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Core Curriculum in Nephrology

Fluid Management in Adults and Children: Core Curriculum 2014

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BACKGROUND: PHYSIOLOGY

Overview

An understanding of fluid compartments, including the structure and function of the cell and capillary membranes and the changes that occur in health and in disease, is key to providing appropriate fluid management. The effective circulating volume is the part of the extracellular fluid that maintains perfusion to tissues. The cornerstone of volume management is to maintain the effective circulating volume to optimize oxygen delivery to tissues early in the disease process while avoiding interstitial edema. Having knowledge of the physiologic principles that determine volume distribution—in other words, knowing what happens to the fluid after a volume challenge has been given—can influence the type and amount of fluid administered.

Intracellular Versus Extracellular Compartments

In adults, total-body water (TBW) comprises ~60% of lean body weight and therefore is the most abundant component in the human body. This varies based on sex (TBW comprises a higher percentage of lean body weight in males than in females) and age (the percentage decreases with age). The variation in water weight is due largely to the amount of adipose tissue in the body, which holds significantly less water than muscle. TBW is divided into the extracellular and intracellular fluid compartments. The distribution of water can be remembered by the "two-thirds/one-third and three-fourths/one-fourth" concept illustrated in Fig 1. There is considerable variation in TBW in children. Neonates, infants, and children carry a significantly higher percentage of TBW compared with adults due to reduced fat content and increased muscle mass proportion. TBW percentage gradually decreases by toddler age (Fig 1B), mirrored by the increase in intracellular fluid volume secondary not only to muscle growth, but also to decreasing rates of collagen production.

Osmolality, Vascular Barrier, and Integrity

Osmotic forces are the main determinant of water distribution and movement throughout the body. Solutes that cannot freely cross the cell membrane exert osmotic pressure on that compartment, resulting in fluid shifts across the membrane. Because water freely crosses almost all cell membranes, a change in osmolality in one compartment will trigger water movement across the cell membrane to the side with higher osmolality. This specifically describes the forces that occur between the intracellular and extracellular compartments across cell membranes. The calculation for serum osmolality is: $2 \times [Na^+] +$ [urea nitrogen]/2.8 + [glucose]/18. It is important to note that while this calculation includes glucose and serum urea nitrogen, both these substances permeate readily across most cell membranes and are ineffective osmoles. Therefore, the most abundant extracellular cation, sodium, greatly affects water homeostasis. Control over serum osmolality is maintained by the intricate feedback loop between the hypothalamus and the juxtaglomerular apparatus in the kidney. Release of arginine vasopressin secondary to hyperosmolarity detected by osmoreceptors in the anteroventral hypothalamus leads to upregulation of aquaporin channels in the collecting duct of the kidney. Simultaneously, osmoreceptors in the juxtaglomerular apparatus detect changes in solute (ie, sodium) delivery and volume status and regulate the renin-angiotensin-aldosterone axis to change fluid and sodium retention in renal tubules. In periods of volume imbalance, the 2 osmoreceptor mechanisms work in tandem with each other and with the sympathetic nervous system to regulate a precise balance of sodium and extracellular water volume (Fig 2). In small children, susceptibility to volume depletion is increased secondary to immature hypothalamic osmoreceptor function and inadequately developed juxtaglomerular apparatus signaling. Additionally, the higher percentage of their body weight in TBW places small children at greater risk of more significant hemodynamic compromise in situations of volume depletion.

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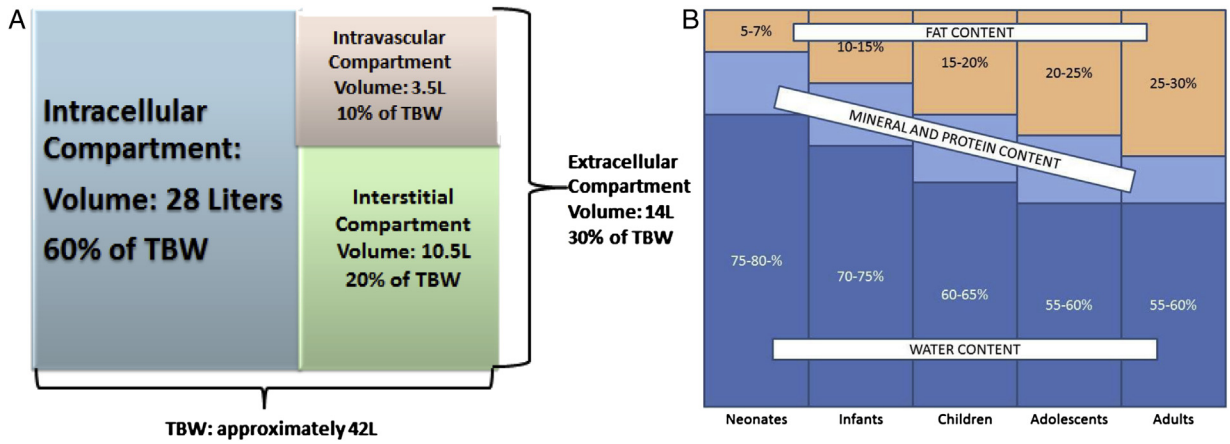

Figure 1. (A) Fluid compartments within the human body. (B) Total-body water (TBW) content by age.

The intravascular and interstitial compartments are separated by capillary membranes, and the mechanism of fluid shift differs from that described, where capillaries and small postcapillary venules act as the sites of exchange. In 1896, Ernest Starling described the classic model of vascular barrier function, specifically that net filtration between plasma and interstitium is determined by physical factors, including hydrostatic pressure, oncotic pressure, and the permeability of the barrier separating the 2. The Starling principle declared that the vascular barrier function is the sole responsibility of the single endothelial cell line. However, more recent data suggest that the healthy endothelial lining is coated with another barrier called the glycocalyx. The glycocalyx is $\sim$1 μm in thickness and binds proteins, thereby increasing oncotic pressure within the endothelial surface layer and further preventing an egress of fluid into the interstitium. In addition, a free space containing minimal oncotic pressure resides just adjacent to the glycocalyx and endothelial layers. A pressure gradient between the glycocalyx and free space is generated, which further reduces fluid shifts across the vascular wall. Thus, the glycocalyx, along with the adjacent endothelial cell layer, forms this double barrier to prevent tissue edema.

