intravenous antibiotics such as ampicillin and gentamycin should be considered.
Work-up for associated anomalies must still be performed. This should include a cardiac echocardiogram, renal ultrasound, and chromosomal studies.

Operative Considerations

If the defect is small (3cm or less), primary closure can be achieved easily. Consider getting an Upper GI study to define whether the baby’s mesentery is narrow and therefore whether volvulus is likely.

Giant omphalocoeles cannot be closed primarily in the newborn period. Keeping the omphalocoele intact creates a biologic dressing much better than artificial dressings such as PTFE. The omphalocoele membrane is 'scarified" by application of ¼ strength betadine paint (mixed with saline) here in CHW. Other hospitals may use silavadene. The dressing is changed daily. The membrane hardens and epithelializes. Closure is done in one or several stage(s) when the baby is one year of age. A Ladd’s procedure is done at this time, if the baby has no feeding problems. The baby with giant omphalocoele is often able to breathe without support and eat without any problems. REMEMBER that omphalocoele babies all have malrotation, so feeding problems should be seriously considered –ie. Upper GI to rule out volvulus.

If an omphalocele is closed in the early newborn period, specific attention should be paid when the globular liver is placed in the abdomen. The hepatic veins are longer than normal in these patients and replacement of the liver in the abdomen can kink these veins causing hemodynamic compromise. This can occur in the operating room or hours after the operation. In addition, replacing all the viscera in the abdomen (with or without a patch) can cause an abdominal compartment syndrome to develop. This
manifests in decrease urine output and acidosis. Vigilance should be exercised in monitoring these patients post-operatively.
VIII. INTESTINAL ATRESIAS

The most common cause of neonatal intestinal obstruction is intestinal atresias and stenosis. Atresia is complete obstruction of lumen of the intestine, and stenosis refers to incomplete obstruction of the lumen. The most common intestinal atresia (in decreasing order of frequency) are duodenal, ileal, jejunal. Colonic atresia is very rare.

Incidence 1 in 2710 live births (equal sex distribution)

Clinical Presentation

Infants with intestinal atresias are often diagnosed prenatally. After birth, they can have abdominal distention and vomiting. Babies with colonic atresia can present with perforation and/or such significant abdominal distension to require ventilatory support.

The differential diagnosis of babies with a bilious vomiting include causes of intestinal obstruction such as malrotation with or without volvulus, intestinal duplication, meconium ileus, Hirschprung disease.

Radiological Presentation

On prenatal ultrasound, findings may include polyhydramnios or dilated, “echogenic” bowel. Postnatally, duodenal atresias often show a double bubble sign (air in the stomach and in the proximal duodenum). Small bowel atresias show dilated (air filled proximal intestine). If a distal contrast enema is done, there is often a microcolon. If peritoneal calcifications are seen, there is likely an in utero perforation.
Classification

Type 1: membranous atresia with intact mesentery

Type 2: blind end with intact mesentery

Type 3a: blind end with defect in mesentery

Type 3b: “apple peel” or “Christmas tree” appearance of bowel as it corkscrews around blood vessel

Type 4: multiple atresias

Duodenal Atresia

Duodenal atresias are thought to be due to failure of canalization of the duodenal lumen. Obstruction of the duodenum may be due to a number of causes. There could be a complete disconnection with blind ending segments of the duodenum. There could be a complete membrane in the duodenal lumen (Type 1) or a perforated membrane (“windsock anomaly”). 85% of duodenal atresias are distal to the ampulla of Vater. Other causes of duodenal obstruction in a newborn include annular pancreas, preduodenal portal vein. Notably, malrotation with volvulus can also cause duodenal obstruction. If the initial KUB shows a “double bubble sign” (air in the stomach and proximal duodenum) and scattered gas pockets distally, malrotation with volvulus should be ruled out (upper GI series).

The presence of an annular pancreas or preduodenal portal vein may not cause an obstruction that is clinically significant. If there is an obstruction at level, it is bypassed with a duodenoduodenostomy. If these congenital anomalies are present,
one should look rule out the presence of asplenia/polysplenia or biliary atresia at the time of exploration.

Trisomy 21 is seen in 30% of patients with duodenal atresia. As such, when duodenal atresia is seen in patients with Trisomy 21, anomalies that are associated with Trisomy 21 should be ruled out (including cardiac defects—AV canal—and Hirschprung disease.

Jejunal/ Ileal Atresia

The pathogenesis of jejunoileal atresias is thought to be due to vascular insufficiency of an intestinal segment. Ileal atresia is the most common intestinal atresia. Jejunoileal atresias may be seen in 15% of gastroschisis patients. Atresias may also be seen in patients with meconium ileus. Multiple atresias may occur. Small intestinal atresias may give rise to small bowel syndrome.

Colon Atresia

Colon atresias may be associated with Hirschprung disease (2%). The atretic segment is typically located in the hepatic flexure. A suction rectal biopsy should be performed before gastrointestinal continuity is re-established in patients with colon atresias.

Management of Atresias
Pre-operatively, an OG tube should be placed for decompression. Fluid losses are replaced. Evaluation for other anomalies should be done as necessary. Prophylactic antibiotics should be administered, but should be discontinued within 24 hours.

Surgical repair for duodenal atresias usually entail an anastomosis between the bowel proximal and distal to the obstruction. If a web is involved, care is taken not to harm the ampulla, since the ampulla can be involved in the web. The ampulla is usually located in the posteromedial aspect of the web.

For jejunal and ileal atresia, resection of the dilated segment and reanastomosis is performed. With all atresias, ruling out the presence of other atresias is mandatory. If only a limited length of intestine is present, the surgeon would refrain from resecting any intestine. An intestinal lengthening procedure (such as serial transverse enteroplasty) may be done in the future to increase intestinal length.

Post-operative management of patients with intestinal atresias typically involves awaiting intestinal function to resume and supporting the patient during this time. Ventilatory support is provided, if needed. Fluid losses from the stomach should be monitored and replaced as necessary. The baby is given parenteral nutrition until ileus resolves as evidenced by stool output and decreasing output from the OG tube. Foregut dysmotility takes at least 2-3 weeks’ time to resolve in duodenal atresia. Some centers start early trophic feeds in children with duodenal atresia after a contrast study documents no leakage through a patent anastomosis.
In patients with short gut (<40 cm of small intestine), one should monitor for malabsorption and diarrhea (reducing substances in stool). Patients who have required ileostomy may have difficulty absorbing sodium. Low systemic levels of sodium would lead to poor weight gain. Random urine sodium should be monitored when these patients are on full enteral feeds. If urine sodium is <5-10, supplemental sodium should be given.

Outcome and Potential Complications

Most patients with intestinal atresia do well. Predictably, those with a limited length of intestine may have issues relatable to short bowel syndrome. If the dilated segment is not resected, problems with motility in this segment may be seen. This functional intestinal obstruction leads to poor peristalsis, impaired digestion and absorption, as well as bacterial overgrowth.
IX. HIRSCHSPRUNG DISEASE (CONGENITAL AGANGLIONOSIS)

Hirschprung disease results from a congenital absence of intramuscular (Auerbach’s) and submucosal (Meissner’s) plexi or autonomic ganglionic cells in segment of intestine.

Peristalsis does not occur in affected segment, which leads to dilation with the passage of time.

The length of aganglionic segment is variable, but the most common location where the “transition zone” between normally innervated intestine to the aganglionotic segment is the rectosigmoid area (85%).

Hirschprung disease is associated with Trisomy 21. Most cases of Hirschprung disease are sporadic. However, familial cases are well-documented. The retprotooncogene has been associated with Hirschprung disease. If there is a family history, the patient may have long segment disease (transition zone above the rectosigmoid area)

Clinical Presentation

A baby with Hirschprung disease presents with abdominal distention and, sometimes, vomiting. A careful history usually elicits that the baby failed to pass meconium within 24 hours after birth.

Often, rectal stimulation with a digital rectal examination allows stool to pass.

Diagnosis
An abdominal X-ray usually shows evidence of distal obstruction in cases of rectosigmoid Hirschprung. A contrast enema would show differential width between the affected (spasm/narrowed) or normal (dilated) bowel. In neonates, there may not be a significant difference between these segments. It is also noted that there is delay in contrast elimination.

The gold standard in establishing the diagnosis of Hirschprung disease is suction rectal biopsy. At the bedside, 3 biopsies [2 lateral and one posterior—1 cm from anal verge] are obtained of the rectal submucosa to look for Meissner’s plexi.

Management

There are institutional differences in the approach to definitive management of Hirschprung disease. In some institutions, once the diagnosis is established, feeds are resumed and rectal irrigations are initiated every 4-6 hours to evacuate the rectum. The patient is sent home with irrigations and the operation “pullthrough” is performed in 4-8 weeks.

If the baby is not doing well with washouts, the pullthrough is performed earlier, or if there is long segment disease, an ileostomy is created.

More commonly, definitive treatment is performed prior to discharge. One of several abdominal-perineal pull-through techniques is performed. The principles of the operation is to definitively identify the level where the normal bowel transitions to the aganglionic segment. The abnormal segment is removed and the ganglionic proximal colon anastomosed to 1 cm above dentate line. This procedure can be
performed conventionally with a laparotomy, or using laparoscopic techniques. In cases of rectosigmoid Hirschprung, a wholly transanal approach can be used.

Total colonic aganglionosis w/small bowel involvement should be treated with ileostomy initially. Any patient with ileostomy has sodium loss. Check urine sodium. Patient may require oral sodium supplements to gain weight.

Complications

Hirschprung Associated Enterocolitis: Some babies may present initially with enterocolitis if the diagnosis of HD is missed within the first few day of life. These babies present with dehydration, lethargy, and distended abdomens. Other symptoms may include refusal to eat, fevers, and vomiting. In the newborns, enterocolitis is associated with no stool output. It is important to note that enterocolitis can be seen in patients who has had the definitive operation for Hirschprung. The presentation is the same as that of a newborn.

A digital rectal examination elicits a forceful evacuation of stool. Abdominal Xray would show intestinal distention and/or air-fluid levels.

Hirschprung associated enterocolitis can be a life-threatening event. When stool is not evacuated from the patient’s colon, enteric bacteria multiply under pressure within the intestine. Clostridium difficile can be seen in this setting. The patient can present in septic shock. The patient should be resuscitated. IV antibiotics should be administered (must cover enteric flora). The
patient is kept NPO. The most important part of therapy is frequent rectal irrigations to evacuate the colonic stool burden.

**Obstructive Symptoms:** Anastomoses can tighten as scars mature. Parents are taught to do dilations for a few months after surgery.

**X. ANORECTAL MALFORMATIONS (IMPERFORATE ANUS)**

Anorectal malfomations occur in 1 in 5,000 live births, occurring more commonly in males. There are no known association with maternal age, parity, race.

Lesions classified as low- or high-type imperforate anus based on position of end of rectum relative to the puborectalis muscle or levator sling.

Anorectal malforations are part of the VACTERL association. Work-up for the other components of VACTERL should be sought out.

**Clinical Presentation**

On physical exam, the lack of a normal anal opening is confirmed by the inability to insert a rectal thermometer. An anal opening that exists anterior to an imaginary line drawn between the two ischial tuberosities is anteriorly displaced.

Females more commonly have a low variant. The most common anomaly seen in a girl is a rectovestibular fistula, where the anal opening lies just inferior to the vaginal opening. The rectal opening can be seen on the perineum as well. Higher lesions (to the bladder neck and bladder) can exist, but occur less frequently.
Males are more at risk to have high lesions. The anal opening can be in the perineum, anywhere along the urethra, bladder neck, or bladder. Meconium staining along the scrotal raphe suggests a low lesion.

When examining a baby with an anorectal malformation, signs are elicited to see whether there is a low or high lesion. Signs of a low lesion include well-formed gluteal muscles, a “bucket handle” skin tag on the area where the anal opening would have been located, meconium “pearls” along the scrotal raphe.

Associated anomalies are more commonly seen in high lesions). Anorectal malformations are part of the VACTERL complex. As such, a work-up to rule out vertebral/rib anomalies, cardiac anomalies, tracheoesophageal fistula/esophageal atresia, genitourinary anomalies, and limb deformities should be initiated. A tethered spinal cord may be present. Anorectal malformations can also be part of more involved dysmorphic anomalies of the lower torso such as sacral regression syndrome, cloacal anomalies, and cloacal extrophy. These more severe malformations require a multidisciplinary approach.

Radiologic imaging would at least include ECHOcardiogram, CXR, renal ultrasound. Further work-up should be dictated by clinical findings.

