Syndrome of Inappropriate Antidiuretic Hormone Secretion in Malignancy: Review and Implications for Nursing Management

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Hyponatremia is a common fluid and electrolyte disturbance in adults with cancer. Hyponatremia has many causes, including the primary tumor, metastasis, diagnostic procedures, and therapeutic interventions, or it can result as a secondary complication (Berghmans, 1996; McDonald & Dubrose, 1993). Although the syndrome of inappropriate antidiuretic hormone (SIADH) secretion is a rare paraneoplastic syndrome (occurring in 1%–2% of adults with cancer), it is a common underlying etiology for hyponatremia (Poe & Taylor, 1989). In fact, several studies have identified that SIADH is among the most common reasons for hyponatremia and accounts for up to one-third of cases (Anderson, Chung, Kluge, & Schrier, 1985; Berghmans, Paesmans, & Body, 2000; Miller, Hecker, Friedlander, & Carter, 1996). Therefore, oncology nurses must be knowledgeable about this syndrome. This article provides a review of the pathophysiology, risk factors, signs and symptoms, diagnosis, treatment, and appropriate nursing management of patients with SIADH.

Pathophysiology

Sodium and water balance is tightly regulated in narrow physiologic ranges. Four mechanisms are involved in the regulation of sodium and water (Terpstra & Terpstra, 2000). The first mechanism is the secretion and regulation of antidiuretic hormone (ADH) from the hypothalamus-neurohypophyseal system. ADH is produced in special neurosecretory cells in the supraoptic and paraventricular nuclei of the posterior hypothalamus (Keenan, 1999; Terpstra & Terpstra). ADH is stored and released by the posterior pituitary gland (Batcheller, 1994). The production and release of ADH is regulated by receptors located in the kidneys, heart, and brain. Normally, ADH is secreted in response to increased serum osmolality and decreased plasma volume (Finley, 1998a). The release of ADH is inhibited by low plasma volume or an increased circulating blood volume. When serum osmolality reaches 295 mOsm/kg, arginine vasopressin (AVP), the biologic active form of ADH, is released (Haapoja, 2000; Metheny, 1982; Terpstra & Terpstra).

The second mechanism of action occurs in the kidneys (Terpstra & Terpstra, 2000). ADH acts on the V1 receptors, which are located in the collecting ducts (Robertson, 2001). The ensuing reaction from the ADH and V1 complex causes water channels to be inserted into the apical cell membrane, making the cell permeable to water (Haapoja, 2000; Robertson). This promotes water reabsorption and decreases urine output (Haapoja; Poe & Taylor, 1989).

The third mechanism of action occurs in the cardiovascular system. The body is able to sense shifts in the circulating blood volume and blood pressure by the stretch receptors in the left atrium and baroreceptors in the aortic arch and carotid sinus (Terpstra & Terpstra, 2000). These receptors release atrial natriuretic peptide (ANP) in response to increased atrial pressure (Smeltzer & Bare, 2002). ANP acts on the distal tubule and collecting ducts to decrease water and sodium chloride reabsorption (Guyton & Hall, 1996).

The fourth mechanism is the stimulation of the limbic system. ADH production is increased by limbic stimulation (Terpstra & Terpstra, 2000). The limbic system is an interconnected complex of basal brain function, and its control center is the hypothalamus (Guyton & Hall, 1996). One major function of the limbic system is to control behavior, but it also controls many internal functions, including osmolality of body fluids (Guyton & Hall). Stimulation of the limbic system, by

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factors such as stress, pain, nausea, or surgery, causes an increased production of ADH (Poe & Taylor, 1989; Terpstra & Terpstra).

When the production and release of ADH continues despite hypotonicity, SIADH occurs. The kidneys continue to absorb water with a proportionate decrease in serum sodium levels. Three mechanisms are most often responsible for SIADH: inappropriate secretion of ADH from the supraoptico-hypophyseal system, ectopic production of ADH, and enhanced action of ADH in the renal distal tubules (Otto, 1997).