Any form of disruption to the glycocalyx can result in increased transendothelial permeability and ultimately in interstitial edema. Tumor necrosis factor α (TNF-α) and other cytokines, known to be indicative of systemic inflammation, have been shown to be associated with a decrease in the thickness and breakdown of the glycocalyx, leading to increased vascular permeability. Similar cases of glycocalyx degradation and increased vascular

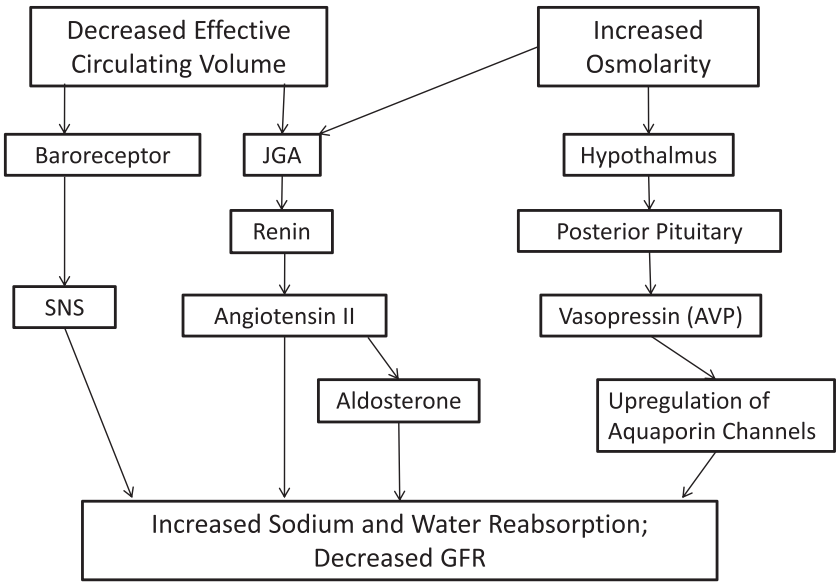

Figure 2. Volume and osmolality homeostasis. Abbreviations: AVP, arginine vasopressin; GFR, glomerular filtration rate; JGA, juxtaglomerular apparatus; SNS, sympathetic nervous system.

Table 1. Crystalloid Solutions

	Na^+ (mEq/L)	K^+ (mEq/L)	Ca^{++} (mEq/L)	Mg^{++} (mEq/L)	Cl^- (mEq/L)	Buffers (mEq/L electrolyte)	Glucose (g/L)	pH	POsm (mOsm/L)
Plasma	141	4.5	5	2	103	Bicarbonate, 26; protein, 16	0.7-1.1	7.4	290
Isotonic									
Normal saline	154	—	—	—	154	—	—	6.0	308
Lactated Ringer's solution	130	4	4	—	109	Lactate, 28	—	6.5	274
Plasma-Lyte	140	5	—	3	98	Acetate, 27; Glucose, 23	—	7.4	294
Hypotonic									
D_5W	—	—	—	—	—	—	50	4.5	252
D_5W $^1/_2$ NS	77	—	—	—	77	—	50	5.0	406
Hypertonic									
7.5% NaCl	1,284	—	—	—	1,284	—	—	6.0	2,568

Abbreviations: Ca^{++}, calcium ion; Cl^-, chloride ion; D_5W, 5% dextrose; D_5W $^1/_2$ NS, 5% dextrose in half-normal saline; K^+, potassium ion; Mg^{++}, magnesium ion; Na^+, sodium ion; NaCl, sodium chloride; POsm, plasma osmolality.

permeability have occurred after ischemia-reperfusion injury. Finally, the release of atrial natriuretic peptide secondary to excessive volume resuscitation can cause damage to the double barrier, further exacerbating tissue edema.

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FLUID TYPES

Overview

Since the first infusion of intravenous fluid in 1832 during the cholera epidemic to present day, when fluids are the most frequently prescribed therapy in the intensive care unit (ICU), the quest for the "best" solution has been a subject of ongoing debate and inquiry.

Crystalloid Solutions

Crystalloids are aqueous solutions of inorganic and small organic molecules and are either hypotonic, isotonic, or hypertonic with respect to plasma. Isotonic crystalloids distribute freely across the vascular barrier; approximately one-fourth of the solution stays within the vascular space, assuming an intact vascular barrier. Clinically, this translates to a 1-L sodium chloride (NaCl) solution bolus resulting in a 250-mL expansion of circulating volume. Therefore, large volumes of crystalloids often are needed to maintain intravascular volume, potentially at the cost of generating interstitial edema. Hypertonic solutions, such as 3% or 7.5% NaCl, often are used in the treatment of severe hyponatremia. Many have advocated for the use of hypertonic saline solution to restore intravascular volume rapidly; however, data do not support its use as a resuscitation strategy. Similarly, hypotonic fluid (ie, half-normal saline solution) is used for treating hypernatremia or free water deficit, but is not an effective resuscitative fluid.

In addition to tonicity, crystalloids can be defined by their electrolyte makeup. Balanced solutions contain a physiologic mixture of electrolytes and buffers in an effort to replicate the makeup of plasma. Examples include lactated Ringer's solution, Isolyte (B. Braun Medical Inc), and Plasma-Lyte (Baxter). Unbalanced solutions do not contain extra electrolytes or addition of a buffer. NaCl solution is the typical unbalanced solution. A summary of the various crystalloid solutions can be found in Table 1. For years, internal medicine specialists have favored the use of NaCl solution as a resuscitation fluid due to concerns that electrolytes added to balanced solution might be harmful in patients with kidney impairment who cannot handle, for example, a potassium load.

However, large-volume resuscitation with NaCl solution results in hyperchloremic metabolic acidosis, which now has been shown to have deleterious consequences. In studies of both animals and humans, excess extracellular chloride is associated with increased afferent arteriolar resistance and subsequent reduced cortical perfusion and diminished glomerular filtration rate. In a surgical study of open-abdomen patients that compared 0.9% NaCl to Plasma-Lyte solution, major complications, including an increased risk of patients requiring renal replacement therapy (RRT), was observed in the chloride-liberal group. A large prospective sequential-period pilot study compared a chloride-liberal approach versus a chloride-restricted regimen through patients' entire ICU stays. Results demonstrated an increased incidence of acute kidney injury (AKI) and RRT in the chloride-liberal group.

