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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 17, 2010. 3 products were added in the *Formulary*, and 6 products were deleted. 12 products were designated nonformulary and not available. 2 interchanges and 2 restrictions were approved. 1 drug was designated a high-priority nonformulary drug.

◆ ADDED

Epoprostenol Injection [Room-temperature-stable] (Veletri® by Actelion Pharmaceuticals)

Glucose Chews (generic)*

**Restricted to CTSI for GSD1*

Liothyronine (Cytomel® Tablet by King Pharmaceuticals)

**Restricted to Shands Vista*

◆ DELETED

Daclizumab (Zenapax®)†

Dalteparin (Fragmin®)†

Influenza H1N1 Virus Monovalent Vaccine†

Pork Insulin (Iletin II®)†

Sodium Bicarbonate Injection (500 mEq/500 mL)†

Treprostinil Subcutaneous Injection (Remodulin®)†

†Nonformulary and Not Available

◆ NONFORMULARY AND NOT AVAILABLE

Alglucosidase alfa (Lumizyme® and Myozyme®)‡

‡Patients must use their own supply

Amlodipine-Hydrochlorothiazide-Olmesartan (Tribenzor®)

Clindamycin-Tretinoin (Veltin®)

Desvenlafaxine (Pristiq®)§

§Interchanged to Venlafaxine

IncobotulinumtoxinA (Xeomin®)

Pentosan (Elmiron®)

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MEDICATION SAFETY

Erythropoiesis-stimulating agents: When good turns evil

There are many types of anemia, each caused by different abnormalities, but all present with similar symptoms. Since one treatment does not fit every anemia, evaluating laboratory tests and medication profiles is vital for individualizing and optimizing therapy. Once the underlying cause of each anemia is determined, the most appropriate therapy can be selected.

◆

Clinicians are advised against using ESAs in patients with high Hgb levels greater than 12 g/dL and in manners that increase Hgb too rapidly.

Erythropoiesis-stimulating agents (ESAs), including epoetin alfa (Epogen®, Procrit®) and darbepoetin alfa (Aranesp®), are synthetic erythropoietins that stimulate red blood cell (RBC) production in the bone marrow. They are used to treat anemia caused by chronic diseases, such as anemia of chronic kidney failure, HIV / AIDS antiretroviral-induced anemia, or cancer chemotherapy-induced anemia. ESAs are also used to prevent the need for transfusions after surgery. There are many implications to ESA therapy that must be addressed by prescribers. A mere diagnosis of one of the aforementioned conditions does not validate indiscriminate use of ESAs, if not for efficacy reasons, then certainly for safety reasons. Because of this, the Shands at UF ESA Policy is vital to assist in better outcomes.

The presence of RBCs alone is not sufficient in carrying oxygen throughout the body. They must be accompanied by adequate iron to be effective. Prescribing ESAs in an iron-deficient person is useless. However, once it is confirmed that iron stores are adequate and that there are no other possible correctable causes for the anemia, the ESA-prescribing process can begin. The many pieces of the puzzle that have to fit for ESAs to be prescribed must remain in place for therapy to be continued. Generally, hemoglobin (Hgb) levels mostly drive the initiation, modification, and discontinuation of ESA therapy.

The National Kidney Foundation recommends maintaining the Hgb of anemic patients above 11 g/dL for efficacy, but not greater than 13 g/dL for safety reasons. In November of 2006, the FDA first issued an advisory statement and attached a black-box warning to ESAs.[1] Clinicians are advised against using ESAs in patients with Hgb levels greater than 12 g/dL and in manners that increase Hgb too rapidly. The danger of not adhering to this comes in the form of increased cardiovascular and thrombotic events and death. When ESAs are used to prevent the need for allogenic RBC transfusion after surgery, a black-box warning informs of the need for prophylactic anticoagulants, like heparin, while ESAs are used. And for patients receiving ESAs for chemotherapy-induced anemia, probably most frightening of all is that ESAs have been linked to increasing tumor growth! Such huge risks, as evidenced by the following literature, warrants extra caution when using these drugs.

