HANDBOOK

OF

PEDIATRIC SURGICAL CRITICAL CARE

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

Marjorie Arca, MD

Editor-in-Chief

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Chapter 1
OXYGEN KINETICS

Marjorie J. Arca, MD

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 (VO_2) and is equal to 100-200 $cc/m^2/min$. Oxygen delivery (DO_2) is equal to 500-600 $cc/m^2/min$.

$$O_2 \text{ Delivery} = CO [(1.34 \times Hgb \times O_2 \text{ sat}) + (0.003 \times PaO_2)].$$

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 O_2 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.

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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= Cardiac Ouput [(1.34 x Hgb x O2 sat) + (PO2 x 0.003)]

DO2= Cardiac Output [Bound O2   + Dissolved O2]

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.

CO = HR x Stroke Volume   (Figure 1)
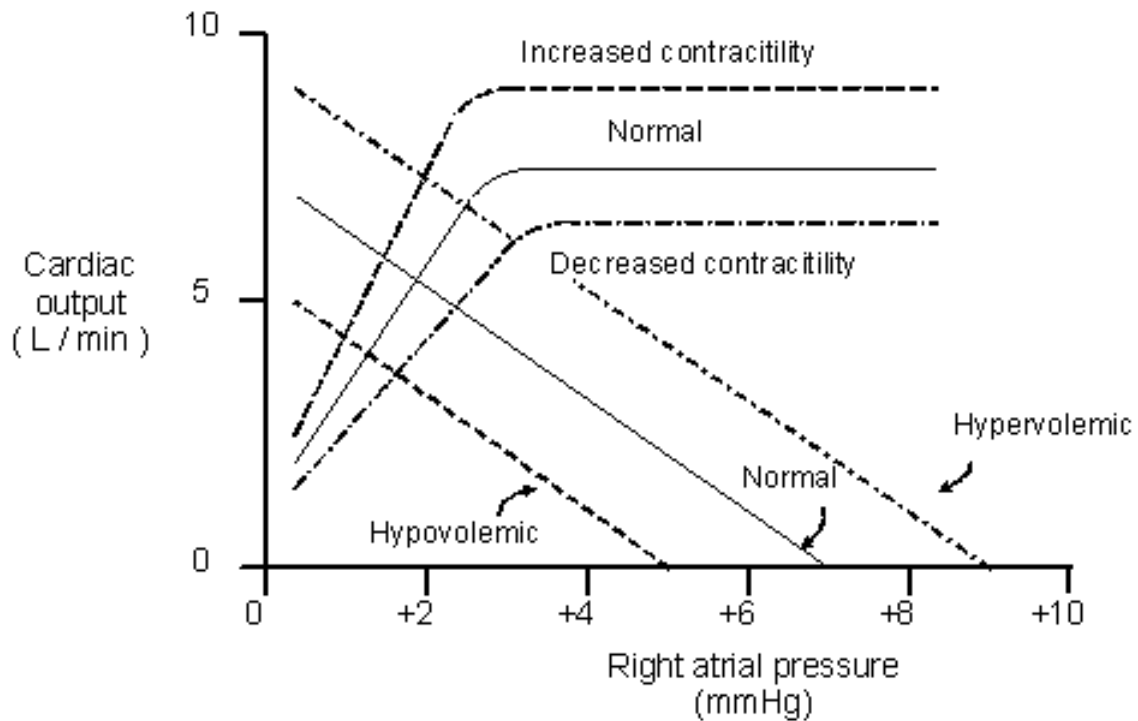
Figure 3

Three cardiac and three vascular function curves plotted on the same coordinate axes.

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.

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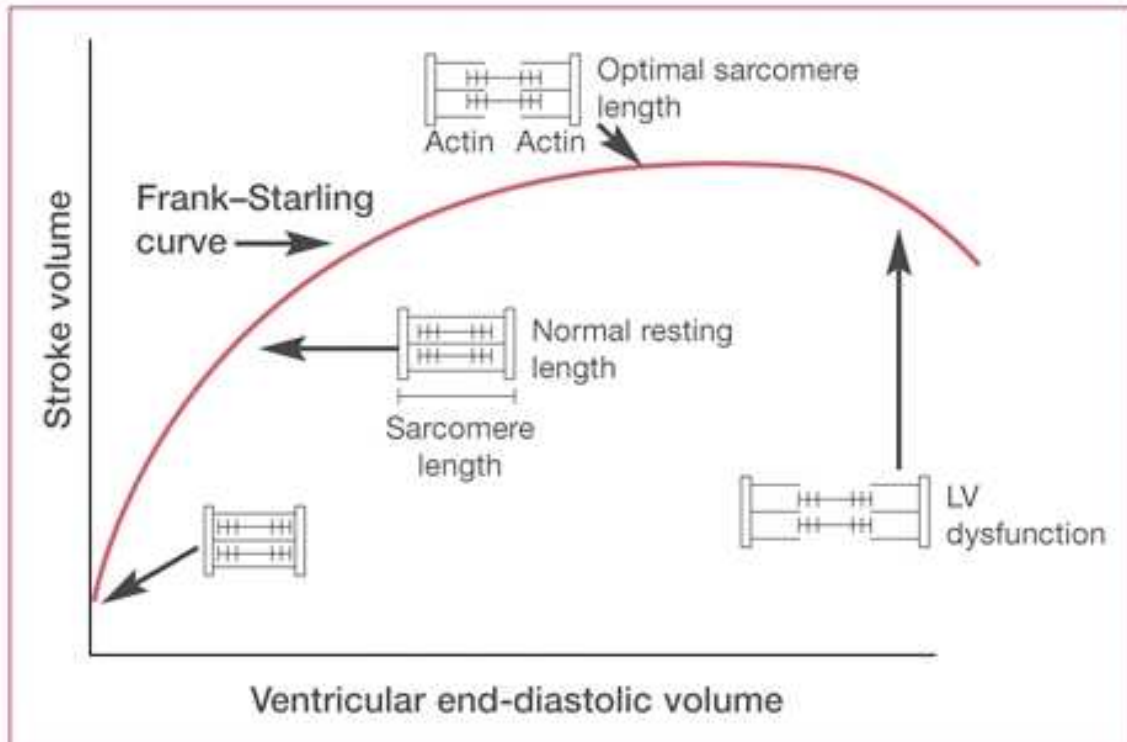
Starling curve.

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 H20. 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 after load 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 after load.

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.

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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 $P_{thoracic}$= -10, the LV has to generate pressure of 110 to obtain systemic

pressure of 100 (must overcome intrathoracic pressure of -10 + 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 $P_{aiarway}$. Effects due to phasic changes such as ΔP 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.

The graph shows Oxyhaemoglobin (% Saturation) on the y-axis (10–100) versus PO$_2$ (mmHg) on the x-axis (10–100).

(Haldane effect: O$_2$ displaces CO$_2$ from Hb)

↑pH
↓DPG
↓Temp

↓pH
↑DPG
↑Temp

(Bohr effect: ↑CO$_2$, ↓pH)
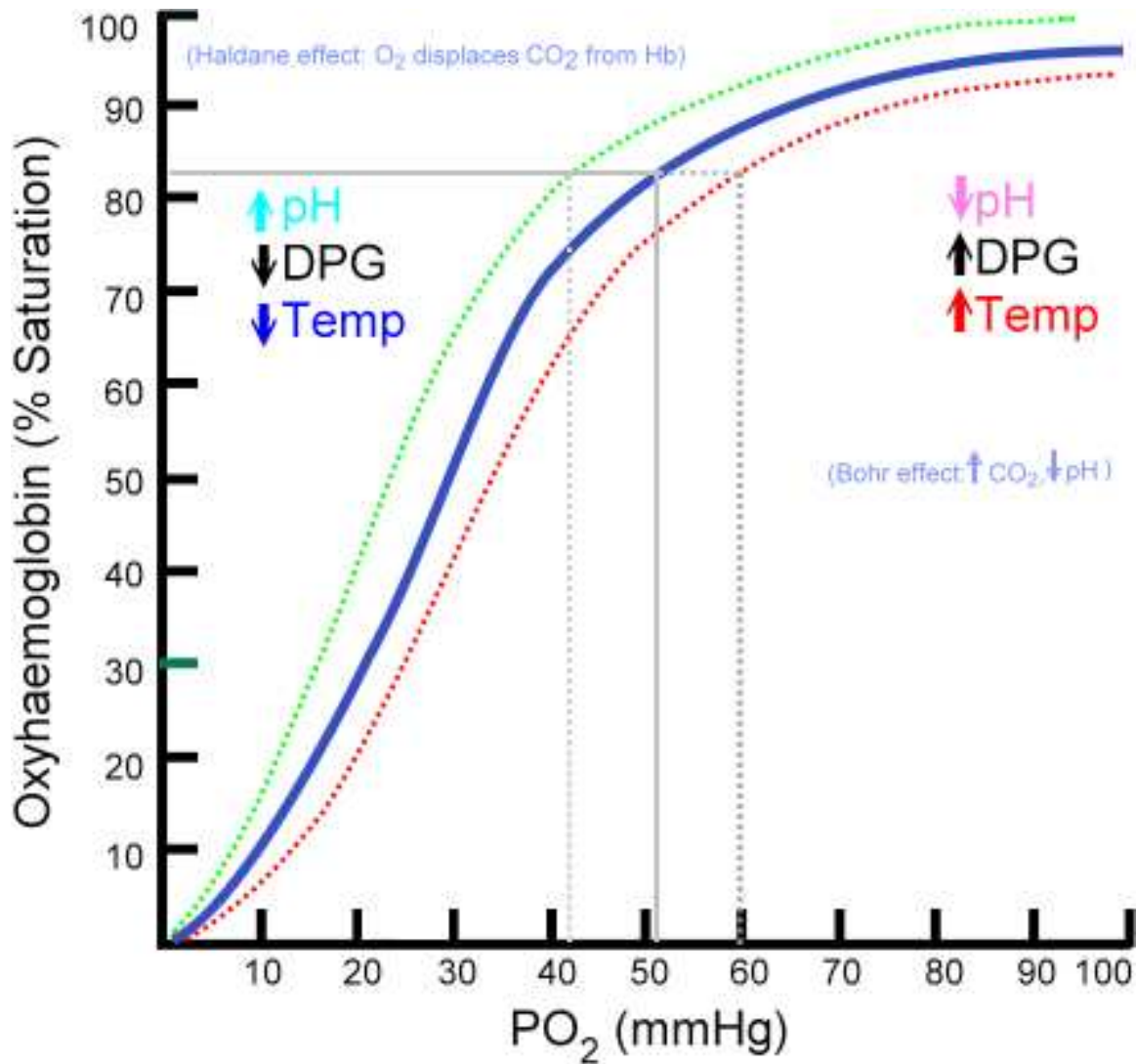
p50 for O$_2$ dissociation is partial pressure of 26-27mm Hg.
In some NICU and PICUs, near infrared regional tissue oximetry to check trends in cerebral and somatic oxygen delivery. Although the absolute value is important the trend of the values provides invaluable dynamic information regarding the 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.

    $$R = 8nL/\pi^4$$ 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.

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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 < 4 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, CO_2 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

$$\frac{Age + 4}{4}$$

However, approximating the size of the ETT to a child's pinky finger or nare is also a well-known maneuver.

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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 $PaCO_2$ (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**)?

Flow over time
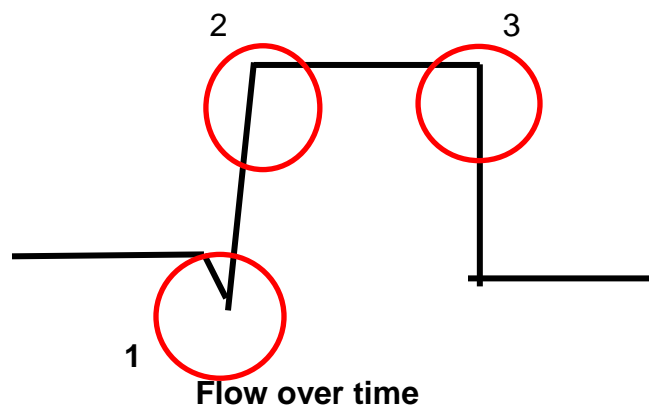
1. Triggering

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 support 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 not 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 (therefor 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…..

COMPLIANCE = Δ Volume / Δ 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)

Pressure Ventilation

Guaranteed pressure, not affected
by the changes in pulmonary mechanics

Compliance ↓
Decreased Tidal Volume
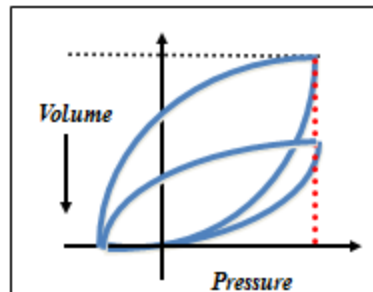
Volume Ventilation

Guaranteed tidal volume, not affected
by the changes in pulmonary mechanics

Compliance ↓
Increased Inspiratory Pressure
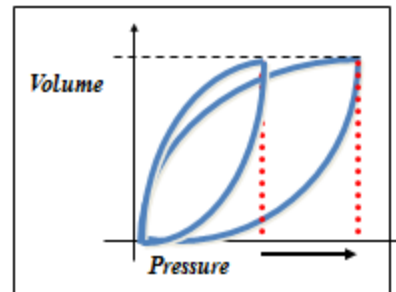
i. Pressure vs. Volume

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
maintain 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.

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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 combine 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.

3. 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 CO_2 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 FiO_2, increasing the PEEP is the most effective way to increase oxygenation (see oxygenation below)

<u>**On VC and PRVC:**</u> 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.

<u>**On PC**</u>: 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.

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E. Troubleshooting

1. Is it working ?

    Look at the patient - Listen to the patient !!

    Look at the data: Pulse Ox, ABG, $ETCO_2$, 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 exam? Atelectasis, bronchospasm, pneumothorax, pneumonia? (Consider needle thoracentesis) Circulation: shock? sepsis?

    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

V_t / PIP   Permissive Hypoxemia: accept PaO2 of 55-65;

SaO2 88-90% in exchange for limiting FiO2 (<.60) and PEEP?

F. NON-INVASIVE VENTILATION…

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.

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Chapter 5
VENTILATION IN THE NICU

Utpala Das, MD

MAKING CONVENTIONAL VENTILATOR ADJUSTMENTS

Increasing PEEP

Benefits:	Risks:
Maintains Functional Residual Capacity (FRC)	Increased risk of air leak
Prevents alveolar collapse	Decreases V_T if no ↑ PIP
Increases Mean Airway Pressure (MAP)	Can cause CO_2 retention
Improves oxygenation	Obstructs venous return
Splints obstructed airways	Less compliant lung

Increasing PIP:

Benefits: **Risks:**

Increases MAP   Obstructs venous return
Improves oxygenation   Increased barotrauma,
Prevents atelectasis   air leak, CLD

Increasing Rate:

Benefits: **Risks:**

Improves ventilation   Inadvertent PEEP
                                                  Inadequate emptying time
                                                  Air trapping

Increasing I-Time:

Benefits: **Risks:**

Increases MAP   Obstructs venous return
Improves oxygenation   Inadequate emptying time
                                                  Leads to slower rates
                                                  Increased barotrauma

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***.

The two conventional ventilators we use in the NICU are:
- Evita XL
- Servo i

Non-conventional ventilation incorporates the following types of ventilators:
- High frequency oscillatory ventilation (HFOV)
- High frequency jet ventilation (HFJV)
- Liquid ventilation

HFJV & liquid ventilation are currently not used in the CHW NICU.

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 V_T for each breath in a newborn depends on their body weight in kg:

Evita XL	=	4-7 cc/kg
Servo i	=	10 cc/kg

The difference is due to where the different ventilators make their measurements of exhaled tidal volume. The Evita takes the measurement at the mouthpiece; the Servo takes the measurement back at the ventilator, so you 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).

This is actually a more physiologic way of ventilating the lung, and is used frequently in the older pediatric and adult population. *However*, this is a little dangerous in newborns, especially prematures, because their lung compliance changes rapidly and we know that high ventilator pressures can result in barotrauma to the still developing lung, which leads to chronic lung disease (CLD).

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.

Where do we set the PIP and PEEP?

Where we set the PIP depends on age, weight, and lung pathology
  Generally, lower PIP's for smaller/premature babies and higher PIP's for larger/term babies.

PEEP is usually set between 4-6
  Again, lower PEEP's for smaller/premature babies and higher PEEP's for larger/term babies.

I-time is usually 0.25-0.45 seconds
    Shorter I-times in infants with RDS
    Longer I-times for older infants with lung disease or decreased compliance

The tidal volume (V_T) is now going to be what varies from breath to breath, but it is a value that is measured by the ventilator and we can follow this number to see how well we're doing with volume delivery on a given PIP.

While in this mode we can *safely* control the amount pressure a newborn lung sees, accepting the fact that the necessary tidal volume may not always be achieved, BUT we'd rather accept lower tidal volumes than use pressures that will induce barotrauma.

We can also follow this value to assist with weaning the ventilator, especially following surfactant administration when compliance changes rapidly. 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

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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. **This is the primary ventilatory mode used in our NICU.**

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). If you are delivering NCPAP using an Evita XL ventilator, you can add a rate, but one must also set a PIP for those breaths (often called, nasal ventilation).

PRVC: PRESSURE REGULATED VOLUME CONTROL
Best of both worlds! Allows one to ventilate with volume, but within pressure limits that are pre-set. Operator sets V_T, PEEP, I-time, and rate, as well as maximum pressure limits the ventilator is allowed to deliver the set tidal volume within. 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.