Due to concerns about the ability of neonatal and infant kidneys to handle high-solute load, hypotonic resuscitative fluids traditionally have been used for restoring adequate circulating effective volume. However, high incidences of hyponatremia and hypoglycemia warranted investigation and comparison with other crystalloid solutions. Isotonic salt solution and isotonic salt solution with dextrose have been demonstrated to reduce the number of electrolyte imbalances (primarily hyponatremia and hypoglycemia) in resuscitation in children. The recent FEAST (Fluid Expansion as Supportive Therapy) Study received worldwide attention by examining resuscitation of more than 1,000 Kenyan, Tanzanian, and Ugandan children presenting with severe infection (~60% malaria) using either normal saline solution bolus, albumin bolus, or no bolus and reported increased mortality in children receiving fluid boluses versus no bolus. Importantly, the cause of death in patients who received the 20- to 40-mL/kg bolus fluids could not be linked to hypernatremia, hyperchloremia, edema, or any direct effect from resuscitative fluids. Unfortunately, randomized data regarding the use of more balanced salt solutions (ie, Plasma-Lyte) versus pure salt solution are unavailable.

Given the body of evidence, the authors of this review recommend the use of balanced over unbalanced crystalloid solutions. However, certain clinical scenarios require individual consideration. Patients with cerebral edema or traumatic brain injury cannot tolerate even relatively hypotonic solutions due to the risk of cellular swelling. Therefore, lactated Ringer's solution, by the nature of its low sodium content, is contraindicated in these patients. In patients at risk of cerebral swelling, we recommend a balanced isotonic solution when resuscitation is necessary. Balanced solutions also should be avoided in patients with alkalemia or severe hyperkalemia. Last, use of lactated Ringer's solution requires intact liver function to convert lactate into bicarbonate and therefore is not recommended in patients with significant liver dysfunction. In children, there currently is not enough evidence to support routine use of balanced salt solutions over unbalanced salt solutions, though pure physiologic data obtained from animal models indicate that unbalanced solutions could be even more detrimental to children than they are to adults.

Colloid Solutions

Colloids are homogenous noncrystalline substances that contain large molecules. In theory, colloids have a greater capacity to remain within the intravascular space and therefore restore hemodynamics with smaller quantities of volume infused. Colloids in clinical practice include human plasma derivatives (albumin, fresh frozen plasma, and blood) and semisynthetic colloids (starches, gelatin, and dextran). Albumin has been used for resuscitating hemodynamically unstable patients for decades. It achieved its greatest popularity after its use in Pearl Harbor victims, in which resuscitative goals were achieved efficiently. Albumin is the most costly of colloid solutions and, as a human body product, contains a very small risk of infectious transmission. It is available in 5% (50-g/L) and 25% (250-g/L) solutions and most often is given in a 250-mL followed by a 50-mL volume. Certain religious groups (eg, Jehovah's Witnesses) forbid its use. Hydroxyethyl starches (HESs) are the most widely used semisynthetic resuscitation fluids. Examples include Volulyte (Fresenius Kabi), Hespan (B. Braun Medical Inc), and Voluven (Hospira). HESs are described by their average molecular weight (130-200 kDa) and degree of molar substitution (ie, the proportion of glucose units on the starch molecule replaced by hydroxyethyl units; typically 0.35-0.5). An HES is described further by its concentration in percent (ie, grams per 100 mL). For example, 6% HES 130/0.4 contains 6% solution of 130-kDa molecules with 0.4% of the glucose molecules substituted. HESs have a lower cost per unit compared to albumin. Dextrans are high-molecular-weight D-glucose polymers that are biosynthesized commercially from sucrose. They are described by average molecular weight: dextran 40 and dextran 70. Dextrans are rarely used in adults. Gelatins are prepared by hydrolysis of bovine collagen. Due to concerns about coagulopathy and bleeding, gelatins were withdrawn from the market in the United States in 1978.

Crystalloid Versus Colloid Solutions: The Data

Despite decades of inquiry and study, there has yet to be a large randomized controlled trial to demonstrate that one type of fluid is superior to the other.

Colloid supporters focus on the large volume of crystalloid needed to achieve intravascular resuscitation goals. Those who favor crystalloids point to the potential side effects of colloids, including hematologic derangement and adverse drug reaction, as well as the higher cost. As stated, under healthy conditions, colloids are too large to permit passage across the capillary membrane and thus restore circulating volume efficiently. However, in the setting of inflammatory conditions and vascular barrier breakdown, the distribution of colloids looks very similar to that of crystalloids because both migrate from the vascular compartment into the interstitial space. This physiologic principle likely is the reason that few studies can demonstrate superiority of one fluid over the other.

Albumin Versus Crystalloids

As the primary determinant of oncotic pressure and driver of fluid distribution between compartments in the human body, albumin has great appeal as a resuscitative fluid. Albumin was a staple for volume resuscitation until a meta-analysis in 1998 showed that it was associated with increased mortality. Opinions changed again after publication of the SAFE (Saline Versus Albumin Fluid Evaluation) trial in 2005 in which survival, number of days spent in the ICU and hospital, and days spent on mechanical ventilation after receiving 4% albumin versus 0.9% NaCl solution were shown to be similar. Subsequent trials have demonstrated albumin's safety. In a SAFE subgroup analysis, patients with severe head injury had worse outcomes when treated with albumin, whereas patients with severe sepsis showed some degree of improvement with albumin compared with saline. Albumin should not be given to patients with traumatic brain injury for this reason. Albumin is indicated in spontaneous bacterial peritonitis as another trial demonstrated a benefit of albumin to survival of cirrhotic patients with the condition. Finally, in dialysis patients who require large-volume ultrafiltration, a 250-mL bolus of 5% albumin can be invaluable in order to maintain mean arterial pressure. In several small studies, primarily limited to patients with malaria and dengue fever in resource-poor areas, albumin appeared to be associated with lower overall mortality than saline solution when used as fluid of choice for resuscitating critically ill children. Unfortunately, there are no current controlled studies examining colloid versus crystalloid resuscitation in children with sepsis or severe hypovolemia in developed nations.