Management
If the child has a distended abdomen, gastric decompression should be initiated. A female with a low lesion (rectoperineal fistula or vestibular fistula) through which meconium is freely expressed may be initially managed with daily dilations through the perineum. An anorectoplasty with or without a diverting colostomy may be formed 1-3 months later, when the sphincter muscle complex is mature. A male with a rectoperineal fistula within the anal complex may undergo an anoplasty, usually without the need for a diverting colostomy. If a child male or female) has a high lesion, a colostomy and a mucus fistula is performed in the newborn period, and the definite repair is performed months later.

Complications

Early complications are related to wound and colostomy issues. In the newborn population, stomas can have up to a 25-30% incidence of complication such as prolapse, retraction, and peristomal complications. Late complications are typically related to the lesions. Low ARM patients have an excellent chance at having continence, but are likely to have problems with constipation. High ARM patients have significant problems with continence and may require life-long measures (such as antegrade enemas) to achieve social continence.
XI. MALROTATION OF THE MIDGUT

In general, rotational anomalies are associated with any diaphragmatic or abdominal wall defect where abdominal contents are trapped outside the abdomen, and therefore preventing normal rotational development.

Malrotation occurs in 1 in 500 live births, 2/3 of patients present in newborn period. Up to 2/3 of neonates with malrotation may also have midgut volvulus.

Embryology

Stage 1: Herniation of midgut

Around 10 weeks of gestation, the midgut protrudes through vitelline sac into base of umbilical cord.

Stage 2: Return to abdomen

At 10-12 weeks gestation, midgut returns into abdominal cavity and in the process rotates 270 degrees counterclockwise around the superior mesenteric artery. Failure of this process may result in a rotational anomaly such as incomplete rotation (i.e. malrotation), paraduodenal hernia, or reversed rotation.

Stage 3: Fixation

After 12 weeks gestation, fixation occurs and continues until birth. Failure to fixate results in mobile cecum or retrocecal appendix.

Clinical Presentation
Malrotation may present as midgut volvulus, vomiting, or asymptomatic. Midgut volvulus can occur in anatomic configurations where the root of the mesentery is narrow. In the course of the regular peristalsis of the gut, the intestine twists in a clockwise fashion. Bilious vomiting is the classic presentation of volvulus, and as such, all babies with green or bright yellow emesis should have an urgent upper GI study. If a volvulus is diagnosed, this requires an EMERGENT EXPLORATORY LAPAROTOMY!

Vomiting may also occur due to abnormal adhesions from the retroperitoneum which can tether the duodenum, causing a partial obstruction. The surgical correction of Ladd’s bands is not as urgent as reduction of volvulus. Sometimes, malrotation is diagnosed from an upper GI series and is asymptomatic. A Ladd’s procedure is still required, but on a more elective basis.

Work-Up

Plain film of abdomen- distended, air-filled loops of bowel

Upper GI study- establish position of duodenal junction (Ligament of Treitz); rule out volvulus

Treatment: Timing of surgical intervention is dependent on the situation. Volvulus requires emergent laparotomy. Partial obstruction due to Ladd’s bands or asymptomatic rotational anomaly may be repaired on a more elective basis.

LADD’S PROCEDURE:

1. Right upper quadrant transverse incision.

2. If volvulized bowel, detorse in a counterclockwise manner until the mesentery is straight. Make sure that the anesthesiologist knows that the bowel is getting
detorsed since he may need fluid or inotropes after detorsing. If the bowel is compromised, wrap in warm and moist guaze and wait to see if it gets pink. If there is a focal segment of dead intestine, consider resection with primary anastomosis. If there is significant compromised bowel (i.e., resection may lead to short gut), consider temposrary closure and second look laparotomy in 24 hrs.

3. Lyse Ladd’s bands around the duodenum, around the mesentery.

4. Open and “widen” mesentery like a book.

5. Appendectomy

6. Replace the intestines in a configuration that keeps the base mesentery straight and wide (small bowel on the right side and colon the on the left side).

POST-OPERATIVE:

1. Extubate as tolerated.

2. If significant ileus is expected, consider PICC line and TPN.

3. Antibiotic therapy should be determined in the OR and communicated clearly with the NICU team.

4. Feeds are started when gut function returns.

XII. CYSTIC MALFORMATIONS OF THE LUNG

Presently, cystic malformations of the lung present as a fetal diagnosis. When a fetus is diagnosed with a thoracic mass, he or she may be considered for fetal
intervention if the following if hydrops fetalis is present. Hydrops is a sign of in utero cardiac failure due to the physiologic effects of the space occupying lesion in the thorax. On ultrasound, signs of hydrops include nuchal or scalp edema, pleural effusion, pericardial fluid, overall fetal edema. For congenital cystic airway malformations (CCAM), there is literature to support that administration of steroids while the fetus is in utero may shrink the lesion. Thoracoamniotic shunts have been used to drain the fluid within the fetal cyst to alleviate signs of hydrops.

Embryology

The classic embryology and histology of congenital cystic malformations of the lung is currently being challenged. In the past, CCAM’s, which may also be referred to as congenital pulmonary airway malformations (CPAM) were differentiated from sequestrations by the presence of systemic blood supply in the latter diagnosis. There was a school of thought that CCAM’s were truncated maldeveloped airways and pulmonary sequestrations are alveolar units that developed without airway connections. However, there is more evidence that these lesions often overlap. Bronchopulmonary sequestrations are classified as either intralobar and extralobar. Sequestrations consist of non-functional pulmonary tissue that does not directly communicate with the bronchial tree. Extralobar sequestrations are invested in their own plural membrane, while intralobar sequestrations are a lobe of the lung, usually the lower lobe. Extralobar and intralobar sequestrations have a systemic arterial blood supply. Venous return is through the systemic or pulmonary venous systems. The systemic vessels associated with extralobar sequestraions may be large, thin walled,
and extend below the diaphragm. The presence and location of these vessels should be identified by imaging preoperatively as inadvertent division of the vessel can result in its retraction of a vessel below the diaphragm and uncontrolled bleeding.

CCAM’s usually occur in the upper lobes of the lungs. Histologically, they are classified according to the size of the cysts within the lesion. Type I CCAM’s have large cysts, type III CCAM have dense small cysts, and type II cysts have a combination of both. CCAM’s may involve one or multiple lobes.

Congenital lobal overinflation (also known as congenital lobar emphysema) is a lesion that typically occurs in the upper lobes, more commonly the left. There is an anatomic defect in the lobar bronchus that does not allow complete emptying of the lobe during exhalation. Overinflation of the lobe can cause mediastinal shift and a tension pneumothorax physiology. These patients may require emergent thoracotomy and lobectomy after birth.

Associated anomalies: Extralobar sequestrations may be seen with a diaphragmatic hernia. 30% of extralobar sequestrations are associated with other anomalies such as cardiac and gastrointestinal anomalies. 10% of intralobar sequestrations may have a communication with the gastrointestinal tract. If a lung anomaly involves the right lower lobe, a Scimitar syndrome should be suspected. This involves anomalous pulmonary venous return into the heart. Depending on the anatomic variant, a baby may require a combined lung lobectomy and cardiac surgery or embolization of anomalous vessels prior to surgery.
Management

Some cystic lung lesions shrink or disappear during gestation. Perinatologists and fetal surgeons recommend that the child undergo postnatal CT or MRI to determine whether abnormal lung tissue still exists. Elective resection is recommended even for asymptomatic lesions. Abnormal lung tissue is a nidus for infection due to abnormal air drainage. In addition, cystic lung lesions and sequestrations have been associated with the development of tumors later in life.

A newborn born with a cystic malformation of the lung should be birthed in a facility that has immediate access to pediatric surgeons and possible ECMO. If a baby is asymptomatic (breathing normally, no tachypnea), a CXR should be performed to document anatomy. The baby should be observed for 24-48 hours to make certain that symptoms do not develop with feeding. Asymptomatic babies are sent home with a follow-up with a surgeon. Typically, imaging with MRI or CT scan is performed prior to the operation. Advanced imaging can identify systemic vascular supply and the precise anatomic lesion. The operation can be deferred for a few months if the baby remains without symptoms.

Symptomatic babies require immediate NICU transfer. If CLO is suspected, an emergent surgical consultation is made in preparation for possible thoractomy. Symptomatic babies with CCAM or sequestration would need an operation prior to discharge. Imaging with CT or MRI is usually required.
I. RESPIRATORY DISTRESS SYNDROME (RDS) & SURFACTANT ADMINISTRATION

RDS results from lack of active surfactant in lung alveoli. In premature infants, this is caused by the absence of mature type II cells. Antenatal steroids may be used to facilitate this maturation. In older infants with RDS, the lack of surfactant may be from a delay in maturation of type II cells as seen in infants born to diabetic mothers. Other causes of RDS stem from a relative lack of surfactant in alveoli such as inactivation from cytokines in infection (sepsis, pneumonia) or chemical inactivation (meconium aspiration). Production may also be impaired by hypothermia, hypovolemia, hypoxemia and acidosis.

Symptoms result from low lung volumes which lead to increased alveolar surface tension and collapse. This manifests as poor compliance, decreased FRC and worsening work of breathing. Clinically, infants have tachypnea, ↑ respiratory effort, hypoxemia, hypercapnia and/or respiratory failure. On CXR, air bronchograms and a “ground glass” appearance of the lung fields may be seen. However, these may also be found in TTN, aspiration syndromes and congenital pneumonia.
Antenatal steroids speed maturation of the lung, increasing surfactant production and decreasing the severity of RDS. The accepted treatment for RDS is surfactant therapy via endotracheal (ET) tube. Replacement/supplementation in the alveoli by commercially prepared surfactants via an endotracheal tube is the current method. In order to dose an infant with surfactant they must be intubated for at least a short time. Some infants may be rapidly extubated (“in and out dosing”). Most infants make surfactant by 3 days of life.

**Surfactant Preparations and Dosing Regimens**

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Preparation</th>
<th>Manufacturer</th>
<th>Dose Amount (ml/kg)</th>
<th>Interval (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survanta</td>
<td>Beractant</td>
<td></td>
<td>Bovine lung mince extract w/ added DPPC, tripalmitin &amp; palmitic acid</td>
<td>Abbott (USA)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Curosurf</td>
<td>Porcine</td>
<td>Surfactant</td>
<td>Porcine lung minced extract</td>
<td>Chiesi Pharm. (Italy)</td>
<td>1st:2.5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>subseq: 1.25</td>
<td></td>
</tr>
<tr>
<td>Infasurf</td>
<td>Calf lung</td>
<td>surfactant</td>
<td>Bovine lung wash</td>
<td>Forrest Pharm (USA)</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>extract</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Surfactant prophylaxis**
- Given to high-risk infants during resuscitation (10-30 minutes after birth)
- Pro: surfactant pool is established before lung damage occurs
- Con: unnecessary treatment?

**Surfactant treatment**
- Given to infants diagnosed with RDS (1-2 hours or even longer after birth)
- Pro: overtreatment is avoided
- Con: delay in treatment may allow lung inflammation and damage to occur

Versus
II. PATENT DUCTUS ARTERIOSUS (PDA)

PDA is the most commonly diagnosed cardiac condition in the NICU. It is often associated with prematurity &/or respiratory distress.

In the fetus, the ductus arteriosus is a direct connection between the main pulmonary artery and the descending aorta. From six weeks gestation to delivery, it is the main outlet of blood flow from the right ventricle allowing blood to bypass the fetal lungs. It carries ~60% of combined ventricular output. The ductus media contains primarily muscular cells in contrast to the aorta and pulmonary artery which are comprised of elastic tissues.

In term infants, the breath taken at birth opens the lungs and rapidly decreases pulmonary vascular resistance. Less blood is diverted from the lung increasing the PaO2.

Closure of PDA occurs in two stages. First, there is the rapid constriction of the muscle cells in the media layer occurring shortly after birth. Second, there is fibrous and anatomic obliteration over a period of weeks to months. Shunting of blood may be bi-directional during the 1st few hours of life, but subsequently becomes left to right. By 24-72 hours of life, in most infants, the PDA is no longer physiologically significant. Sensitivity of ductal closure to increased PaO2 increases with gestational age.
Factors that encourage continued patency of the ductus include prematurity, RDS, surfactant therapy, hypoxia, anemia, hypervolemia, and high altitude.

In the clinically significant PDA, a murmur may be auscultated and is systolic or continuous heard best in the left upper sternal border. The baby often has a widened pulse pressure (>30 mmHg) with corresponding bounding peripheral pulses (palmar pulses). Additional findings include respiratory insufficiency, hepatomegaly or a hyperactive precordium. A CXR may show an enlarged heart and increased vascular markings. Echocardiography is used to confirm a PDA. Its continued presence may result in heart failure, ventilator dependency, CLD and potential increased susceptibility to NEC, IVH or CLD.