In the Correction of Hemoglobin in Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) study, it was demonstrated that when epoetin alfa was used to correct anemia of chronic kidney disease with higher target Hgb levels (13.5 g/dL), patients experienced more serious and life-threatening cardiovascular events compared to those with lower

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Formulary update, *from page 1*

◆ INTERCHANGES

Finasteride (Generic) for **Dutasteride** (Avodart®)

Venlafaxine IR or SR (Generic) for **Desvenlafaxine** (Pristiq®)

◆ CRITERIA-FOR-USE CHANGES

Cidofovir (Vistide®)*

**Restricted: ID or Anti-Infective Stewardship Approval Required*

Dexmedetomidine (Precedex®)*

**Pediatric Dexmedetomidine Order Form Required*

◆ REVIEWED BUT NOT ADDED

Aztreonam, Inhaled (Cayston®)¶

¶High-priority Nonformulary Drug: Restricted Distribution

Epoprostenol is a prostanoid vasodilator used in the treatment of pulmonary hypertension. It achieves its therapeutic effects through direct vasodilation of the pulmonary and systemic arterial vasculature and by inhibiting platelet aggregation.

Room-temperature-stable (RTS) epoprostenol is now available as the brand name Veletri®. Its main advantage over Flolan® (epoprostenol sodium) and generic versions of Flolan® is that it does not have to be refrigerated. Flolan® must be refrigerated after reconstitution and during administration. It can only be used at room temperature for 8 hours. Additionally, Flolan® has a proprietary diluent and the RTS epoprostenol uses normal saline. Flolan® and its generics are not AP-rated to Veletri®.

The equivalence of these products is unclear, although differences are not anticipated. The prescribing information for these products is identical in terms of indications, clinical studies, and adverse reactions. Inhalation of Veletri® is inappropriate because of its high pH.

With the addition of Veletri®, all epoprostenol use will be converted to a new procedure. Instead of a constant rate, we will use standard concentrations. This decreases waste and matches patients' home use of epoprostenol. Establishment of a new epoprostenol policy will delay the availability of Veletri®.

Glucose chews are used an alternative to other dietary methods for the management of hypoglycemia in diabetic patients receiving hypoglycemic agents. In June 2009, glucose chews were designated nonformulary and not available. There was concern that the use of glucose chews by hospitalized patients could confound the results of routine glucose checks, leading to unwarranted adjustments in insulin regimens. (A rise in glucose due to self-treatment [without notifying the healthcare team] may be mistakenly perceived to be an indication for increased insulin requirements.) Therefore, glucose chewable tablets were designated nonformulary and not available. Patients were not allowed to use their own supply. In adult patients receiving subcutaneous insulin, the approved standardized treatments for hypoglycemia are dextrose 50% and orange juice.

This restriction applied to the Clinical and Translational Sciences Institute (CTSI), which revealed a potential problem with this formulary designation. The CTSI has patients with type-1 glycogen storage disease (GSD1), a metabolic defect that prevents the conversion of fructose or galactose (found in fruit juice or table sugar) to glucose. Usually cornstarch is used as an energy source, but this may not act rapidly enough in some patients. Therefore, glucose chewable tablets were added in the *Formulary* and restricted to use in the CTSI in patients with GSD1.

Liothyronine is a synthetic version of the endogenous thyroid hormone triiodothyronine. For many years, liothyronine has been considered a therapeutic option for augmentation strategies in patients suffering from refractory major depression.

Numerous trials have looked at liothyronine's addition to tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). However, most of these trials have had small sample sizes, open-label designs, and limited efficacy data. In a randomized, multicenter, placebo-controlled trial (STAR*D), liothyronine was compared to lithium for augmentation of treatment in refractory depression. The results of this study revealed a nonsignificant difference in the rate of remission between the 2 treatment groups. However, liothyronine had a more favorable adverse effect profile compared to lithium.

Patients who are intolerant to treatment with lithium augmentation may benefit from treatment with liothyronine as an alternative augmentation agent. This inference is supported by the generalizability of the STAR*D trial and by the results of other trials using liothyronine as augmentation to either TCAs or SSRIs among treatment-naïve and treatment-resistant depressed patients. Patients who have responded to liothyronine therapy generally do so within the first 3 weeks of therapy.