Starch Versus Crystalloids

HESs have been under increasing scrutiny in recent years. In 2008, the VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) trial showed that patients who received 10% pentastarch (HES 200/0.5) solution were twice as likely to develop AKI and trended toward increased mortality. Subsequent trials, including 6S (Scandinavian Start for Severe Sepsis/Septic Shock) and CHEST (Crystalloid Versus Hydroxyethyl Starch Trial), compared lower weight HES with crystalloid solutions and again showed an association between HES exposure and the need for RRT. As a result of these findings, a European task force on colloid therapy recommends that starch solutions not be used outside the context of clinical trials. The present Surviving Sepsis Campaign states that fluid resuscitation should begin with crystalloid, albumin should be considered in patients who continue to require substantial amounts of crystalloid, and HES should be avoided. Combining the available evidence, guidelines, and costs, we favor the use of balanced crystalloid solution with sparing use of albumin for the conditions outlined.

Though less expansive, results from studies in children comparing unbalanced to balanced electrolyte solutions mirror data obtained from adult studies. For example, comparison of HES (HES 130/0.42/6:1) in normal saline solution (ns-HES) to balanced salt solution (bal-HES) for perioperative resuscitation demonstrated a significantly higher incidence of hyperchloremia in the ns-HES group and improved safety for bal-HES use in neonates and small infants.

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FLUID MANAGEMENT

Targets of Fluid Resuscitation

Securing adequate intravascular volume and ensuring optimal perfusion is the primary goal of resuscitation in critical care management. The study by Rivers et al demonstrated that early resuscitation using a goal-directed algorithmic approach improved survival. Although this study has not been validated in a multicentered randomized trial (currently in progress) and many aspects of an early goal-directed therapy protocol have been contested, the importance of recognizing inadequate tissue perfusion and oxygen debt early is emphasized by this study's findings. The time-honored method of assessment is based on physical findings, including tachycardia, hypotension, dry mucous membranes, altered mentation, and decreased urine output, are not reliable indicators of intravascular volume. Hypotension is a late indicator of shock and reflects failure of compensation or volume loss $> 20\%$. Hypotension also may reflect pure vasodilation (eg, a side effect of anesthesia) and not volume depletion. In the trial by Rivers et al, average mean arterial pressure in the early goal-directed therapy group was 76 mm Hg, while the control group's was 76 mm Hg, and yet lactate values were > 4 mEq/L, indicating hemodynamic compromise. Urine output is not a reliable indicator either, especially in a setting in which renal blood flow alone may not be the cause for oliguria, for example, sepsis-induced AKI.

The primary target of resuscitation in children may simply be timely resuscitation. Unfortunately, volume correction in children offers several unique challenges that are not present in adults. Robust data, starting with a landmark study by Carcillo et al demonstrating a marked improvement in survival in patients with septic shock who received 40 mL/kg of fluid in the first hour versus those who did not, support instituting early and rapid correction of volume deficit in children. More recent retrospective studies published in the past 3-5 years support the use of early and rapid infusion of fluids. Unfortunately, rapid infusion of fluids in children often is easier said than done. Catheter properties limit the speed of fluid delivery secondary to Poiseuille's law, which states that resistance is inversely proportional to the radius to the fourth power, a physical principle that becomes significant with the 20-, 22-, and 24-gauge peripheral lines that sometimes are necessary in small children presenting in extremis. Additionally, this assumes that access can be obtained readily, which often is not the case in a small unstable patient. Second, the availability of proper infusion equipment is not widespread. The rapid infusers that are used with some regularity in adult medicine are not commonly used outside of tertiary-care pediatric trauma bays, operating theaters, and ICUs. Knowledge of the speed of fluid delivery of standard intravenous fluid pumps also is lacking (eg, most providers would be unaware that a 20-mL/kg bolus in a child weighing 15 kg would take 18 minutes to complete for a pump running at "maximum": 999 mL/h). Finally, the need to obtain access and institute fluids rapidly is not universally appreciated in pediatric care, an oversight that global sepsis and shock recognition movements are now addressing.

Clinical examination plays a relatively larger role in resuscitating children. Assessment of volume and oxygenation debt by thorough examination of the critically ill child consists of a precise time-stamped inspection of perfusion, capillary refill, skin temperature, skin turgor, mucous membranes, lung auscultation, cardiac examination, mental status examination, and vital signs. Owing in part to the inability to obtain reliable invasive measurements (described in some detail next), pre- and post-examinations of children with fluid resuscitation rest on the cornerstones of changes in these physical examination findings.

Unlike physical signs and symptoms, using surrogates of oxygen delivery, including mixed venous oxygen saturation (Svo_2), central venous oxygen saturation ($Scvo_2$), and serum lactate concentration, better represents the imbalance between the body's metabolic demands and the adequate delivery of oxygen to body tissues. The Svo_2 measurement is acquired from the distal port of a pulmonary artery catheter (PAC). Oxygen consumption exceeding its

supply or oxygen delivery being compromised reduces subsequent oxygen venous return to the right side of the heart. An $Svo_2 < 65\%$ (reference range, 65%-75%) reflects an imbalance. An $Scvo_2$ level obtained from the distal port of a subclavian or internal jugular central catheter can act as a surrogate for the PAC-derived Svo_2. Although the 2 values (Svo_2 and $Scvo_2$) are not equivalent, they have been shown to correlate well. $Scvo_2 < 70\%$ denotes inadequate oxygen delivery and should trigger an intervention. High serum lactate concentration and the inability to clear this lactate can reflect mitochondrial dysfunction, often as a consequence of inadequate oxygen delivery. As demonstrated by the study by Rivers et al, a high lactate level can occur even in the setting of normal blood pressure and heart rate, and therefore one should have a very low threshold for obtaining a lactate level in a patient who meets systemic inflammatory response syndrome criteria. If lactate level is high (in general we use a cutoff of 2.0 mmol/L), fluid resuscitation followed by rechecking the value 6 hours later to ensure clearance is a reasonable approach. Studies have shown that lactate clearance $\geq 10\%$ is associated with improved outcomes and is the basis for this strategy.