PDA closure may be accomplished medically or surgically. Indomethacin or ibuprofen may be administered, but should not be given in patients with creatinine >1.6 mg/dl, platelet count <50,000, or suspicion of NEC. Surgical ligation is indicated when medical treatment is unsuccessful or when NSAID administration is contraindicated.

There may be an initial hypertensive episode resulting from closure of the ductus. This may be followed by potential hypotension, which may require pressor support. Some of the hypotension observed may be in response to surgical conditions such as thoracostomy, sedation and paralysis. Additionally, some infants may have low cardiac output due to alterations following ligation (post ligation syndrome). Pressor support is therapy for this initial change.
## Pharmacological Closure of PDA Dosage Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
<th>Prophylactic dose</th>
<th>Route of Administration</th>
<th>PDA Closure Rate</th>
<th>Adverse Effects</th>
<th>Reopening rate</th>
</tr>
</thead>
</table>
| Indomethacin | Age < 48 hours:  
1st dose: 0.2mg/kg  
2nd dose: 0.1 mg/kg after 12 hours  
3rd dose: 0.1mg/kg 24 hours after 2nd dose  
Age > 48 hours: 0.2mg/kg/dose at 12-24 hour intervals for total of 3 doses | 1st dose (<24 hours age, preferably <12 hours age): 0.1-0.2 mg/kg  
Subsequent 2 doses: 0.1mg/kg every 24 hours | IV over 30 minutes | 70-80% | Renal function+: oliguria, rising creatinine  
GI: bleeding, perforation, NEC, electrolyte disturbance | 20-30% |
| Ibuprofen   | Loading dose: 10mg/kg  
Subsequent doses: 5mg/kg for 2 doses at 24 hour intervals | 1st dose: 10mg/kg IV or oral at < 6 hours age  
Subsequent 2 doses: 5mg/kg at 24 and 48 hours age | IV or Oral | 70-80% | Oliguria, rising creatinine  
Higher serum bilirubin  
Bleeding-less common | 30% |
| Paracetamol | Oral dosing: 15 mg/kg every 6 hours  
Duration: 48-72 hours for 3 doses | Oral IV* | Needs Further Study | Elevated liver enzymes | Needs Further Study | Elevated liver enzymes | 30% |
III. APNEA AND BRADYCARDIA

Apnea is defined as respiratory pause lasting 20 seconds--or less if associated with bradycardia (HR <100). The risk of apnea decreases with increasing gestational age.

Apnea may be classified as follows:

1. **Central apnea:** due to immaturity in brain stem & respiratory center. There is no evidence of either respiratory effort or obstruction
2. **Obstructive apnea:** due to pharyngeal collapse. Breathing movements are seen without air movement
3. **Mixed apnea:** most common form of apnea. Central apnea is followed by obstructed respiratory efforts.
4. **Periodic breathing:** IS NOT TRUE APNEA. Characterized by a repeating sequence (>=3) of prolonged pauses (>=3s) in breathing with periods of normal respiration (<20s). While commonly seen in nearly all infants, careful clinical assessment to rule out true apnea is necessary. This is generally benign and requires no treatment.

If apnea is recurrent, consider checking CBC (impending sepsis or anemia), electrolytes, calcium, magnesium and glucose, a blood gas, CXR, head ultrasound, or EEG. Review the medications. Review timing to apnea to determine whether apnea may be due to reflux.
For those infants <60 weeks PMA, apnea is a significant risk in the 24 hours after an anesthetic.

Treatment for apnea

1. Xanthines such as caffeine, aminophylline and theophylline are central stimulants that may improve diaphragmatic contraction and inhibit hypoxia-induced ventilation. Caffeine citrate (IV or enteral has a loading dose of 20 mg/kg and maintenance of 5-8 mg/kg q 24 hrs). Theophylline (po) and aminophylline (IV) has a loading 5 mg/kg, with a maintenance of 1.2-2mg/kg/dose every 6-8 hrs.

2. Additional therapy may include the use of nasal CPAP, which splints upper airway with positive pressure and stimulates breathing with increased flow. CPAP may stabilize Functional Residual Capacity. NCPAP is started at 5 - 8 cm water pressure (maximum of 10-12 cm water). It may exacerbate reflux.

ANEMIA OF PREMATURITY

At birth, the hematocrit ranges ~40-60% For term babies, hemoglobin, declines to ~9 g/dl by 10 wks. In premature infants, Hgb declines to ~7-8 g/dl by 7-8 wks. Physiologic anemia of prematurity is often long-term and not necessarily pathologic. Neonatal red cells have short life spans and stressed marrow may exacerbate anemia.
Erythropoiesis is indicated by a reticulocyte count > 5%. When transfusing, consider overall physiology and perfusion. Recall that transfusion will inhibit the marrow and blunt the reticulocyte response.

When transfusing in infants, use CMV-negative packed red blood cells. Immunodeficient, preterm, and lymphopenic (<500/mm³) require CMV-negative irradiated packed red blood cells 15 cc/kg over 3-4 hrs.

IV. CHRONIC LUNG DISEASE (CLD) / BRONCHOPULMONARY DYSPLASIA (BPD)

Chronic lung disease of prematurity (CLD), or bronchopulmonary dysplasia (BPD), is an important cause of morbidity and mortality in the pre-term infant. The NIH consensus definition of BPD defines it as the treatment of >21% oxygen for at least 28 days. Further subclassification of severity is based on gestational age and chronologic age. The incidence is 20% at those born <1500gm and 40% in those <1kg.

Contributing factors to CLD include prenatal exposures such as acute or chronic maternal infection and smoking. Postnatal factors are related to immaturity such as ventilator associated injury (oxygen toxicity, barotrauma/volutrama, atelectasis), sepsis, pulmonary infection and poor nutrition. It is higher in males and there are likely genetic factors.
Infants with CLD have longer hospital stays, increased re-hospitalizations, more pulmonary hypertension, higher rate of neurologic impairment, higher incidence of poor growth, and increased risk of mortality.

Early Xray findings include diffuse haziness and a ground glass appearance. Later, the film may show pulmonary edema, airway cuffing, atelectasis, cystic changes, and air trapping.

Treatment / Management of CLD
The best way to manage CLD is to prevent or minimize it. The time on a ventilator should be decreased as much as possible. There should be a conscious effort to minimize the pressure and oxygen levels. Enhancement of growth of normal lung tissue is accomplished in the absence of a ventilator and excess oxygen. This means aggressive weaning and extubations of the infant to CPAP or nasal cannula as soon as possible, accepting higher pCO2s (50-60mmHg) and lower oxygen saturations (89-95%).

Other therapies for CLD used acutely and chronically, are steroids, diuretics, and beta agonists, but have not shown to be universally beneficial. Again, lung protective therapies such as avoidance of infection, ventilation and hyperoxia, as well as ensuring good nutrition are critical to long-term growth.
Infants with CLD have reactive airways, frequent ER visits and hospitalizations, difficulty with RSV and other respiratory infections. They also have impaired growth due to increased caloric needs and may need to be on increased calorie formulas. Since lung parenchyma continues to grow until age eight, symptoms usually abate with time.

Corticosteroid use in infants for CLD

In premature infants, corticosteroid therapy is very controversial, long-term follow-up studies from the initial groups that received post-natal therapy have revealed significant risks for neurodevelopmental delay. The risks seem to be associated with length of course and bulk dose exposure. NO STEROID REGIMEN HAS PREVENTED CLD. Current practice is to resort to steroids in order to attenuate the inflammation related to (CLD) when demands of mechanical ventilation for the infant threaten long-term outcomes. Another indication for corticosteroid therapy is to supplement the corticosteroid insufficient infant.

Dexamethasone (Decadron) dose ranges from 0.05-0.5 mg/kg/day IV (more commonly, 0.25 mg/kg/dose q12hrs for 3 days is used). Courses have currently trended to 3 day bursts with a steroid-free period between bursts. Dexamethasone also has a very long half-life in the premature infant.
Hydrocortisone Stress dose: 2-6 mg/kg/day, physiologic replacement 1-2 mg/kg/day. Dose may be divided q12hrs. It has a more physiologic half-life and agent is eliminated from body within 24hrs of dosing. This agent has been utilized in both treating the steroid deficient infant and supplementing the stressed premature infant.

Methylprednisolone (Solu-Medrol) Loading dose is 1-2 mg/kg IV. Subsequent dosing is 2 mg/kg IV divided in to 4 doses. This agent is more commonly used in older premature infants, who are ventilator dependent secondary to severe CLD, and currently during hospitalization when evaluation for possible tracheostomy.

Inhaled steroids may play a role in decreasing CLD. Beclomethasone has limited systemic effects.

V. INTRAVENTRICULAR HEMORRHAGE (IVH)

While the overall incidence has fallen sharply in the last 20 years, the incidence is 5-11%. IVH is more common in preterm infants and its incidence is directly proportional to the degree of prematurity (e.g., 45% in infants born at 500-749 grams). Studies have shown that 450 % of all IVH occur within the first 24 postnatal hours of age and 78% within the first 72 hours. These infants are at increased risk for seizures, hydrocephalus, and death. Surviving infants may have neurodevelopmental and cognitive difficulties.
IVH occurs when small, fragile vessels in the subependymal germinal matrix bleed. The hemorrhage may extend either into the ventricular space and/or the surrounding parenchyma of the lateral ventricle. The germinal matrix is adjacent to lateral ventricles and the site of neuronal and glial cell production and subsequent migration; it is a highly vascular area that involutes by 36 weeks gestation. IVH can occur in term infants; most originate from choroid plexus and are generally benign.

**Classification of IVH (Papile classification)**

**Grade I:** subependymal germinal matrix hemorrhage

**Grade II:** IVH without ventricular dilatation

**Grade III:** IVH with ventricular dilatation (blood fills >50% of the ventricle)

**Grade IV:** IVH with extension into parenchyma (Parenchymal hemorrhage in the absence of IVH may be classified as a Grade IV)

The infant’s degree of prematurity is the primary risk factor that supersedes all other risks. Other factors include presence of PDA, rapid shifts in blood pressure, PaO2 or PCO2, HIE, hypertonic infusions (glucose, bicarbonate), exchange transfusions, hypoxia, DIC.

Head ultrasound is the main diagnostic modality and classification is based on this modality of detection. The ultrasound probe is placed over the anterior fontanel. Subarachnoid hemorrhages or secondary parenchymal injuries may be difficult to detect. CT or MRI may be used to clarify findings.
Management consists primarily of supportive care; i.e. anticonvulsant therapy for seizures, blood pressure support, transfusion if indicated, etc.

Grade I: Serial HUS to rule out extension of IVH, if no extension, follow clinically
Grade II: Serial HUS

If ventricular size is unchanged, follow clinically as with Grade I If ventricle enlarges, treat as with Grade III
Grades III & IV: Serial HUS to track size of ventricle

If ventricles continue to enlarge, serial lumbar punctures (LP) may be required. The frequency of LP is dictated by clinical status and response to LP. An intraventricular reservoir to tap CSF may be necessary.

Because of the increased incidence of IVH in the NICU population, as well as the increased incidence of periventricular leukomalacia (PVL) in the same subset, at-risk infants (<1500gm or depressed infants) in the NICU are screened at 1 week, 1 month and/or 36weeks CGA, unless clinical status necessitates earlier evaluation.

VI. PERIVENTRICULAR LEUKOMALACIA (PVL)

The most common form of brain injury in preterm infants is diffuse PVL. It is also the most common cause of neurologic deficit and cerebral palsy in at risk infants. PVL refers to focal necrosis and gliosis of white matter dorsal and lateral to the exterior
angles of the lateral ventricles. Associated with PVL is corresponding cortical volume loss overlying these areas.

Two types of PVL are encountered.

Cystic PVL is found in 5% of all VLBW infants. It is characterized by focal cystic necrotic lesions deep in the cerebral white matter. These may be seen at any time after birth, but generally appear between 2 and 4 weeks. May be seen on head ultrasound.

Diffuse PVL is the most common cause of brain injury in preterm infants. It is the major cause of cognitive defects and impaired neurodevelopment in this population. MRI is the preferred modality for diagnosis.

There is increasing evidence that the presence of PVL correlates more strongly to cerebral palsy (CP) than any of the grades of IVH. Also, there are trends in the literature suggesting that the highest predictors of PVL are the presence of intrauterine infections, hypoxia, or ischemia. Screening for PVL in the NICU is accomplished by head ultrasound performed at 1 month of life or later. PVL is a lesion that appears 2-3 weeks following the inciting insult.