These are general concepts of conventional mechanical ventilation. Different ventilators, however, have different names for some of these modes as follows.

Differentiating the Ventilator Modes on the Evita XL from the Servo i

EVITA XL	SERVO I
CMV	VC (+/- VS OR PS)
SIMV	PC (+/- VS OR PS)
MMV	PRVC
PCV	SIMV (PRVC + PS, VC + PS, PC + PS)
PCV(+)	AUTOMODE (VC+VS, PC+PS, PRVC+VS)
PCV(+) ASSIST	
(N)CPAP/PS	

Evita XL Modes:

- CMV: Conventional Mechanical Ventilation
  Volume Control (VC) ventilation only. Patient receives a set rate of fixed V_T breaths from the ventilator. Spontaneous breaths between the delivered ventilator breaths are NOT supported. User sets V_T, PEEP, I-time, and rate.

- SIMV: Synchronized Intermittent Mandatory Ventilation
  Volume Control (VC) ventilation plus Pressure Support (PS). Just like CMV, but now any breaths the patient initiates between the breaths delivered by the ventilator are supported with a set amount of pressure that is above PEEP, but still less than PIP.   User sets V_T, PEEP, I-time, rate, and PS.

- MMV: Mandatory Minute Ventilation
  This is an Assist Control (AC) mode using volume ventilation. Every breath the patient initiates is a fully supported breath with however much volume the patient needs for that breath. The patient sets his/her own rate and I-time. If patient becomes apneic, the ventilator will switch into CMV mode. User sets min/max V_T, PEEP, and rate below which ventilator will sense apnea and switch into CMV.

- PCV: Pressure Control Ventilation
  Pressure Control (PC) ventilation only. Patient receives pre-determined rate of fixed pressure breaths from the ventilator. Spontaneous breathing between delivered breaths is NOT supported. User sets PIP, PEEP, I-time, and rate. Just like CMV, only using pressure ventilation

- PCV(+): Pressure Control Ventilation plus Pressure Support
  Pressure Control (PC) ventilation plus Pressure Support (PS). Just like PCV, but now any spontaneous patient breaths are supported with PS. User sets PIP, PEEP, I-time, rate, and PS. Just like SIMV, only using pressure ventilation. **This is our most commonly used mode of ventilation on this ventilator.

Evita XL Modes (continued):

- PCV(+) Assist:
  This is an Assist Control (AC) mode of ventilation using pressure. Every breath the patient initiates is a fully supported pressure breath. The patient sets his/her own I-time and rate. If patient becomes apneic, ventilator will switch back to PCV(+) mode. User sets min/max PIP, PEEP, and rate below which ventilator will sense apnea and switch back into PCV(+). Just like MMV, only using pressure ventilation.

- CPAP/PS: Continuous Positive Airway Pressure + Pressure Support
  This is simply PEEP with PS for spontaneous breaths if patient is still intubated. User sets PEEP and PS. If delivering CPAP through nasal prongs (NCPAP), PS cannot be added. However, a delivered rate can be added, but you must set a PIP for those breaths (nasal ventilation).

Servo i Modes:

- VC: Volume Control
  Straight volume control (VC). Patient receives pre-determined rate of fixed tidal volume breaths. There is no support for spontaneous breaths in between delivered ventilator breaths. User sets V_T, PEEP, I-time, and rate. Either volume support (VS) or pressure support (PS) can be added if you want to provide that for your patient.

- PC: Pressure Control
  Straight pressure control (PC). Patient receives pre-determined rate of constant pressure breaths. There is no support for spontaneous breaths inbetween delivered ventilator breaths. User sets PIP, PEEP, I-time, and rate. Either volume support (VS) or pressure support(PS) can be added if you want to provide that for your patient.

- PRVC: Pressure Regulated Volume Control
  Ventilates with a fixed tidal volume, but within pressure limits that are pre-set. User sets V_T, PEEP, I-time, rate, and maximum pressure limits the ventilator is allowed to deliver the tidal volume of air within. Every breath the patient initiates will be a fully supported breath.

- SIMV: Synchronized Intermittent Mandatory Ventilation

This is simply the feature that allows the ventilator to synchronize its delivered breaths with the inspiratory effort of the patient. It will also automatically support any spontaneous breaths by the patient with pressure support. It can be added to VC, PC, and PRVC modes. **SIMV PC + PS is our most commonly used mode on this ventilator.

Servo i Modes (continued):

- Automode:
  Basically, this is a feature that can be added to VC, PC, and PRVC to turn them into Assist Control (AC) modes. The patient breathes spontaneously in the chosen mode (VC, PC, or PRVC) and every breath he/she initiates is supported with either PS or VS. If the patient becomes apneic, the ventilator will switch back into the mode of delivered breaths.

Nasal Continuous Positive Airway Pressure (NCPAP):
Continuous flow of air that the infant breaths around. Usually set at 4-6 cm. Can be delivered using either long or short prongs. The long prongs are preferred if you are planning on adding delivered ventilator breaths to your patient on NCPAP, although they can become easily obstructed. NCPAP can be delivered on the following devices:

- Flow-Driver: will only deliver flow
- Evita XL: will also allow for delivered breaths
- Infant Star: will allow for synchronized delivered breaths

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 CO_2 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 7-10 rib expansion on chest x-ray, so you should always get a CXR within 30 minutes of putting someone on HFOV. Because the MAP is directly related to oxygenation, you can 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.
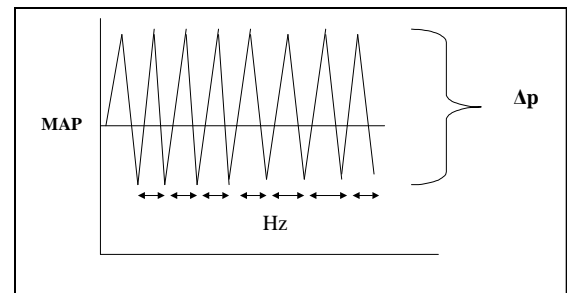
HFOV depends on achieving the optimal lung inflation with the optimal MAP. The aim is to obtain maximal alveolar recruitment without causing over distension. Consequences of inappropriate lung inflation are:
- Under-inflation results in elevated pulmonary vascular resistance and higher O2 requirements. 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 CO_2 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 ↓CO_2)
- Decrease in ΔP → geometric decrease in ventilation (will ↑CO_2)

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 ↑CO_2)
- Decrease in Hz → linear INCREASE in ventilation (will ↓CO_2)

Think of adjusting the Hz in the direction you want the CO_2 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

Chapter 5
EXTRACORPOREAL MEMBRANE OXYGENATION/ EXTRACORPOREAL LUNG SUPPORT

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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.

Circuit Pressure Monitors

Artificial Lung

Pump

Anticoagulation Level Test Device

Heat exchanger

S_vO_2 Monitor

Heater Water Bath

Bladder box controller

Backup Battery
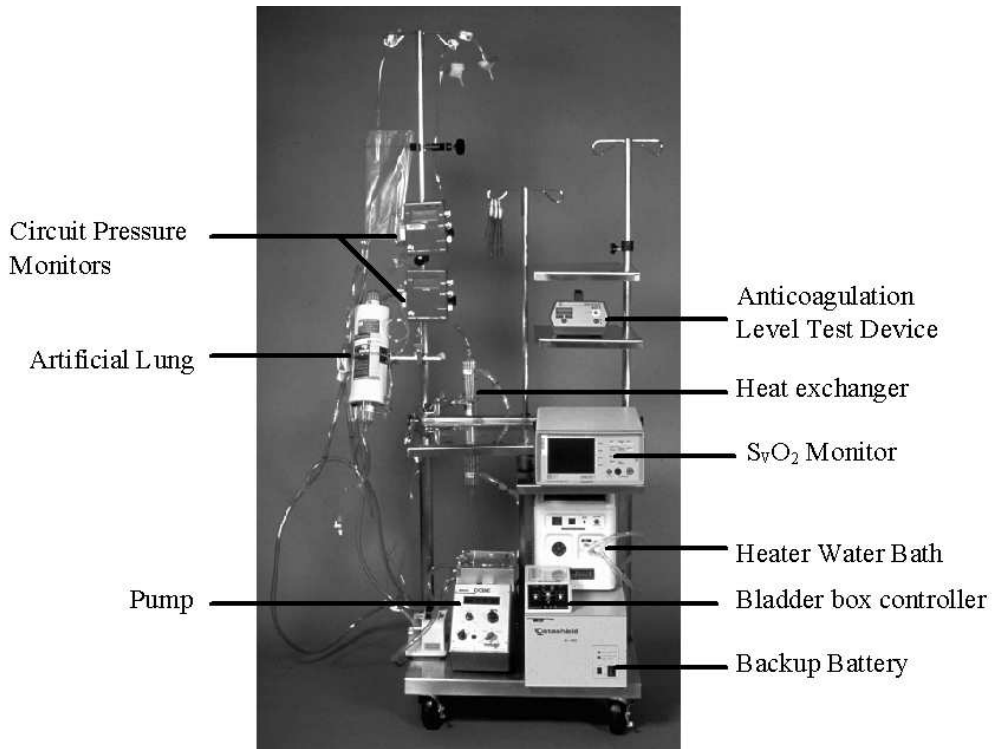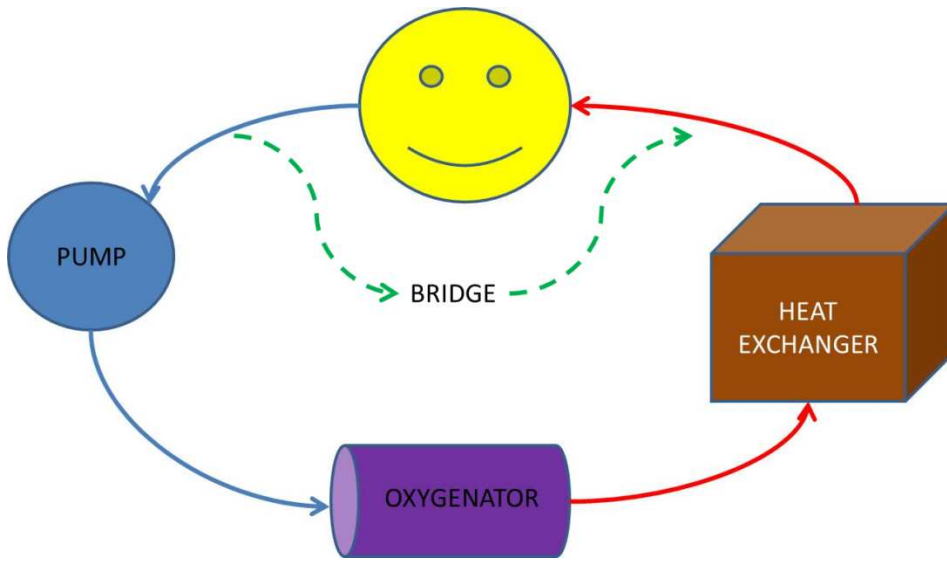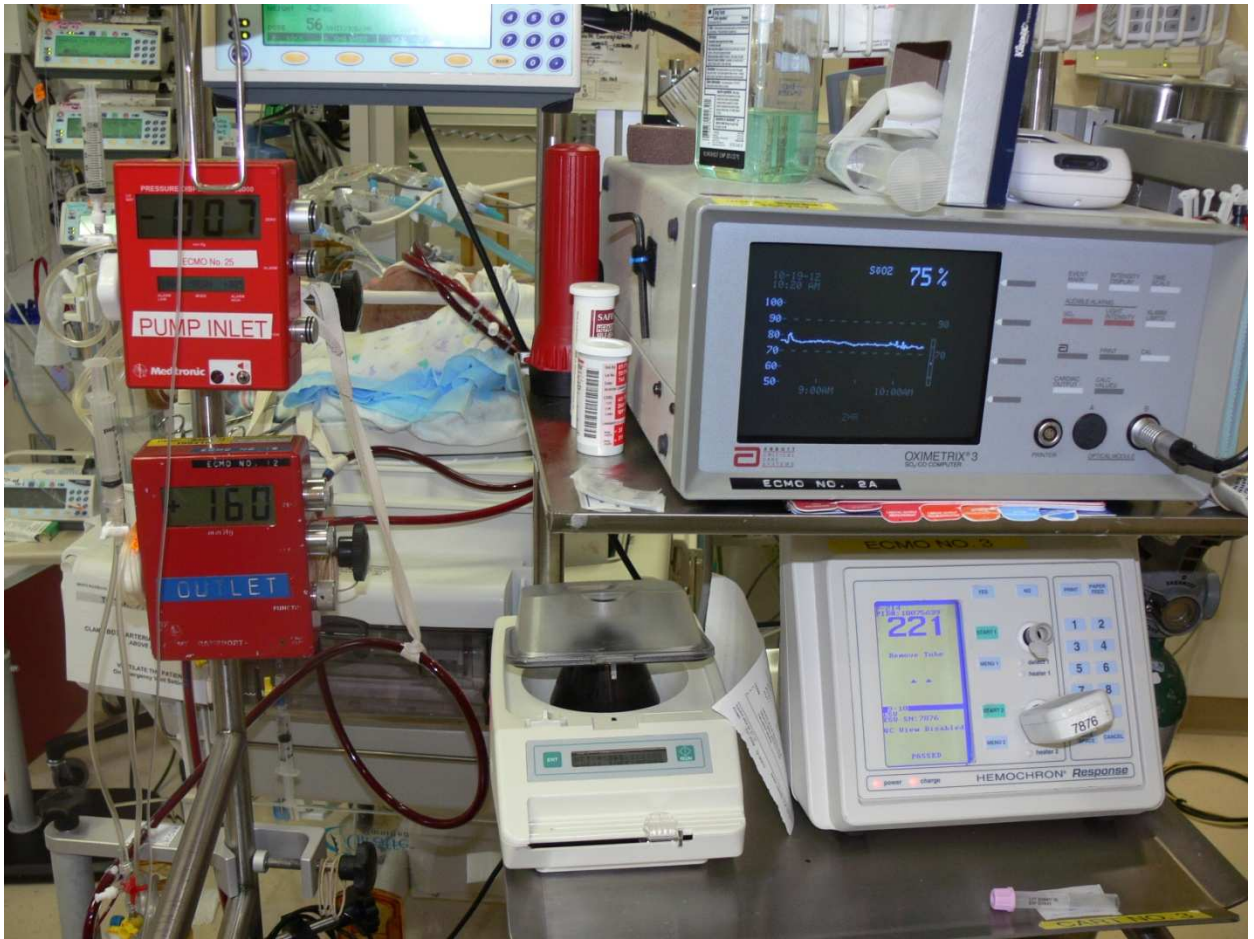
II. Anatomy