Assessment of Fluid Resuscitation Targets

Overview. Given adequate hemoglobin and oxygen saturation levels, cardiac output is the main determinant of oxygen delivery. Therefore, fluid management should be based on whether giving a bolus of fluid infusion augments cardiac output and thus improves perfusion and oxygen delivery (ie, whether cardiac output is fluid responsive). This relationship between preload and cardiac performance is depicted by the Frank-Starling curve, whereby a change in preload will produce a significant change in cardiac output only if both ventricles operate on the ascending limb of the Frank-Starling curve (Figs 3 and 4). Conversely, if preload value is low, yet operates on a flat portion of the Frank-Starling curve, volume expansion will not improve cardiac performance and will only contribute to volume overload. It is this physiologic concept that governs why a static value of preload does not predict the extent that stroke volume will respond to a volume challenge.

In children, the response of the myocardium to volume resuscitation is different than in adults. The myocardium in neonates and infants is immature secondary to numerous cardinal properties: a lower contractile to noncontractile ratio, different shape (more circular than elongated/fibrillar), less extracellular matrix elements that confer more tensile strength, decreased myocardial compliance, and less ready regulation of calcium current for depolarization. Though the Starling mechanism is intact, the curve is shifted to the left and requires less volume loading to reach higher pressure. In aggregate, volume loading the immature myocardium leads to a relatively decreased effect on augmenting cardiac output compared to the mature heart. In addition, the maturation process and relative compliance of the ventricles, along with intraventricular dependence, change dramatically in the first year of life. Though the right

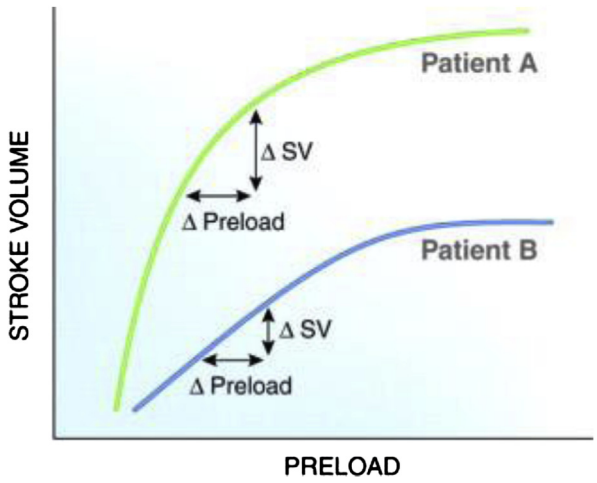

Figure 3. Patient A has a steeper Starling curve than patient B. Although patients A and B have the same initial preload value and identical changes in preload (ie, fluid bolus), patient A has a greater increase in stroke volume (SV) than patient B. Patient A is said to be "volume responsive." Reproduced from Davison & Junker ("Advances in critical care for the nephrologist: hemodynamic monitoring and volume management." *Clin J Am Soc Nephrol.* 2008;3[2]:554-556) with permission of the American Society of Nephrology.

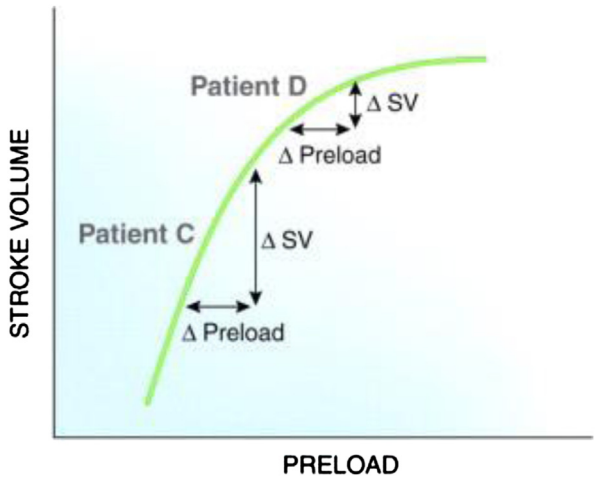

Figure 4. Patient C is on the steep portion of the curve. Patient D is on a flat portion. Identical changes in preload (ie, fluid bolus) result in different stroke volumes (SVs). Reproduced from Davison & Junker ("Advances in critical care for the nephrologist: hemodynamic monitoring and volume management." *Clin J Am Soc Nephrol.* 2008;3[2]:554-556) with permission of the American Society of Nephrology.

ventricle is always more compliant than the left ventricle, the relative abundance of contractile elements in the right ventricle decreases significantly relative to the left within the first 3 months of postnatal development. Finally, it is important to recognize the inverse relationship of heart rate and stroke volume (or rather, the incomplete inverse relationship) in neonates and infants. Because the myocardium is limited in tensile strength, neonatal and infant hearts are more dependent on heart rate as a means to augment cardiac output. Taken together, properties of the myocardium are important to recognize because a significant proportion of mortality from shock and volume depletion in children occurs in the neonatal period.

Static measurements. Static markers of preload include pulmonary artery occlusion pressure (or "wedge") and central venous pressure. Despite their common use in the critical care setting, these parameters are poor surrogates of volume status and fail to predict fluid responsiveness, as demonstrated by numerous studies. In clinical practice, central venous pressure is used as a surrogate for right atrial and right ventricular volumes. Likewise, in theory, pulmonary artery occlusion pressure represents the volume of the left side of the heart. Use of these filling pressures as a parameter of volume status assumes a constant relationship between pressure and volume. However, there are several clinical scenarios in which this relationship is altered. In the noncompliant "stiff" heart, central venous pressure and pulmonary artery occlusion pressure may be elevated even if the ventricles are underfilled. The high pressure values would indicate that the patient is volume replete when in actuality, cardiac performance may still benefit from volume. External pressures, including high ventilator pressures, abdominal compartment pressures, and vascular compliance, can alter the relationship between central venous pressure, pulmonary artery occlusion pressure, and ventricular volume, making them an inaccurate gauge of volume status. Use of central venous pressure measurement to estimate fluid dynamics in children outside the immediate postoperative congenital cardiac surgery setting has no literature support. In addition, the relatively higher pressure of the right ventricle in neonates and infants (vs the left as a function of age) affects the reliability of the static central venous pressure measurement.

We strongly recommend against the use of static preload markers to define volume status or guide resuscitation.

