In a healthy adult, nearly all fluid is contained in the intracellular, intravascular, or interstitial spaces, with the intracellular space holding about two-thirds of total body water. Normally, fluid moves freely between these three spaces to maintain fluid balance (see Water, water everywhere).

Third-spacing occurs when too much fluid moves from the intravascular space (blood vessels) into the interstitial or “third” space—the nonfunctional area between cells. This can cause potentially serious problems such as edema, reduced cardiac output, and hypotension.

In this article, I’ll describe why third-spacing occurs and how to intervene to restore balance. Let’s start with a brief physiology review.

What’s behind third-spacing?
Fluid volume, pressure, and levels of sodium and albumin are the keys to maintaining fluid balance between the intracellular and extracellular (intravascular and interstitial) spaces. Capillary permeability and the lymphatic system also play a role. A problem with any of these components can cause fluid to shift from the intravascular space to the interstitial space. Let’s look more closely at each component.

- **Increased fluid volume** can be caused by overzealous fluid replacement or renal dysfunction. Volume overload can lead to peripheral edema, pulmonary edema, hepatic dysfunction, cerebral edema and mental changes, and decreased cardiac output. Other signs of fluid overload include jugular vein distension, hypertension, and a pathologic S3.
- **Increased capillary hydrostatic pressure** often accompanies heart failure. Right-sided heart failure is characterized by an increase in venous pressure that causes edema in the liver and the periphery. Left-sided heart failure causes pulmonary edema.
- **Decreased sodium level**, or hyponatremia, may result from sodium loss; for example, gastrointestinal losses during diarrhea or fluid losses caused by medications such as diuretics. Hyponatremia can also arise from volume overload. Also called dilutional or hypervolemic hyponatremia, this can occur with overzealous fluid replacement, heart failure, hepatic cirrhosis, renal disease, hypothyroidism, or administration of vasopressin.
- **Albumin losses** disrupt colloid osmotic pressure. Plasma proteins are crucial to maintaining colloid osmotic pressure. Albumin, the major protein constituent of the intravascular space, accounts for up to 60% of total protein. Any condition that destroys tissue or reduces protein intake can lead to protein losses and third-spacing. Some examples are hypocalcemia, decreased iron intake, severe liver diseases, alcoholism, hypothyroidism, malabsorption, malnutrition, renal disease, diarrhea, immobility, burns, and cancer.
Increased capillary permeability results from burns and other forms of tissue trauma. Edema due to an increase in capillary permeability can be local, as with a localized trauma, or systemic as with anaphylaxis or disseminated intravascular coagulation.

Lymphatic system obstruction is commonly caused by lymph node removal to treat cancer. An obstruction typically leads to localized edema; fluid and plasma proteins accumulate and can’t be drained into the general circulation because of the lymphatic obstruction [see The role of the lymph system]. Postmastectomy lymphedema is an example of this type of third-spacing.

**Phases of third-spacing**

Third-spacing has two distinct phases—loss and reabsorption.

In the loss phase, increased capillary permeability leads to a loss of proteins and fluids from the intravascular space to the interstitial space. This phase lasts 24 to 72 hours after the initial insult that led to the increased capillary permeability (for example, surgery, trauma, burns, or sepsis). Fluid loss from diarrhea, vomiting, or bleeding can be measured, but fluid loss from third-spacing isn’t so easy to quantify. Signs and symptoms include weight gain, decreased urinary output, and signs of hypovolemia, such as tachycardia and hypotension.

During the reabsorption phase, tissues begin to heal and fluid is transported back into the intravascular space. Signs of hypovolemia resolve, urine output increases, the patient’s weight stabilizes, and signs of shock (if any) begin to reverse. If the patient was given fluid resuscitation during the loss phase, monitor for fluid overload as interstitial fluid shifts back to the intravascular space.

**Determining the cause**

In some cases, the cause of third-spacing may be subtle and require a diagnostic workup, including a complete blood cell count (CBC), complete metabolic profile, and serum osmolality. The CBC may give clues to volume status and factors contributing to third-spacing, such as infection or necrosis. Elevated hemoglobin and hematocrit values may indicate hypovolemia; decreased values may indicate hypervolemia. The metabolic panel will give clues to renal and hepatic function as well as electrolyte balance [especially sodium], and levels of protein, including albumin.