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

[5][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.
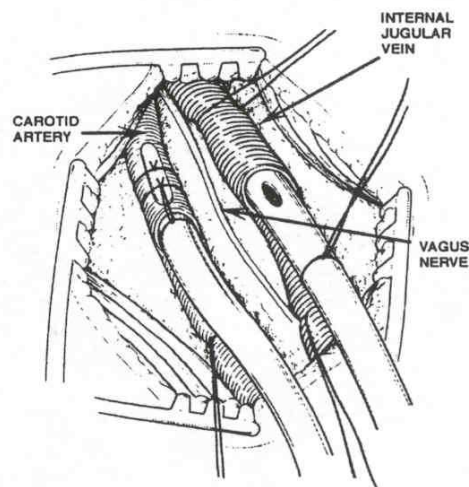
Percutaneous access to the internal jugular and femoral vein is the preferred approach to cannulation in adults and children over 3 years of age.[3] Sequentially larger dilators are placed over a wire using a Seldinger technique. A variety of cannulas are available for percutaneous venous and arterial 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
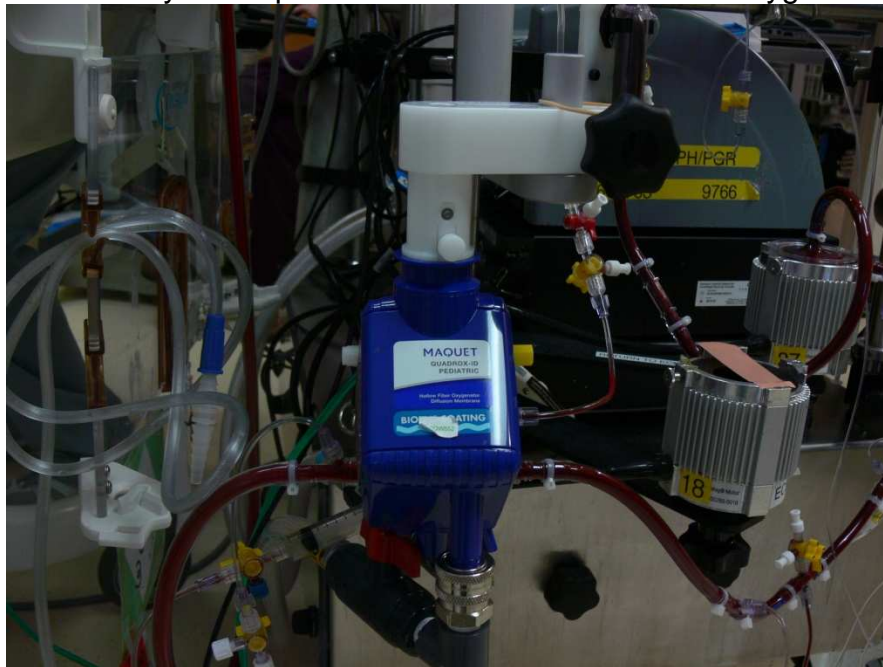
Gas exchange devices (traditionally called oxygenators) are designed to oxygenate and ventilate the blood. "Rated flow" is the amount of desaturated (75%) venous blood with hemoglobin of 12 gm/dL that can be nearly fully saturated (95%) per minute.[4] The maximal oxygen delivery (typically 4-5 mL O2/dL), 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
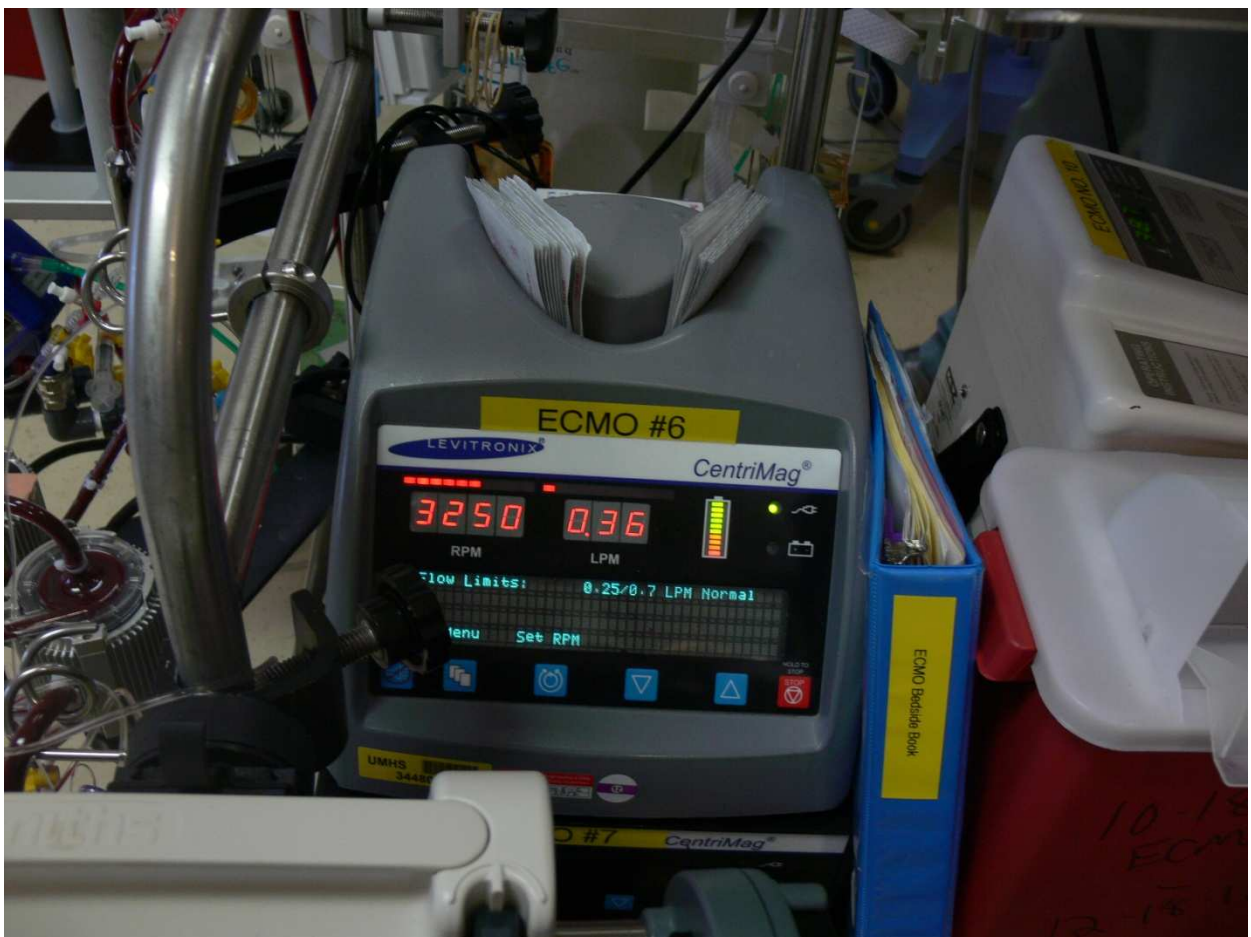
a neonate.

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.[4] 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.[4] 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.[4] 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: $OI = (MAP \times FiO_2 \times 100)/PaO_2$.[15] 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 $[(A-a)DO_2]$ value of $\geq$ 610 torr despite several hours of maximal medical management is associated with a very high mortality.[16] 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 ELCS, 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

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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/mm^3, 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 SvO_2. 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

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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

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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

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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

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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.

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Chapter 6
MONITORING IN THE ICU

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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.

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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 $P0_2$ 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 it's 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

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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 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.

ETCO$_2$ mm Hg

Normal time base

ETCO$_2$ mm Hg

Trend time base
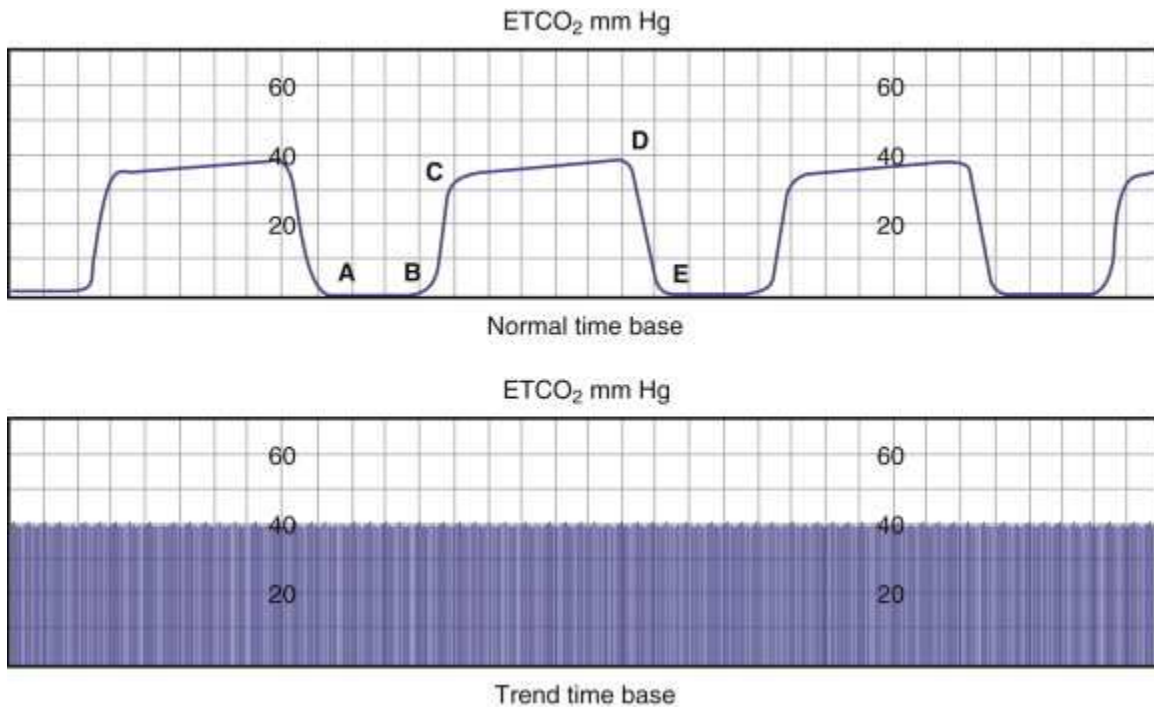
D. Transcutaneous Monitoring

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 PCO2, underestimation of arterial PO2, and sensitivity to variations in cutaneous perfusion. These devices are generally used in neonates only.

IV. Cardiac Monitoring

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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 (SvO_2=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 4th 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.
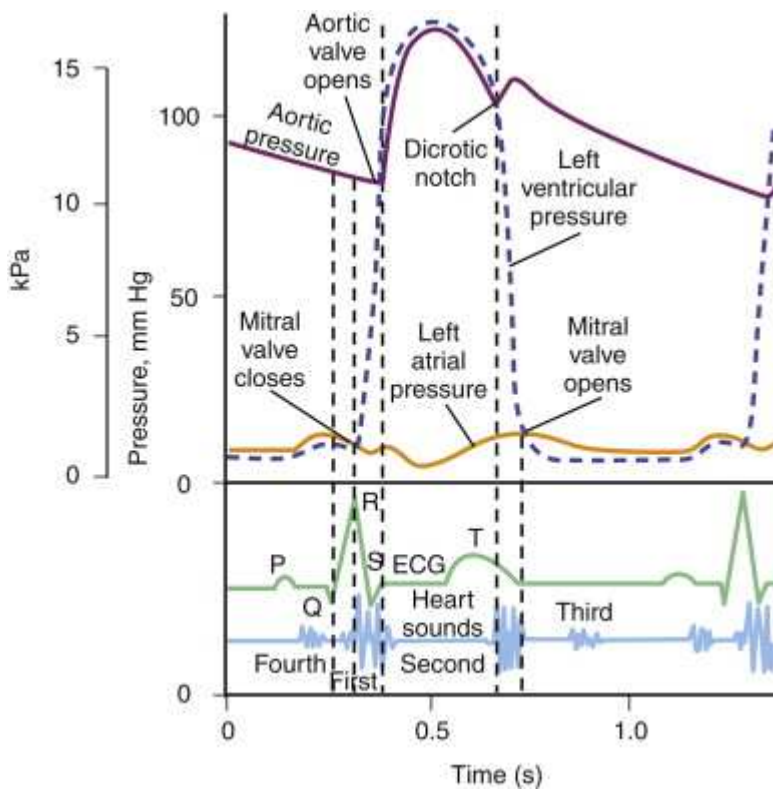
FIGURE 1: FURHMAN FIGURE 21-7. NEED PERMISSION.

Volume Status and Cardiac Performance Monitoring

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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.
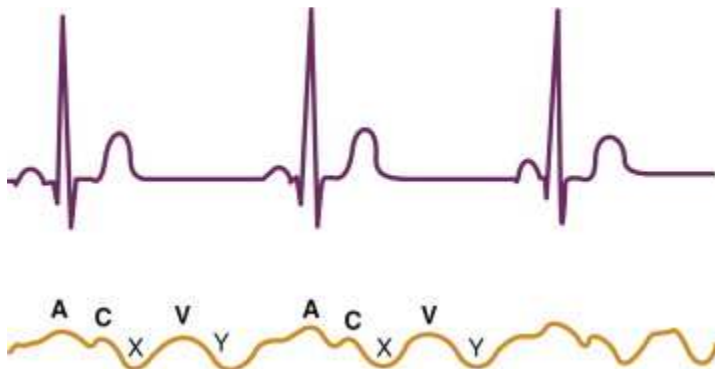
FIGURE 2FUHRMAN FIGURE 21-5 NEED PERMISSION

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 H_2O. 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 ($ScvO_2$) 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 (SvO_2) as measured from the pulmonary artery. $ScvO_2$ should be measured from the SVC, as IVC measurements are highly variable with changes in mesenteric circulation and do not correlate with true SvO_2. $ScvO_2$ has been utilized to guide early goal-directed therapy for adult sepsis with good outcomes. Normal SvO_2 is 65-75%, with lower

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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.
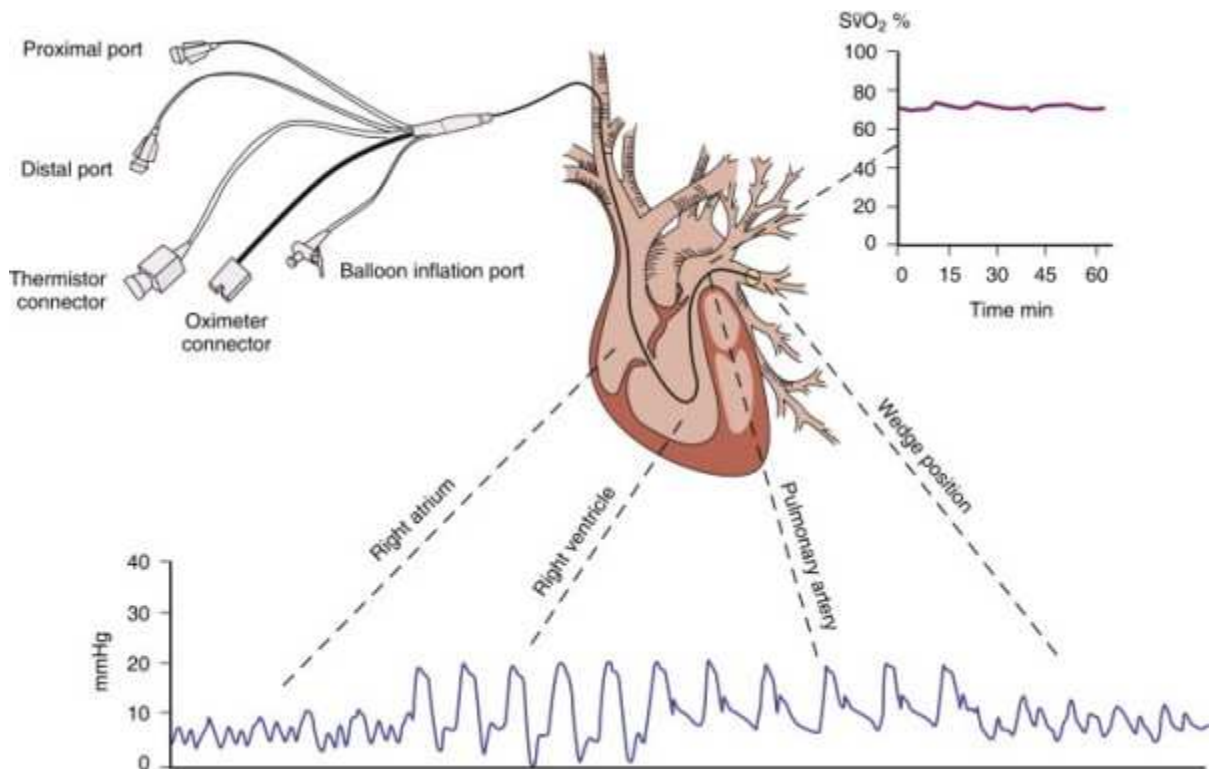
FIGURE 3 FUHRMAN FIGURE 21-10 NEED PERMISSION

E. Cardiac Output Monitoring

Cardiac output monitoring can be measured by two methodologies: the Fick method (calculated from oxygen consumption--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.

Chapter 7
SHOCK,
LOW CARDIAC OUTPUT,
AND INOTROPIC SUPPORT

Pramod S. Puligandla, MD

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 <u>is not equivalent to hypotension</u>. 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 3^0C. 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

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

(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

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measurement of arterial-venous oxygenation gradients (A-V O_2), mixed venous

saturations (SvO_2), acid base, and lactate.

A-V O_2 is the difference between arterial oxygen saturation and SvO_2, and

is normally <30%. Changes in A-V O_2 are reflective of variations in CO when

oxygen demands are stable in the absence of anemia or hypoxia. A high A-V O_2

in combination with elevated serum lactate could indicate an inability of the

tissues to consume oxygen the cellular level.

SvO_2 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. PaO_2). Normal SvO_2

values range from 70-75%. Values <65% suggest increased oxygen extraction at

the tissue level and is indicative of impaired tissue perfusion. Importantly, SvO_2 is

affected by all 4 components that affect oxygen delivery (CO, Hgb, PaO_2, and

SaO_2). Furthermore, an increase in oxygen consumption without a compensatory

increase in oxygen delivery will also lead to low SvO_2 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 PaO_2 and $PaCO_2$ 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 DO_2. 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. SvO_2 and lactate measurements should be obtained with the goal to be >70% and <2 mmol/L, respectively.

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 bicabonate 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 SvO_2 > 70% (i.e. warm shock), consideration should be given to the use of norepinephrine and/or vasopressin. In patients with an SvO_2 <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 SvO_2 <70%, low blood pressure and poor peripheral perfusion (i.e.) cold shock, optimization of Hb > 10 g/dL and an

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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 have been obtained. Urinary cortisol measurements are another alternative prior to steroid supplementation..

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 cylic 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 norepineprine (6). 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 ventricvular 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 intra-pulmonary shunting (i.e. reduced PaO_2), 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

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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

Agent	D_1	D_2	Alpha $_1$	ß_1	ß_2	V_1
Dopamine	0.5-10	0.5-10	>10	3-10		
Norepinephrine			+++			
Epinephrine			0.1-1.0+	0.05-0.1	0.05-0.1	
Isoproterenol					+++	
Phenylephrine			+++			
Dobutamine				++	+	
Vasopressin						++

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].

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Chapter 8

SEPSIS

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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)*

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At last two of the following criteria, one being abnormal temperature or leukocyte count.

- **Hyper or hypothermia**, defined as core temperature of > 38.3℃ or < 36℃.