Dynamic measurements. Dynamic markers consist of variations in stroke volume and arterial pressure that result from heart-lung interactions during positive pressure ventilation. Many studies have documented that these parameters better predict whether volume administration will improve cardiac performance. Mechanistically, dynamic measurements are acquired as follows. With each positive pressure breath, there is a decrease in venous return. If the right ventricle is preload dependent, there also will be reduced right ventricular outflow. There is a subsequent decrease in left ventricular outflow (after a few cardiac cycles, given the 2-second transit time for blood to pass through the lungs). The opposite occurs during exhalation: venous return is increased and cardiac output is amplified. This cyclic variation in stroke volume and blood pressure is most pronounced when stroke volume is preload dependent. Therefore, high variations suggest that hemodynamics will benefit from volume expansion. Clinically, these markers include systolic pressure variation, pulse pressure variation, and stroke volume variation. An example of this physiologic concept is depicted in Fig 5. These values can be measured on an arterial wave form tracing (systolic pressure variation and pulse pressure variation) or calculated and displayed continuously by hemodynamic devices (described next). At our institution, we use stroke volume variation as a guide to volume expansion. Stroke volume variation greater than 10%-13% indicates that the patient is fluid responsive. If a patient has a stroke volume variation $< 10\%$ and cardiac output unresponsive to volume, that patient's hypotension would be managed with either vasopressors alone or inotropes, depending on cardiac function (Fig 6).

The use of dynamic markers to predict fluid responsiveness has limitations. These markers are most accurate when used in a mechanically ventilated patient with consistent breaths, which usually occur during deep sedation or paralysis. Few studies have validated its use in spontaneously breathing patients. Similarly, in the open-chest patient, ventilator-

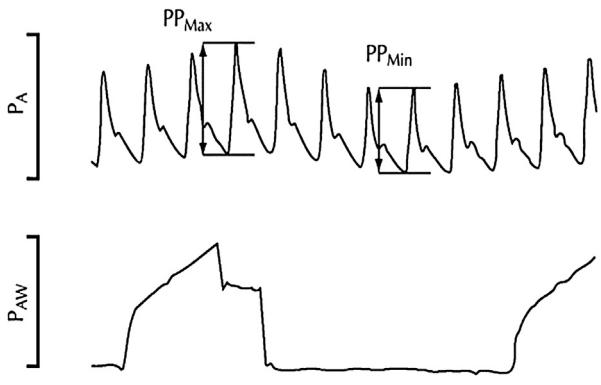

Figure 5. Dynamic markers. Pulse pressure (PP) variation relative to peak airway pressure (Paw) during inspiration and expiration. Reproduced from Davison & Junker ("Advances in critical care for the nephrologist: hemodynamic monitoring and volume management." *Clin J Am Soc Nephrol.* 2008;3[2]:554-556) with permission of the American Society of Nephrology.

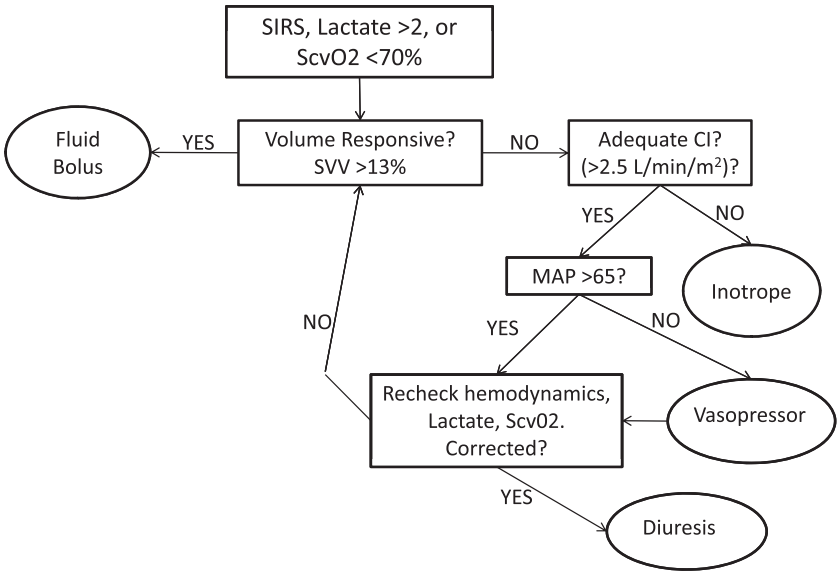

Figure 6. Bedside strategy for fluid management. Abbreviations: CI, cardiac index; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome; $Scvo_2$, central venous oxygen saturation; SVV, stroke volume variation.

induced variation in stroke volume loses its accuracy. Stroke volume variation is not accurate in patients with arrhythmias.

Dynamic markers of fluid responsiveness have not been assessed adequately in infants, children, and adolescents. Pulse pressure variation and systolic pressure variation analysis in neonates and infants is discrepant from children and adolescents secondary to the differences in chest wall elasticity and lung compliance as a function of age.

Other functional dynamic measurements. Two other dynamic mechanisms by which fluid responsiveness can be measured include the passive leg raise and variation in inferior vena cava (IVC) diameter. During the passive leg raise test, a recumbent patient raises the lower extremities above the heart, which increases right and left cardiac preload. If no other monitoring device is present, the effect of passive leg raise on blood pressure and heart rate is used to guide the decision of whether more fluid is indicated. The passive leg raise test reproduces the effects of a volume challenge and therefore also plays a therapeutic role. The passive leg raise test has proved accurate in nonintubated patients, which differentiates it from the other dynamic parameters. The passive leg raise test cannot be performed in immobilized patients (eg, those who have traumatic brain injury or open abdomen). IVC diameter measured by echocardiogram is another method to measure fluid responsiveness. Like the other dynamic parameters, variation in IVC diameter depends on the variation in venous return as a result of changes in thoracic pressure during mechanical ventilation. Variation in IVC diameter is calculated as the change in IVC diameter during inspiration compared with expiration (approximately >20% variation indicates volume responsiveness). Measuring IVC diameter variation requires echocardiography, which is highly dependent on operator skill. Neither passive leg raise test results nor IVC diameter variation can be measured in a continuous fashion and therefore are not useful for ongoing assessment of hemodynamic instability. Tests of reliability for IVC diameter measurement in children have not been performed and informal assessments of interuser consistency demonstrate a lack of appropriate standards. However, in children, in lieu of a passive leg raise test, direct pressure applied to the inferior surface of the liver edge often is used as a test of volume responsiveness.

