

Drugs & Therapy

B * U * L * L * E * T * I * N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met January 20, 1999. No drugs were added in the *Formulary* and 3 amino acid solutions were deleted. One drug was evaluated, but not added in the *Formulary*.

• **ADDED**
None

• **DELETED**

Amino Acids, Intravenous
(FreAmine HBC® by McGaw)

Amino Acids, Intravenous
(HepatAmine® by MrGaw)

Amino Acids, Intravenous
(RenAmine HBC® by Clintec)

• **EVALUATED BUT NOT ADDED**
Becalpermin
(Regranex® by Ortho-McNeil)

FreAmine HBC®, HepatAmine®, and RenAmine® are specialty crystalline amino acid solutions used in the preparation of total parenteral nutrition (ie, TPN). These intravenous solutions were designed to meet special protein requirements of patients with high metabolic stress or sepsis (ie, FreAmine HBC®), hepatic failure (ie, HepatAmine®), and renal failure (RenAmine®). These products were deleted from the *Formulary* because of low usage and questionable benefit over standard amino acid solutions.

FreAmine HBC® is a mixture of essential and nonessential acids with a high concentration of branched-chain amino acids (ie, HBC. Branched-chain amino acids (ie, isoleucine, leucine, and valine) were thought to improve nitrogen balance and prevent muscle

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OUTPATIENT PHARMACY

Charity Care Formulary changes

For years the Shands Outpatient Pharmacy has provided medications to ambulatory patients with a household income at or below the 150th percentile of the federal poverty guidelines. Most of these prescriptions (~60%) are for elderly patients on Medicare who have difficulty paying

program and is now 20% of the prescriptions filled in the Outpatient Pharmacy. The expenses associated with the *CC Formulary* are again increasing at an alarming rate. Additional limitations on the program are necessary to make it possible to continue to meet the needs of as many patients as possible.

Ideally, a more defined *CC Formulary* will decrease resource consumption while continuing to make available medications for targeted medical conditions. An ad hoc committee was established to study this issue and made recommendations to the P&T Committee. In addition to a more limited list of covered medications, a more defined geographic definition was established.

The geographic limitation was established considering the existence of other health care facilities in a 30- to 50-mile radius and the ability of local governments to support the health care of county residents. Transplant and oncology patients were exempted from this geographic limitation. The lines were drawn using zip codes.

The final limitation is that the formulary will apply only to patients seen at Shands at the University of Florida (1600 SW Archer Road) or the Shands Medical Plaza-Cancer Center (2000 SW Archer Road).

A formulary of approximately 130 drugs has been adopted that covers specific disease states or drugs that are **easily** obtained from manufacturers. New expensive agents with

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**A more defined
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for their prescriptions. Over the last few years, steps have been taken to control the increasing expenses associated with the provision of this program.

In 1995, the Charity Care Formulary (*CC Formulary*) was established. At that time, the hospital was the payor for approximately 15% of outpatient prescriptions. The Charity Care Formulary placed some restrictions on the drugs that would be available (eg, 1 H2-blocker, selected birth control pills). It also required patients to pay a \$5 co-pay, similar to other managed-care formularies. As new drugs were considered for the inpatient *Formulary*, some drugs were explicitly excluded from the *CC Formulary* (eg, zolpidem).

These changes, along with accessing programs from drug manufacturers, have helped decrease the budgetary impact of the charity care drug program from nearly a million dollars a year to a few hundred thousand per year. Unfortunately, this program has been so good it has drawn patients from distant locations to access the

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- New drugs in '98
- Urokinase

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wasting in patients experiencing metabolic stress. Amino acid mixtures with high branched chain amino acid content are more expensive and the published data supporting improved outcomes in stressed patients is weak.

HepatAmine® is also a mixture of essential and nonessential amino acids. Like FreeAmine HBC®, HepatAmine® has a higher concentration of branched chain amino acids than generic amino acid solutions (eg, Travasol®) HepatAmine® is also relatively low in aromatic amino acidst (ie, phenylalanine, tyrosine, and tryptophan). High concentrations of aromatic amino acids are thought to favor octopamine production which was thought to contribute to the symptoms of hepatic encephalopathy. HepatAmine® is also more expensive than standard amino acid solutions with questionable benefits.