- **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 <10th percentile for age in the absence of external vagal stimulus, β-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:

AGE	TACHYCAR DIA (beats/min)	BRADYCARD IA (beats/min)	TACHYPN EA (breaths/mi n)	LEUKOCYTOSIS/ LEUKOPENIA (WBC x 10^3/mm)
0-7 days	>180	<100	>50	>34
8-30 days	>180	<100	>40	>19.5 or <5
30 days -1 year	>180	<90	>34	>17.5 or <5
2-5 years	>140	n/a	>22	>15.5 or <6
6-12 years	>130	n/a	>18	>13.5 or <4.5
13-18 years	>110	n/a	>14	>11 or <4.5

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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

Organ System	Definition of Organ Dysfunction	
Cardiovascular (dysfunction despite volume expansion with ≥ 40 ml/kg of isotonic fluids in 1 hour)	Need for vasoactive medications at any dose (dopamine >5 mcg/kg/min)	**OR:** Presence of at least 2: Oliguria, Lactic acidosis (>1 mmol/L), Unexplained metabolic acidosis, Capillary refill > 5 sec, Mottling, Core to peripheral temperature gap >3°C
Respiratory (dysfunction unrelated to congenital heart disease or chronic lung disease	PaO_2/FiO_2 <300 **OR** $PaCO_2$ >65 **OR** $PaCO_2$ 20 mmHg >baseline **OR**	FiO2 >50% for O2 saturation >92% **OR** Need for invasive or noninvasive positive pressure ventilation
Neurologic	GCS ≤ 11 or decrease by ≥ 3 from abnormal baseline	
Hematologic	Thrombocytopenia (<100,00/mm^3) or decrease by 50% over course of 3	**OR** Coagulopathy with INR > 2

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	days, if already chronically low	
Renal	Acute Kidney Injury (AKI): Creatinine ≥ 2 times normal for age	**OR** Doubling of the baseline creatinine
Hepatic	Hyperbilirubinemia (>4 mg/dl) *excluding newborns	OR: ALT ≥ 2 times normal for age

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 sings 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 with children 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 phosphodiasterase 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.

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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 blood stream 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 deesclation 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

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 classifies 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

+

Consider undiagnosed congenital heart disease

+

Fluid resistant Shock

Catecholamine resistant shock

Persistent Shock

Refractory

Shock

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.

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Chapter 9
FLUIDS, ELECTROLYTES & NUTRITION

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I. Nutritional Physiology

Provision of nutritional support for critically ill patients is an important element of their care, especially for infants and children who have requirements for growth and development in addition to maintenance requirements. Surgical patients have further supplementary requirements 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 nutrient 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. 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 (CO_2/O_2) 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 further 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 affects both short and long term outcome.

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 of these various half-lives explains why patients with a low pre-albumin are malnourished even if the albumin 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 are significant. Protein losses can be measured but estimates range from 12-29 grams per liter. [2, 3]

II. Maintenance Fluids

While maintenance fluid requirements for adults allow a wide range of administration from 2-3 liters per day, the provision of fluid for infants and

children is more closely calibrated with their lean body mass. Several issues can affect the suggested rate of fluid administration including age, environment, patient-related factors and disease-related factors. Age requirements are essentially related to body surface area in the infant. In addition, during the first week of life, infants are expected to lose 10-15% of body weight and a greater percentage for the more 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.

Birth Weight (gm)	DOL 1 (ml/kg/d)	DOL 2 (ml/kg/d)	DOL 3 (ml/kg/d)
<700	100	120	120-140
700-2500	80	100	120
>2500	60	80	100

Electrolytes are not needed initially so that 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 1-2, urine output and serum sodium are the most useful parameters to follow in determining the appropriate rate of fluid administration. Abnormal serum sodium levels should be managed by changing the rate of fluid

administration and not by adding Na supplementation. Hyponatremia is most frequently due to excess fluid administration. Conversely, hypernatremia is most frequently due to dehydration.

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. In a child > 4 weeks of age, D5 0.45NS with 20 mEq KCl/L is used.

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 a higher body surface area leading to greater evaporative loss. These patients require a bolus of 20 ml/kg of crystalloid after birth and increase of the maintenance infusion by 20-25% until coverage of the intestines is accomplished. Concurrent gastrointestinal fluid losses are especially important for surgical patients. Losses should be replaced with consideration of both volume and electrolyte concentration of fluids. 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 or 0.9% normal saline. Urine output should be monitored to ensure adequate perfusion.

Gastrointestinal Fluid Losses

Electrolyte Composition	Na+	K+	Cl-	HCO3

(mEq/L):				
Gastric	20-80	5-20	100-150	
Bile	120-140	5-15	80-120	40
Small bowel	100-140	5-15	90-130	
Diarrhea	10-90	10-80	10-110	

Because the electrolyte concentration of gastrointestinal fluids is variable, laboratory analysis aids the precision of replacement.

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 cation and major osmotic component of the serum being essential for growth as well as fluid balance. 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 are also affected by the administration of naturetics including theophylline, caffeine, furosemide and dopamine.

Potassium is an essential electrolyte for proper cardiac and neurologic function. Daily requirements are 1-2 mEq/kg/day in the first week of life, increasing to 2-3 mEq/kg/day thereafter. The potassium replaces the obligatory

renal loss of potassium. Consequently, for decreased renal function, careful adjustment and often cessation of potassium supplementation is 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. Chloride deprivation occurs over several days and is rare. 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 formulas such as catheter insertion complications or malfunction, sepsis, and metabolic complications. 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. 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 intestintal lengthmay benefit from the addition of pectin, psylium 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 elemental formula alternatives. Nutritional supplementation can be accomplished by adding Duocal (fat and carbohydrates, 42 kcal/tbsp), vegetable oil, 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 few months of life. Donated expressed breast milk (EBM) can be used when the mother cannot produce sufficient amounts. 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, are used in infants with lactose 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 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), 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 metabolism such as disaccharidase deficiencies.   Diet powder 3232A, which is free of monosaccharides and disaccharides, is a bovine milk protein hydralysate 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 individual addition of carbohydrate.

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 develop significant morbidity if starvation exceeds 5-7 days. This is especially true for patients with head injuries or burns. 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 the 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 more closely as their glucose level may fall more rapidly and 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 fail to maintain 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, infusion of dextrose should be initiated. Symptomatic hypoglycemia should be treated with 2 ml/kg bolus of D10W followed by a continuous glucose infusion. Glucose levels should then be checked at 30 minutes 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 (LA) are considered pro-inflammatory (prostaglandin and ARA precursor), while Omega 3 (ALA) are considered anti-inflammatory (DHA precursor). The ratio is important because of competition by these two fatty acids for the same enzymes in physiologic processes. The omega 6 to omega 3 ratios found in the diet are currently very high with ratios of 10:1 or higher, markedly different from the 1:1 ratio assumed to occur in the diet of our evolutionary ancestors. The situation has been implicated in promoting inflammation, thrombosis and vascular constriction leading to a variety of

vascular and neurologic medical conditions. 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. Among vegetable oils, flax seed oil has a ratio of 1:3, canola 2:1, soybean 7:1 and olive oil ranges from 3-13:1. Corn oil has a very high proportion of omega 6 fatty acids with a ratio of 46:1. Sunflower, cottonseed, peanut and grapeseed oils all have very little omega 3 fatty acids.

The most common intravenous solution for lipid administration is Intralipid, made from soybean oil. Both the 10% and the 20% solutions of soybean oil each 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]

Fat is generally required for skin integrity but especially for brain growth and development and proper functioning. The balance of essential fatty acids appears to be the most important factor to providing healthy lipid nutrition, but patients rarely can develop essential fatty acid deficiency syndrome. Neonates, especially premature infants, can develop this syndrome within a few days of life

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without the provision of fatty acids. The syndrome is characterized by dry skin, defective wound healing and respiratory distress. Provision of at least 5% of calories as fat is preventive. As a practical point, each ml of 20% Intralipid provides 1.1 kcal of linoleic acid. EFA needs would be met in an infant with 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 protein catabolism and decreased extrahepatic protein synthesis. Evidence of this increased need is found by measurement of urinary nitrogen loses which are 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 presumed 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.

	TROPHAMINE 1.6%	TRAVASOL 1.6%
ESSENTIAL AMINO ACIDS		
Isoleucine	131	76
Leucine	224	100
Valine	125	73
Threonine	67	67
Methionine	53	93
Tryptophan	32	29
Phenylalanine	77	100
Lysine	131	93
SEMI-ESSENTIAL AMINO ACIDS		
Histidine	77	70
Tyrosine	37	6
Cysteine	0	0
Taurine	4	0
NON-ESSENTIAL AMINO ACIDS		
Glycine	59	331
Alanine	85	331
Proline	109	67

Serine	61	0
Arganine	195	166
Aspartate	51	0
Glutamine	80	0

Special situations require specific formulations of amino acids in parental nutrition. Branch chain amino acids (valine, leucine, isoleucine) are the main proteins used in parenteral nutrition. 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 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. The 10% calcium gluconate solution is typically used providing 1 mEq of calcium, which equals 200 mg of calcium. 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 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 occurs with chloride administration. Acetate is especially important in the preterm neonate who normally excretes excess bicarbonate. Any time that acetate is used to treat the metabolic acidosis, the cause of the metabolic acidosis must be assiduously sought.

Trace elements are required for growth and normal metabolism in such small amounts that individual supplementation is not feasible. The trace

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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 gastrointestinal losses administration of 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 dermatitis, glossitis and alopecia. Chromium deficits cause hyperglycemia. Copper deficits cause an anemia that is not responsive to ferrous sulfate.

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

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 is 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 children usually receive 35 kcal/kg/day. Term infants should receive 80-100 kcal/kg/day; preterm infants 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](p S29) In addition, overreliance on glucose causes excessive CO_2

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production which 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 immune function. Lipids may provide up to 50% of total calories. Fat 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 follow 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 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

$$\frac{\% \text{ glucose x ml/kg/day}}{144} \quad or \quad \frac{\% \text{glucose x ml/hr}}{6 \text{ x body weight (kg)}}$$

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. 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 show that this complication can be prevented or treated with restriction of soy based lipid formulations and replacement by fish oil. 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 are checked with each increase in lipids. After a few days of stable values, these items are checked twice weekly. Liver enzymes, bilirubin, alkaline phosphatase and CBC are checked every other week.

Adequacy of nutrition can be calculated with indirect calorimetry and measurement of the respiratory quotient. $RQ = CO_2/O_2$. Patients with an RQ of 1

indicate mainly carbohydrate utilization while an RQ of 0.7 indicates pure fat

utilization. Intermediary values indicate a mixture of fuels. Lipogenesis occurs

with overfeeding and is indicated by a RQ of 1.1 or greater. Estimations of

energy needs may either too high or too low when compared to measurement by

indirect calorimetry. [4] Estimation of RQ may be helpful when trying to wean a

patient off ventilatory support. Breaking down mostly carbohydrate substrate

(i.e., RQ = 1), requires more production CO_2; substituting a more fat-based

nutritional source may be considered in this situation.

Urine urea nitrogen (UUN) is

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.

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Chapter 10
RENAL PHYSIOLOGY, ACUTE RENAL FAILURE AND RENAL REPLACEMENT THERAPY IN CHILDREN

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I. 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 without depending on maternal regulatory mechanisms. This adaptation includes a tight homeostasis of water and electrolytes.

One of the first events in the adaptation process is the "physiologic weight loss" in which a normal neonate loses approximately 10% of the body weight in the first week of life. This loss is due to the elimination of excess total body water and sodium through the kidney and represents a loss primarily from the extravascular extracellular (EC) compartment. As expected, decreases in the EC water are undertaken without compromising the circulatory volume; homeostasis is achieved by slow mobilization of water into the intravascular compartment from existing reservoirs in skin and muscle. This important phenomenon is believed to be regulated by prolactin and aimed to eliminate excess water from the neonatal tissues.

Failure to recognize this normal adaptation 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 as they have a decreased area of reabsorption (due to small and immature proximal tubules) and ineffective interstitial reabsorptive capacity and sodium transport mechanisms. Sodium is mainly reabsorbed in the proximal tubules and distal tubules under the influence of aldosterone, which is produced by the adrenal cortex more effectively in term than pre-term infants. The responsiveness to aldosterone is therefore better in term infants.

Physiologic mechanisms of sodium reabsorption in the proximal tubule include Na/H exchange transporters, Na-Pi 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. Other systems of sodium reabsorption utilize amiloride-sensitive sodium channel (ENaC).

Renal fluid and electrolyte balance is possible not only by a fully functional tubular system but by mature renal interstitium capable of concentrating urine. This mechanism is important to regulate 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 mentioned physiologic changes are more pronounced in prematures 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.

The renal function of infants approaches adult state at the end of the first year of life. Useful parameters to assess the renal function in children less than 1 year of age are the glomerular filtration rate (GFR), urine output, urine concentrating capacity, sodium balance, acid/base balance and plasma renin activity.

II. GFR

Glomerular filtration rate (GFR) refers to the amount of serum filtrated across the glomerulus each minute. A GFR of 50 mL/min per $1.73m^2$ is considered normal in the first week of life, increasing to 86 mL/min per $1.73m^2$ at the end of the first year. Adult levels of GFR are attained around three years of age, as the lean body mass increases and steady creatinine production is achieved (90-140 mL/min). [25]

Inulin clearance is the standard method to determine the GFR because it is excreted 100% by the kidney after its administration. The test involves the

measurement of 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:

$$C = UV/P,$$

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

The results are corrected according the surface body area applying the following formula:

Height x Weight x 0.007184

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:

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

(140 – age)(body weight in kg)/72 x PCr,

where PCr=plasma creatinine

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

K x height (cm)/PCr (mg/dL),

where 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.

III. Urine output

Adequate urine output (UO) is a clinical indicator of an 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.

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. Similarly, children in the ICU receiving drugs that increase the UO by inducing diuresis, even with deteriorating renal function, will often have an acceptable UO. Examples of these are diuretics, dopamine and mannitol.

IV. 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.

GFR decrease >75%

UO<0.3 mL/kg/h X 24h
or
Anuria X 12h

Increased
creatinine X 3

GFR decrease >50%

UO<0.5 mL/kg/h X
12h

Increased creatinine
X 2

Loss renal function
>4wks

GFR decrease >25%

UO<0.5 mL/kg/h X
6h

Increased creatinine
X 1.5

ESRD

I   F   L   R   E
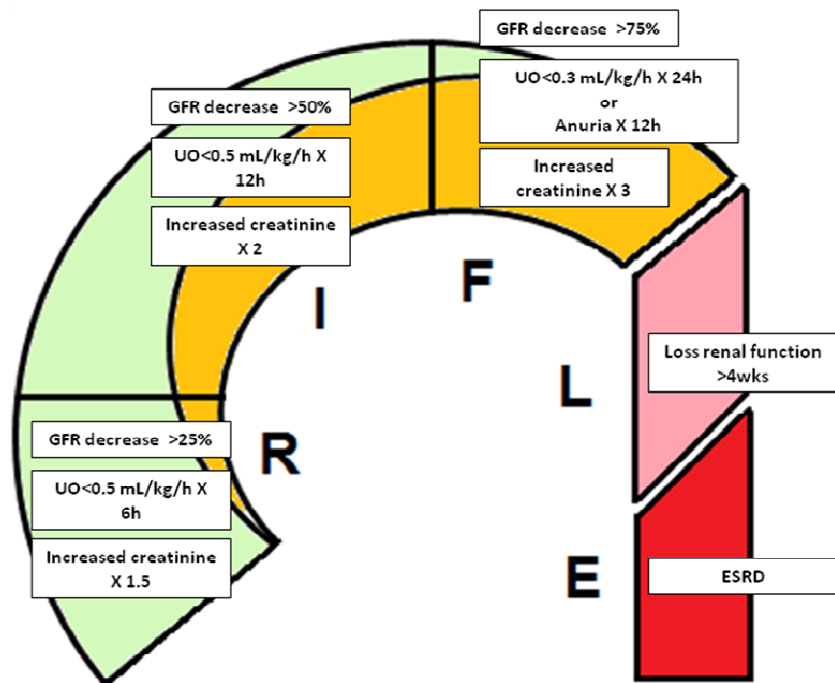
A. Renal failure criteria

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 overcome 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 these criteria, the acute deterioration of the kidney function follows a series of steps to progress to a complete and permanent cessation of renal function. These criteria are known as the RIFLE criteria for acute renal

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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 application of the RIFLE criteria was investigated in depth in order to determine its correlation with outcomes from renal failure. Some groups identified that the initiation of RRT in early stages or "less severe" renal failure (RIFLE-R, RIFLE-I) was 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]
A recent review demonstrated that the RIFLE criteria were inconsistent when used to determine the morbidity and mortality outcomes in children with RF. [28]

To apply the RIFLE criteria and estimate the stage renal function however, it is important to know the baseline creatinine level. This may be difficult when baseline laboratory is not available but can be estimated using the "modification of diet in renal disease" (MDRD) formula. MDRD 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. We 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]

B. Causes of renal failure

In developed countries, only 10% of cases of ARF are due to primary kidney disease. The majority of causes are secondary to cardiac surgery for congenital heart disease, ATN, 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*
1. Hypovolemia
    - Hemorrhage
    - Extensive burns
    - Diarrhea
2. Decreased pre-load
    - Increased intrathoracic pressure with ventilation
    - Pneumothorax
    - Cardiac tamponade
3. Cardiac pump failure
    - Heart failure
    - Cardiomyopathy
4. Renovascular disease

5. Drugs that impair renal auto regulation (ACE inhibitors, anti-inflammatory drugs)

6. Liver failure

In pre-renal failure, the kidney attempt to retain sodium and water to increase the intravascular volume by means of activation of the renin-angiotensin-aldosterone axis. Non-steroidal anti-inflammatory medications inhibit this physiologic response causing renal insufficiency during states of hypoperfusion

During renovascular disease and renal hypoperfusion, the release of angiotensin promotes vasoconstriction of the efferent arteriole providing this way enough pressure for transglomerular filtration. The administration of ACE inhibitors, inhibit this compensatory mechanism by dilating the efferent arteriole.