Liothyronine was added in the *Formulary* for use at Shands Vista. Patients must have normal thyroid function at baseline to be eligible for augmentation. Patients must not be suicidal (based on clinical evaluations) at any time during augmentation therapy. Patients must not have evidence of structural heart disease at any time during augmentation therapy. Patients should receive at least 3 weeks of liothyronine therapy, and if no effect is seen within 3 weeks, then augmentation therapy should be discontinued.

Daclizumab is a monoclonal antibody that binds to IL-2. It is an immunosuppressant with a labeled indication for the prevention of kidney transplant rejection. Its manufacturer has made a business decision to stop marketing this product. This decision was based on the availability of alternative treatments and diminishing market demand and is not due to any safety issue.

Dalteparin is a low-molecular-weight heparin (LMWH) used for the prevention and treatment of thromboembolic diseases. Compared with enoxaparin (Lovenox®), the LMWH listed in the *Formulary*, it is rarely used. Since a generic version of enoxaparin was recently approved, there was no incentive to keep dalteparin listed in the *Formulary*.

Influenza A [H1N1] monovalent vaccine was added in the *Formulary* to make it readily available for inpatients who met the Centers for Disease Control (CDC) criteria for vaccination. This inactivated vaccine injection was developed and made just like the inactivated seasonal influenza vaccine injection, except it contained only the antigens from a unique strain of influenza (ie, A/California/7/09-like virus).

Vaccination using the seasonal influenza virus vaccines for this year has already begun. The FDA's Vaccine and Related Biological Products Advisory Committee selected the following strains for this season's vaccine A/California/7/09 (H1N1)-like virus, A/Perth/16/2009-like virus, and a B/Brisbane/60/2008-like virus.

In June 2010, the US Public Health Emergency for the 2009 H1N1 ("Swine") Influenza expired. In August, the World Health Organization declared the end to the 2009 H1N1 pandemic globally. The H1N1 virus strain is now covered in the seasonal vaccine. Experts expect the H1N1 virus to persist for years to come, similar to other seasonal influenza viruses.

Insulin from pork sources was discontinued in 2006. Some patients continue to import this product for personal use; however, it has not been used at Shands for years.

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Formulary update, *from page 2*

The **500 mEq/500 mL vials of sodium bicarbonate** have been discontinued and there is no alternative source. Therefore, this dosage form was deleted from the *Formulary* and designated nonformulary and not available.

Treprostinil is a prostaglandin analogue used for the treatment of pulmonary arterial hypertension. It was first marketed as a continuous subcutaneous infusion in 2002. In 2004, the intravenous (IV) administration of treprostinil was approved. The subcutaneous (SQ) route of administration is rarely used and has not been used at Shands at UF for years. It was rarely used because of the pain that occurs at the injection site.

Lumizyme® is **recombinant human alglucosidase alfa**, similar to Myozyme®. Although Lumizyme® and Myozyme® are both alglucosidase alfa, these products are not identical because of differences in the production methods, which result in differences in some product attributes. Both are enzyme replacements for patients with Pompe disease who have endogenous acid alpha-glucosidase deficiency. The lack of this endogenous enzyme results in the accumulation of glycogen in lysosomes in the heart, liver, and skeletal muscles. Patients develop cardiomyopathy, progressive muscle weakness, and impaired respiratory function without replacement therapy.

Lumizyme® has a labeled indication for patients 8 years and older with late (non-infantile)-onset Pompe disease, who do not have evidence of cardiac hypertrophy. Myozyme® has a labeled indication for the treatment of Pompe disease, but is targeted for infantile-onset Pompe disease.

Alglucosidase alfa trials show that it is superior to placebo or to a historical control group that received no treatment. These studies evaluated survival and ventilator-free survival as measures of efficacy. Unfortunately, a limited number of studies are available to review due to the rarity and nature of the disease.

Myozyme® and Lumizyme® have black-box warnings for anaphylaxis and severe allergic reactions, which may occur up to 3 hours after infusion and may be life-threatening. Infusion-associated reactions were seen in all the studies examined.