The albumin-to-globulin ratio (normally slightly greater than 1:1) will elicit more information about colloidal osmotic pressure than total protein and albumin levels alone. Albumin molecules are large and don’t diffuse freely through the vascular endothelium, making this protein a major source of plasma colloidal osmotic pressures.

Noninvasive assessment tools include an echocardiogram, which may yield information on cardiac function and volume status, and weighing the patient daily. Invasive hemodynamic monitoring of central venous pressure, right atrial pressure, and pulmonary artery occlusive pressure also help track volume status and the patient’s response to treatment for hypervolemia or hypovolemia. However, some patients aren’t candidates for hemodynamic monitoring, and some facilities aren’t equipped for this type of monitoring.

Treatment of third-spacing depends on the cause, the phase, and the factors involved. Stabilizing your patient’s hemodynamic status is the first priority. During the loss phase, your focus is on preventing hypovolemia and hypotension, which can lead to shock and renal failure. During the reabsorption phase, focus on preventing circulatory overload and hypertension, which can lead to pulmonary edema.
Which fluid is best?

To stabilize the patient’s volume status, you’ll administer crystalloids, colloids, or a combination of these. Crystalloids replace electrolytes and restore normal serum osmolality; colloids replace the proteins responsible for maintaining plasma colloid osmotic pressure. Crystalloids are most commonly used, and can also treat hyponatremia. Remember, you’re trying to replenish intravascular volume, not deplete the third space.

Crystalloid fluids can be hypotonic, isotonic, or hypertonic. Hypotonic solutions, such as 0.45% sodium chloride solution, aren’t appropriate for volume resuscitation because very little of the fluid would remain in the intravascular space.

Isotonic solutions such as lactated Ringer’s solution and 0.9% sodium chloride solution, which are similar to plasma in tonicity and osmolality, are used for resuscitation, with 0.9% sodium chloride solution preferred if the patient is hyponatremic.

Hypertonic solutions, such as 3% sodium chloride solution, contain large amounts of sodium and have been rarely used for resuscitation because of their potential for cellular dehydration and overexpansion of the intravascular space. However, a recent study found that hypertonic crystalloids were better than isotonic crystalloids for reducing abdominal third-spacing and abdominal compartment syndrome that often occur with massive fluid resuscitation in patients with extensive burns. Another study of critically ill patients found that even though smaller volumes of hypertonic solutions are needed for fluid resuscitation, there wasn’t enough evidence to determine whether hypertonic solutions were safer or more effective than isotonic solutions.

In 2004, the SAFE (saline versus albumin fluid evaluation) study evaluated fluid resuscitation with albumin, a colloid, compared with crystalloid. The study found that albumin wasn’t associated with higher morbidity and mortality in critically ill patients. In young adult trauma patients without preexisting cardiovascular or pulmonary disease, resuscitation with albumin or 0.9% sodium chloride solution may not make a difference except in cost: Albumin is considerably more expensive. However, with older adults, patients with associated traumatic brain injury, and patients with cardiovascular or pulmonary disease, colloid use was found to be associated with increased morbidity and mortality compared with crystalloid use. At present, due to

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the cost of colloids and the potential for adverse reactions, especially if human albumin is used, research doesn’t support using colloids instead of crystalloids.4

No matter which type of fluid he receives, monitor your patient’s response to treatment to determine if the goals of intravascular resuscitation have been met.

What the future holds
Although they’re valuable indicators of a patient’s condition, vital signs, weight, and urine output don’t tell us what’s going on at the capillary level. Future goals for treating third-spacing may focus less on the type of fluid given than the patient’s capillary health as defined by capillary permeability and perfusion.

Someday soon, we may be able to not only monitor capillary health at the bedside, but also to determine which factor or combination of factors led to third-spacing so that interventions can be tailored more precisely to the patient’s condition. ❖

REFERENCES

RESOURCES

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