VII. RETINOPATHY OF PREMATURITY (ROP)

Retinopathy of prematurity is a disorder of vascular and retinal development in preterm infants resulting from prematurity and oxygen use. In severe forms, retinal scarring, traction folds, and detachments can lead to blindness. Screening for ROP should meet the Joint Statement by the AAP, AAO and AAPOS (Pediatrics 117(2):572, 2006).
All infants with birth weight ≤1500 g or born at <32 weeks are screened.

In addition, selected infants born at >32 weeks gestational age deemed at risk (complicated clinical course). Infants are screened when they are 4-6 weeks chronological age, or 31-33 weeks postconceptual age.

ROP is classified by the clinical stage and the retinal zone.

Retinal Zones

**Zone 1:** Vessels extend less than twice the distance between the disc and macula. A very immature retina with great potential for severe disease.

**Zone 2:** Vessels extend further, but potential for severe disease still exists.

**Zone 3:** Vessels are quite mature. There is a small risk for severe disease.
Clinical Stages
Stage 1: A demarcation line separates avascular retina anteriorly from vascular retina posteriorly.

Stage 2: The demarcation line is now a ridge with height, width and volume. The ridge extends above the plane of the retina. This regresses spontaneously without sequelae in 80% of patients.

Stage 3: A ridge is seen with extraretinal fibrovascular proliferation. This is severe disease with some sequelae to vision expected.

Stage 4-5: Retinal detachment. There is poor prognosis, even with surgery


Follow-Up
Based on retinal maturity & severity of disease.
<= 1 week
  Stage 1 or 2 ROP: zone 1
  Stage 3 ROP: zone 2
1 to 2 weeks
  Immature vascularization: zone 1—no ROP
  Stage 2 ROP: zone 2
  Regressing ROP: zone 1
2 weeks
Stage 1 ROP: zone 2
Regressing ROP: zone 2
2 to 3 weeks

Immature vascularization: zone 2—no ROP
Stag 1 or 2 ROP: zone 3
Regressing ROP: zone 3

Threshold Disease Is
Stage 3 in Zone 1
Stage 3 in 5 continuous clock hours or 8 total clock hours
Stage 3 in Zone 2 with presence of Plus disease

Intervention
Treatment is initiated within 72 hours for:

Zone 1 ROP: any stage with plus disease
Zone 1 ROP: stage 3, no plus disease
Zone 2 ROP: stage 2 or 3 with plus disease

Ablative therapy is considered if threshold disease exists (cryotherapy, laser photocoagulation
Anti-VEGF injection with Avastin (Genetech/Roche, South San Francisco, CA)

Most often occurs at 38 wks post-conceptional age
Complications of therapy:

Myopia, retinal detachment, necrosis, corneal hemorrhage, corneal or iris burns, tunnel vision

Eye Exams in the NICU

In preparation for the ophthalmologic exams in the NICU, infants are treated with dilating agents

Common Side Effects of Eye Examinations

Exacerbations of apneas/bradycardias

Feeding intolerance
THERMOREGULATION IN THE NEONATE

Modes of Heat Generation

- Metabolic activity (moderate source for neonate)
- Voluntary muscle activity (insignificant source for neonate)
- Peripheral vasoconstriction (insignificant source for neonate)
- Thermogenesis
  - Shivering (insignificant source for neonate)
  - Nonshivering (uses brown fat, a significant source of heat production in neonate)

Nonshivering Thermogenesis (NST)

- Skin temperature falls immediately after delivery.
- This fall is halted when the umbilical cord is clamped, initiating NST to raise body temperature.
- NST in prematurity
  - Neonates born at greater than 30 wga do not have dorsal surface NST.
  - SGA neonates show markedly decreased NST compared to AGA.
  - It is only during the third trimester that neonates can produce heat to overcome cold stress.
- NST is mediated by brown fat
Brown Fat

- Compared to white fat, brown fat cells have many more mitochondria and fat vacuoles.
- Has abundant sympathetic innervation as well as blood supply located in the neck, intrascapular area, mediastinum, surrounds spinal cord and kidneys.
- Functions to elevate core body temperature.

Thermal Neutral Zone

- First proposed by Cross & Hill in 1959.
- Defined as range of ambient temperatures at which
  - Metabolic rate is at a minimum
  - Temperature regulation is achieved by control of sensible (non-evaporative) heat loss

Modes of Heat Loss

- Conduction – transfer of heat energy from the body to a solid object and/or surface in direct contact with the body (e.g. heat loss from neonate to a weighing scale)
- Convection – transfer of thermal energy from the body to an adjacent gas (air).
  - Heated gas (heat coming off of body) expands and is displaced upwards by cooler surrounding gas (Boyle’s law).
  - Contributes of convective heat loss
    - Position of body (flexed or extended)
    - Body surface area
- Body weight
- Air temperature
- Air currents in room or incubator
- Maturity of neonate’s skin

- Evaporation – heat transfer by energy-carrying water from the skin and respiratory tract to a drier environment
  - Affected by
    - Maturity of neonate’s skin
    - Wet skin (newly born neonate, prior to drying off)

- Radiation – net rate of heat loss in the form of electromagnetic waves between the body and environmental surfaces not in contact with the body
  - Dependent on temperature differences between the body and solid objects facing it.
  - Radiant heat loss factors
    - Skin temperature
    - Exposed surface area
    - Distance and angles to irradiated objects (e.g. incubator walls, nearby windows)
  - NB
    - Radiant heat loss is independent of air temperature
    - Cold stress is possible if surrounding walls or windows are sufficiently cold
Equipment Used To Minimize Heat Loss In Neonates

- Radiant Warmer
  - Provides ease in visualizing and handling infant.
  - A large difference in surface temperature between exposed and unexposed areas exists; therefore, insensible water loss (evaporative heat loss) is approximately 50% higher than that of convective incubators.

- Convective Incubator
  - Humidity controlled and therefore reduces evaporative heat loss
  - Double walls serve to decrease radiative heat loss
  - Portholes serve to decrease convective heat loss
  - Incubator rubber foam mattress serves to decrease conductive heat loss.
  - 3 Modes of Temperature Control
    - Skin temperature servocontrol
      - Heater power output automatically adjusts to changes in temperature based on skin temperature probe
      - Variable air temperature
      - Constant skin temperature
      - Best mode for very low birth weight and extremely low birth weight neonates
    - Air temperature servocontrol
      - A constant air temperature within incubator is maintained
      - Stable air environment
      - Neonate not part of thermal feedback loop
· Best for neonates weaning to open crib
  · Manual control
    · Temperature is manually adjusted in response to intermittent
      measurement of skin temperature or air temperature.
    · Seldom used for neonates.

Weaning to Open Crib
· Generally thermal competence is achieved between 1500 to 2000 grams.
· Done gradually
· Infant is
  ▪ Fully dressed
  ▪ Wrapped in blankets
· Incubator portholes are kept open
· Temperature of incubator is allowed to drop
· If infant’s temperature remains stable, infant is transferred to a bassinet.

Fever
· An infrequent sign of sepsis
  ▪ Less than 10% of febrile infants have culture-proven sepsis.
  ▪ Nonetheless, sepsis is most feared cause of neonatal fever.
  ▪ Septic infants most commonly present with hypothermia.
· Mechanism of neonatal fever is poorly understood.
Most commonly results from interactions between central heat conservation and heat dissipation at the hypothalamic level.

- May be caused by immunogenic pyrogens – most commonly PGE-2.
- Generally, neonates react to pyrogens with hypothermia rather than fever.

- Etiologies of increased temperature
  - Increased metabolic rate
    - Status epilepticus
  - Excessive environmental heat
    - Poor incubator monitoring
    - Excessive swaddling

**BILIRUBIN & JAUNDICE**

**2004 AAP Guidelines**

Jaundice occurs in most neonates; most is benign. However because of the potential toxicity of bilirubin, it is important to recognize hyperbilirubinemia and be aware of the risk factors for it. The 2004 AAP recommendations are for newborns > 35 weeks gestation, and “do not indicate an exclusive course of treatment or procedure to be followed”.

One third of healthy breast-fed infants have persistent jaundice beyond 2 weeks of age. Jaundice beyond 3 weeks of age merits investigation.
Bilirubin may be toxic to the brainstem. In jaundiced term infants who do not have hemolysis, an association that might exist between any one total serum bilirubin (TSB) level and later serious neurologic abnormality of hearing deficit remains unproven. There is some evidence, however, that subtle differences in outcome might be linked to TSB levels.

The **goal** is to reduce the incidence of severe hyperbilirubinemia as well as acute bilirubin encephalopathy (the clinical central nervous system findings associated with bilirubin toxicity) and the more chronic kernicterus while minimizing harm such as increased parental anxiety, decreased breastfeeding and unnecessary costs and treatments.

**AAP GUIDELINES RECOMMEND**

The promotion and support of successful breastfeeding, the measurement of total serum bilirubin or transcutaneous bilirubin in any infant jaundiced within the first 24 hours of life, recognizing that visual estimation of the degree of jaundice can lead to errors, interpret bilirubin levels according to the infant’s age in hours, recognize that infants born at less than 38 weeks gestation, especially if breastfed are at a higher risk for hyperbilirubinemia, perform systematic review of risk factors for hyperbilirubinemia in all infants prior to discharge, especially if discharge takes place before age of 72 hours, arrange appropriate follow up based on risk assessment and time of discharge.
Poor caloric intake and/or dehydration may contribute to the development of hyperbilirubinemia. Increasing the frequency of nursing may decrease the likelihood of hyperbilirubinemia in breastfed infants.

Jaundice should be assessed whenever vital signs are checked but at least every 8-12 hours. Jaundice is usually seen in the face first and progresses caudally, but visual estimation can lead to errors. A serum or transcutaneous bilirubin level should be checked in every infant who is jaundiced within the first 24 hours of life, or if there is any doubt about the degree of jaundice in any infant. All bilirubin levels should be interpreted according to the infant’s age in hours using the nomogram. The cause of jaundice should be investigated in any infant receiving phototherapy or if the level is rising rapidly (crossing percentiles on the nomogram).

Infants with an elevated direct reacting bilirubin (conjugated) should have a urinalysis and urine culture. Sepsis work up should be done if the history or exam indicates. Sick infants or those jaundiced beyond 3 weeks should have a total and direct bilirubin level checked to identify cholestasis. Results of the newborn screen should be checked for thyroid abnormalities and galactosemia. G6PD levels should be checked on any infant receiving phototherapy or if the response to phototherapy is poor (G6PD deficiency is common in certain ethnic groups).
Major risk factors for severe hyperbilirubinemia

- Total Serum Bilirubin (TSB) or Transcutaneous Bilirubin (TcB) in the high risk zone (see Figure 1)
- Jaundice in the first 24 hours
- ABO incompatibility or other hemolytic disease (eg, G6PD deficiency)
- Gestational Age 35-36 weeks
- Phototherapy in a previous sibling
- Cephalohematoma or other significant bruising
- Exclusive Breastfeeding, and if not nursing well and weight loss >10%
- East Asian race

AAP recommendations on evaluation of the healthy term infant with jaundice

- Maternal blood type and indirect Coombs test
- Cord blood type and direct Coombs (DAT-AHG) test
  - If maternal type and Coombs not known or if mother is Rh negative
- Consider possibility of hemolytic disease and G6PD deficiency
- TSB level if infant is jaundiced within the first 24 hours of life
- Physical exam of infant

NOTE: If the total serum bilirubin is at a level at which exchange transfusion is recommended (see figure 3) OR if the level is 25mg/dL or higher, THIS IS CONSIDERED A MEDICAL EMERGENCY AND THE INFANT SHOULD IMMEDIATELY BE ADMITTED.
Techniques to lower the level of TSB include:

- ↑ fluid intake to maximize renal excretion (not proven to be effective, but may improve bilirubin level if dehydration is a factor)
- ↑ enteral intake to stimulate intestinal motility & excretion of bilirubin via stool
  - Bilirubin is enterohepatically circulated in intestinal lumen and recycled
  - Glycerin suppository to stimulate intestinal motility
- Phototherapy (Note that photoproducts are excreted in both urine and bile)
- IVIG for Coombs positive or ABO incompatibility patients

Exchange transfusion

**PHOTOTHERAPY**

Please see Figure 2 as a guide on when to start phototherapy. Efficacy is affected by: the spectrum of light, energy output (irradiance) in the blue light range, and infant’s exposed surface area. To achieve maximal efficacy, use special blue (narrow spectrum) tubes. They carry the marking “F20 T12/BB”. Placing the light as close to the infant as possible optimizes irradiance. Irradiance of at least 30 W·m⁻² is confirmed with an appropriate irradiance meter. A fiberoptic blanket on the infant’s underside increases surface area exposed to blue light. The eyes should be covered to minimize/eliminate theoretical retinal harm. There should be a demonstration of a decrease in total bilirubin concentration after 4-6 hours of phototherapy.
Phototherapy is contraindicated in infants with porphyria or those on photosensitizing drugs.