Patients who require hospitalization are permitted to use their own personal supply of alglucosidase alfa from their home healthcare agency. The cost of this therapy can be as much as $300,000 per year.

Tribenzor® is an oral combination tablet with a labeled indication for the treatment of hypertension. It contains the angiotensin receptor blocker (ARB) **olmesartan**, the calcium channel blocker **amlodipine**, and the diuretic **hydrochlorothiazide**. Olmesartan is currently nonformulary and not available and is automatically interchanged to valsartan. Patients may use their own supply of Tribenzor® or be switched to amlodipine, hydrochlorothiazide, and valsartan instead of olmesartan.

Veltin® Gel is a combination of the topical antibiotic **clindamycin** and the retinoid **tretinoin** with a labeled indication for the treatment of acne vulgaris in patients 12 years or older.

Desvenlafaxine succinate is an extended-release serotonin-norepinephrine reuptake inhibitor with a labeled indication for the treatment of major depressive disorder. It is the major active metabolite of the formulary medication venlafaxine, a medication used to treat major depressive, generalized anxiety, social anxiety, and panic disorders. Desvenlafaxine's efficacy is thought to be related to potentiation of serotonin and norepinephrine in the central nervous system.

The labeled dosage is 50 mg once daily. Daily doses up to 400 mg have been used in clinical studies, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events and discontinuations were more frequent at higher doses.

Efficacy data are limited to comparisons with placebo as there are no published trials directly comparing desvenlafaxine to other available antidepressants. The promoted benefit of desvenlafaxine is the lack of significant interaction with cytochrome P450 2D6, thereby reducing the potential for drug interactions and minimizing the potential for a variable response due to cytochrome P450 2D6 genetic polymorphism. To date this has been supported only with pharmacokinetic drug studies and case reports.

The most commonly observed adverse events are comparable to those of venlafaxine. While there are no published data available to establish therapeutically equivalent dosages of desvenlafaxine and venlafaxine, the two compounds are reported to be equivalent. To accommodate patients currently treated with desvenlafaxine, they are allowed to use their own medication supply. If a patient currently treated with desvenlafaxine cannot provide their own medication, orders for desvenlafaxine 50 mg or 100 mg daily will be interchanged to Effexor® XR 75 mg daily. An order for desvenlafaxine 150 mg daily will be interchanged to Effexor® XR 150 mg daily. An order for desvenlafaxine 200 mg daily or greater will be interchanged to Effexor® 225 mg daily. Orders for desvenlafaxine 50 mg every other day will be automatically interchanged to Effexor® XR 75 mg every other day.

IncobotulinumtoxinA is a type A botulinum toxin, similar to abobotulinutoxinA, which was designated nonformulary and not available in January 2010. IncobotulinumtoxinA has labeled indications for the treatment of cervical dystonia and blepharospasm.

All botulinum toxins have new generic names, which differentiate among the various forms of botulinum toxin. Different products have different potencies. Thus, the units for these agents are NOT equivalent. By limiting the formulary agents, the goal is to prevent medication errors.

Botulinum toxins are used for a variety of uses where the "toxin" paralyzes muscle. The agent listed in the *Formulary*, Botox® (onabotulinumtoxinA), has been on the market the longest and has the most labeled and off-labeled uses. Theoretically, any botulinum toxin could be used for these uses as long as the appropriate dose is used. Botox® has labeled indications for blepharospasm, cervical dystonia, facial wrinkles, hyperhidrosis, and strabismus. Some off-labeled uses include achalasia, neurogenic bladder, sialorrhea, and spasticity.

Pentosan is a synthetic polysaccharide, which structurally resembles glycosaminoglycan, that has approximately 1/15th the anticoagulant activity of heparin. Pentosan polysulfate sodium has a labeled indication for the relief of the symptoms of interstitial cystitis (IC). Pentosan was proactively reviewed due to a recent increase in nonformulary usage.

Pentosan polysulfate sodium's mechanism of action to relieve the symptoms of IC is not completely understood. However, it is believed that pentosan acts in the bladder to augment the natural barrier between bladder fluids and tissues resulting in irritation to these tissues and propagation of an inflammatory response and symptoms of IC.