Mechanical ventilation or other situations that increase the intrathoracic pressure under conditions of inadequate cardiac filling volumes leads to renal hypoperfusion and renal failure.

b) *Renal*

1. Acute tubular necrosis (ATN)

   - Shock states

   - Sepsis

   - Radiocontrast dye

   - Myoglobinuria

   - Acute tumor lysis syndrrome

2. Segmental glomerulosclerosis

3. Cardiac and aortic surgery

4. Acute interstitial nephritis (AIN)

   - Nephrotoxic drugs (Antibiotics, carbamazepine, NSAID's, diuretics, ACE inhibitors)

   - Infectious (Bacterial, viral)

   - Glomerulonephritis

   - Systemic lupus

   - Acute transplant rejection

Parenchymal damage prevents the kidney to normally absorb water and electrolytes and elimination of products 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 AIN, inflammatory infiltrate of the extraglomerular structures (tubules and interstitium) and activation of proinflammatory cytokines lead to acute epithelial injury and renal dysfunction. This process is secondary to an hypersensitivity reaction to medications. AIN is most of the times self-limited 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 with limited

blood flow, the enormous metabolic demand easily leads to interstitial hypoxia and subsequent renal injury.[32]

c) *Post-renal*

1. Obstruction of the urinary outflow

   - Papillary necrosis

   - Posterior urethral valves

   - Urethral stricture

   - Retroperitoneal mass

   - Prostatic hypertrophy

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

D. Clinical assessment of the child with acute renal failure

The clinical evaluation of a child with suspected renal failure should include the 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 to 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 will 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 levels higher than 500 mOsm/L.

  In renal/parenchymal failure, the inability to conserve water leads to a more diluted urine hence urine osmolality is less than 300 mOsm/L

- *Urinary sodium*

  The measurement of urinary sodium may indicate 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 will be low or less than 20 mEq/L.

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

- *FE_{Na}*

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

Calculation of FE_{Na}:

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

- *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 in creatinine 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]

E. Initial management

1. *Determine the cause of renal dysfunction*

Patients with oliguria and rising plasma creatinine levels should immediately be investigated. Urinary electrolytes and FeNa, 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 failure. 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 the central venous pressure (CVP) and the central venous oxyhemoglobin saturation ($ScvO_2$).

Commonly, children with oliguria from low circulatory volume 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 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 iothalamete 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.

When needed, IV contrast agents should be used at least 5 days apart. Several hydration strategies have been recommended in the literature. One strategy consists of administering 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. Another commonly used protoool is 0.9% NaCl at 1 mL/kg/hr for 12 hours pre-procedure and 12 hours post-procedure.[33]. Acetylcysteine (Mucomyst) have questionable benefits to prevent 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 and data supporting the use dopamine in infants and children to improve renal function. [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 has deleterious effects in the GI, endocrine, immunologic and respiratory systems and its use is no longer justified in patients with 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 WNK 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 hyperkalemia is 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]

V. 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 treplaces most of the kidney's metabolic functions.

A. 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)

B. Modes of RRT

1. Ultrafiltration

2. Hemodialysis

3. Peritoneal dialysis

4. Renal transplantation

VII. Continuous renal replacement therapy (CRRT) [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 an effective mechanisms than intermittent hemodialysis.

1. CUF (continuous ultrafiltration), removes only water

2. CVVH (continuous veno-venous hemofiltration) –uses convection, requires replacement solution which causes convection. Helps remove medium to large molecules. Replacement solutions are electrolyte and bicarbonate-based solutions

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.

3. CVVHD (continuous veno-venous hemodialysis) – uses diffusion, requires dialysate solution for diffusion due to concentration gradient across semi permeable membrane. Helps remove small molecules. No replacement solution is required. Dialysate solution uses buffering agents, electrolytes and glucose at normal plasma values. The concentrations can be changed according to the indications for RRT.

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

4. CVVHDF (continuous veno-venous hemodiafiltration) – uses both convection and diffusion, requires both dialysate and replacement solution.

1. *Convection*

    During convection, a pressure gradient "forces" water and solutes to pass through a filter, including large molecules. The hemofilter is impermeable to proteins and cells due to the small size of its pores.

2. *Diffusion*

    Is the mechanism by which, solutes are transported across a semipermeable membrane according to a concentration gradient. Solutes move or "diffuse" to the side of the membrane that has lower concentration of that solute.

3. *Adsorption*

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

4. *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, cytokines

5. *Sieving coefficient.*

    Is the ability of a molecule to pass through the membrane/filter. A Sieving coefficient of 1 means 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.

A. CRRT Circuit (Fig 3)

1. Central double-lumen veno-venous hemodialysis catheter
2. Extracorporeal circuit and filter
3. Blood pump
4. Dialysate pumps
5. *Replacement fluid pump*

- 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]

- Anticoagulation. 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.

- 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 polyarylethersulfone (PAES) membranes to avoid this reaction. Others are made of polysulfone, polyamida, polyacrylonitrile

- 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 its use in patients with associated liver compromise. Furthermore, due to its vasodilator

properties and non-physiologic pH, could cause hypotension and worsen acidosis due to accumulation of lactate.

- CRRT solutions for dialysate and replacement fluid

  Bicarbonate based fluid are preferred over lactate based due to the risk of metabolic acidosis leading to cardiac dysfunction, vasodilatation, and as a result, 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.

- *Circuit blood flow rate*

  Blood flow (Qb) should be started below the goal rate and advanced to maximum rate over 30 min. Flow rates vary from 2-4 mL/kg/min in older children and adolescents to10-12 mL/kg/min in neonates. [7]

.B. 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 7Fr, 6 to 15 kg require 8 Fr, 15 to 30 kg require 9 Fr and >30 kg 10Fr [3]

- *Catheter insertion*

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

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.

Tunneled dialysis catheters can be used in children who will require prolonged HD and in those waiting for renal transplantation.

In a retrospective review of radiologically inserted HD catheters in children, Adeb et al showed a technical success of 100%, higher catheter survival rates but higher catheter mechanical and infectious complication rates especially in small children. [4]

C. 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.

D. CRRT dosing

In CRRT, dosing is expressed as filtrate volume/kg per time. There are no studies addressing CRRT dosing (delivered ultrafiltrate flow) in children. Rates of 20-25 mL/kg/h are optimal for clearance in the majority of adult cases reported in the literature. [10-11] Higher rates could potentially lead to clearance of medications needed for the support of critically ill children. Also loss of phosphorus and protein are seen with high rates and phosphate and protein supplementation should be considered.

E. Hyperammonemia due to inborn errors of metabolism

In children with hyperammonemia due to inborn errors of metabolism, rapid and continuous clearance of ammonia is desired. Peritoneal dialysis is inadequate to

achieve clearance rates and intermittent HD predisposes to rebound hyperammonemia.

Higher rates of clearance are needed during CRRT hence, the replacement of phosphates and other electrolytes and amino acids are essential.

F. Outcomes of CRRT [12]

Primary diagnosis	Number of patients	Number of survivors	Survival
Sepsis	81	48	59%
Stem cell transplant	55	25	45%
Cardiac disease/transplant	41	21	51%
Renal disease	32	27	84%
Liver disease/transplant	29	9	31%
Malignancy (w/o tumor lysis)	29	14	48%
Ischemia/shock	19	13	68%
Inborn error of metabolism	15	11	73%
Drug intoxication	13	13	100%
Tumor lysis syndrome	12	10	83%
Pulmonary disease/transplant	11	5	45%
Other	7	5	71%

The outcomes of children receiving CRRT are largely related 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]

VIII. Peritoneal dialysis

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

A. Indications and contraindications of PD

PD is preferable 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 exstrophy, obliterated peritoneal cavity and peritoneal membrane failure. [20]

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

B. Technique

1. Catheter placement

2. Dialysate solutions

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.

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 child on PD.

3. 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.

C. Complications of PD

Complications of PD include peritonitis and catheter site 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.

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Chapter 11

Transfusion and Anticoagulation
Robert L. Ricca, 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 bood products. As a rule of thumb, use the following table for specific patients in the ICU.

Blood Product Type	Patient
CMV negative	Severely immunodeficient patients who are CMV negative. CMV negative transplant patients
Irradiated (prevents GVHD)	Infants,congenital immunodeficiency, cancer, HSC
Pharesed/leukofiltered	Everyone
Washed PRBC	Patients known to have exposed antigen-causing hemolytic reaction

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 exits. A sample guideline is listed below:

Transfuse with PRBC's if:

- HCT < 35% and intubated (or on CPAP > 8cm H20) with FiO2 > 0.35

- HCT < 30% and intubated (or on CPAP) with FiO2 < 0.35

    o Undergoing surgery

    o Poor weight gain for one week (< 10gm/day)

    o 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:

    o Birthweight less than 1500 grams

    o Exchange transfusion

    o Directed donor of relative's blood

    o 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*

- *Hematocrit of > 35%*

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.

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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 following 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 (ie ASA therapy), regardless of the platelet count

VI. Transfusion Reactions

There are several types of tranfusion 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 send

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

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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 myelosuppresive therapy

- Patients with congenital immunodeficiency syndromes

TABLE: TYPES OF TRANSFUSION REACTIONS

TYPE OF TRANSFUSION REACTION	CAUSE	SYMPTOMS	TREATMENT
Hemolytic, immediate	ABO incompatibility	Fevers, chills, back pain, hemolysis, red urine At risk for renal failure	Measures to reduce risk of renal failure such as hydration with crystalloid solution and osmotic diuresis
Hemolytic, delayed	SCD patients	Fever, hemolysis 5-14 days after transfusion	
Infectious	Hepatitis B, C, HIV, CMV, bacteria		Appropriate antimicrobial treatment, as needed
Febrile	Donor WBC's produce cytokines. Older blood products more likely to cause reaction	Fever	Pre-treatment with acetaminophen and washing blood products are helpful. Otherwise, supportive measures once it develops
Allergic	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	Can be as mild as skin rash or anaphylaxis	Diphenhydramine and/or support for allergic reaction (i.e., epinephrine) if needed
GVHD	Donor leukocytes attacking immuno-compromised host	Skin rash, diarrhea, liver dysfunction. Can be life threatening	Supportive care. Treat as GVH
TRALI	Complement activated WBC	Occurs 4 hrs after transfusion.	Supportive care and steroids

	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

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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 lepuridin and argatrobam should be done.

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Chapter 12
SEDATION AND ANALGESIA

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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

    o sufentanil: fentanyl derivative that is 10x more potent than fentanyl. Used commonly in cardiac anesthesia.

        ▪ Doses of 15-30mcg/kg

    o 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:

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

    o bradycardia

3. Methadone [13]

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

4. Codeine [13]

- 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

6. Meperidine [13]

- 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

    - 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 indications: induction and maintenance of anesthesia. Procedural sedation. No analgesic properties.

- Clinical effects: ultra-short acting non-barbiturate hypnotic

  - Minimal cardiovascular effects – often used in patients with impaired cardiovascular function

  - Dose dependent depressant respiratory effects

- Decreases cerebral metabolic rate, causing dereased 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 – hydroxlase, which is necessary for the production of cortisol.
    - Avoid in patients in septic shock due to the adverse consequences of adrenal suppression

- o Prolonged infusions not recommended due to risk of propylene glycol toxicity.

- o Use with caution in patients with seizure disorders. May cause EEG burst suppression at high doses.

2. NSAIDS [13]

- Clinical indications: potent analgesic and anti-inflammatory. Treatment of mild to moderate pain.

- 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:

  - o GI bleeding

  - o hepatotoxicity

  - o interferes with platelet function

  - o 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]

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- 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.

- o Effects on CNS to decrease sympathetic tone, stimulates central parasympathetic outflow, decreases sympathetic outflow.

  - o 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; moya moya disease or patients who have had a stroke; concomitant use of clonidine

V. Common Anesthetics

A. Systemic Anesthesia

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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

  o Clinical effects dissipate quickly with discontinuation of infusion

  o Negative ionotropic effects

  o Potent vasodilator

- Dosing: initial bolus 1-2 mg/kg. Infusion 75-250 mcg/kg/minute

- Onset & elimination: Rapid onset – within a minute of injection.

  o 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

  o 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 would 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 guildelines 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

    o duration of therapy

        ▪ develops 10-21 days of morphine use

    o infants in early developmental stages develop long term tolerance to developing brain

    o greater tolerance with shorter acting opioids

- Approaches to address tolerance

    o dose escalation

    o use longer acting opioids

    o add non opioid analgesics

    o add drugs that prevent or delay tolerance

B. <u>Tachyphylaxis</u> [13]: rapid loss of drug effects caused by compensatory neurophysiologic mechanisms due to exhaustion of synaptic neurotransmitters

C. <u>Dependence</u> [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. <u>Withdrawal</u> [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

  o gradual wean

  o conversion to long acting enteral medications (i.e. methadone, clonidine, lorazepam),

  o 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]

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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

  o Conversion to intermittent dosing: give dose for 24-48 hours before any subsequent wean is made

  o Goal to decrease drug by 10-20% of the original total dose per day

  o If withdrawal symptoms develop, then stop weaning for 24 hours

  o 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.

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Table 1. Initiation Doses for Common Opioids

Agent	Load/prn	Infusion Range
Fentanyl	1mcg/kg	1 - 5mcg/kg/hr
Morphine	0.05 - 0.1mg/kg	0.05 - 0.1mg/kg/hr
Hydromorphone	0.015mg/kg	10 - 15mcg/kg/hr

Table 2. Initiation Doses for Common Sedatives/Anesthetics

Agent	Load/prn	Infusion Range
Midazolam	0.05 - 0.1 mg/kg	0.05 - 0.1 mg/kg/hr
Lorazepam	0.05 - 0.1 mg/kg	-----
Pentobarbital	0.5 - 1 mg/kg	1 - 2 mg/kg/hr
Chloral hydrate	25 - 100 mg/kg	------
Ketamine	0.5 – 1 mg/kg	1 - 2 mg/kg/hr
Clonidine	2 – 5 mcg/kg/day (transdermal patch 100 – 300 mcg, change q 7 days)	
Dexmedetomidine	0.3 - 1 mcg/kg	0.2 - 0.7 mcg/kg/hr
Propofol	2 - 3 mg/kg	75 - 250mcg/kg/min

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Table 3. Maximum Local Anesthetic Dosing

	Dose without epinephrine (mg/kg)	Dose with epinephrine (mg/kg)	Duration (hours)
Bupivacaine	2*	3*	3 - 6
Lidocaine	5	7	1
Ropivacaine	2	3	3 - 6

* Reduce dose by 50% in neonates

Yaster, M. Easley RB. Brady KM. Pain and sedation management in the critically ill child. Pediatric Critical Care Medicine. 2012; 13(2): 149.

Table 4. Neuromuscular Blocking Agents

Drug	Intubating dose	Continuous infusion
Pancuronium	0.1 mg/kg	NA
Vecuronium	0.1 mg/kg	1 mcg/kg/min
Rocuronium	0.6 - 1.2 mg/kg	3 - 10 mcg/kg/min
Cisatracurium	0.1 mg/kg	0.4 - 4 mcg/kg/min

Yaster, M. Easley RB. Brady KM. Pain and sedation management in the critically ill child. Pediatric Critical Care Medicine. 2012; 13(2): 158.

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

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

Curley MA, Harris SK, Fraser KA, et al. State Behavioral Scale (SBS) A sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatric Critical Care Med. 2006. 7(2): 107-114.

Table 6. State Behavioral Score (SBS)

Score	Description	Definition
-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)

Curley MA, Harris SK, Fraser KA, et al. State Behavioral Scale (SBS) A sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatric Critical Care Med. 2006. 7(2): 107-114.

Table 7. FLACC Behavioral Pain Assessment Tool

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

Voepel-Lewis T, Merkel S, Tait AR, et al. The reliability and validity of the Face, Legs, Activity, Cry, Consolability observational tool as a measure of pain in children with cognitive Impairment. Anesth Analg. 2002. 95:1224-1229.

Table 8. PIPP Pain Assessment Tool

Process	Indicator	Description	Score
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	
	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	
	Eye squeeze	0 – none 1 – minimum 2 – moderate 3 – maximum	
	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

Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. Clinical Journal of Pain. 1996. 12(1): 13-22.

