

February 2004

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medication update

New Formulary Drugs

Botulism IVIG

BabyBIG® is indicated for the treatment of infant botulism caused by toxin type A or B. We do not expect a lot of use here at Children's Hospital. The cost of a single injection therapy is **\$22,900**, however, it is anticipated to save weeks of ICU costs.

Although the manufacturer does not allow us to stock the product in our pharmacy, they will provide the drug within 24 hours if we have a patient needing it. Due to the high cost, a neurology consult is required prior to its use.

Advate®

This new factor VIII drug is considered the product of choice for newly diagnosed hemophilia A patients. Advate® is free of human plasma-derived proteins, and therefore, there is no risk of transmission for human-associated infectious agents.

NovoSeven®

This recombinant factor VIIa product is now on formulary for the treatment of bleeding in patients with hemophilia A or B and with inhibitors to factor VIII or IX. There has also been recent interest, through anecdotes and case reports, in using this product for uncontrolled hemorrhage in surgical patients. Due to its cost, the P&T Committee has selected to restrict NovoSeven® to patients on the Hem-Onc service. In the setting of surgical hemorrhage, approval from the Medical Director at the Blood Bank is required prior to use.

Aripiprazole

Abilify® is used in children with a primary psychotic disorder or autism. Its benefits compared with other atypical antipsychotic agents are an absence of both weight gain and QTc prolongation. Unfortunately, the pediatric dosing information is limited as published literature on use in children is lacking.

Other Formulary Changes

Drugs deleted – mostly due to low usage:

- VoSol
- Otic Domeboro
- Cortisone
- Propine ophthalmic
- Chloramphenicol injection
- Chloramphenicol ophthalmic ointment
- Fluoride
- Midodrine
- Mexiletine
- Quinidine
- Nicardipine
- Triple Dye
- Poly Vi Flor
- Vidaylin F
- Beef heparin (no longer manufactured)

Formulary Clarifications:

- Combivir (lamivudine/zidovudine) is now officially on formulary (used in needle poke protocol)
- Clindamycin Gel has been replaced with clindamycin topical solution
- Pancrease plain is on formulary
- Nasacort AQ is now stocked by pharmacy
- Cyproheptadine – has been re-added
- Bath Oil is now stocked by CS

Moxifloxacin ophthalmic solution

Moxifloxacin eye drops were reviewed for formulary consideration. Due to its cost (\$11 more than ciprofloxacin), therapeutic duplication on formulary, and minimal concern for resistant organisms, the P&T Committee decided NOT to add this product to formulary.

ADHD Drugs Streamlined

Due to therapeutic duplication and risk for mix-ups (in particular, long acting methylphenidate products), P&T Committee recommended to remove Metadate® CD and dextroamphetamine from formulary.

Critical Drug Shortages

IV Erythromycin – unavailable; consider IV azithromycin

Amphotericin B –Regular amphotericin B is unavailable. During this shortage period, AmBisome is available for SCCA use without ID restriction

Methadone injection – unavailable from manufacturer

Senna Granules – unavailable from manufacturer

ADEKs multivitamin liquid - temporarily unavailable from manufacturer

Ganciclovir capsules – very short supply, if any at all

Valganciclovir – Temporarily unavailable, due to ganciclovir shortage

Hydrochlorothiazide oral liquid – discontinued by manufacturer

Piperacillin injection – temporarily unavailable

Gonadorelin injection – temporarily unavailable

Watch List:

Meropenem, succinylcholine, Humalog insulin, bacitracin for irrigation, ganciclovir injection, sirolimus, indomethacin injection, pantoprazole injection, thioguanine tablets, thiopental, azithromycin, conjugated estrogen injection and pralidoxime kit.

Methylprednisolone injection, hydrocortisone injection – please try to use oral route when possible in order to preserve our injectable supply

Shortage Resolved:

Tamiflu® liquid is readily available at Children’s Hospital.

Proton Pump Inhibitors: Is IV Really Necessary?

Intravenous pantoprazole is 92 times more costly than oral lansoprazole. Therefore, in conjunction with the Pharmacy and Therapeutics Committee, Children’s Pharmacy performed a Medication Usage Evaluation (MUE). The pharmacy looked at 225 patient days of pantoprazole use (over a period of 20 days). The results of the MUE indicated that 55% of the patients receiving IV pantoprazole were using it for stress ulcer prophylaxis. Another 27% of patients had an upper GI bleed, and 18% were using it for gastroesophageal reflux disease (GERD). The correct dose was ordered 95% of the time. The indication for use was documented in the chart 2 out of 3 times.