Figure 1: The nomogram above designates hyperbilirubinemia risk for
- Well newborns at \( \geq 36 \) weeks’ gestation with a birth weight of \( \geq 2000 \) grams OR
- \( \geq 35 \) weeks’ gestation with birth weight \( \geq 2500 \) grams

(From Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Reproduced with permission from Pediatrics, Vol. 114, Page 301, Copyright © 2004 by the AAP)
Figure 2 (above): **AAP Guidelines** for **phototherapy** in hospitalized infants of ≥ 35 weeks’ gestation. The nomogram in Figure 1 led to the development of this graph.

(From the AAP Clinical Practice Guidelines "Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation" Reproduced with permission from *Pediatrics*, Vol. 114, Page 304, Copyright © 2004 by the AAP)
The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy. Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, reticulosis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.

- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Figure 3: AAP Guidelines for exchange transfusion in infants ≥ 35 weeks' gestation.

(From the AAP Clinical Practice Guidelines “Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation” Reproduced with permission from Pediatrics, Vol. 114, Page 305, Copyright © 2004 by the AAP)
Term infants who are sick or who have hemolysis require full evaluation. As a rule of thumb, start phototherapy early, and begin preparing for exchange transfusion when TSB reaches 15mg/dL. Any infant who is jaundiced and manifests signs of the intermediate or advanced signs of bilirubin encephalopathy should have immediate exchange transfusion.

Recognize that the preparation time required for a double-volume exchange transfusion (often 4-6 hours). It is prudent to send blood for typing and cross-matching to the Blood Bank as soon as it is recognized that an exchange is possible. Dialogue with the Blood Bank may be essential for proper composition of the whole blood required for the procedure.

In the outpatient management of the jaundiced infant, it is an AAP recommendation that breastfeeding should be continued. It is also an option to temporarily interrupt breastfeeding and substitute formula. Supplementing the breastfed infant receiving phototherapy with expressed breast milk or formula if intake is inadequate, the weight loss is excessive or the infant seems dehydrated.

**SEIZURES**

Seizures in the newborn period can present in many ways. Often presentations are not in the classical “tonic-clonic” form and can range from asymptomatic to many other ways such as apnea, lip smacking, staring, BP instability, cyanotic spells. Etiology
include infection, SAH, hypoglycemia, drug withdrawal, intracranial pathology, electrolyte abnormalities

First line anticonvulsants used include Phenobarbital, Keppra and benzodiazepines (lorazepam [Ativan], diazepam [Valium]) in the newborn period. Also, it is imperative to treat the underlying cause, if it can be determined (i.e. correct glucose, electrolyte abnormalities, treat the infection, etc.).

Phenobarbital: loading dose 20 mg/kg IV; side effects include respiratory depression and hypotension. Very long half-life in the infant (days).

Keppra: 10mg/kg/day divided BID, same dose for PO and IV; most common side effects include decreased appetite and diarrhea; half-life in neonates is approximately 5 hours.

Benzodiazepines: Ativan 0.1 mg/kg, Valium 0.1 mg/kg; half-life measured in minutes-hours; ideal for use in treating uncertain seizures or in situations where airway management may be compromised.

NOTE: Other anticonvulsants such as phenytoin (Dilantin), carbazepam (Tegretol) and phosphenytoin are used in the infant, but have many additional considerations such as bilirubin displacement and/or drug interactions. These tend to be second-line agents and are used primarily in conjunction with a neurology consult.
HYPOXIC-ISCHEMICENCEPHALOPATHY (HIE)

Hypoxic-ischemic brain injury may occur during the perinatal period. These injuries may often be independent of any symptoms during labor or delivery period. In fact, some of these injuries occur antenatally or may result of specific conditions or abnormal anatomy. It is often difficult to pinpoint when exactly the event did occur.

Babies with HIE may preset with lethargy, hypoglycemia, bradycardia, seizures, abnormal breathing patterns, ↑ renal function tests, ↑ liver function tests.

The prognosis for HIE is highly variable and only the most severe and tragic cases are the easiest to assess. Several generalizations for HIE are as follows.

1. The fewer symptoms, the better

2. The quicker the recovery, the more optimistic the outcome

3. Uncontrollable seizures portend a bad outcome.

4. Brainstem effects indicate a higher degree of severity

5. Absence of gray-white matter differentiation on CT suggestive of poor outcome

HIE is treated with supportive care, such as treating seizures and normalizing blood pressure abnormalities. In 2005, three multicenter randomized controlled trials were published showing that induction of mild hypothermia resulted in significantly improved neurodevelopmental outcome in neonates 36 weeks gestation with acute perinatal HIE.
Evaluation of HIE

Sarnat's Scale is common method to evaluate the degree of HIE in an infant. This scale was initially presented several years ago in a small study. The advantage of the scale is it uses physiologic parameters to define a common vocabulary to describe an infant's condition. It is summarized below.

<table>
<thead>
<tr>
<th>Sarnat &amp; Sarnat Classification of HIE</th>
<th>Stage 1 (Mild)</th>
<th>Stage 2 (Moderate)</th>
<th>Stage 3 (Severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENSORIUM</td>
<td>Jittery, irritable</td>
<td>Lethargic</td>
<td>Stuporous</td>
</tr>
<tr>
<td></td>
<td>Hyperalert</td>
<td>Dulled sense</td>
<td></td>
</tr>
<tr>
<td>MUSCLE TONE</td>
<td>Normal</td>
<td>Hypotonic at rest</td>
<td>Flaccid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertonic on stim</td>
<td>Unresponsive</td>
</tr>
<tr>
<td>POSTURE</td>
<td>Mild distal</td>
<td>Strong distal</td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td>flexion</td>
<td>flexion</td>
<td>decerebrate</td>
</tr>
<tr>
<td>STRETCH REFLEXES</td>
<td>Overactive</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>MORO REFLEX</td>
<td>Strong</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>SUCK REFLEX</td>
<td>Normal</td>
<td>Weak</td>
<td>Absent</td>
</tr>
<tr>
<td>SEIZURES</td>
<td>None</td>
<td>Focal or multifocal</td>
<td>Decerebrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>posturing</td>
<td></td>
</tr>
</tbody>
</table>
**Long-term Follow-Up of HIE**

These children need neurodevelopmental follow-up in the Developmental or Neuro clinics. This should occur at about 6 months of age and then subsequent evaluations as dictated by the specialist. Many children "normalize" within the first year. Others require early intervention.

**SUBARACHNOID and SUBDURAL HEMORRHAGE**

In the context of this passage this refers to primary subarachnoid hemorrhages which are bleeds that are not extensions of parenchymal bleeds. Ultrasonography is not helpful in diagnosis; CT/MRI must be performed.

The clinical presentation can vary widely from asymptomatic and an incidental finding to infants presenting with seizures to, extremely rarely, an infant with a catastrophic deterioration. Supportive and symptomatic treatment is the course. Small bleeds are common in vaginal deliveries, but for a larger one or if symptomatic, evaluation is indicated. Work-up of coagulopathies and confirmation of vitamin K administration should be done in the symptomatic cases.

~90% of infants presenting with seizures will be normal in follow-up. Infants presenting in catastrophic demise and survive tend to have neurologic sequelae in follow-up.
INTRODUCTION:
Persistent pulmonary hypertension of the newborn (PPHN) occurs when the pulmonary vascular resistance (PVR) fails to decrease at birth. It can occur as a complication of lung diseases that cause respiratory failure in the newborn. These include perinatal aspiration syndrome, pneumonia or respiratory distress syndrome. PPHN can also occur by itself as idiopathic PPHN without associated parenchymal lung disease. PPHN accounts for 10% of admissions to tertiary care NICUs and can range in spectrum from mild and transient to severe or chronic pulmonary hypertension. PPHN is also a common complication of lung hypoplasia which occurs with space occupying anomalies in the chest, such as congenital diaphragmatic hernia or with oligohydramnios due to prolonged leakage of amniotic fluid or renal dysplasia/agenesis. Finally, PPHN is a complication of some lethal causes of respiratory failure such as alveolar-capillary dysplasia (ACD) and genetic defects in surfactant synthesis. MAS accounts for majority of cases (40%), followed by Pneumonia/sepsis (15%) and RDS (15%) and idiopathic PPHN accounts for approximately a third of the cases (27%).

Infants who survive neonatal PPHN are at an increased risk for long term neuro-developmental impairments and/or late hearing loss and need careful follow-up after discharge.
NORMAL PULMONARY VASCULAR TRANSITION:

At birth, physiologically high PVR decreases and there is 10 to 15-fold increase in pulmonary blood flow. The initial decrease in PVR is fairly steep at birth, followed by a gradual decrease over the 2 months of life.

Fetal Circulation:

- Pulmonary and Systemic pressures are nearly equal in utero.
- High PVR ensures that 90% of right ventricular output flows across the PDA to descending aorta and then to placenta for gas exchange.
- Low fetal oxygen tension (PaO2 of 20-25 torr) contributes to fetal pulmonary vasoconstriction
- Fetal Hb with high O2 affinity and high systemic blood flow (both ventricles pumping in parallel into aorta) ensure that O2 delivery is optimal
- Streaming of umbilical venous blood, which has the highest O2 saturation in the fetus, across PFO to left atrium ensures that O2 delivery is maximized to brain and heart
- Placenta is a low resistance/low pressure vascular bed, which favors right ventricle pumping into the systemic instead of pulmonary circulation

Postnatal transition: Pulmonary artery pressure drops from removal of lung liquid, expansion of the lungs, increase in arterial oxygen tension and release of vasoactive mediators from vascular endothelium. Oxygen, increases in pH and decreases in PaCO2 also directly cause vasodilation.
Systemic pressure rises from: Removal of placenta from circulation and rise in left ventricular output, aided by increased preload on LV from higher pulmonary blood flow returning to LA and LV.

Closure of fetal shunts: Increase in left atrial pressure from higher pulmonary venous return leads to functional closure of PFO and cessation of right to left atrial shunt. Drop in PA pressure and constriction of PDA from higher oxygen tension lead to cessation of right to left PDA shunt and eventual anatomical closure of PDA.

**PATHOPHYSIOLOGY OF PPHN:**

Abnormally constricted lung vasculature: The failure of normal adaptation Some cases of idiopathic PPHN may be related to maternal intake of medications that cause fetal ductal constriction (NSAID) or pulmonary vasoconstriction (NSAID and/or SSRI intake). The pathophysiology specific to common parenchymal lung diseases associated with PPHN are described below.

**Meconium aspiration syndrome:**

Meconium causes mechanical obstruction to the airways → resulting in air trapping, hyperinflation, ↑ risk for pneumothorax, inactivation of surfactant, release of vasoconstrictors. Chemical pneumonitis leads to release of cytokines and leukotrienes that can increase pulmonary vasoconstriction. Recognition of the role of surfactant inactivation in MAS lead to clinical trials of surfactant replacement therapy for neonates.
with MAS requiring mechanical ventilation. Surfactant decreases the need for ECMO in MAS.

**Pneumonia/Sepsis:**
Bacterial endotoxin causes release of vasoconstrictors. They also cause loss of surfactant function and decreased aeration of lungs and induce pulmonary edema by increasing vascular permeability.

**Respiratory Distress syndrome:**
Increased reactivity of pulmonary arteries after 34 weeks of gestation predisposes late preterm infants with RDS to pulmonary hypertension when gas exchange is impaired because of surfactant deficiency. With the increase in late preterm deliveries since mid-90s, RDS has become an important risk factor for PPHN.

**Idiopathic PPHN:**
Structurally abnormal pulmonary vasculature may occur in idiopathic PPHN. These changes consist of abnormal thickening of media and adventitia of pulmonary arteries and hypoxemia in the absence of recognizable parenchymal lung disease. As pointed out above, prenatal ductal constriction from maternal intake of NSAIDs can lead to this altered adaptation. However, these structural changes can also occur in severe meconium aspiration syndrome, lung hypoplasia and ACD.
Lung hypoplasia:

Congenital diaphragmatic hernia, an important cause of lung hypoplasia, is often associated with PPHN. CDH affects 1 in 3000 live births. Pulmonary hypertension occurs in CDH because of the decreased number of blood vessels and increased reactivity of the vessels in the hypoplastic lungs. Similarly, prolonged rupture of membranes and renal dysplasia and agenesis are associated with lung hypoplasia and PPHN for similar reason.

CLINICAL PRESENTATION: Respiratory symptoms occur at birth or during first day of life. Primary symptom is respiratory distress with cyanosis (hypoxemia). Labile oxygenation is characteristic of PPHN. Physical exam may show tachypnea and retractions from respiratory disease. Active precordium and systolic murmur of tricuspid insufficiency may be appreciated on cardiac exam.