Figure 1. NICU ANALGESIA AND SEDATION ALGORITHM
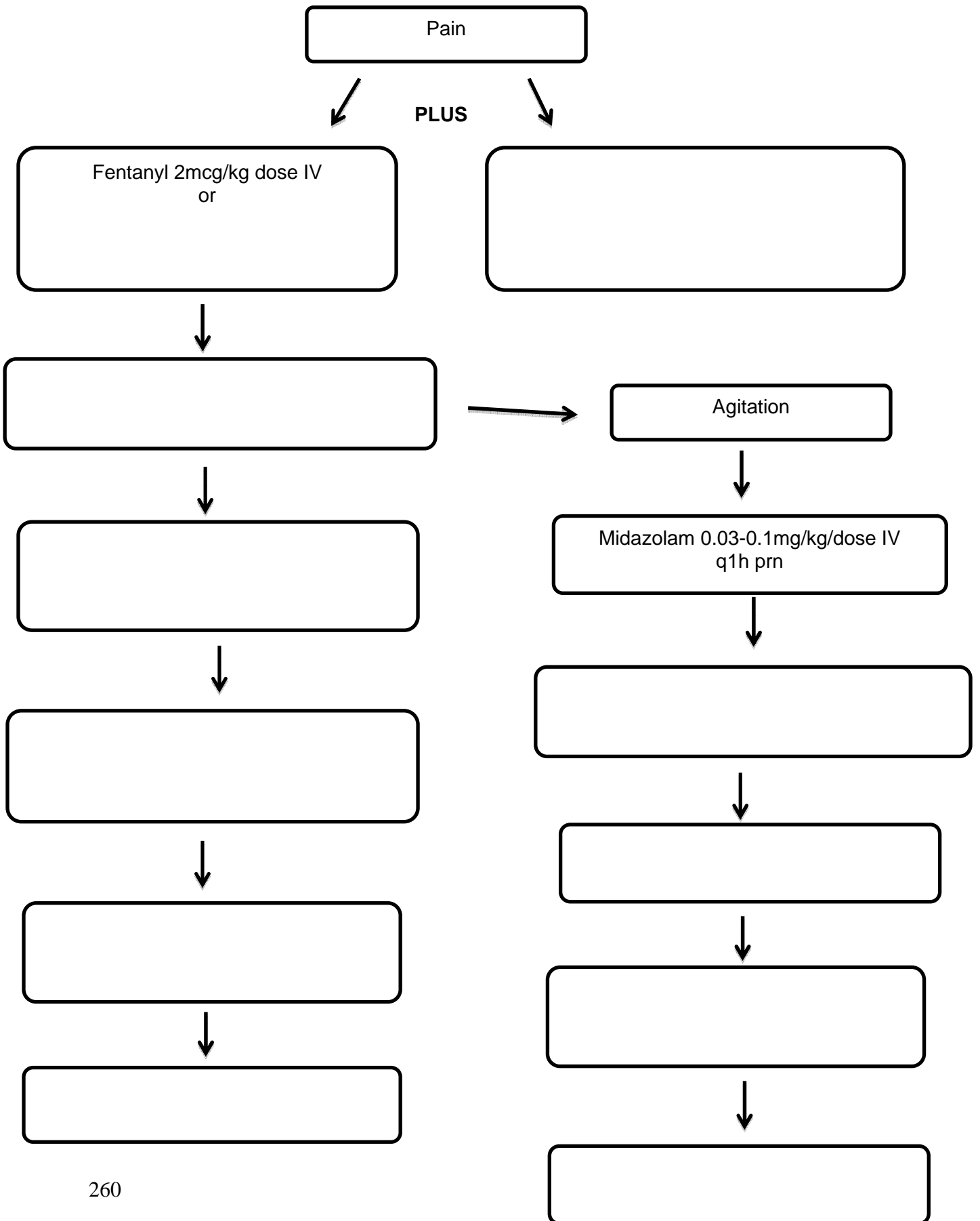
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        │ Fentanyl 2mcg/kg     │    │                      │
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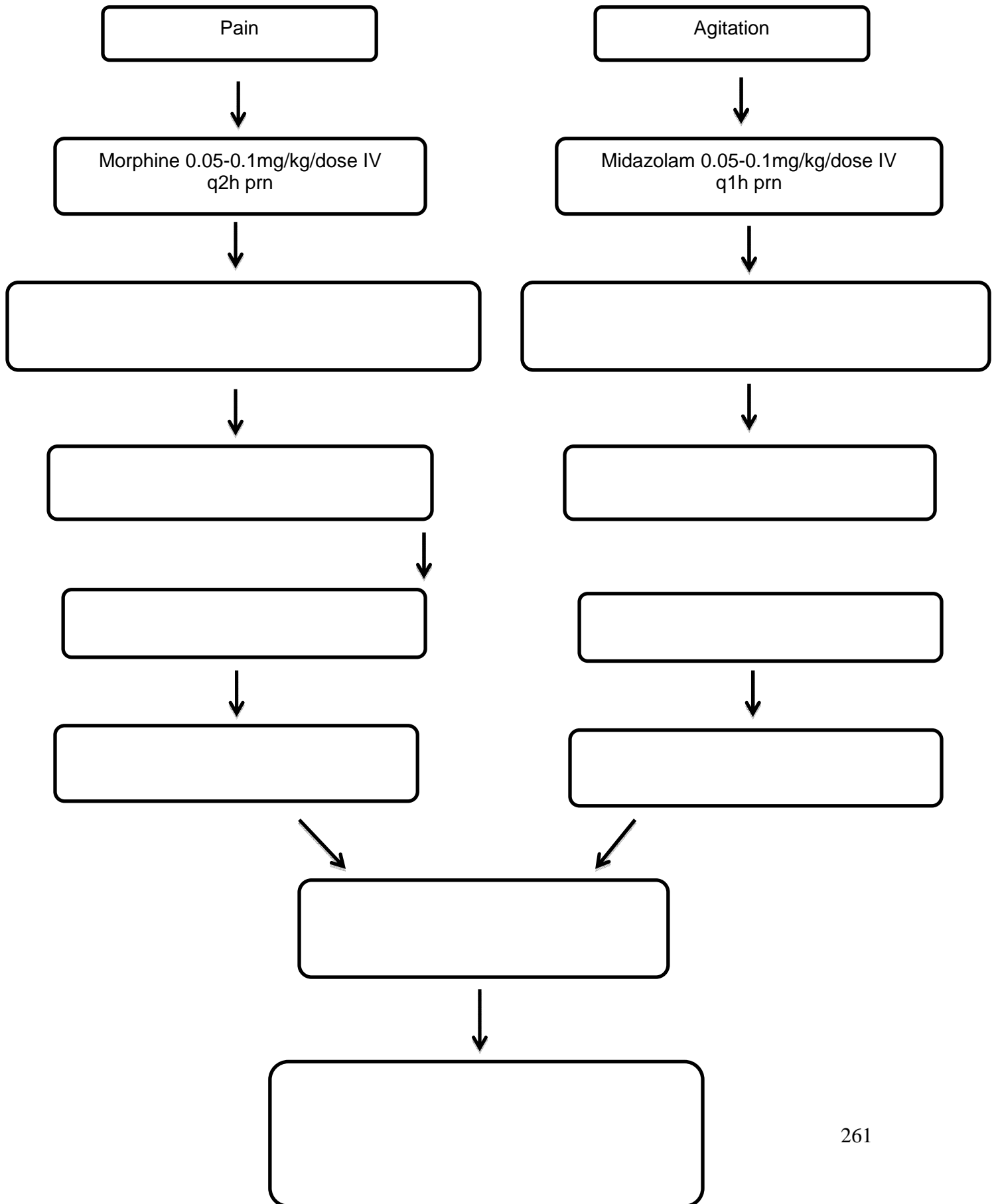
Figure 2. PICU SHORT **T**ERM **E**XTUBATION **A**LGORITHM **(<3 days)**

| Pain | | Agitation |

| Morphine 0.05-0.1mg/kg/dose IV q2h prn | | Midazolam 0.05-0.1mg/kg/dose IV q1h prn |

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Figure 3.PICU Long Term Extubation Algorithm (>3 days or chemically paralyzed)

Morphine 0.05 mg/kg/hr IV to maintain comfort	**AND**	Midazolam 0.05 mg/kg/hr IV to reduce physiologic stress and anxiety

Figure 4. NICU/PICU Titration Algorithm

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        │ Titrate narcotic and benzodiazepine│
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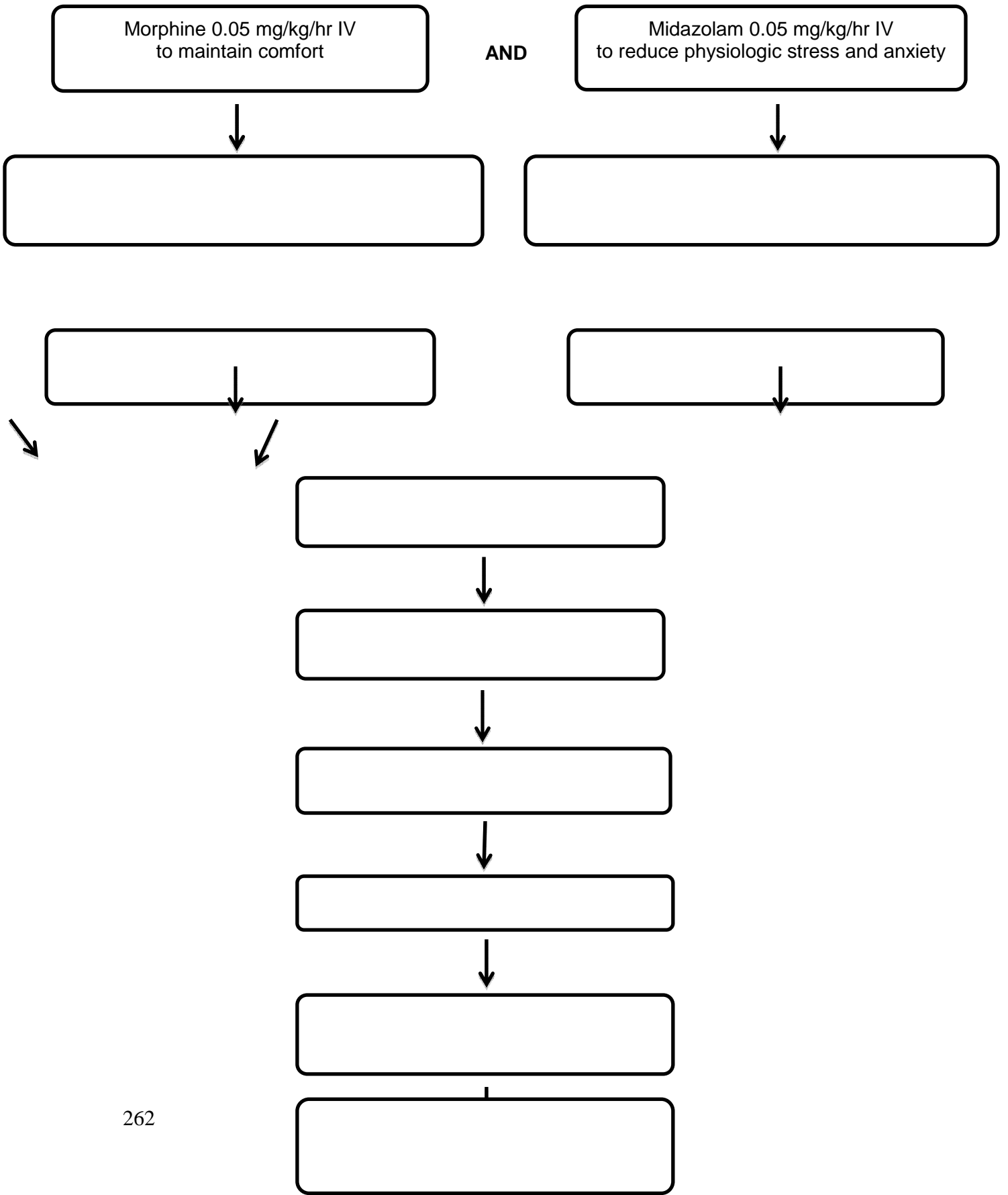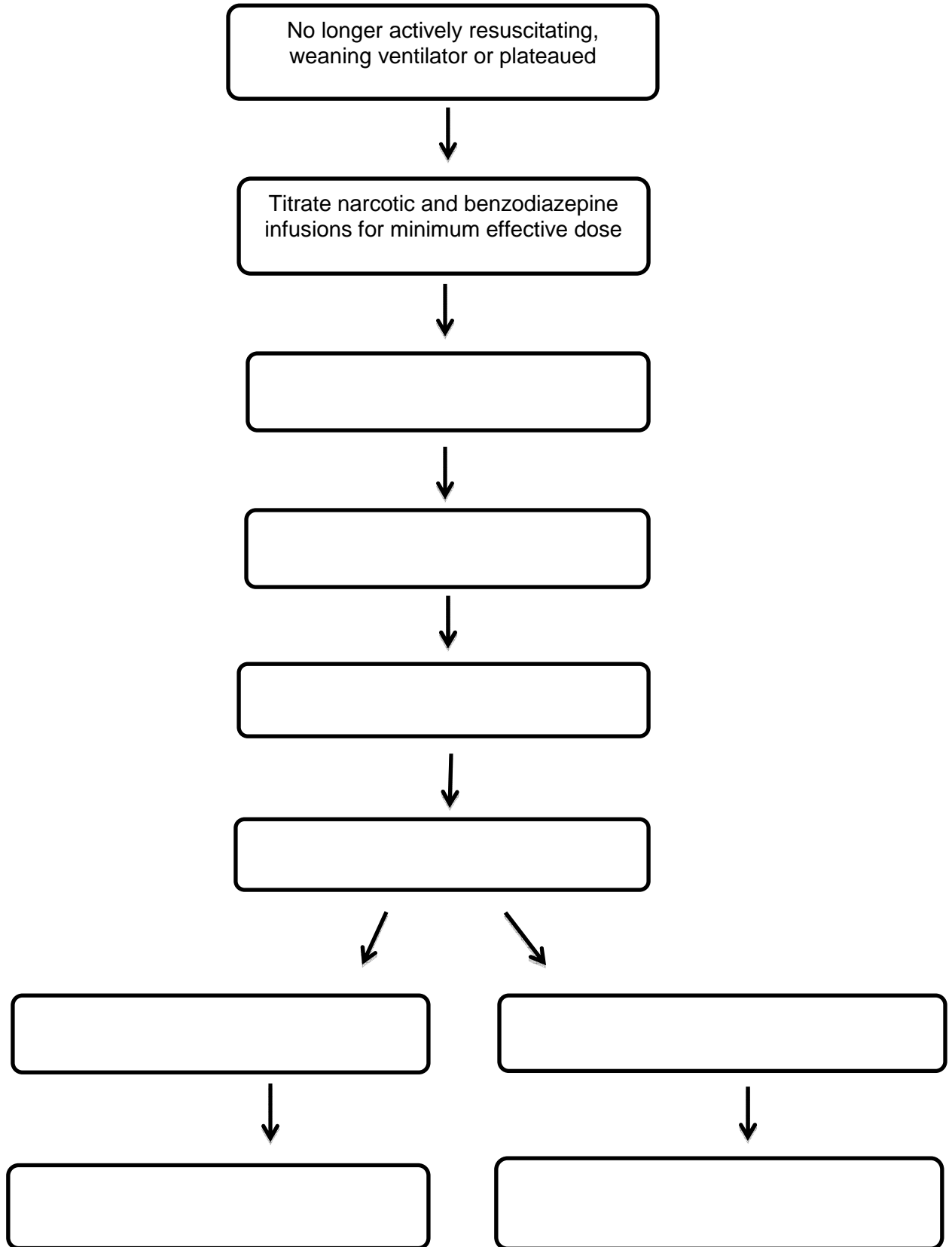
Chapter 13
PEDIATRIC NEUROTRAUMA

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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

Subdural	Age of injury (days)
Acute	< 3
Subacute	3-10
Chronic	>10

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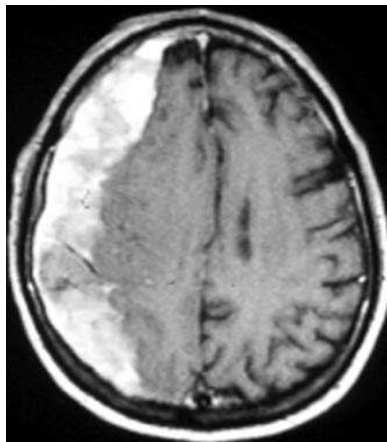
Figure 2: Subdural hematoma: Note the concave or crescent-shaped appearance associated with mass effect and loss of ventricles.

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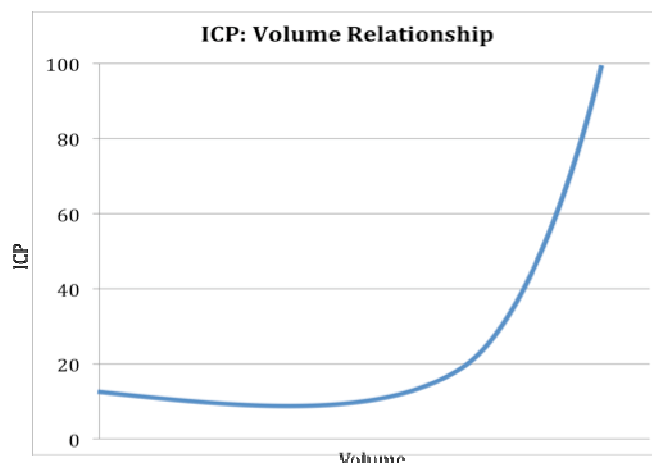
Figure 5: ICP and volume relationship: Initially the ICP remains unchanged with increasing volumes due to compensation mechanisms, however at elevated ICP's, small volume increases cause a significant change in pressure.

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.[17] 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)

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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

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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.[8] 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

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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

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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].

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Chapter 14
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 systemtic 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 cinician 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

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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 pracitical 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

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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 abilituy 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. [24] 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 cholangiopancreaticogram). 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 thickess 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 protoctoscopy 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 modaility 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.[50] Operative repair of duodenal injuries are tailored to the extent of the injuires. 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 comparment 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 stocpock. 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 H_2O.

Abdominal Perfusion Pressue 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.

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Chapter 15
Pediatric Burns

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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^oF (54^oC) 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^oF (60^oC), 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^oF (77^oC).

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

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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}Xe) scanning in which the radioactive tracer, ^{133}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

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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 abdoment, 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 modailities 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 bacritracin/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)

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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.

Escharatomy

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 escharatomy +/- 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 that 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

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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.

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Chapter 15
THE SURGICAL NEONATE

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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, in utero 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	Hydronephrosis
Hydroureter	Renal vein thrombosis
Mesoblastic nephroma	Wilms tumor
Neuroblastoma	Adrenal hemorrhage

Midabdominal

Mesenteric cyst	Ovarian cyst
Duplication of intestine	Meconium ileus

Upper abdominal

Liver tumor	Splenic cyst
Choledochal cyst	Splenic hematoma
Subcapsular hematoma of liver	

Lower abdominal

Bladder	Hydrometrocolpos
Sacrococcygeal teratoma	Urachal cyst
Anterior meningocele	

iV. CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Congenital diaphragmatic hernia is can be 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.