Devices Used for Fluid Management at the Bedside

Pulmonary Artery Catheter

Monitoring devices that display cardiac output and facilitate the measurement of volume responsiveness can allow for more precise resuscitation and minimize unwanted side effects. The gold standard for measuring bedside cardiac output is the PAC. The PAC uses the thermodilution technique to calculate cardiac output, and it is the mechanism against which all other devices are measured. Central venous pressure, right atrial pressure, pulmonary artery pressures, pulmonary artery occlusion pressure, and $Scvo_2$ also can be obtained from the PAC. Newer fiberoptic PACs allow for continuous cardiac output monitoring, which adds significant clinical value when monitoring trends and changes in intervention. Use of PACs has declined in the past 20 years for 2 major reasons. First, despite a large body of research, the PAC has never been shown to improve outcomes. Second, the advent of newer devices that are less invasive and provide dynamic parameters to assess

volume responsiveness are making the PAC increasingly obsolete. Though no evidence demonstrates proven efficacy of the PAC at reducing mortality across the wide range of critically ill children, there also is no solid evidence indicating an increase in mortality or complications. The available data support using PACs in select children (those with pulmonary hypertension and refractory shock). Pediatric critical care practitioners continue to use PACs, though at lower numbers, driven by clinical context.

Less Invasive Hemodynamic Devices

Echocardiography. Echocardiography is a noninvasive technique that uses ultrasound waves to generate real-time images of the heart. It is used increasingly by intensivists to gain a snapshot of ventricular function and volume status. It rarely is used in a continuous fashion outside the operating room and therefore has its limitations for ongoing management of critically ill patients.

Esophageal Doppler. This technique estimates aortic blood flow through a Doppler ultrasound inserted into the esophagus. It is based on the physiologic concept that the velocity of blood flow through the aorta is inversely proportional to aortic diameter and directly related to flow. This technique requires that the patient be intubated on insertion and that flow is laminar throughout the aorta. Turbulent flow secondary to atherosclerosis or an aneurysm will distort the calculations of cardiac output. This technique also relies heavily on operator skill for proper placement of the device in the esophagus. Despite these drawbacks, data suggest that esophageal Doppler is a reliable measure of continuous cardiac output.

Thoracic electrical bioimpedance. Bioimpedance is the electrical resistance of the thorax to an alternating electrical current transmitted through the chest. This is accomplished by 8 electrodes placed on the patient's thorax and connected to the thoracic electrical bioimpedance device. The patient's cardiac output is calculated using the impedance of the thoracic aorta, which varies with blood flow. Thoracic electrical bioimpedance is noninvasive; however, it loses accuracy in the settings of pulmonary edema, pleural effusions, and chest wall edema due to the fluid interference. Studies have not demonstrated that thoracic electrical bioimpedance is an accurate measure of cardiac output; it should be used in only a select set of patients.

Transpulmonary thermodilution. The transpulmonary thermodilution technique uses thermodilution similar to that of the PAC. However, it requires use of a standard central venous catheter in the internal jugular or subclavian vein, as well as a distal thermistor tip in the femoral artery. Cold injectate is infused into the central line and the temperature change as measured in the downstream femoral artery thermistor is used to calculate cardiac output. Assuming minimal loss of injectate and only one pass from the proximal to distal thermistor, this is an accurate measure of cardiac output. A unique feature of the transpulmonary thermodilution technique is that it also allows for calculation of global end-diastolic volume and extravascular lung water, which reflect cardiac filling and pulmonary edema, respectively. Studies have shown this technique to be a reliable measure of cardiac output in the critically ill patient population.

Lithium dilution. In this technique, a bolus of lithium is injected into a venous catheter. Blood then is drawn from a distal arterial catheter that contains a lithium sensor. The dilutional curve over time is used to estimate cardiac output. Unlike the transpulmonary thermodilution technique, lithium dilution does not require a central venous catheter, but it requires arterial access and is dependent on accurate sodium and hemoglobin concentrations. Lithium dilution is contraindicated in patients receiving lithium therapy, those who weigh <40 kg, and those who are pregnant. Lithium dilution also can calculate extravascular lung water and compares well when measured against other thermodilution techniques.

Pulse contour analysis. Pulse contour analysis is a unique monitoring system that displays cardiac output and cardiac index, stroke volume and stroke volume index, and the dynamic marker stroke volume variation, all in a continuous fashion. Pulse contour analysis is based on the notion that the pulse pressure arterial waveform is proportional to stroke volume and inversely related to compliance of the vessel. Cardiac output is calculated from the analysis of the pulse contour. PICCO (Pulsion Medical Systems), PulsCO (LidCO Ltd), and FloTrac (Edwards Lifescience LLC) are the 3 pulse contour analysis devices available on the market. We use the FloTrac at our institution, which is the only device that does not depend on recalibration and requires only an arterial line. PICCO must be recalibrated using the transpulmonary thermodilution technique and therefore requires both central venous access and a femoral arterial catheter. PulsCO must be recalibrated every 8 hours and uses the lithium dilution technique to do so. Although most studies have demonstrated that the pulse contour analysis technique is accurate and reliable, there are some limitations. Because it relies on the shape of the arterial waveform, a dampened arterial line tracing, the presence of atherosclerosis, or any arrhythmias, including frequent premature ventricular contractions, can generate inaccurate data. Alterations in chest wall compliance or certain ventilator settings (eg, elevated positive end-expiratory pressure) can affect the accuracy of pulse

contour analysis. This monitoring system has not been validated in spontaneously breathing patients. Last, these devices can be costly and therefore might not available in settings in which resources are limited.

Optical-based assessment of tissue perfusion. Near-infrared spectroscopy is a transcutaneous monitoring system that acts as a surrogate for tissue metabolism. Displaying results as regional oxygen saturation, near-infrared spectroscopy technology relies on the emission of infrared light to millimeters deeper than the traditional pulse oximeter. This technique differentiates between oxygenated and deoxygenated moieties (not simply red blood cells). The algorithm within the individual near-infrared spectroscopy devices is able to detect changes in deoxy/oxy components of the subdermal microcirculation and acts as a real-time sensor of oxygen delivery and consumption. Though rigorous study and evaluation of near-infrared spectroscopy currently is unavailable, there are numerous reports of near-infrared spectroscopy monitoring systems foretelling acute decompensation events, near-infrared spectroscopy values responding to vigorous resuscitations (ie, code events) and fluid resuscitations, and cerebral near-infrared spectroscopy being a sensitive indicator of acute brain attacks (strokes). However, this technology remains unproved versus gold-standard measurements.