The inappropriate secretion of ADH from the supraoptic-hypophyseal system occurs most often in patients who have central nervous system disorders or those who have had shock, pain, stress, or recent surgery. These conditions increase intrathoracic pressure or decrease venous return to the heart, thereby stimulating ADH secretion. Malignant cells can secrete ADH or ADH-like substances, creating ectopic sources for production of ADH. Patients with malignancies or pulmonary infections may develop SIADH by this mechanism. Finally, many medications cause SIADH by enhanced action of ADH in the renal distal tubules or increased release of ADH (Chan, 1997). The most common medications that have been associated with SIADH are narcotics, tranquilizers, barbiturates, general anesthetics, thiazide diuretics, hypoglycemic agents, antidepressants, and certain chemotherapy agents.

**Risk Factors**

Patients with cancer often have multiple factors that put them at risk for SIADH (Otto, 1997). Figure 1 provides a list of conditions and medications that are associated with an increased risk of SIADH. The most common risk factors associated with SIADH are the primary diagnosis, medications, concomitant diseases, advanced age, or a combination of factors. The most common diagnosis associated with SIADH is a malignancy. About two-thirds of patients who are diagnosed with SIADH have an underlying malignancy (Otto), and small cell lung cancer accounts for approximately 80% of all cases of SIADH (Haapoja, 2000; Keenan, 1999). One percent of patients with non-small cell lung cancer and 3% of patients with head and neck cancer experience SIADH (Ferlito, Rinaldo, & Devaney, 1997; Streveler, 1998). Other malignancies that can cause SIADH are pancreatic, prostate, duodenal, or colon carcinoma; Hodgkin’s and non-Hodgkin’s lymphoma; thymoma; and primary brain tumors (Otto; Poe & Taylor, 1989; Terpstra & Terpstra, 2000). SIADH also can be caused by pulmonary infections or central nervous system disorders (Haapoja).

Patients with AIDS also are at risk for SIADH. Hyponatremia is seen in 40%–60% of hospitalized patients with AIDS. The two most common causes of hyponatremia in patients with AIDS are SIADH and volume depletion (Akillin, Chandrakantan, Keane, & Hamburger, 2001). Factors that put these patients at high risk for SIADH are secondary malignancies, opportunistic infections (e.g., tuberculosis, pneumocystis carinii pneumonia), and medications such as pyrazinamide or ethambutol used to treat tuberculosis (Akillin et al.).

After surgery, patients are at increased risk for SIADH. One factor associated with this increased risk is that fluids often are replaced with hypotonic IV solutions such as 5% dextrose in water, which dilutes plasma electrolyte concentrations and predisposes patients to hyponatremia (Smeltzer & Bare, 2002). Another factor is that patients on mechanical ventilation and/or positive pressure breathing devices have a decrease in ANP production, which stimulates the release of ADH (Metheny, 1982; Otto, 1997). Similarly, pain, stress, shock, trauma, general anesthesia, and opioid medications stimulate ADH release, leading to SIADH (Chan, 1997; Haapoja, 2000; Otto). All of these factors combined put postoperative patients at risk for SIADH.

Increased age is another risk factor for SIADH (Miller et al., 1996). Older patients are at greater risk for SIADH from any disease state when compared with younger patients because of normal physiologic changes associated with aging, such as elevated ADH and atrial natriuretic hormone levels and an increased responsiveness to osmotic stimulation (Miller, 2001). Moreover, fluid and electrolyte balance and sodium regulation is not as effective when treating the elderly. This is because of decreased total body fluids and glomerular filtration rate as well as impaired renal diluting capacity and sodium conservation (Miller). Multiple medications also put older patients at risk for SIADH (Terpstra & Terpstra, 2000). The typical patient in a nursing home receives about seven medications, and many of these medications are associated with SIADH (Terpstra & Terpstra).