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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.

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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.

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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 desribed 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 pCO_2 in the immediate post-operative period. This is due to the CO_2 insufflation that is required for a minimally invasive approach. Slight hyperventilation (increased rate and or 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.

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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 tupe 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	Renal ultrasound
Cardiac ECHO --visualize cardiac anomalies and the side of the aortic arch & descending aorta. This determines the side of the thoracotomy for surgical repair.	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

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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 pre-determined 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 a 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 sually 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. Baloon 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 apenea 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 directl to the OR, vascular access should be established. Gastroschisis 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 the 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

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(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 omphalocele is ~ 1 in 6,000-10,000 live births

Like gastroschisis, omphaloceles are now most commonly diagnosed prenatally. Unlike gastroschisis, the defect is contained within umbilical cord, unless ruptured. Even in small sized omphaloceles, the bowel is nonrotated. In the large omphaloceles, there usually is a globular liver within the sac.

Associated anomalies seen in at least 50% of cases: These include

Cardiac	Neurological
Tetralogy of Fallot, VSD	Genitourinary
PS, coarctation, AV canal	Imperforate anus

Bladder &/or cloacal exstrophy

Gastrointestinal

Skeletal

Diaphragmatic hernia

Malrotation

Chromosomal

Pentalogy of Cantrell:

Trisomy 21

omphalocele combined with

Beckwith-Wiedemann

ectopia cordis

Syndrome

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 itact 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 membrahe 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 referes 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, finings 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 failur 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 obsruction. If the initial KUB shows a "double bubble sign" (air in the stomach and proximal duodenum) and scattered gas pockets distally, malrotaion 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 inn 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 continuitiy 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 ret-protooncogene 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 Xray 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 diseas 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 theoperation "pullthrough'"is performed in 4-8 weeks.
If the baby 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 peformed. The principles of the operation is to definitively identify the level where the normal bowel transitions to the agangllionated segment. The abnormal segment is removed and the ganglionated 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

<u>Hirschprung Associated Enterocolitis</u>: 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 MALFORATIONS (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 malforation, 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

Embrology

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 vovulus, vomiting, or asymptomatic. Midgut volvulus can occur in anatomic configurations where the root of the mesentery is narrow. In the course of the regular peristatlsis 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 urgen 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 sitution. 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.

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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 intotropes 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 closre 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.

Embrology

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.

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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 determined 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 addtion, 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.

Chapter16
MEDICAL CONDITIONS IN THE NEONATAL ICU

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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. 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).

Symptoms include tachypnea, ↑ Respiratory effort, hypoxemia, hypercapnia. On CXR, air bronchograms and "ground glass" may be seen..

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 and ventilated for at least a short time. Surfactant prophylaxis is

given to infants <29 weeks EGA at birth.

Surfactant Preparations and Dosing Regimens

| Surfactant | | | | Dose | |
Trade Name	Generic Name	Preparation	Manufacturer	Amount (ml/kg)	Interval (hrs)
Survanta	Beractant	Bovine lung mince extract w/ added DPPC, tripalmitin & palmitic acid	Abbott (USA)	4	6
Exosurf	Colfosceril palmitate hexadecanol, tyloxapol	DPPC w/9% hexadecanol, 6% tyloxapol	Burroughs Wellcome Co. (USA)	5	12
Curosurf	Porcine Surfactant	Porcine lung minced extract	Chiesi Pharm. (Italy)	1st:2.5 subseq: 1.25	12
Infasurf	Calf lung surfactant extract	Bovine lung wash	Forrest Pharm (USA)	3	12

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. Blood bypasses the fetal heart. It carries ~60% of combined ventricular output

In term infants, the breath taken at birth decreases pulmonary vascular resistance. More blood is diverted to the lung increasing the PaO_2. Closure of PDA

occurs in two stages: the rapid constriction of the muscle cells in the media layer of th

ductus occuring after birth and the 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, the PDA is no longer

physiologically significant. Sensitivity of ductal closure to increased PaO_2 increases with

gestational age.

Factors that encourage continued patency of the ductus include,prematurity,

RDS, surfactant therapy, hypoxia, anemia, hypervolemia, and high altitude.

Clinically, the murmur associated with PDA is systolic or continuous heard best in

the left upper sternal border. The baby will have a widened pulse pressure (>30 mmHg)

and has bounding peripheral pulses. A CXR may show an enlarged heart and increased

vascular markings. An echocardiogram confirms its presence. Its continued presence

may result in heart failure, ventilator dependency, CCLD and potential increased

susceptibility to NEC, IVH or CLD.

PDA closure may be accomplished medically or surgically. Indomethacin 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 indomethacin 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. Pressor support is a more direct therapy for this

initial change.

Dosing of Indomethacin for Closure of PDA   (Neofax 2004)

AGE AT 1st DOSE	DOSE (mg/kg)		
	1st	2nd	3rd
<48 hours	0.2	0.1	0.1
2-7 days	0.2	0.2	0.2
>7 days	0.2	0.25	0.25

IV doses are administered by syringe pump over 30 minutes in order to minimize

adverse side effects on renal, cerebral, & GI flow velocities. Generally, 3 doses are

given per course, with a maximum of 2 courses. Indomethacin is dosed at 12-24 hour

intervals with close monitoring of urine output. Subsequent doses may be held in the

event of severe oliguria or anuria.

III. APNEA AND BRADYCARDIA

Apnea is defined as respiratory pause lasting 20 seconds--or 10 seconds if associated with bradycardia. The risk of apnea increases with prematurity . Apnea may be classified as follows:

1. Central apnea: due to immaturity in brain stem & respiratory center. Clinically a lack of breathing movements seen

2. Obstructive apnea: due to pharyngeal collapse. Breathing movements are seen without air movement

3. Mixed apnea: most common form of apnea, consists of obstructive and central components

4. Periodic breathing: IS NOT TRUE APNEA. Characterized by a repeating sequence of prolonged pauses in breathing that is under 20 seconds in duration. While commonly seen in nearly all infants, careful clinical assessment to rule out true apnea is necessary

If apnea is recurrent, consider checking CBC (impending sepsis or anemia), blood gas, head ultrasound, or EEG. Review the medications. Review timing to apnea to determine whether apnea may be due to reflux.

Treatment for apnea 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. 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 2040 mg/kg and 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.

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/mm^3) require CMV-negative irradiated packed red blood cells
15 cc/kg over 3 hrs.

Infection risk with allogenic blood transfusion.
Residual risk of virus transmission.

- · HIV   1 in 2.1 million
- · HTLV   1 in 3.0 million
- · HCV   1 in 1.9 million
- · HBV   1 in 205,000

Ref: Dodd, RY, et al:*Transfusion* 2002:42975–079**.**

IV. CHRONIC LUNG DISEASE (CLD) / BRONCHOPULMONARY DYSPLASIA (BPD)

Chronic lung disease of prematurity, or bronchopulmonary dysplasia (BPD), is an important cause of morbidity and mortality in the pre-term infant. It is defined as being O_d dependent at 36 weeks corrected age or 28 days postnatal age, with persistent clinical symptoms and radiologic findings consistent with the disease.

CLD in <1500 gram BW infants in 2 large databases is **23-26%** and is inversely related to birth weight and gestational age. Infants with CLD have longer hospital stays, increased re-hospitalizations, higher rate of neurologic impairment, higher incidence of poor growth, and increased SIDS rate.

Contributing factors to CLD include pulmonary immaturity, ventilator toxicity (oxygen toxicity, barotrauma/volutrama, atelectasis), excess fluid administration, sepsis, and infection. It is higher in males and Caucasian race.

Xray findings include 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 ventilator should be decreased as much as possible. There should be a conscious effort to minimize the pressure and oxygen levels. There are data showing that endogenous NO is created in the nasal mucosa of babies. Intubation bypasses this endogenous NO getting to the lung. Enhancement of growth of normal lung tissue is accomplished in the

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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.

Other therapies for CLD used acutely and chronically, are steroids, diuretics, and beta agonists. Again, lung protective therapies such as careful fluid management, "gentilation", use of HFOV, should be foremost.

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. This is designed to

limit both lengthy and bulk exposure. 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. 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.

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V. INTRAVENTRICULAR HEMORRHAGE (IVH)

IVH is more common in preterm infants. Studies have shown that 40-50 % of all IVH in very low birth weight (VLBW, BW<1500 gm) infants occur within the first 6-8 postnatal hours of age. 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 which 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. Therefore, IVH risk decreases with increasing gestational age.

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

Grade IV: IVH with extension into parenchyma

The infant's degree of prematurity is the primary risk factor supersedes all other risks. Other factors include presence of PDA, rapid shifts in blood pressure, exchange transfusions, hypoxia, DIC.

~50% of IVHs will occur within the first 24 hours of life

>95% of IVHs will have occurred by 7 days of life.

Head ultrasound is the main diagnostic modality. The ultrasound probe is placed over anterior fontanel. Subarachnoid hemorrhages or secondary parenchymal injuries may be difficult to detect. CT 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 enlarging, may require serial lumbar puncture (LP)

Frequency of LP dictated by clinical status and response to LP

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, we screen at-risk infants in the NICU at specific intervals.

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VI. PERIVENTRICULAR LEUKOMALACIA (PVL)

PVL refers to necrosis of white matter dorsal and lateral to the exterior angles of the lateral ventricle. Lesion is observed in the premature infant, infants with IVH, infants with evidence of an antenatal maternal placental-fetal infection. PVL may be seen in term infants as a result of a hypoxic-ischemic episode occurring at varying times of gestation as well as postnatally. Pathologic features includes focal necrotic lesions in periventricular regions and diffuse cerebral white matter injury

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, particularly those that progress to placental-fetal involvement.

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 wks following the inciting insult.

VII. RETINOPATHY OF PREMATURITY (ROP)

Retinopathy of prematurity is a disorder of vascular and retinal development in preterm infants. 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 100: 273, 1997).

All infants with birth weight ≤1500 g or born at $<28^{0}/_{7}$ weeks are screened. In addition, elected 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.

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.

Stage 4-5: Retinal detachment. There is poor prognosis, even with surgery

"Plus disease": Inflammatory changes. Hazzy vitreous. Poor pupil dilation. Synechiae.

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.
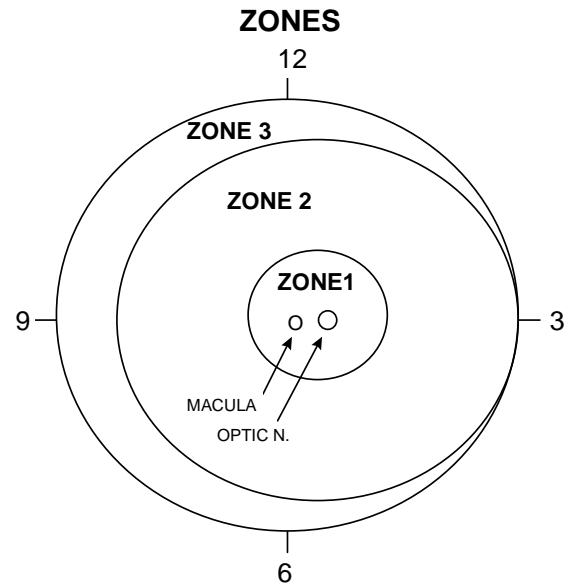
ZONES

Follow-Up
Based on retinal maturity & severity of disease.

ROP or immature vessels Zone 1:q wk

Immature vessels Zones 2 or 3, but no ROP: q 2-4 wks.

Intervention
Ablative therapy is considered if threshold disease exists
Most often occurs at 38 wks post-conceptional age

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

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 intolerances

BILIRUBIN & JAUNDICE

AAP Guidelines

Jaundice occurs in most neonates, and is mostly 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 AAP recommendations "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.

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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

Follow up assessment should include

Infant weight and change from birth weight

Assessment of intake

Pattern of voiding and stooling

Presence or absence of jaundice

NOTE: If the total serum bilirubin is at a level at which exchange transfusion is recommended **OR** if the level is 25mg/dL or higher, this is considered a medical emergency and the infant should immediately be admitted to a hospital pediatric service. THESE INFANTS SHOULD NOT BE ADMITTED TO AN EMERGENCY DEPARTMENT, BECAUSE OF THE DELAY IN TREATMENT.

Techniques to lower the level of TSB include:

↑ fluid intake to maximize renal excretion (not proven to be effective)

↑ 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. Placing the light as close to the infant as possible optimizes irradiance. 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.

Jaundice in the first 24 hours merits a complete physical exam and work up.
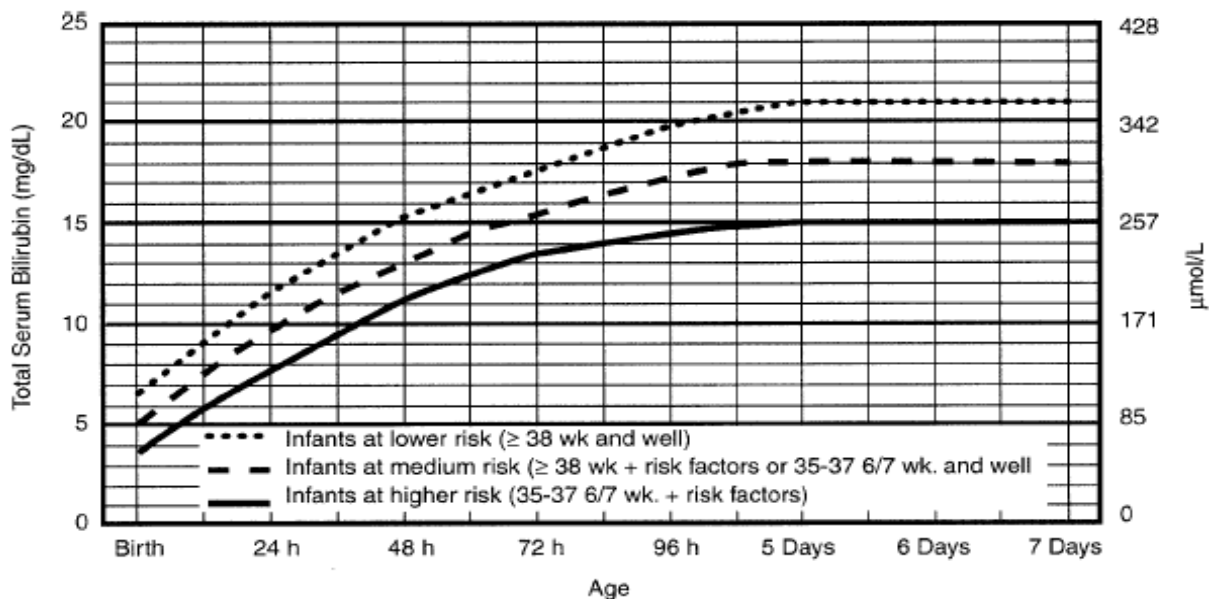
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Figure 1: **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" Pediatrics Vol 114, No. 1, July 2004 pp.297-316)

Figure 2: **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" Pediatrics Vol 114, No. 1, July 2004 pp.297-316)

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.

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, narcotic withdrawal, intracranial pathology, electrolyte abnormalities

First line anticonvulsants used include phenobarbital or 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).

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-ISCHEMIC ENCEPHALOPATHY (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.

Sarnat & Sarnat Classification of HIE			
	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
SENSORIUM	Jittery, irritable Hyperalert	Lethargic Dulled sense	Stuporous
MUSCLE TONE	Normal	Hypotonic at rest Hypertonic on stim	Flaccid Unresponsive
POSTURE	Mild distal flexion	Strong distal flexion	Intermittent decerebrate
STRETCH REFLEXES	Overactive	Decreased	Absent
MORO REFLEX	Strong	Incomplete	Absent
SUCK REFLEX	Normal	Weak	Absent
SEIZURES	None	Focal or multifocal	Decerebrate posturing

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 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. 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.

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN) / PERSISTENT FETAL CIRCULATION (PFC)

Transition of Fetal to Newborn Circulation

In the normal fetus, pulmonary and systemic pressures are near equal. The placenta is a low resistance/low pressure vascular bed. The arterial oxygen tension in the fetus is low. Fetal Hemoglobin has a high affinity for oxygen and there is a easy transfer of O_2 at placental interface.

At birth, in a normal newborn, pulmonary pressures drop from lung expansion, and increase in arterial oxygen tension. In addition, inspired oxygen acts as a pulmonary vasodilator. Systemic vascular pressures rise from the removal of the placenta, stress response. This results in an increase systemic pressures >> pulmonary pressures.

These physiologic changes allows change to adult circulatory patterns:

PDA ---> closure

Ductal tissue constriction begins

PFO ---> "Functional" closure

Equilibration of pressures across the PFO

Pulmonary Vascular Resistance (PVR) is drastically reduced

Anatomic/functional isolation of systemic and pulmonary circulation

Persistent Fetal Circulation (PFC) can result from

1. Rise in pulmonary pressures to near or suprasystemic

     (i.e. meconium, other aspirations, RDS, idiopathic, pneumonia)

2. Severe fall in systemic pressures to near or below normal pulmonary

     (i.e. Sepsis, pneumonia, asphyxia, SVT, congenital heart disease)

3. A combination of pulmonary hypertension and systemic

     hypotension such that resultant pulmonary pressures are near or

     above resultant systemic pressures

     (i.e. Sepsis, Asphyxia states, pneumonia)

Persistent Pulmonary Hypertension occurs when the adjustment of the

fetus to newborn life is either interrupted or reversed. This interruption causes

PVR to approach or become greater than systemic vascular resistance (SVR) (or

SVR to be reduced to levels approximate to PVR). This results in abnormal right-

to-left shunting through a PDA and PFO.