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Dangers of Fluid Resuscitation

As emphasized, early targeted fluid resuscitation to optimize tissue perfusion is the key to managing patients who are hemodynamically unstable. However, continued volume resuscitation beyond what will improve hemodynamics has detrimental effects. Increasing evidence is demonstrating that a positive fluid balance is associated with worse outcomes. Single-center data initially suggested that increased fluid overload percentage at the time of RRT initiation was associated with higher mortality in 2001. Since that time, data from more than 13 separate centers in the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry comprising 300 patients continues to indicate that a high fluid overload percentage is associated with worsened outcomes (higher mortality and longer duration of mechanical ventilation). Note that the calculation for fluid overload percentage (FO%) is: FO% = (cumulative fluid in− cumulative fluid out)/weight (kg). Data from adults have paralleled this finding. A summary of the organ-specific consequences of overzealous fluid therapy is next.

Vasculature

Mediated by atrial natriuretic peptide release, excess fluid can lead to degradation of the glycocalyx barrier, ultimately increasing vascular permeability and promoting tissue edema. A viscious cycle of repeated boluses to maintain intravascular volume may ensue, which further contributes to the underlying pathophysiology.

Cardiac

Increased ventricular wall stretch, functional mitral and tricuspid insufficiency, resultant pulmonary hypertension, and exacerbation of diastolic dysfunction are all consequences of fluid accumulation.

Lungs

The consequence of fluid overload is most apparent in the lungs, in which pulmonary congestion causes increased workload and reduced compliance. The FACTT (Fluids and Catheters Treatment Trial) demonstrated that patients who received a restricted fluid regimen compared to a liberal regimen spent less time on the ventilator and less time in the ICU. Similar findings were seen in an observational study of brain-dead organ donors in which a restricted fluid strategy resulted in an increase in number of lung

procurements. The fluid restriction did not negatively affect kidney transplant function. In a single-center study of 80 mechanically ventilated children, fluid overload began to be correlated positively and independent with worsening oxygenation index at 15% relative volume accumulation.

Kidneys

As an encapsulated organ, the kidney has limits of expansion when edematous. On a mechanistic level, an increase in kidney venous pressure due to fluid overload decreases kidney arterial perfusion, increases interstitial pressure, and stimulates the renin-angiotensin system, which worsens fluid accumulation. There are convincing data to show that volume overload at the time of dialysis initiation is associated with heightened mortality and decreases the likelihood of recovering kidney function. Moreover, no randomized controlled trials have demonstrated that a positive fluid balance prevents kidney injury during acute illness, whereas a 5%-10% increase in water weight is associated with worsening organ function in patients with AKI.

Gastrointestinal/Abdominal Compartment

Postoperative ileus and malabsorption are prolonged as a consequence of fluid overload. A restricted fluid strategy has been shown to be associated with decreased incidences of complications after colorectal surgery, including anastomotic leaks, pulmonary edema, wound infection, and AKI. Intra-abdominal hypertension and abdominal compartment syndrome are major consequences of imprudent resuscitation. Intra-abdominal hypertension causes decreased venous return, decreased ventilator compliance, reduced renal blood flow, and subsequent development of shock and AKI.

Tissue Edema

Once thought of as simply a cosmetic concern, tissue edema now is linked to impaired oxygen diffusion, obstruction of capillary blood flow and lymphatic drainage, poor wound healing, and the development of pressure ulcers.

Immune System

The innate immune response, particularly to sepsis, may be aberrant in fluid overload states. Responses of humoral cytokines such as TNF-α, IL-4, IL-6, IL-10, and monocyte chemotactic protein 1 reportedly have been altered in animal models of sepsis with fluid overload. Additionally, response of the Toll-like receptor family to pathogen-associated molecular patterns may be hampered in fluid overload states.

Fluid is a drug and should be treated as one. Given the body of evidence reviewed, we propose that intravenous fluid be viewed as a prescribed medication with indications, contraindications, and side effects. The correct "dose" is specific to each individual based on his or her physiologic needs and can change dramatically within hours of illness presentation. Recognizing and maintaining adequate oxygen delivery with fluid administration early in the course of illness will improve outcomes. However, when a patient is volume replete, we advise a strategy of fluid restriction and diuresis to prevent or manage volume overload. Too often, fluid management is left to the discretion of an inexperienced physician who indiscriminately gives a fluid bolus to the hypotensive or oliguric patient. Based on dynamic parameters and hemodynamic monitoring, this patient may benefit from other interventions, such as pressors, inotropes, or diuresis. Figure 6 provides a schematic algorithm that can help the bedside clinician in ensuring organ perfusion while avoiding volume overload.

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TAKE HOME POINTS

Without evidenced-based guidelines to direct volume management, it is essential to understand the underlying physiology, including vascular integrity and fluid shifts, in order to make a rational choice

of the type, amount, and mechanism by which to monitor fluid therapy.

In today's health care environment, in which cost savings and patient safety are paramount, focusing on the overall cost and side effects of each individual fluid should be the main determinant of which fluid to choose. We recommend using balanced crystalloid solutions for resuscitative purposes, with the addition of albumin in select patients.

Securing adequate intravascular volume to optimize the delivery of oxygen to tissues is the primary goal of resuscitation. Using surrogates of delivery and extraction, including Svo_2, $Scvo_2$, and lactate levels, can help identify patients with global oxygen debt.

The main determinant of oxygen delivery to organs is cardiac output. Static measurements, including central venous pressure and pulmonary artery occlusion pressure, are not valid markers of intravascular volume status. Dynamic monitors better assess whether volume will improve cardiac output and the delivery of oxygen to tissues.

Monitoring devices that display dynamic variables and cardiac output in a continuous fashion can be instrumental to ensuring that bolus administration is both timely and appropriate.

Continued volume resuscitation beyond what will improve hemodynamics has detrimental effects. Fluid is a drug and is prescribed, dosed, and delivered like all other medications. Overdose is a possibility and too often is a reality. When hemodynamic goals have been met, one should consider a strategy of fluid restriction or diuresis.

Resuscitation of children must take into consideration the unique features of children's physiology, particularly in neonatal and infant patients who have less myocardial and pulmonary reserve in addition to immature capabilities of handling salt and water.

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