Medications can cause SIADH either through stimulation of ADH release from the central nervous system or an enhanced ADH effect in the kidneys (Keenan, 1999), Chemotherapeutic and biotherapy agents that are implicated in SIADH are cisplatin, cyclophosphamide, ifosfamide, interferon alpha or gamma, and vinca alkaloids (Chan, 1997; Kirch, Gachot, Germann, Blot, & Nitenberg, 1997; Miaskowski, 1997). Case studies of vinorelbine and docetaxel causing SIADH have been reported (Garrett & Simpson, 1998; Langer-Nitsche, Luck, & Heilmann, 2000). Other medications that can cause SIADH are narcotics, tranquilizers, barbiturates, general anesthetics, thiazide diuretics, hypoglycemic agents, and antidepressants. An in-depth discussion of medications that cause SIADH is beyond the scope of this article, and readers are referred to another, more comprehensive source (Chan).

**Signs and Symptoms**

The key presenting sign of SIADH is hyponatremia associated with serum hyponatremia and continued urinary sodium loss (Haapoja, 2000; Miller, 2001; Sorenson, Anderson, & Hansen, 1995). Early symptoms associated with SIADH often are subtle but, if left untreated, may progress to life-threatening seizures, coma, and death (Haapoja; Heater, 1999). Because oncology nurses have frequent and ongoing contact with patients, they are in an ideal position to recognize patients who are at increased risk for SIADH and those who present with early symptoms.

Early signs and symptoms are mild and can be attributed mistakenly to other causes. Therefore, nurses must maintain a high index of suspicion in patients who are at potential risk for SIADH. Early signs and symptoms associated with mild to moderate hyponatremia are nausea, anorexia, thirst, weight gain, oliguria, weakness, fatigue, and muscle cramps, all of which usually become apparent when serum sodium falls to the 115–120 mEq/l range. Neurologic signs may include headache and mild altered mental status (Keenan, 1999; Poe & Taylor, 1989).

Nurses must recognize that the severity of the symptoms of SIADH depends not only on sodium level but, more importantly, on how rapidly the syndrome develops. Symptoms develop because of water retention leading to water intoxication (Keenan, 1999). As sodium levels decrease, progressive symptoms include mental status changes such as lethargy, irritability, disorientation, and mental confusion. Late, severe symptoms are seizures and coma as a result of cerebral edema (Haapoja, 2000). Death can occur in adults if serum sodium decreases below 110–115 mEq/l or below 128 mEq/l in children unless the decrease is corrected promptly (Poe & Taylor, 1989).

**Diagnosis and Treatment**

The diagnosis of SIADH is based on findings of hyponatremia, decreased serum osmolality, euvolemia (hypotonic hyponatremia), high urine specific gravity, urine sodium less than 20 mEq/l, urine osmolality greater than
1,400, normal or decreased blood urea nitrogen (BUN) and creatinine, hypouricemia, and normal renal, adrenal, and thyroid function (Terpstra & Terpstra, 2000) (see Table 1). Other potential causes of hyponatremia (e.g., congestive heart failure, cirrhosis, adrenal insufficiency, Addison’s disease, and hypothyroidism) must be evaluated and ruled out during the diagnostic workup.

A water-loading test may be performed to establish the diagnosis of SIADH. Patients are instructed to drink 20 cc water per kg of body weight over 15–20 minutes, and urine is collected hourly for five hours and tested for specific gravity and osmolality. In the case of SIADH, the specific gravity is normal or increased and less than 80% of the water is excreted (Finley, 1998b). Before beginning the test, the sodium level must be greater than 125 mEq/l and patients should be asymptomatic (Otto, 1997). A water test rarely is needed to make a definitive diagnosis of SIADH (Arnold, Patchell, Lowy, & Foon, 2001; Otto).

Once the diagnosis of SIADH is established, the primary treatment is to identify and treat the underlying cause. If a disease is causing the SIADH, treatment for the underlying disease must be initiated as quickly as possible, whether it is a malignancy, pulmonary infection, or condition of the central nervous system. If a medication is the suspected reason for SIADH, the medication should be discontinued and the patient should be monitored for resolution of SIADH.