In addition, it was noted that in three out of four courses of therapy, the patient was taking oral feeds or other oral medications. It is estimated that if patients with functional gastrointestinal activity received oral lansoprazole instead of IV pantoprazole, the hospital could have saved \$32,000 a year on drug costs plus approximately another \$3000 on syringe pump tubing.

The CIS will be modified to remind practitioners of the cost differential.

Is that ATG from a Horse or Rabbit?

by Tom Nemeth, PharmD

Anti-thymocyte globulin comes in two different forms: Atgam® and Thymoglobulin®. Different services have their favorite product, however you cannot assume that a service will only use one product over another. It is critical to know which product you are using!

ATGAM®	Thymoglobulin®
Equine (horse)	Rabbit
10-15 mg/kg/dose	1-1.5 mg/kg/dose
Needs an inline filter (0.2-1 micron)	Needs an inline filter (0.22 micron)
NS or ½ NS only NOT D5W	D5W or NS only
Run over 4-8 hours	Run over 6-8 hours
High flow vein is recommended	High flow vein is required
Skin test recommended by manufacturer	No skin test recommended by manufacturer

Use of Tamiflu® in Very Young Children

Based on new preclinical safety data in juvenile rats, Roche Laboratories and FDA issued a warning against the use of Tamiflu® (oseltamivir) in children less than 1 year. Oseltamivir is indicated for the treatment of acute illness due to influenza infection in patients who have been symptomatic for no more than 2 days. High exposures of oseltamivir in juvenile rats (about 250 times the usual dose in children) resulted in a lethal drug level in the brain around 1500 times those observed in adult animals. The immature blood-brain barriers in these juvenile animals are likely the cause of the high exposures. Due to the uncertainty of the significance of these results in relation to exposure of oseltamivir in young children with immature blood-brain barrier, Tamiflu® should only be used in patients 1 year of age.

Amphotericin B Products: Hydration and Pre-medications: To give or not to give?

Acute infusion-related reactions with amphotericin B generally consist of fever, chills and rigors, but may include nausea, vomiting, anorexia, headache, dyspnea, tachypnea and hypotension. They are most acute and frequent with initial doses and may occur within 30 minutes to 1 hour after initiation of conventional amphotericin B infusion. The occurrence of these reactions lessens with continuation of therapy but may reappear if conventional amphotericin B is reinitiated after an interruption. As much as 50-90% of patients receiving conventional amphotericin B experience some degree of adverse reactions associated with initial doses. These acute reactions have also been associated with all lipid amphotericin formulations. However, Wong-Beringer et al observed an occurrence that appears to follow this order of frequency based on various studies:

Liposomal AmB < ABLC ≤ conventional AmB < ABCD

AmB amphotericin

ABLC amphotericin B lipid complex

ABCD amphotericin B colloidal dispersion

The exact mechanism that causes these acute infusion reactions is not well known, although an increase in prostaglandin synthesis has been implicated. Routine administration of both acetaminophen and diphenhydramine are generally recommended prior to each administration of conventional amphotericin B due to the high incidence of acute infusion reactions. Meperidine should also be available on an as needed basis to treat rigors.

Nephrotoxicity with conventional amphotericin B is another major concern. It ranges from elevated serum creatinine, azotemia, renal tubular acidosis, hypokalemia, hypomagnesemia, and nephrocalcinosis to renal failure. A lytic action on the membranes of renal tubular cells and vasoconstriction of renal arterioles are both involved in the development of nephrotoxicity. Renal function impairment of varying degree occurs in over 80% of patients receiving conventional amphotericin B. In a study by Bates et al, acute renal failure was reported to develop in up to 30% of conventional amphotericin B-treated patients (hydration prior to amphotericin was not addressed). Avoidance of other nephrotoxic drugs and adequate hydration (i.e. saline bolus) in patients receiving conventional amphotericin B are routinely recommended in order to lower the risk and severity of renal damage.

Liposomal amphotericin B (AmBisome®) is currently the only lipid amphotericin formulary agent at Children’s Hospital. There are no specific guidelines regarding either premedications or hydration prior to liposomal amphotericin B. Infusion reactions with liposomal amphotericin B can be severe but seem to occur with less frequency and intensity than conventional amphotericin B. They usually do not reappear if subsequent infusions are prolonged. A cautious approach is to prescribe acetaminophen and diphenhydramine prior to initial doses of liposomal amphotericin B in all patients. When the patient appears to tolerate infusion without problems, premedications may be discontinued.