RenAmine® is a mixture of essential and nonessential amino acids with added histadine which is considered conditionally essential in renal patients. Supplying primarily essential amino acids is supposed to minimize ureagenesis by eliminating the need for higher concentrations of nonessential ammo acids. Recycled urea nitrogen can serve as a precursor for nonessential amino acid synthesis. Therefore administration

of RenAmine® to uremic patients is supposed to result the utilization of retained urea, which would resolve many azotemic symptoms. Like the other modified amino acid solutions deleted, RenAmine®'s increased cost is difficult to justify because of its unproven effects on patient outcomes.

Becaplermin is a recombinant human platelet-derived growth factor (rhPDGF-BB). Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor (PDGF) into the yeast, *Saccharomyces cerevisiae*. Becaplermin has biological activity similar to that of endogenous PDGF, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair and enhancing the formation of granulation tissue. PDGF promotes cell mitogenesis and synthesis of protein and extracellular matrix components, thereby enhancing the formation of granulation tissue contributing to tissue regrowth and wound healing.

Becaplermin has a labeled indication for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. The efficacy of becaplermin for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers has not been evaluated.

It is estimated that a 15-gram tube should last about 3 weeks for an average-size ulcer. A 15-gram tube costs \$327. Therapy could last 20 weeks or more, which would be a total cost of approximately \$2300.

The published data on the efficacy of becaplermin are sparse. Good wound care appears to be most important in whether ulcers heal. After 20 weeks, about 1/2 of patients in the published clinical trials had complete healing with becaplermin gel. Good wound care and placebo healed about 1/3 of the patients ulcers. If becaplermin is effective, it could save the considerable expenses needed for surgical treatment of neuropathic diabetic ulcers that will not heal. Pharmacoeconomic data supporting this conclusion have not yet been published, however.

Patients receiving becaplermin, placebo gel, and good ulcer care alone had a similar incidence of ulcer-related adverse events such as infection, cellulitis, or osteomyelitis. Erythematous rashes occurred in 2 % of patients with becaplermin gel and placebo gel. Patients treated with becaplermin did not develop neutralizing antibodies against becaplermin.

Becaplermin was not added in the inpatient Formulary, It will also not be available the outpatient CC Formulary. Becaplermin is, however, available from the Outpatient Pharmacy,

DRUG USE EVALUATION

Imipenem use OK but costly

Imipenem is a broad-spectrum antibiotic with activity against important aerobic and anaerobic pathogens. It is used for serious infections caused by susceptible organisms causing lower respiratory tract infections, urinary tract infections, intra-abdominal infections, gynecological infections, septicemia, bone and joint infections, skin and soft tissue infections, endocarditis, and polymicrobial infections. Imipenem is also useful for serious infections when the causative organism is not known or when resistance may be suspected. Cephalosporin-resistance or other difficult-to-treat organisms may warrant imipenem therapy.

A medication use evaluation was done during a 1-month period in the fall of 1998. 32 patients (27 adults and 5 children) were started on imipenem during this time. Much of this use was in a critical care unit.

Imipenem was most frequently prescribed for intra-abdominal infections (31 %), nosocomial pneumonia (25%), pancreatitis (16%), cellulitis-osteomyelitis (13%), sepsis (6%), and

cystic fibrosis (6%). Most of the use was for suspected (62%) versus documented (38%) infections. However, 20% of the patients with suspected infections at the start of therapy subsequently were documented as culture-positive. The following organisms were documented: *A. anitratus*, *C. diversus*, *E. aerogenes*, *E. coli*, *K. pneumoniae* (2), and *P. aeruginosa* (6).

Most patients (66%) were treated with another antibiotic before imipenem was used. This indicates that imipenem is usually being reserved for more severe infections with resistant pathogens. Imipenem is a very expensive option compared with other antibiotics or antibiotic combinations. Imipenem's broad spectrum also often

leads to fungal infections. Therefore, it is important that it be reserved for difficult-to-treat organisms that are resistant to other antibiotics.

Although imipenem is usually being used appropriately, there were instances when a less costly, but equally effective antibiotic or antibiotic combination could have been used. The table shows a cost comparison of imipenem with other possible options.

During this audit, the average duration of imipenem therapy was 10.5 days. This would be over \$8000 for imipenem therapy. This emphasizes the need to streamline to equally effective therapy, especially oral therapy, as soon as possible.