Mild hyponatremia (serum sodium levels of 125–134 mEq/l) is treated with fluid restriction of 800–1,000 ml per day (Haapoja, 2000). Serum sodium levels and symptoms generally improve over three to five days (Haapoja). In severe hyponatremia (less than 115 mEq/l) accompanied by seizures or coma, patients are treated in an intensive care unit (Haapoja). A fluid restriction of 500 ml per day is initiated. IV fluid administration of 3%–5% saline at a rate of 1–2 ml/kg is administered over two to three hours, and IV furosemide is given at a dose of 1 mg per kg of body weight (Finley, 1998b, Haapoja). The administration of furosemide inhibits free water reabsorption and also may interfere with the action of ADH in the kidneys (Terpstra & Terpstra, 2000). Serum sodium levels are taken every one to two hours to guide the initial stages of therapy. Serum sodium levels can be raised safely at a rate of 1–2 mEq/l per hour (Terpstra & Terpstra). Hypertonic solutions are discontinued when the serum sodium level is from 120–125 mEq/l and neurologic symptoms subside (Haapoja).

An important consideration when initiating treatment for SIADH is whether the hyponatremia developed acutely or over hours to days (less than 24–36 hours) or if it developed insidiously and lasts more than 48 hours (Hojer, 1994; Keenan, 1999). Slow sodium correction (0.5 mmol/l per one hour) in patients with chronic hyponatremia and rapid correction (1–2 mmol/l per one hour) to a moderately hyponatremic level in those with acute development are recommended (Chan, 1997). In cases where the rate of development cannot be determined, rapid correction with sodium chloride and furosemide for three to four hours followed by slow correction therapy is suggested for patients with seizures or those in coma (Hojer).

Overaggressive correction of hyponatremia must be avoided because it can lead to central pontine myelinolysis, a condition that causes a breakdown of the blood-brain barrier mainly in the pons and thalamus.
Demeclocycline, a tetracycline derivative, is given at doses of 600–1,200 mg orally on a daily basis (Keenan, 1999). Peptide V₂ receptor antagonists are another potent group of drugs that selectively block the action of ADH in the collecting ducts and are available in both an IV and oral form (Keenan, 1999; Serradeil-Le Gal et al.). V₂ receptor antagonists block the antidiuretic effects of AVP by preventing the insertion of the AVP water channels into the luminal membrane of the collecting ducts. (Serradeil-Le Gal et al., 2002). Two such receptor antagonists that are being tested are SR121463 and OPC-31260 (Saito et al., 1997; Serradeil-Le Gal et al.). Saito et al. reported that in human subjects, a single IV dose of OPC-31260 significantly increased sodium levels during a four-hour observation period. YM-087 (conivaptin) is a V₁A and V₂ vasopressing receptor antagonist that is being tested in clinical trials (Serradeil-Le Gal et al.; Udelson et al., 2001). In human subjects, conivaptin produced increased urine output and significantly reduced urine osmolality as well as demonstrated a favorable change in hemodynamics (Udelson et al.). The CenterWatch Clinical Trial Listing Service Web site lists clinical trial sites for conivaptin, and more information can be accessed at www.centerwatch.org/patient/studies/stu20175.htm.

**Nursing Management**

First and foremost, oncology nurses must have a high index of suspicion in patients who have multiple risk factors for SIADH because the symptoms often are nonspecific. Knowledge about the early signs and symptoms associated with SIADH and careful nursing assessment also are critical for early identification of the syndrome. Nursing assessment consists of conducting a thorough history and physical examination and reviewing the appropriate laboratory values.

Oncology nurses should focus assessment on detecting subtle signs of hyponatremia, which may mimic side effects of chemotherapy, dehydration, and neurologic disorders. Assessment of hydration status focuses on checking the skin turgor, condition of mucus membranes, intake and output, and daily weights. In assessing patients who are at high risk for SIADH, nurses must monitor patients for fluid overload. Specific signs to watch for are fluid intake more than urine output as well as weight gain (Menethy, 1982). Laboratory values also provide information about hydration status and aid in the diagnosis of SIADH. Laboratory values must be reviewed, paying close attention to the electrolytes, BUN, creatinine, serum osmolality, urine osmolality, and specific gravity. Table 1 provides a description of the laboratory abnormalities that commonly are seen in SIADH. Assessment of neurologic status focuses on early assessment of changes in the level of consciousness. Early signs and symptoms include headache and mild altered mental status. These symptoms may become progressively worse and include lethargy, irritability, disorientation, mental confusion, seizures, or coma.