In clinical trials, pentosan has been compared to cyclosporine in terms of a reduction in the number of voids per day. Pentosan appeared inferior to cyclosporine for this outcome. Other measures of disease response include subjective disease criteria such as the global response assessment, the O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index, and the Patient's Overall Rating of Symptoms Index. Results from 1 subgroup analysis of a larger clinical trial showed better efficacy for pentosan in recently diagnosed IC. Various placebo-controlled, randomized, clinical trials have yielded mixed results, with a maximum

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Formulary update, *from page 3*

response measured by subjective disease criteria of 16% compared to placebo.

Consistent with pentosan's pharmacology, it should not be used in patients at high risk for bleeding episodes. Patients receiving pentosan should be carefully monitored for adverse effects such as rectal hemorrhage, ecchymosis, epistaxis, or gingival bleeding. Concurrent administration of drugs that inhibit the clotting cascade, platelet activity, or potentiate these drugs should be avoided due to the risk of adverse outcomes.

Finasteride and **dutasteride** are 5-alpha-reductase inhibitors that inhibit the conversion of testosterone to 5-alpha-dihydrotestosterone (DHT). DHT is a potent form of testosterone that is associated with the stimulation of growth of prostate tissue. Both have labeled indications for the treatment of benign prostatic hyperplasia (BPH). Dutasteride is nonformulary and not available, while finasteride is listed in the *Formulary.* A 5-mg dose of finasteride is roughly equivalent to a 0.5-mg dose of dutasteride and the interchange of dutasteride 0.5 mg to finasteride 5 mg was approved. Patients that have their own supply of dutasteride can continue to use their own supply upon request.

Cayston® is an **inhaled** version of the monobactam antibiotic **aztreonam**. It has a labeled indication for improving respiratory symptoms in patients with cystic fibrosis and *Pseudomonas aeruginosa* infection of the lungs. It is approved for use in patients 7 years of age or older with moderate to severe lung disease (FEV_1 25% to 75% of predicted). Cayston® is an alternative to TOBI® (inhaled tobramycin).

Only designated pharmacies can stock Cayston®. Shands cannot stock Cayston, so it cannot be considered for addition in the *Formulary.* If patients are admitted on this medication, they will have to use a supply provided by the specialty pharmacy. It must also be administered via a special nebulizer that is specific for this drug.

Cayston® was designated a high-priority nonformulary drug so that prescribers will be notified that Shands at UF cannot provide this agent [and to prevent a delay in appropriate care.] Options include switching to an alternative agent or using a product provided by the specialty pharmacy.

Cidofovir is an antiviral agent with a labeled indication for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). It has been used off-label to treat other CMV infections.

Renal impairment is the major toxicity of cidofovir. To reduce the risk of nephrotoxicity, intravenous prehydration with normal saline and administration of probenecid must be used with each cidofovir infusion. Renal function must be monitored.

Cidofovir is contraindicated in patients receiving agents with nephrotoxic potential. Nephrotoxic agents are supposed to be discontinued at least 7 days before starting cidofovir. Over a 1-year period from 2008 to 2009, alerts were generated for concomitant use of foscarnet, vancomycin, lipid amphotericin, and ibuprofen. Over the last year, only 6 patients received cidofovir.

Following a review of the evidence, it was determined there are circumstances when the use of cidofovir and "nephrotoxic" agents are the only possible options; therefore, concomitant use should be permitted in specified circumstances. The circumstances would be that there is no alternative for cidofovir and no alternative for the "nephrotoxin."

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Formulary update, *from page 4*

Since most of the "contraindicated" concomitant drugs are anti-infective agents, cidofovir was restricted to approval by either the Adult or Pediatric Infectious Diseases Services or the Anti-Infective Stewardship Program so that drug interactions can be properly evaluated and alternatives identified, when appropriate. Cidofovir and ibuprofen continue to be contraindicated.