RELATIVE DAILY COST COMPARISON OF SELECTED ANTIBIOTICS

Imipenem	\$82.08
Ciprofloxacin IV-Metronidazole IV	\$38.70
Ticarcillin-Clavulanate IV	\$33.44
Trovafloxacin IV (alatrofloxacin)	\$28.80
Cefepime-Metronidazole IV	\$24.50
Ciprofloxacin PO-Metronidazole PO	\$ 6.42
Trovafloxacin PO	\$ 5.61

Outpatient Pharmacy, from page 1 indigent programs that are administered through physicians offices will be excluded from the CC *Formulary*. If patients meet the geographic and income limitations and they are prescribed a drug not available in the CC *Formulary* or through a company sponsored, office based indigent program, patients can receive these non formulary drugs from the Outpatient Pharmacy at acquisition cost plus \$6. For high cost medications, this should be the least expensive option for patients who need these products.

Realizing that these are major changes, every effort has been made to get this information first to the prescribers then to the patients that it will affect. In January, letters were sent to physicians who prescribe medications for patients who will no longer be covered by the program. One week later, a letter was sent directly to each patient. Patients were given an opportunity to make other arrangements for obtaining their prescriptions, if cost plus \$5 is not their best option. Most patients who no longer qualify live too far away from the medical center.

Some patients may qualify for other charity care programs. Shands staff will assist with financial assessment to see if patients qualify for Medicaid, Medically Needy drug industry sponsored programs, or other programs.

The P&T Committee will maintain the CC *Formulary*. Every effort will be made to include the most cost-effective agents, especially for those conditions that may cause acute problems in patients. For example some of the asthma medications listed include inhaled steroids (eg beclomethasone inhalers) beta agonists (eg albuterol), and sustained release theophylline.

The site for filling charity care prescriptions has been moved from the Outpatient Pharmacy near the Atrium to the Shands Medical Plaza (SMP) Pharmacy. This change has significantly decreased waiting times and phone traffic to the Outpatient Pharmacy near the Atrium. This has improved service levels for discharging patients on site clinics and employees. The SMP Pharmacy has a separate financial counseling area that facilitates the process of filling prescriptions for charity care patients without holding up service to other patients.

NEWS

New drugs in 1998

The FDA approved 30 new drugs in 1998 (see table). This was a decrease from last year's 39 and much lower than the 53 new drugs approved in 1996. Unlike previous years, only a few drugs were approved in December. Traditionally, a disproportionate number of drugs are approved at the end of the year. This has been attributed to the FDA trying to make their numbers look good to demonstrate they are meeting their goals of getting drugs to market.

Approval times in 1998 were shorter than in previous years. The average approval time for a new drug was 12.5 months compared with 17 months in 1997. The quicker approvals and, perhaps, the lack of approvals at the end of the year, have been attributed to user fees that the FDA collects from drug companies to help with the approval process. Built into this program are deadlines that the FDA must meet in order to collect its fees.

Like last year, drugs for neurological and cardiovascular diseases dominated approvals. Neurological drugs approved included 2 for migraines, and 1 each for depression, narcolepsy, and Parkinson's disease. Cardiovascular drugs approved include 2 each for hypertension and acute coronary syndrome. There were also several anti-infective agents approved. Two drugs for HIV infection, a drug for CMV-retinitis, and a drug for TB were approved.

Included in the table are 6 important new biologics approved in 1998. More biotechnology products are being approved compared with previous years. Monoclonal antibodies (ie, biologics ending with "mab") were more common this year. Not listed in the table are 3 new vaccines that were approved (ie, for Diphtheria-Tetanus-[acellular] Pertussis, Rotavirus [oral], and Lyme disease).