Nurses are responsible for the safety needs of patients with neurologic manifestations of their disease. Seizure precautions are initiated when serum sodium levels fall below 125 mEq/l (Finley, 1998b). Nursing interventions include assessing patients for mental status changes and any associated muscle weakness and assisting patients with activities of daily living and ambulation (Menethy, 1982; Otto, 1997; Terpstra & Terpstra, 2000). Other safety measures include keeping the immediate area well lit.

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### Table 1. Laboratory Values: Normal Limits and Alterations Seen With Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Secretion

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Values</th>
<th>Values in SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium</td>
<td>135–145 mEq/l</td>
<td>&lt; 135 mEq/l</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>275–295 mOsm/kg</td>
<td>&lt; 275 mOsm/kg</td>
</tr>
<tr>
<td>Urine sodium</td>
<td>50–220 mEq/l</td>
<td>&gt; 220 mEq/l</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>400–1,200 mOsm/kg</td>
<td>&gt; 1,200 mOsm/kg</td>
</tr>
<tr>
<td>Typical range</td>
<td>500–800 mOsm/kg*</td>
<td>–</td>
</tr>
<tr>
<td>Range</td>
<td>50–1,400 mOsm/kg*</td>
<td>–</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>1.025–1.032</td>
<td>&gt; 1.032</td>
</tr>
<tr>
<td>Water load test</td>
<td>&gt; 80% of water load excreted in five hours</td>
<td>&lt; 40%–80% of water load excreted</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>reaches low of &gt; 100 mOsm/kg during second or third hour</td>
<td>No diuresis occurs</td>
</tr>
<tr>
<td>Urine specific gravity decreased</td>
<td>than the plasma osmolality</td>
<td></td>
</tr>
</tbody>
</table>

* Values have been updated based on information from Smeltzer & Bare, 2002.

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(Haapoja, 2000). Symptoms associated with this condition occur because of shrinkage of the central nervous system neurons resulting in progressive muscle weakness, dysarthria, dysphagia, cerebral edema, and seizures that typically occur two to six days after the hyponatremia is corrected (Keenan, 1999; Poe & Taylor, 1989). Nurses must recognize that this neurologic disorder can lead to permanent brain damage or death (Miller, 2001).

Fluid restriction is the mainstay of management of chronic SIADH (Keenan, 1999). The amount of fluid restriction prescribed is related to the severity of the hyponatremia such that as the severity of the hyponatremia increases, the fluid intake restriction also increases. Many patients have difficulty complying with this over a long period of time; therefore, pharmacologic agents are used to effectively treat SIADH in the ambulatory oncology setting. Pharmacologic intervention is added in the form of demeclocycline, lithium, or urea. Demeclocycline and lithium block the action of ADH in the collecting tubules (Poe & Taylor; Robertson, 2001). Patients do not need to adhere to a fluid restriction while on these medications. Demeclocycline, a tetracycline derivative, is given at doses of 600–1,200 mg orally on a daily basis (Keenan). This medication is taken one to two hours before or after meals and should not be taken with aluminum, magnesium, iron, or calcium products because they delay absorption of the medication (Poe & Taylor). Because demeclocycline can cause renal dysfunction, serum BUN and creatinine are monitored on a regular basis. Other potential side effects associated with this medication are nausea, vomiting, diarrhea, and photosensitivity. Demeclocycline is preferred over lithium because it is better tolerated and may be more effective (Terpstra & Terpstra, 2000). Occasionally, urea is used as an osmotic diuretic (Haapoja, 2000). The usual dose for urea is 30–60 mg per day (Finley, 1998b). Gastrointestinal upset is a potential side effect associated with urea (Finley, 1998b).