MANAGEMENT OF PPHN: It is very important to differentiate idiopathic PPHN or PPHN due to lung disease from pulmonary hypertension, which also occurs in congenital heart disease. Use of pulmonary vasodilators, like inhaled NO are contraindicated in congenital heart disease associated with right to left shunts (HLHS, coarctation of the aorta) and in TAPVR. Traditionally, responses to hyperoxia or hyperoxia +/- mechanical ventilation have been used to distinguish PPHN from cyanotic congenital heart disease. Although these criteria are still useful, certain caveats have to be considered to avoid errors in diagnosis. Some neonates with congenital heart disease and right to left shunt at PDA may experience increase in saturations with
administration of Oxygen (HLHS); neonates with severe PPHN may not show improvement in saturation with oxygen. In addition, increased pulmonary interstitial markings in TAPVR can be mistaken for RDS or transient tachypnea, particularly in late preterm infants. Echocardiography is needed to make a more accurate diagnosis in neonates with hypoxic respiratory failure and PPHN.

**DIAGNOSIS:**

1. **X-ray chest:** may be normal or show "black out" lung fields or haziness/patchy infiltrates from parenchymal lung disease (meconium, pneumonia or RDS)

2. **ABG:** In the presence of right to left shunting via PDA, pre ductal PaO2(right radial artery) is higher (10-15 mm of Hg) than post ductal PaO2(umbilical artery, left radial artery, or posterior tibial artery). However, 2-site sampling for arterial blood is invasive and is not recommended for diagnosis.

3. **Oxygen saturation:** A difference of >5% between pre ductal and post ductal oxygen saturations is considered indicative of right to left ductal shunt seen in PPHN. However, this difference is also seen in CHD with right to left shunts. Monitoring pre- and post-ductal saturations is useful in gauging the response to pulmonary vasodilator therapy. Neonates with TGA may have higher postductal than preductal saturation.

4. **Echocardiogram:** Helpful to distinguish cyanotic congenital heart disease from PPHN. ECHO also documents the presence of right-to-left or bidirectional shunts at the level of the PDA or PFO and estimate the pulmonary artery pressure from Doppler velocity measurement of the tricuspid regurgitation jet. Echo can also allow assess the progression of PPHN over time.
5. **OXYGEN INDEX**: Important estimate of the severity of respiratory failure in neonates- primarily based on oxygenation in relationship to level of ventilator support and FiO2.

\[
\text{OI} = \frac{(\text{Mean Airway Pressure} \times \text{FiO2\%})}{\text{PaO2}}
\]

OI<15, mild; OI 15-25 moderate and OI >25 severe respiratory failure.

New evidence suggests better outcomes if INO initiated at OI of 15-20. Traditionally INO has been started at OI≥ 25

OI>30: Refer baby to ECMO Center and/or initiate pre-ECMO studies

OI>40 despite optimal therapy, including use of INO and other pulmonary vasodilators, consideration of ECMO

**TREATMENT:**

Since PPHN is often a complication of underlying lung disease, treatment strategies should also address associated lung disease. It is important to consider the lungs and heart as one unit, connected by pulmonary circulation. Ideal management will involve optimizing lung expansion and cardiac output while achieving pulmonary vasodilation and maintaining systemic pressure. The target for PaO2 is 60-90 and should be achieved while maintaining normal PaCO2. It is important to avoid excessive levels of
oxygen or ventilator pressures that can injure the lung. Hyperventilation can also have adverse effects on cerebral perfusion and induces hearing loss (blood supply to cochlea is part of cerebral circulation).

Initial treatment:
- Treat metabolic derangements: correct hypoglycemia, hypocalcemia, hypothermia and metabolic acidosis as they can aggravate PPHN

- Optimize lung recruitment: mechanical ventilation, use high frequency oscillator as indicated, surfactant treatment for parenchymal lung disease. Optimize cardiac output and left ventricular function: ensure optimal preload with volume expansion, use inotropic agents, vasopressors

Pulmonary vasodilators: Inhaled nitric oxide (INO) is the primary agent used in PPHN. INO causes selective pulmonary vasodilation when administered directly into the lungs. INO has been shown to decrease the use of ECMO/mortality in RCT. INO can also be safely given through CPAP or nasal cannula. INO is started at a dose of 20 parts per million (PPM); higher doses don’t improve the response rate and increase the risk of methemoglobin (MetHb) formation. 70% of hypoxic neonates with PPHN show a positive response (increase in PaO2 by at least 20 torr). Once the baby is stable, wean FiO2 and ventilator pressures. INO can be weaned every 6-12 hours once ventilator settings are at a reasonable level. The weaning algorithm is 20-10-5-4-3-2-1-0.5PPM and then off. MetHb level should be checked at 24 and 48 hours after starting INO and
repeated as necessary (if still on 20ppm, repeat once a day). MetHb levels are not required once below 5 PPM. If a baby never had a response, wean off quicker. Never discontinue INO abruptly even in neonates that had no response to INO- sudden decompensation and crisis can be precipitated by intense pulmonary vasoconstriction if INO is suddenly discontinued.

Alternate therapies: Alternate agents are needed when oxygenation fails to improve with INO and/or PPHN persists by ECHO. These agents are often needed in babies with CDH. If a baby with PPHN fails to respond to INO and other measures, consider alveolar capillary dysplasia (ACD) in the differential.

- Type V Phosphodiesterase inhibitor (sildenafil): Blocks degradation of cGMP and works synergistically with NO. Usually given by oral or NG tube at a dose of 0.5-2mg/kg repeated every 6-8 hours. IV sildenafil is available- speak to the pharmacist about the dosing. IV sildenafil use needs approval of attending neonatologist. IV sildenafil is associated with higher incidence of hypotension

- Inhaled prostacyclin analogs (iloprost, prostacyclin) are given by nebulizer, usually for babies on a ventilator. Prostacyclin increases cAMP levels in smooth muscle cell. Iloprost is the preferred agent since it can be given by intermittent nebulization, every 2-6 hours, depending on the duration of response.

Phosphodiesterase III inhibitor, Milrinone: This is given by continuous infusion and usually started without a bolus in neonates. Usual doses are 0.2-0.5 micrograms/Kg/Min. IV milrinone can cause hypotension and is typically used in
conjunction with vasopressor agents. Milrinone works synergistically with inhaled prostacyclin in the same signaling axis.

ECMO: Decision to institute ECMO support is a complex process and involves coordination of services. Pre-ECMO studies typically done are cardiac ECHO to rule out CHD and head US to rule out IVH. Although OI>40 are typically used for consideration of ECMO, overall assessment of cardiopulmonary stability is more important than any single number.

**MEASURES OF OXYGENATION**

A-a GRADIENT

Alveolar PO2 = PAO2

Alveolar PCO2 = PACO2

In 100% O2, PAO2 = Atmospheric pressure - water vapor pressure - PACO2

Assume PACO2 = PaCO2

\[
\text{PAO2} = \text{Atmospheric pressure} - \text{water vapor pressure} - \text{PACO2}
\]

\[
= (760 - 47 - \text{PACO2}/0.8)
\]

Alveolar-arterial gradient is calculated by:

A-a Gradient = (713 - PACO2/0.8) - PaO2
OXYGENATION INDEX:

MAP x FIO2

PaO2
There are several reasons why a pediatric heart may require support. When looking at the components of the cardiac output equation.

\[ CO = HR \times SV \]

Since SV is dependent upon preload, myocardial contractility and afterload, one recognizes that two of the components preload and afterload are extrinsic to the heart. To be sure, this is a gross oversimplification. Time contributely relies on preload, etc. However, in this summary, Heart Rate and contractility are properties intrinsic to the heart itself and will be discussed.

**HEART RATE and RHYTHM**

Work performed by the heart can be compromised if the heart has ineffectively time beats or irregular beats. In the ICU setting, arrhythmia can be classified as fast or slow, atrial or ventricular, hemodynamically important or unimportant. Again, this is an over simplification, but categorizes treatment options well.

Mechanically, tachyarrhythmia can be classified as 1) reentry, 2) automaticity, 3) triggered activity. Reentry occurs when there are differential rates of conduction and is
triggered by a premature beat. Automaticity is a function of phase and depolarization ectopic activity, action potential.

Slow rates (bradycardia) can be from the atrium (sinus bradycardia) or the ventricle. In children, some bradycardia might be a manifestation of hypoxemia. Other causes include sinus disease (post-operative) hypercalcemia hypermagnesemia. Treatment includes identifying the cause if one is present, epinephrine, atropine, or pacemaker, Ventricular bradycardia are functional blocks, stable patients are treated with epinephrine, unstable patients are paced.

Fast rates (tachycardia) can stem from the atrium or the ventricle and may be hemodynamically problematic or not. The atrial tachycardias includes:

Sinus tachycardia – Consider hyperdynamic states (fever, seizures, sepsis, thyrotoxicosis, or hypoglycemia). Treatment is treating 1° disease atrial tachyarrhythmias include atrial flutter, paroxysmal atrial tachycardia atrial fibrillation and SUT. Atrial Muttler (saw tooth pattern rate 150) should get a trial of procainamide, digoxin or ibutilide (0.1 mg/kg).

Supraventricular tachycardias can be classified as ectopic or reentrant. Ectopic SVT is when a different pacemaker from above the AV modes sets the rate. The abnormal rhythm is insidious in onset, SVT is variable. Adenosine does not ablate this SVT, use esmolol, sotalol or flecainide. Reentrant tachycardias are usually sudden in onset, rate
is fixed. Adenosine 50-200 mg/kg is the first agent. Magnesium (25-50 mg/kg up to 2 grams) may also be used.

Post operative junctional ectopic tachycardia seen in VSD repairs, insides Amiodarone, calcium channel blockers or procainamide. SVT’s which cause hemodynamic instability should be considered for cardioverters.

The first question regarding ventricular tachycardias should be “is it a shockable rhythm?” Should be defibrillated, unstable VT should be defibrillated. Otherwise, use of antiarrhythmia such as procainamide should be considered.

CONTRACTILITY

In the chronically failing heart, there therapeutic interventions that have been shown to improve survival. These include:

- RAAS Modulators
- B Blockers
- Implantative cardioverters/detibrillary
- Cardiac Resynchronization therapy
- Mechanical ventricular assist device

RAAS (Figure)
Sensed by Juxtaglomerular Cells in Macula Densa of Kidney

Renin release

Angiotensinogen (made by liver) → Renin → Angiotensin I → Circulates ACE (lung) → Angiotensin II

Adrenal Cortex

Conserve Na → Produce Aldosterone → Conserve fluid

Captopril, enalapril are ACE Inhibitors

Nesitiride – reduces Na absorption in proxima and distal tubules. It causes natriuresis, decreases rennin production and angiotensin II production.

In acute decompensated heart failure, there are no medications that are associated with increased survival.
Loop diuretics – can be useful to achieve euvolemic state but must be used judiciously in patients who may need elevated filling pressures. Patients must not be overdiuresed as this may complicate renal function.

Catecholamines

Positive inotrope agents
  Milrinone
  Dobutamine

Vasodilators – May be considered to improve cardiac output. Reserve inotropes for patients with hypertension.

B naturetic factor is a protein secreted by the ventricles. It inhibits the renal angiotensin aldosterone (RAAS) system and promotes vasodilation, natreusis and diuresis.

Levosimendan is a calcium sensitizer and prolongs the bridging time of action and myosin by stabilizing the troponin – calcium interaction.

Theoretically, the end point of therapy is to achieve a great stroke volume for the same or lower preload.

CARDIOPULMONARY RESUSCITATION
Pediatric CPR delivered with arrest is associated with 60% return of spontaneous circulation. 27% of the pool of patients are able to be discharged to home and 80% of the cohort of patients have no neurologic sequelae.

When a “code” is called, determine whether there is a shockable ($V_F/V_T$) or nonshockable rhythm. $V_F/V_T$ is treated and defibrillation, epinephrine first.

If it is not $V_T$ or $V_F$ → epinephrine and CPR are the only modalities.

<table>
<thead>
<tr>
<th></th>
<th>Breath</th>
<th>Rate</th>
<th>Depth (inches)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>20/min</td>
<td>100/minute</td>
<td>1/3 to ½ of chest</td>
</tr>
<tr>
<td>Pediatric</td>
<td>20/min</td>
<td>100/minute</td>
<td>1/3 to ½ of chest</td>
</tr>
<tr>
<td>Adult</td>
<td>12/min</td>
<td>100/minute</td>
<td>At least 2</td>
</tr>
</tbody>
</table>

Infant—newborn to 1 year of age

Pediatric—up to 8 years

Adult—Greater than 8 years

CPR delivers 25-33% of normal cardiac output. Ventilating deeply makes cardiac output decrease even further.