Morbidity of PFC comes in 2 phases. The first phase is related to the

primary insult causing entry into PFC/PPHN physiology (e.g., asphyxia,

infection). The second phase is the morbidity resulting from the treatment of

PFC/PPHN such as oxytrauma, barotrauma. Other possible morbidiites include

cerebral hemorrhage (ECMO), seizures, poor feeding.

The mortality of PFC stems primarily from cardiovascular failure: R or L heart failure, prolonged hypoxic damage to organs, stroke, sepsis.

PPHN Feedback Loop

Insult

Hypoxia

Acidosis

Vasoconstriction
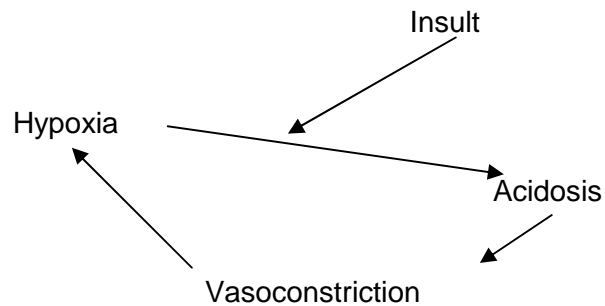
Diagnosis of PPHN

- Chest X-Ray: "blackout" of lung fields from decreased pulmonary blood flow, patchy infiltrates from meconium or pneumonia

- Hyperoxia Test: ABG on 100% FiO2; must be drawn from L arm or feet (postductal)

- Pre-/Post-ductal Sats: Postductal sats at least 5% less than preductal sats

- Echocardiogram: R→L Shunting through the PFO & evaluation of cardiac structure and function and to R/O congenital cardiac disease

OXYGENATION INDEX (OI): Measurement of the ventilatory work required achieving

the respective level of O_2 saturation; units are not necessary

$$OI = \frac{(Mean\ Airway\ Pressure\ \ x\ \ FiO_2\%)}{PaO_2}$$

Utilized for:

1. ECMO criteria (largely > 30)

2. iNO criteria (>25)

Treatment/Therapy of PFC/PPHN Basics

These therapies can be provided in any nursery and are looked upon as the first

line of treatment/prevention.

Recognition of at risk infants: both pre-/post-natally screen

If the PFC is secondary, treat the primary cause

Surfactant, antibiotics, etc.

Oxygen! Oxygen! Oxygen!

Supportive Therapy of PFC/PPHN

Interventions geared towards treatment of presenting infant or the ill at-risk infant

1. Intubation & mechanical ventilation (either conventional or HFOV)

2. Address oxygenation; surfactant therapy if indicated

3. Vascular access (UAC, UVC, peripheral arterial line, PICC line)

4. Blood pressure support (volume, pressors)

Strategies in treating full-blown PFC/PPHN

These therapies may have varying responses in different patients

1. Alkalization (pH>7.4)

   a. Hyperventilation (pCO$_2$ 30-35 range)

   b. Bicarbonate: either bolus or drip

2. Sedation

3. Paralysis

4. Peace and quiet

5. Surfactant

   Mainly in infants with RDS, meconium

6. Nitric Oxide: see accompanying section

7. ECMO

GENERAL GUIDELINES & PITFALLS IN TREATING PFC/PPHN

Guidelines

- Wait for signs of well-being

    o Urine output improves

    o Diuresis/mobilization of fluids

    o Tolerance of care

    o Stabilization of blood pressure

- Management Pearls

    o Association: recognize the possibility of PFC in at risk infants

    o Be aggressive with initial therapy: liberal use of oxygen, volume

      expansion, sedation

    o Alkalization: pH goals of 7.4 or higher

       do NOT tolerate pH's less than 7.25 in a near term newborn

    o Access: vascular access is a must

    o Anticipation: try to treat ahead of necessity

      volume expand before HFOV or sedation

      have consents/machines ready ahead of time

    o Avoid agitation: minimal stimulation

    o Attenuate abrupt management changes

Pitfalls

- Hypotension is a crucial foe

    o Need an adequate pressure head to perfuse/oxygenate lungs

    o Many interventions cause hypotension, such as

       high frequency oscillatory ventilation, sedation, paralysis

- Under-use of oxygen

- Lack of adequate volume expansion

- Narcotic Tolerance

- Many of these infants do not tolerate physical stimulation during acute

   phase of disease

    This may aid in determining when disease runs its course, as care is

   tolerated better

- There are rapid swings/declines in clinical status

   Vigilance is necessary in order to anticipate obvious and subtle changes in

   clinical status

INHALED NITRIC OXIDE THERAPY

NITRIC OXIDE (NO)

Endogenous NO: vasodilator continuously released by vascular endothelial cells

Nitric oxide synthase (NOS) releases NO from oxidation of l-arginine

Regulation of endothelial (type 3) NOS activity is a complex process

Affected by availability of substrates (oxygen, l-arginine) and co-factors

Activity / expression of lung endothelial NOS increases during maturation of the fetus

Endogenous NO release is critical in normal postnatal decrease of pulmonary artery pressure and pulmonary vascular resistance in the transition to adult circulation at birth.

Persistent pulmonary hypertension of the newborn (PPHN): is associated with↓ NO release secondary to ↓ NOS activity and ↓ lung expression. PPHN is associated w/pulmonary vasoconstriction and increases in pulmonary artery pressure and PVR. Right-to-left shunting occurs, often through a patent ductus arteriosus or a patent foramen ovale. The use of inhaled NO to facilitate pulmonary vasodilation in PPHN is a logical extension of research done in the perinatal transition of lung.

Exogenous NO (also known as inhaled NO (iNO)):

Colorless, odorless, highly diffusible gas

Enters alveolar space when mixed w/ inspired O_2 in a ventilated infant

Diffuses from alveolar space to pulmonary arterial smooth muscle

It then increases cyclic GMP levels and causes smooth muscle relaxation

Leads to pulmonary vasodilation and an increase in lung perfusion

Inhaled NO is selective for the pulmonary circulation because any NO that reaches the pulmonary arterial blood is inactivated by hemoglobin, thereby making it unavailable to systemic circulation.

INHALED NO THERAPY (INO)

Shown to improve oxygenation and

Decreases need for more invasive therapies -- extra-corporeal membrane oxygenation (ECMO)

Follow-up of infants treated with iNO until two years of postnatal age did not show evidence of adverse effects on lung function or development. Based on these clinical studies, inhaled NO therapy has been approved for clinical use for near term and term infants (>34 weeks) with severe respiratory failure.

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CURRENT APPROVED INDICATIONS FOR iNO:

- Gestational age ≥ 34 wks

- Respiratory failure not due to structural congenital heart disease

- Oxygenation index (OI) >25 on two blood gases or

- OI >25 on a single arterial blood gas if:

   Significant worsening from previous blood gas   AND

   Mechanical causes for deterioration ruled out

      eg pneumothorax, blocked or misplaced ET tube

Dose of iNO:

   iNO therapy is begun at 20-ppm dose

   If no increase in PaO_2, may consider 40-ppm dose

   Higher doses are not beneficial and increase methemoglobinemia risk

   In addition, there may be an unacceptable decrease in FiO2 with higher doses of NO (for eg, FiO_2 decreases to 0.88 with 80 ppm dose of NO with typical ventilator flow rate of 8-10 L/min).

   IF RESPONSE IS POOR:

   Ensure that lungs are adequately ventilated

Combination of ɪNO and high frequency ventilation has been shown to improve the oxygenation response compared to iNO + conventional ventilation

Surfactant therapy also improves the response to INO in babies at 34-37 weeks gestation and in meconium aspiration syndrome with parenchymal lung disease

Weaning ɪNO:

Weaning is attempted after the infant has been stable for a 12-hour period

At each wean, the dose of ɪNO is reduced from 40-20, 20-10 and 10-5 ppm

Weaning attempts are made every 12 hours

 or every 6 hours if the infant is doing well and oxygenation index is < 10

Weaning below 5 ppm is done in 1 ppm decrements

Dose is weaned to 0.5 ppm before final discontinuation

After each wean, when the baby is acutely ill, PO_2 should be monitored to ensure that it dosen't drop precipitously. When the infant is recovering and is stable, it is reasonable to watch the saturations alone to gauge the success of weaning attempts.

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Weaning of iNO should be planned in consideration of ventilator weans. If infant is on 100% O_2 and high MAP, it is reasonable to wean those parameters and defer NO wean by 12 hours.

iNO should never be abruptly discontinued from a patient as this may lead to life threatening decreases in oxygenation, even in babies that did not appear to respond to iNO.

BEFORE DISCONTINUATION OF iNO…:

Infant should have PO_2> 60 and OI<10 or pulse ox sat >95% on <80% FiO_2

AFTER DISCONTINUATION OF iNO…:

Expect a transient drop in saturation/PO_2 with discontinuation of iNO

Infant's sats and/or PO_2 should return to baseline in 20-30 min.

It is appropriate to increase FiO_2 by 10-20% to overcome decrease in sats/PO_2

POTENTIAL ADVERSE EFFECTS OF iNO:

- METHEMOGLOBINEMIA. Some increase in metHb levels are common during therapy and are well tolerated at levels <5%. If the metHb levels increase to 5% or higher, weaning of NO gas with close monitoring of these levels should be performed. MetHb levels should be obtained every 12 hours during first 24 hrs and every 24 hrs subsequently until the infant is off NO.

- Exposure to NO_2. NO_2 is toxic to the lung, continous monitoring of NO_2 levels should be performed and if NO_2 levels are >1 ppm, weaning of NO dose should be done.

Term infants with severe respiratory failure (i.e. those commonly treated with INO/ECMO) have a high incidence of hearing loss that may develop late in infancy or early childhood. These infants are also at higher risk of neuro-developmental sequelae. Parents should be informed of these risks and should be advised to bring babies for follow-up to Dr. Laurel Bear's clinic.

ECHOCARDIOGRAPHY is useful to rule out structural heart disease, but documentation of PPHN is not required to initiate iNO therapy. iNO may improve oxygenation by improving ventilation/perfusion match.

MEASURES OF OXYGENATION

A-a GRADIENT

Alveolar $PO_2 = P_AO_2$

Alveolar $PCO_2 = P_ACO_2$

In 100% O_2, P_AO_2 = Atmospheric pressure - water vapor pressure - P_ACO_2

Assume $P_ACO_2 = P_aCO_2$

P_AO_2 = Atmospheric pressure - water vapor pressure - P_ACO_2

= (760 - 47 - P_ACO_2/0.8)

Alveolar-arterial gradient is calculated by:

A-a Gradient = (713 - P_ACO_2/0.8) - P_aO_2

OXYGENATION INDEX

$$\frac{MAP \times F_iO_2}{P_aO_2}$$

Chapter 17
CARDIOLOGY BASICS

Marjorie J. Arca, MD

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 after load 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 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 hpyermagnesemia. Treatment includes identifying the cacuse 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 ibutalide (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

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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 Resynchromization therapy
- Mechanical ventricular assist device

RAAS (Figure)

```
┌─────────────────┐
│  ↓   Perfusion  │
│                 │
│  ↓   Na         │
└─────────────────┘
        ↓        Sensed by

Juxtoglomecular Cells in Macula Densa of Kidney

        ↓

Renin release
            ==Vasoconstriction==


Angiotensingen      Renin        Angiotensin I    ACE (lung)    Angiotensin II
(made by liver)                  circulates                           ↗
                                                                      │
                                                                      ↓
                                                               Adrenal Cortex

                                                                      │
                                                                      ↓

                        Conserve Na ←─────────          Produce
Aldosterone
                        Conserve fluid
```
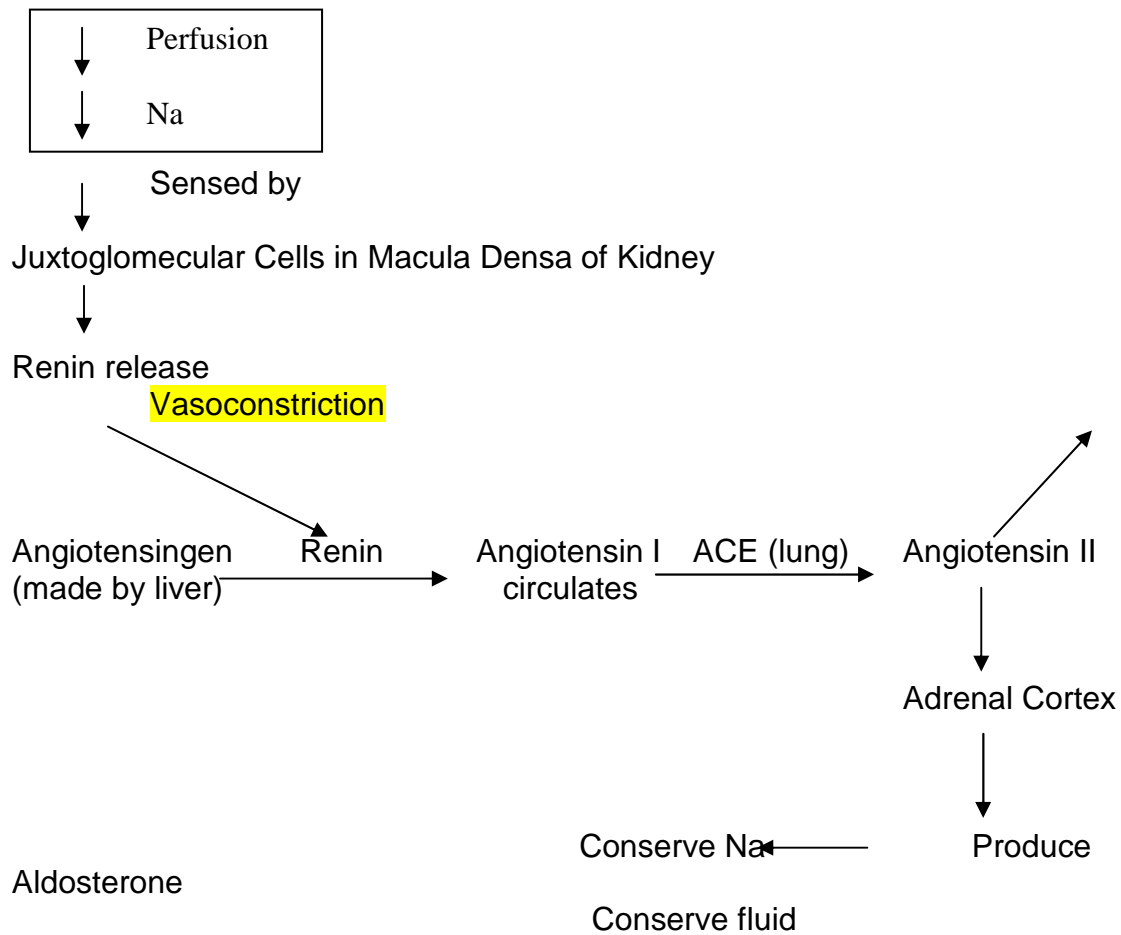
Captopril, enalapril are ACE Inhibitors

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 <u>no</u> 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
    Milninone
    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 sequlae.

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.

	Breath	Rate	Depth
Neonate			
Pediatric			
Adult			1 ½ - 2

Correlated with return of spontaneous circulation

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 CO_2 should be documented and measured continuously, if possible. If epinephrine is given endotracheally, and is given in an acidic carrier, the indicator may turn yell. 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 $ETCO_2$ is O, since pulmonary blood flow is needed for $ETCD_2$ 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 dejects (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 $\rightarrow$ lungs AND body $\rightarrow$ heart), rather than in series (R heart $\rightarrow$ lungs $\rightarrow$ L heart $\rightarrow$ body $\rightarrow$ R heart).

Mixing of blood in Single Ventricle Physiology can occur at three levels:

- Atrial level mixing (PFO, ASD)

o At times, this must be emergently established via balloon septostomy

- Ventricular level mixing (VSD)

- Ductal level mixing (PDA)

o 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

o Examples include:

▪ Hypoplastic Left Heart Syndrome

▪ Critical Aortic Stenosis

▪ Interrupted Aortic Arch

o In such situations, Qs is primarily dependent on a R $\rightarrow$ 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.

o If this condition is not diagnosed prenatally, these babies will often present in cardiogenic shock when their PDA closes.

- Pulmonary (Right-Sided) Outflow Obstruction

o Examples include:

▪ Tricuspid Atresia

- Pulmonary Atresia

- Tetralogy of Fallot with Pulmonary Atresia

- Severe Ebstein's Anomaly

- Critical Pulmonary Stenosis

o 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.

o 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.

$Qp/Qs = (SaO_2 - SmvO_2) / (SpvO_2 - SaO_2),$

Where SaO_2 = oxygenation saturation of arterial blood,

$SmvO_2$ = oxygen saturation of mixed venous blood,

$SpvO_2$ = 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 $SpvO_2$ 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 ($SaO_2 - SmvO_2$) will be about 25%. Thus the above equation can be simplified to:

$Qp/Qs = 25 / (100 - SaO_2).$

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 O_2 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 isolettes 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 $\leq$ 30 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.

Chapter 18
A PRIMER ON CLINICAL RESEARCH AND QUALITY IMPROVEMENT IN CRITICAL CARE

Peter Minneci, MD

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 including 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 hospita- acquired infections and the Center for Disease Control has published evidenced-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 of 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

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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.

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