Several new agents have demonstrated promising results in early clinical trials. One group of agents selectively targets AVP receptors in the kidneys (Haapoja, 2000). The peptide antagonists that are not specific to the V₂ receptors are available only in parenteral form and become less effective with chronic use (Haapoja). Peptide V₂ receptor antagonists also have limited clinical usefulness because of marked species differences, poor oral bioavailability, and short biologic half-life (Verbalis, 1998, 2002). The nonpeptide V₂ receptor antagonists are another potent group of drugs that selectively block the action of ADH in the collecting ducts and are available in both an IV and oral form (Keenan, 1999; Serradeil-Le Gal et al., 2002). V₂ receptor antagonists block the antidiuretic effects of AVP by preventing the insertion of the AVP water channels into the luminal membrane of the collecting ducts. (Serradeil-Le Gal et al., 2002). Two such receptor antagonists that are being tested are SR121463 and OPC-31260 (Saito et al., 1997; Serradeil-Le Gal et al.). Saito et al. reported that in human subjects, a single IV dose of OPC-31260 significantly increased sodium levels during a four-hour observation period. YM-087 (conivaptin) is a V₁A and V₂ vasopressing receptor antagonist that is being tested in clinical trials (Serradeil-Le Gal et al.; Udelson et al., 2001). In
 Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Secretion  
(Hyponatremia, Low Sodium Level)

SIADH
SIADH can be caused by many different things, but cancer is the most common reason. Cancer cells can give off antidiuretic hormone (ADH). In the kidneys, ADH causes water to be taken back into the body. This causes the sodium (salt) levels in your blood to drop.

Signs of SIADH
• Loss of appetite
• Difficulty thinking or concentrating
• General tiredness
• General weakness
• Headaches
• Muscle cramps
• Increased thirst
• Weight gain without swelling in feet, legs, or elsewhere
• Low urine output
• Feeling irritable
• Confusion

Things you should do
1. Weigh yourself daily.
• You can have ____ cups of fluid each day.
• Try drinking orange juice, tomato juice, or beef and chicken broth.
2. Limit the amount of fluids you drink.
3. If your mouth is dry, try brushing your teeth with a mild toothpaste and rinsing your mouth several times a day. Avoid using mouthwashes that contain alcohol or lemon glycerin swabs. Try using sugarless gum or candy.
4. ________ has been ordered to treat your SIADH.
• Take ____ tablets ____ times a day.
• Take your medication with/without food. (Circle one answer.)
• Do not stop your medication without first talking to your doctor or nurse.
5. Smoking and tobacco products make your mouth dry or may make your SIADH worse. Ask your doctor or nurse for help to stop smoking.

Call your doctor or nurse for
• Any of the previous signs of SIADH or if the symptoms get worse, especially weight gain, low urine output, increased thirst, or personality changes
• Uncontrolled pain
If your caregiver observes you having seizures or has difficulty waking you, he or she should call 911 or take you to the emergency room.

Clinic telephone number:
After clinic hours, call:

FIGURE 2. PATIENT EDUCATION SHEET

Conclusion

Oncology nurses play a key role in the successful management of SIADH. Nurses should be aware of which patients are at risk, early signs and symptoms of SIADH, and appropriate medical and nursing management for SIADH. Early recognition of SIADH in patients who are at high risk is critical to allow for initiation of appropriate treatment interventions and the prevention of neurologic complications (Keenan, 1999; Poe & Taylor, 1989). Treatment includes eliminating the underlying cause and managing the hyponatremia. Assessment of the effectiveness of interventions continues on ongoing bases. Patient and family education is an integral part of nursing management, so nurses must recognize that patient and family learning needs must be reevaluated during clinic visits.

References

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Rapid Recap

**Syndrome of Inappropriate Antidiuretic Hormone Secretion in Malignancy: Review and Implications for Nursing Management**

- Syndrome of inappropriate antidiuretic hormone (SIADH) is a rare, paraneoplastic syndrome occurring in 1%–2% of patients with cancer.
- SIADH is caused by abnormal or sustained production of antidiuretic hormone that results in water retention and dilutional hyponatremia.
- Patients with cancer can be at risk for SIADH because of their diagnosis (small cell lung cancer is the most common cause of SIADH), comorbidities, medications, or age.
- Early signs and symptoms of SIADH mimic common side effects of chemotherapy, such as nausea, anorexia, muscle cramps, weakness, and fatigue.
- Progressive symptoms include lethargy, irritability, disorientation, and mental confusion.
- The primary treatment of SIADH is to treat the underlying cause and restrict fluids.