Dexmedetomidine is a relatively selective alpha$_2$-adrenoceptor agonist with centrally mediated sympatholytic, sedative, and analgesic effects. Its pharmacology has always been intriguing; however, there are few data suggesting that outcomes, like time to extubation, are better than with other agents used for general sedation in a critical care setting.

The P&T Committee approved the use of dexmedetomidine in the pediatric intensive care unit in mechanically ventilated pediatric patients requiring sedation who have "failed" traditional therapy. Failure is defined as escalation of sedative and analgesic infusions beyond "conventional therapy" without achieving sedation goals (ie, patient has failed escalating doses of fentanyl [dose exceeds 3 mcg/kg/hr], midazolam [dose exceeds 0.3 mg/kg/hr], ketamine [dose exceeds 1 mg/kg/hr], and intermittent barbiturates [dose exceeds 2 mg/kg/hr]). It was also approved for use in patients who need frequent central nervous system (CNS) assessments beyond 24 hours. Propofol use beyond 24 hours has been associated with a high rate of propofol infusion syndrome. Use of a *Pediatric Dexmedetomidine Order Form* requiring fellow/attending approval with some uses requiring approval of a clinical pharmacist was also mandated by the P&T Committee.

Drug information questions?

Contact the Drug Information Service

Call 265-0408

Or submit your question online at www.shands.org/professionals/druginfo/default.asp

- This service is for referring physicians and other healthcare professionals taking care of Shands patients
- Phones are staffed from 9 am to 4:30 pm, Monday – Friday
- All answers are thoroughly researched and referenced

For emergent questions that do not need thorough research, go to the pharmacy servicing your area.

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EDITOR, DRUGS & THERAPY BULLETIN
Randy C. Hatton, PharmD

DIRECTOR, PHARMACY SERVICES
Alan Knudsen, MS, RPh

CHAIRMAN, PHARMACY & THERAPEUTICS COMMITTEE
Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION
Shands HealthCare's Publication Svcs.

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Medication safety, from page 1
Hgb goals (11.3 g/dL).[2] The primary endpoint of the study was a composite of cardiovascular events, including all cause mortality, congestive heart failure (CHF), hospitalization, non-fatal heart attack, or non-fatal stroke. This endpoint was statistically significantly higher in the study arm with a goal Hgb level of 13.5 g/dL (17.5% vs 13.5%). Death occurred in 7.3% of the target Hgb 13.5 g/dL vs 5% of the target Hgb 11.3 g/dL group. CHF occurred in 9% vs 6.6%. Non-fatal heart attacks occurred in 2.5% vs 2.8%. Nonfatal strokes occurred in 1.7% of both groups. Despite these increased risks, quality of life was not improved with higher Hgb levels. The researchers conclude that higher Hgb goals pose higher risks without providing additional benefits and recommend a target Hgb level between 11-12 g/dL.

A recent review of clinical trials concluded that patients with chemotherapy-related anemia being treated with darbepoetin alfa experienced higher mortality rates when their Hgb goal was 14 g/dL vs 10 g/dL (35% vs 29%).[3] The incidences of nonfatal heart attacks and thrombosis were higher and contributed to the difference in mortality between the groups. The increase of cardiovascular risks of ESAs has been used to question the safety of using ESAs in cancer patients. And if the risk of death from cardiovascular events was not worrisome enough, the risk of death from increased tumor growth will definitely make patients think twice about using ESAs.[4] The FDA's Risk Evaluation and Mitigation Strategy (REMS) on ESAs has resulted in the APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program. Prescribers of ESAs for chemotherapy-induced anemia must train and enroll in the program. Before administering the drug, medication guides and counseling about the risks of ESA therapy must be provided to patients, and documentation is required.

After research evidence and recommendations from the FDA and National Kidney Foundation, the importance of clinicians monitoring patients receiving ESAs has been further emphasized. As guided by evidence and the policy at Shands at UF, ESAs should be discontinued if Hgb levels surpass 12 g/dL, or doses should be decreased if a patient's Hgb rises too quickly. The smallest dose required to prevent blood transfusions should be used. By close management of these agents, we may be able to retain their benefits and mitigate their risks.

By Shimaa Ghonim, PharmD

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