In children, getting an arterial diastolic BP > 30 and ET > 15 has been associated with return of spontaneous circulation, but not to long term survival.
Cerebral protection should be achieved by normalizing BP, avoiding hyperglycemia and avoidance of hyperthermia. There is a current study on whether hypothermia is helpful in the pediatric patient. Hypothermia after arrest has been documented as beneficial in neonates.

End tidal CO₂ should be documented and measured continuously, if possible. If epinephrine is given endotracheally, and is given in an acidic carrier, the indicator may turn yellow. Esophageal intubation can turn the litmus paper yellow for a few breaths if patient has carbonated beverages in the stomach. If there is no chest impressions and only resure breaths are given ETCO₂ is O, since pulmonary blood flow is needed for ETCD₂ to rise.

Outcomes from apneic arrest are worse than ventricular fibrillation arrest.

**CONGENITAL CARDIAC MALFORMATIONS**

This is a very brief introduction about congenital cardiac malformations, focusing on the critical preoperative issues and the most common post-operative problems.

**SHUNT LESIONS**
Atrial septal defects (ASD): Most ASD’s have left to right shunt and may present with right ventricular volume overload. Other lesions that mimic physiology of ASD include partial anomalous pulmonary venous return, LV to RA shunt.

Most common post-operative problems in ASD are atrial dysrhythmias and left ventricular noncompliance. Certain types of ASD may be predisposed to certain operative issues. For instance, coronary sinus ASD may be more predisposed to heart block, sinus venosus ASD may have SA dysfunction and SVC narrowing, IVC type ASD may have cyanosis (baffling) and primum ASD may have mitral valvular problems.

Ventricular septal defects (VSD) also have left to right shunting preoperatively. This manifests as increased pulmonary blood flow and subsequent left ventricular overload since shunting occurs during systole. Lesions with similar pathophysiology include large ductus arteriosus and aortopulmonary window. Post-operative problems encountered include junctional ectopic tachycardia (RR 7180bpm, AV dissociation), or heart block.

AV canal is a lesion by which blood mixes in a common chamber. There is increased pulmonary blood flow and pressure. There may be biventricular overload and AV regurgitation. Postoperative issues may include pulmonary hypertension, AV valve regurgitation, heart block and junctional ectopic tachycardia.
OBSTRUCTIVE CARDIAC LESIONS

Tetralogy of Fallot (TOF) is an eponym for a large VSD, dynamic right ventricular outflow tract obstruction (RVOT), right ventricular hypertrophy (RVH), smaller PA and overriding aorta. There are many different variations of this theme including:

TOF with stenotic shunt

DORV with subpulmonary pulmonary stenosis

SV with submembranous stenosis

Post operatively, restrictive

A Ross procedure implants the pulmonary artery to the LVOT.

After post-operative repair of coarctation of the aorta, hypertension can occur. In the first 24 hours after surgery, the hypertension is due to a catecholamine surge and should be treated with sympatholytics such as labetalol. Beyond 24 hours, the hypertension is due to renin-angiotension system and would require ACE-inhibitors.
such as captopril and enalapril. Diastolic hypertension is more pronounced and spasm of the mesenteric arteries can be seen.

DUCTAL DEPENDENT LESIONS

Duct-dependent lesions can be divided into malformations that depend on the ductus for pulmonary lesions include tricuspid atresia and Ebsteins’ anomaly. One should be judicious with fluid with these lesions.

PRE-OPERATIVE SINGLE VENTRICLE PHYSIOLOGY*

*For this discussion, single ventricle physiology will refer to situations in which cardiac output to the pulmonary and systemic circulations involves mixing of deoxygenated and oxygenated blood. Not all examples described will be true single ventricle lesions or refer to situations that result in true single ventricle anatomy after eventual repair.

“Single Ventricle Physiology” describes situations in which there is mixing of deoxygenated and oxygenated blood providing the cardiac output to the pulmonary (Qp) and systemic (Qs) circuitry. Thus, blood supply to the lungs and body tends to be in parallel circuitry (heart → lungs AND body → heart), rather than in series (R heart → lungs → L heart → body → R heart).
Mixing of blood in Single Ventricle Physiology can occur at three levels:

- Atrial level mixing (PFO, ASD)
  
  - At times, this must be emergently established via balloon septostomy

- Ventricular level mixing (VSD)

- Ductal level mixing (PDA)
  
  - The most common way to provide appropriate mixing is via Prostaglandin E1 infusion (dose 0.01 – 0.05 mcg/kg/min)

Single Ventricle Physiology can result from:

- Systemic (Left-Sided) Outflow Obstruction
  
  - Examples include:
    - Hypoplastic Left Heart Syndrome
    - Critical Aortic Stenosis
    - Interrupted Aortic Arch
  
  - In such situations, Qs is primarily dependent on a R → L ductal shunt.
    
    The amount of shunt flow depends on relative pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). As PVR drops after birth, Qp will increase at the expense of Qs.

  - If this condition is not diagnosed prenatally, these babies will often present in cardiogenic shock when their PDA closes.

- Pulmonary (Right-Sided) Outflow Obstruction
Examples include:

- Tricuspid Atresia
- Pulmonary Atresia
- Tetralogy of Fallot with Pulmonary Atresia
- Severe Ebstein's Anomaly
- Critical Pulmonary Stenosis

In such situations, forward-flow Qp (ie, out the pulmonary artery) is absent or severely limited. Thus, mixing of deoxygenated blood with oxygenated blood must occur. This most often happens via a R → L shunt at the atrial level. This mixing will lead to cyanosis.

If atrial level mixing is insufficient and the pulmonary outflow obstruction is severe, cyanosis may be profound. In such a scenario, an emergent atrial septostomy may be needed to establish an alternate source of Qp.
**Qp/Qs**

Qp/Qs describes the ratio of pulmonary and systemic blood flow in single ventricle physiology. The portion of total cardiac output directed Qp or Qs depends on the specific heart lesion (various degrees of obstruction) and the vascular resistance to flow in the pulmonary and systemic circuits. Through manipulation of the Fick equation, one can calculate Qp/Qs.

\[
Qp/Qs = \frac{(SaO_2 - SmvO_2)}{(SpvO_2 - SaO_2)},
\]

Where

\[
SaO_2 = \text{oxygenation saturation of arterial blood},
\]
\[
SmvO_2 = \text{oxygen saturation of mixed venous blood},
\]
\[
SpvO_2 = \text{oxygen saturation of pulmonary venous blood}
\]

Obviously, not all of these variables can be easily measured in an infant prior to cardiac surgery. However, an estimate of Qp/Qs can be obtained with a pulse oximetry measurement and a few assumptions. If the patient has healthy lungs, then one can assume that the SpvO₂ on room air approaches 100%. If the patient is not severely anemic or septic, and has good cardiac function, one can also assume that the systemic arterial-venous oxygenation difference (SaO₂ – SmvO₂) will be about 25%. Thus the above equation can be simplified to:

\[
Qp/Qs = \frac{25}{100 - SaO_2}.
\]
Thus, if your pulse ox is 75%, your Qp/Qs is roughly 1,
if your pulse ox is 80%, your Qp/Qs is roughly 1.25,
if your pulse ox is 85%, your Qp/Qs is roughly 1.67,
if your pulse ox is 90%, your Qp/Qs is roughly 2.5.

NOTE: Remember, Qp increases at the expense of Qs. Thus, higher saturations are not the goal!! As PVR drops over time, it can be very difficult to prevent pulse ox sats from increasing.

Again, these are approximate calculations based on many assumptions. Other data that can help the clinician assess the patient’s overall status include:

- Urine output
- Capillary refill
- Heart rate
- Base deficit

**PROSTAGLANDINS**

Prostaglandin E1 (Alprostadil) promotes vasodilation of the ductus arteriosus. This allows for the ductus to provide blood flow to structures when the cardiovascular development creates a situation in which oxygenation or perfusion is impaired by congenital heart disease.

Side effects include
- Vasodilation and capillary leak
- Hypotension
- Jitteriness
- Temperature elevation
- Hypocalcemia
- Inhibition of platelet aggregation
- Apnea (one must be ready to intubate when starting Prostaglandins!)

Long term adverse effects

- **Infusions > 120 hours:** gastric outlet obstruction, reversible cortical proliferation of the long bones. Widened fontanels, pre-tibial swelling and soft tissue swelling are seen in infusions > 9days.
- **Infusions > 3 months:** cortical hyperostosis and periostitis which resolves over weeks after therapy is discontinued

Dosing

- Initial dose: 0.05-0.1 mcg/kg/minute by continuous IV infusion
- Maintenance dose: 0.01-0.03 mcg/kg/minute
- If possible, initial dose should be weaned to minimize side effects

When on prostaglandins, maintenance fluids should be increased by 20% because of capillary leak.
Caffeine can be given (10mg/kg caffeine base load, followed by 5 mg/kg daily dose) in an attempt to reduce the prostaglandin induced apneic events.

In most cases, infants on prostaglandins will be kept NPO or provided only trophic feeds because of the risk of necrotizing enterocolitis.
MONITORING OF DUCTAL DEPENDENT LESIONS IN THE NICU

All newborns with ductal dependent cardiac defects requiring prostaglandin infusion (regardless of whether they are ventilated or not)

Minimum lab work:
EVERY 8 HOURS arterial blood gases
EVERY 24 HOURS electrolytes, BUN and creatinine and calcium (total or ionized)

If an infant has no arterial line, lab frequency can be modified, but consideration should be given to daily laboratory monitoring of acid base status and electrolyte profile.

Sign-out of these infants off shift should include the acceptable parameters for the laboratory work that will be done and who to contact (sub-specialty services) for changes in clinical status.

REGIONAL SATURATION (i.e. BRAIN & RENAL) MONITORING

Under normal conditions:

- Oxygen consumption in the brain should be greater than that of the kidney.
- For example, if the pulse ox is reading 80%, the brain regional sat monitor should be about 20 points lower (60). The renal sat monitor should be 5-10 points lower (70-75).
However, in the face of pending shock, brain perfusion will be preserved (sats still about 20 points lower than pulse ox reading), while renal perfusion will be reduced (renal sats will now drop to lower than brain sats).

RESUSCITATION IN THE DELIVERY ROOM (DR) – A BRIEF OVERVIEW

Management of the infant in the delivery room is directed at thermoregulation, oxygenation, and ventilation.

The neonate’s temperature falls precipitously immediately after birth. Cold stress increases free fatty acids, which promote insulin secretion and can cause a reactive hypoglycemia.

To counter these heat losses:

- Pre-heat the radiant warmer
- Have the transport Isolette pre-warmed
- Have warm towels available
- Gently dry the infant and remove wet linens quickly
- Put a hat on the infant → greatest area of heat loss is through scalp
- Very immature infant: Saran™ Wrap may be used to cover head (but not face) and limbs

About 90% of babies are born vigorous. The provider has 30 minutes to determine steps for the resuscitation of the baby.
First steps are to warm the baby, position the baby (sniffing position), dry and stimulate the baby to breathe (slap or flick soles of feet, gently rub back. Assess HEART RATE, RESPIRATIONS, and COLOR

HR needs to be >100 beats per minute (8 beats in 6 seconds)

Blow-by O₂ should be quickly offered to any child not “pinking-up” quick enough. If there is no response to blow-by O₂, positive-pressure ventilation (PPV) should be administered with bag-valve-mask should established. Intubation should follow if there is no further response. PIP should be less than 20 mm Hg, with rates of 30 breaths/minute.

CPR is rarely needed in the delivery room. Bradycardia is almost always due to a suboptimal airway and failure to achieve adequate oxygenation. When necessary, 90 compressions per minute are given (1 breath per 3 compressions per minute, resulting in 120 events/minute)

Management of the circulation generally takes place in the NICU. Occasionally difficult resuscitations require volume expansion in the delivery room. Normal saline (NS) 10-15 cc/kg given as a push (given over 30-60 minutes for preemies) is usually the most readily accessible form of volume expansion. An umbilical venous catheter may need to be placed in an urgent fashion.
In-house deliveries require transport from labor and delivery (L&D) to the NICU. This is accomplished in a warm transport Isolette. These isoletes have a ventilator attached as part of the unit. Pulse oximetry and cardiorespiratory (CR) monitoring are also part of many units.

MINIMIZING LUNG INJURY

1. ARDS net Trial: NEJM 2006
   
   TV of 6 mL/kg of 1BW and Pplat \(<\ 30\ \text{cm/LH20}\) decreased all cause 28 day mortality.