NEW DRUGS & SELECTED BIOLOGICS APPROVED BY FDA IN 1998

GENERIC NAME	TRADE NAME	INDICATION
abacavir**	Ziagen®	HIV infection
antithymocyte globulin, rabbit†**	Thymoglobulin®	renal transplant rejection
basiliximab†	Simulect®	renal transplant rejection
brinzolamide	Azopt®	open-angle glaucoma
candesartan	Atacand®	hypertension
capecitabine	Xeloda®	breast cancer
celecoxib**	Celebrex®	NSAID for rheumatoid & osteoarthritis
citalopram	Celexa®	SSRI for depression
efavirenz*	Sustiva®	HIV infection
etanercept†	Enbrel®	rheumatoid arthritis
eptifibatid	Integrelin®	acute coronary syndrome
fomivirsen	Vitravene®	CMV retinitis
infliximab†	Remicade®	Crohn's disease
leflunomide	Arava®	rheumatoid arthritis
lepirudin*	Refludan®	anticoagulant for heparin-induced thrombocytopenia
loteprednol	Lotemax®	ocular inflammation
modafinil**	Provigil®	narcolepsy
montelukast*	Singulair®	asthma
naratriptan	Amerge®	migraines
palivizumab†*	Synagis®	RSV disease prevention
paricalcitol*	Zemlar®	hyperparathyroidism in renal failure
rifapentine	Priftin®	tuberculosis
risedronate	Actonel®	Paget's disease
rizatriptan	Maxalt®	migraines
sacrosidase	Sucraid®	congenital sucrase-isomaltase deficiency
sevelamer	RenaGel®	phosphate binder in renal failure
sildenafil	Viagra®	erectile dysfunction
technetium Tc-99m	Diatide®	diagnostic for venous thrombosis
telmisartan	Micardis®	hypertension
thalidomide	Thalomid®	erythema nodosum leprosum
thyrotropin alpha	Thyrogen®	diagnostic for thyroid cancer
tirofiban	Aggrastat®	acute coronary syndrome
tolcapone	Tasmar®	Parkinson's disease
tolterodine	Detrol®	urinary frequency & incontinence
trastuzumab†	Herceptin®	breast cancer
valrubicin	Valstar®	bladder cancer

† Biologic

* In the Shands Formulary

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NEWS

Catheter patency—Is urokinase our only option?

In December, Abbott Laboratories issued a letter about its inability to supply urokinase. The FDA observed problems with Abbott's production guidelines and placed a hold on urokinase. The subsequent shortage raised the question, "What are the options for maintaining catheter patency if urokinase is not available?"

In January the FDA released a letter recommending that urokinase "be reserved for only those situations where a physician has considered the alternatives and has determined that the use of urokinase is critical to the care of a specific patient in a specific situation." With this statement, 9 lots of urokinase were released.

The FDA is concerned that urokinase may be contaminated with infectious agents (eg, tropical diseases, HIV, hepatitis C, and other unspecified microbes). Abbott claims to have performed tests on the product, but the FDA wants these tests validated. Over 4 million patients have received urokinase and there have been no case reports associating urokinase use with infection. However, practitioners may not have thought to relate an infection with urokinase use.

Urokinase is the only product with a labeled indication for IV catheter clearance. There are several other thrombolytic agents on the market that should be effective in clearing IV catheters, including streptokinase, anistreplase, reteplase, and alteplase.

All thrombolytic agents enhance the conversion of plasminogen to plasmin, which results in fibrinolysis. Alteplase and reteplase are tissue plasminogen activators. Both alteplase and reteplase are produced using recombinant DNA technology. References list alteplase 2 mg (2 mL) injected into a blocked catheter as an unlabeled use. In theory reteplase should also be effective, but the dose is not established.

Urokinase, streptokinase, and anistreplase are thrombolytic enzymes. Streptokinase is derived from beta-hemolytic streptococci. Because streptokinase is a bacterial protein, it can cause allergic reactions. Anistreplase is a derivative of streptokinase and can also cause allergic reactions. These reactions should be considered when streptokinase and anistreplase are used systemically. However, if the 1st dose of thrombolytic clears the

catheter, no drug should be introduced into systemic circulation. This minimizes the risk of antibody production. When a 2nd dose is needed, some product will be pushed systemically, which may result in antibody production to streptokinase or anistreplase.

Streptokinase has an indication for use in the occlusion of arteriovenous catheters. The dose used is 250,000 IU in 2 mL of solution placed into the occluded catheter for 2 hours. Streptokinase could be used for IV catheter clearance, but the dose is unknown.

The cost of these agents should also be considered. Urokinase is the most cost effective product. The costs of urokinase, streptokinase, and alteplase for catheter clearance are \$46.77, \$94.75, and \$42.96, respectively. If the IV center prepares urokinase from a 250,000-unit vial (verses using the 5000-unit vial), the 5000 unit dose cost only \$7.70.

The risks and benefits must be considered when deciding whether to use urokinase. If urokinase is not available or if the assumed risk is too great, alteplase is a reasonable alternative for clearing an occluded IV catheter.

by Allison Miller, PharmD