2. FACT trial: NEJM
   
   CVOP= 4 or PAOP= 8, Increased ventilator five days by 0.6 days, decrease ICU days. There was a trend to reduced mortality (underpowered). There was an increase in the use of vasopressors.

3. JAMA 2008
   
   2 groups were randomized to PEEP 5-9 and higher PEEP while keeping Pplat (28-30). There were no mortality benefits with higher PEEP.

4. Late steroid rescue study for ARDs NEJM 2006: 354; 1671. No significant difference between steroid vs no steroids regarding mortality.
i. Introduction

Ideally, there would be clinical evidence to use to determine which therapies should be administered to each of our patients. Unfortunately, this type of evidence is not readily available for many of the treatments that we use on a daily basis in our ICUs, and when evidence is available, oftentimes it is not generalizable to the patient you are actively treating. In order to deliver the best care possible for our patients, we must be able to review the available literature that exists about the diseases and treatments that we encounter and use in our ICUs; this requires an awareness of the various types of clinical research and how to interpret them. In addition, quality improvement (QI) science is increasingly being used to improve outcomes in critical care. QI programs are now pervasive in many hospitals and intensive care units and it is important that the practicing intensivist understand the basic fundamental principles of the QI process. The following chapter will provide a brief overview of the various types of clinical research and the techniques and tools of QI.

II. Clinical Research in Critical Care

Broadly defined, clinical research is an investigation that looks at a disease process and reports characteristics about the disease process or outcomes from the disease; outcomes research focuses on studying medical or surgical outcomes from a disease process; and comparative effectiveness research (CER) compares specific
treatments for a disease process to determine if they lead to differences in a particular outcome.

The most common and simplest forms of clinical research are case reports and case series or institutional experiences. These types of reports make up a large portion of the pediatric surgical literature as many of the diseases we treat are rare and not amenable to large prospective trials. These studies have inherent biases as they are retrospective and usually represent either a single surgeon or single center’s experience. Despite these limitations, these reports do provide at least an expert opinion or experience that can be used to draw some information about a disease or treatment and outcomes.

Case-control studies represent retrospective CER studies that will compare the effectiveness of two treatments on outcomes. The value of these types of studies is limited by selection bias but, often, they are the only types of data available. In addition, they can provide evidence to support prospective studies; retrospective case-control studies demonstrating the benefits of low tidal volume ventilation in patients with ARDS eventually led to large multi-institutional randomized controlled trials examining this therapy [1-5].

On a larger scale, outcomes studies or comparative effectiveness studies are being performed using databases. The databases for these studies can be institutional registries or data warehouses, multi-institutional registries such as the Extracorporeal Life Support Organization registry, state or national registries such as the National Trauma Data Bank, or large multi-institutional administrative databases such as the Pediatric Health Information System database or the Kids Inpatient database.
Database studies range in their objectives and can include: descriptive studies of cohorts of patients with a specific disease; longitudinal natural history studies of specific patient populations; resource utilization studies reporting on costs, length of stay, or other variables at a single institution or across institutions; studies of practice variation for a particular disease or treatment across institutions; benchmarking studies comparing rates of specific procedures, outcomes, or complications across institutions; or comparative effectiveness studies comparing two treatments across all patients in the database (single institution or multi-institutional). In all database studies, groups of patients, treatments or outcomes of interest must be identified. It is critical that the identification and grouping of patients, treatments, and outcomes be described and validated as completely as possible. This is where the reliability and validity of these studies must be carefully evaluated. For example, most administrative databases are based on ICD-9 coding; the determination of the presence of a disease, receipt of a treatment, or occurrence of an outcome in a patient is based on an ICD-9 code for that factor being included in the database record for that patient. Therefore, the patients included in a study and the study's results depend on how well coding is performed at each institution and how many ICD-9 codes are included in the various fields of the database (e.g. diagnoses, procedures). Each database will have varying levels of reliability with different rates of misclassification of variables and missing data. These limitations should be addressed and reported as completely as possible in each study.

Prospective observational studies or prospective registries represent slightly higher levels of evidence. These studies identify variables to be collected and then prospective collecting the data. These are less biased because the data is defined and
collected prospectively for important variables, which can control for severity of illness. Although valuable, these studies are limited to establishing associations between variables or treatments and outcomes and cannot directly prove causality.

The traditional “gold” standard of clinical evidence is the randomized controlled trial (RCT) which directly tests a treatment against a “control”. The major advantages of a RCT are that randomization can control for selection bias and the design allows for a causal link to be drawn between an intervention and changes in the primary outcome. However, RCTs require significant financial resources for study staff, treatment interventions, and data collection, monitoring, and analysis. In addition, for conditions that occur infrequently, recruitment of enough patients to adequately power a trial may not be feasible or may require a large multi-institutional effort, which would significantly increase the cost. In addition, the generalizability of the results of a RCT may be limited depending on the inclusion/exclusion criteria; studies that are too restrictive are not generalizable and those that are too inclusive may not show a difference or may include subgroups that did not benefit or were harmed by the investigated treatment. For example, many RCTs of novel anti-inflammatory or anticoagulant therapies for sepsis and septic shock demonstrated that these therapies were only beneficial in the most severely ill patients with the highest risk of death and were potentially harmful in less severely ill patients [6-11]. In addition, the results from RCTs performed in critically ill adults may not be directly translatable to children as was demonstrated with clinical trials of activated protein C (APC) [7, 12-17]. Therefore, it is critical to determine if the patient you are treating is similar to the patient population studied in a RCT before applying its results. Another important aspect to consider when evaluating a RCT is the
appropriateness of the control group in the trial; specifically, did the control group receive routine care as it is practiced at your hospital? For example, if your ICU routinely maintains blood glucose <150 and a RCT of glycemic control demonstrates that an intervention group with blood glucose <90 did better than a “control group” with blood glucose <200, should your ICU change your practice to maintain blood glucose <90? If the control group in a RCT is not reflective of usual care in clinical practice, then the results of the trial cannot be assumed to better than usual care [18-21]. Many landmark RCT trials in critical care have utilized control groups not reflective of usual care, thereby limiting the validity of their conclusions and generalizability [1, 17-27]. Furthermore, the treatment effects in a RCT may not be reproducible outside of the trial setting. This was demonstrated with APC in which phase IV post-marketing studies showed higher rates of bleeding complications with smaller improvements in mortality [15, 17, 28].

Further available types of clinical research include systematic reviews and expert consensus guidelines. Systematic reviews are literature reviews about a particular treatment that will use techniques of meta-analysis to understand the effectiveness of a therapy across multiple studies. These reviews can provide measures of the consistency of the treatment effects of a therapy across studies, insights into why different trials had varying results, and when appropriate, combine the results of the individual studies to provide an overall estimate of the treatment effect of a therapy [9, 10, 27]. Expert consensus guidelines are becoming more common in critical care with multiple guidelines being developed and sponsored by medical societies such as the Society of Critical Care Medicine, American Thoracic Society, American College of
Cardiology, and Infectious Disease Society of America. A consensus guideline is typically developed by a group of national and international experts who review and grade the available literature on a specific disease or therapy, and then make varying levels of treatment recommendations based on the strength of evidence to support the recommendation. An important example of consensus guidelines in critical care is the “Surviving Sepsis Campaign: International Guidelines for the Management of Severe Sepsis and Septic Shock”; these guidelines are sponsored by several medical societies and are periodically revised to incorporate the latest available research [29-32]. The 2012 revision of these guidelines will be published in early 2013.

An additional issue for pediatric critical care physicians is the availability of a large number of studies in adult patients with limited or no data available in children. Specific issues to consider prior to translating these studies to pediatric surgery are the specific endpoints measured and the length follow-up. Much adult critical care research will report in-hospital or 30 day primary outcomes such as death, pulmonary embolism, stroke, deep venous thrombosis, or myocardial infarction. Although these outcomes are important, they occur much less frequently in children and may not be the best primary outcome measures to determine the effectiveness of therapy in our patient population. In addition, our patient population is unique in that they are growing and developing, therefore measuring longer term outcomes, including assessments of the developmental and social impacts of our therapies, should be considered in pediatric critical care trials.
III. Quality Improvement in Critical Care

Despite high levels of evidence or established guidelines with recommendations for “best practices”, adoption of specific treatments that lead to improved outcomes in patients are difficult to obtain using traditional physician level implementation [33, 34]. As an example, hand hygiene has been documented to decrease hospital-acquired infections and the Center for Disease Control has published evidence-based guidelines for hand hygiene [33, 35]. Despite institutions providing the necessary products and supplies for compliance and high levels of staff member awareness of these guidelines, Larson et al demonstrated that hand hygiene compliance was only 56% across 40 member hospitals of the National Nosocomial Infection Surveillance System [33]. Alarmingly, this rate is similar to rates of hand hygiene compliance reported for the past few decades prior to the guidelines. The combination of an increasingly complex patient population, an exponentially increasing medical literature, and variations in physician awareness and interpretation of the available information lead to wide variations in care and adoption of beneficial treatments for our patients.

The quality improvement (QI) process aims to improve care by adopting practice-based approaches to care that can reduce variation and make it easy to apply “best practices” during the treatment of our patients [36]. The principles, processes, and practice of QI science applied to critical care represent ordinary opportunities to use existing knowledge to create extraordinary improvements in the care and outcomes of our patients.

QI represents the science of process management with a learning based approach to understand and then improve the process. In medical care, this translates
into identifying a high priority disease or treatment as the “process” to improve and then applying a series of principles to understand it, identifying areas that can be improved, implementing steps to reduce variation, and ultimately measuring outcomes to document improvement.

One key principle for a successful QI initiative is leadership [36]. This entails having support from the administration or supervisors for the project and identifying a project champion who functions as the team leader. QI initiatives are more likely to be successful if there is institutional leadership support and involvement in the process. The most successful environments for QI are those in which there is an institutional culture that is open to identifying areas for improvements and accepting of changes to existing processes. In addition, successful QI requires the development of a team that includes members involved in all levels of the process including the frontline practitioners. Depending on the process involved, this may include physicians, nurses, respiratory therapists, nutritionists, environmental staff or others. This “bottom up” approach allows the involvement of personnel most intimately involved with the process who can offer unique insights into the process and potential areas for improvement. It also develops a sense of shared ownership or responsibility across all members of the team at all levels of care which will increase the likelihood of adoption of the intervention and the sustainability of successful changes; members of the QI team become champions for the initiative to their respective peer groups and to the multi-disciplinary team. Previous successful studies of QI initiatives to improve hand hygiene and reduce rates of ventilator-associated pneumonia (VAP), central line-associated bloodstream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI) in pediatric
medicine have demonstrated the importance of including a multi-disciplinary team with members from all levels of the process including leaders and front-line staff [37-41].

Fundamental components of the QI process include developing mission and aim statements that summarize the importance of the problem being addressed and the value or goal of the initiative [36]. In particular, the aim statement should identify the intervention targeted with expected levels of change within a specified timeframe. The aim is developed by “mapping” out the process using tools like key driver diagrams, conceptual flow models, or cause and effect diagrams to identify leverage points that represent the best opportunities for improvements. The team will subsequently develop interventions that can affect one or several of the key drivers and lead to successful change to achieve the aim. Interventions to be tested should be specifically defined including how to measure compliance and what outcome to measure to determine success. In critical care, the intervention may be developing a “best practice protocol” using the available literature, guidelines, local and national expert opinions and the experience of the QI team members to come to a consensus protocol that can be implemented in their ICU. Importantly, the QI team should recognize that compliance with an intervention is more likely if it is easily implemented and can be incorporated into everyday workflow. The integral relationships between developing an aim, identifying key drivers, and developing feasible interventions have been well documented in previous QI initiatives [36, 38, 41].

Other key components for a successful QI initiative are measuring and providing feedback on compliance and understanding reasons for non-compliance [36]. Providing feedback to the involved staff will raise awareness about the intervention and lead to
self-driven motivation for improvement. Understanding reasons for non-compliance may identify barriers to implementation that need to be addressed or parts of the protocol that may need to be adjusted. Simple checklists completed at the bedside can be used to collect data on intervention compliance [37]. Monitoring and provision of real-time feedback of compliance were instrumental in the successful implementation of previous hand hygiene and VAP-reduction QI initiatives [38-41].

Key elements of the QI process include continued improvement in compliance with protocols leading to continued improvement in the measured outcomes [36]. This is typically achieved by providing continuous feedback to improve compliance with the intervention and either adjusting the intervention or adding a new intervention if maximum compliance with the initial intervention has been obtained.

QI is a continuous process. Successful adoption and maintenance of an intervention into practice will establish new baseline levels or rates for the measured outcome. These new rates can then be further improved upon by developing new initiatives. QI methods can improve outcomes in pediatric critical care by reducing variation in care and increasing the reliable use of consistent “best” practices.
References