All lipid amphotericin B products show comparative risk of nephrotoxicity, which is significantly reduced when compared to conventional amphotericin B. Once again, specific recommendation on hydration with liposomal amphotericin is lacking. Given its improved nephrotoxicity profile, it seems prudent to base the need for pre-hydration on the clinical situation of each patient, such as fluid status and renal function. If fluid overload is an issue, one may wait on prescribing hydration and follow renal function closely. On the other hand, pre-hydration may be beneficial for the patient with preexisting renal impairment or the patient who receives other nephrotoxic medications concomitantly.

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Outpatient Rx Corner Barb Marquardt, RPh, Ruth Kindy, RPh, Rose Velikanje, RPh, Cindy Larsen, RPh



Welcome to our new section in the newsletter. Outpatient pharmacy is located on Train 3, next to the inpatient pharmacy. Hours are 9AM- 8PM Mondays through Fridays and 8AM-4:30PM on Saturdays and Sundays. Prescriptions after hours will be dispensed by the inpatient pharmacy. Messages can be left on 206-987-2138 for refills.

Do you ever wonder what quantities to dispense on liquid products? Our pharmacy stocks most products in bulk bottles. Indicate the number of doses to be dispensed and pharmacy will calculate the quantity.

Use the tablet form of dexamethasone in acute asthma diagnosis. Dexamethasone solution contains 30% alcohol and with larger doses the alcohol content is significant. Parents can crush the tablet and put in food. The dose for acute asthma is 0.6 mg/kg/dose (up to 16 mg/dose) once daily for 2 days.

Zonegran® (Zonisamide, an anticonvulsant): 25mg and 50mg capsules are now stocked in the pharmacy.

Miralax™ – Medicaid will only pay for Miralax for the treatment of occasional constipation and the patient must have tried and failed a less costly alternative (for example docusate).

Do you know that in 1 out of 21 discharges, the patient leaves the hospital without picking up one or more prescriptions from the outpatient pharmacy? The two most common reasons for not picking up their medications are: parents do not want or need the medication and parents are unaware that the medication is available in the pharmacy. What can you do?

- Carefully review the discharge medications with your patient.
- Ask if they need a new prescription or if they have an adequate supply at home.
- Ask if they want to fill their prescription at Children’s Pharmacy or elsewhere.

Medication Turn Around Time - Great News for Patients!

Prior to the start of our process improvement project, the median time was **1 hour and 15 minutes**. With great work by pharmacy and unit coordinators, we reduced the median turn around time to **52 minutes**. Now with the help of CPOE, our current medication turn-around time is now **23 minutes!** Great work!

Unsafe and Unaccepted Abbreviations

The following abbreviations have been deemed **UNSAFE** and should not be used in anywhere in charting! Remember, as a pediatric institution, we are particularly vulnerable to SERIOUS dosing errors.

Review the following list – and determine how you need to change your practice!

u or IU	Avoid a 10 fold error! Spell out the word UNITS
QD / QOD	These can be mistaken for each other – spell out once-daily or every other day.
µg	This can look like milligrams.
MS, MSO₄, MgSO₄, ZnSO₄	Any of these abbreviations can be mistaken for each other.
AZT	Azathioprine or zidovudine?
CPZ	Compazine or chlorpromazine?
HCl	Hydrochloric acid or potassium chloride?
HCTZ	Hydrochlorothiazide abbreviation can be mistaken for hydrocortisone.
MTX	Methotrexate or mitoxantrone?
TAC	Triamcinolone or tetracaine/adrenaline/cocaine?

In addition, follow these SAFE decimal practices:

1. Avoid the naked decimal – (e.g., .5 mg). Write this as **0.5 mg**, and avoid a 10-fold error.
2. Avoid the trailing decimal – (e.g., 5.0 mg). Write this as **5 mg**, and avoid a 10-fold error.

Vancomycin Monitoring: Are both peak and trough levels necessary?

by Susan Jacob, PharmD

Background In 1958, vancomycin was 'fast-tracked' by the FDA and made available for general use for staphylococcal and streptococcal infections. Even as the first trials were being conducted, vancomycin (nicknamed 'Mississippi Mud') was being purified. Early preparations contained pyrogens and impurities that produced not only its brownish, muddy appearance, but also high fevers, hypotension, severe dose-limiting phlebitis and possibly the nephrotoxicity that was observed anecdotally with its first recipients.²

Why trough? Vancomycin displays time dependent killing¹, which means that effective bacterial killing requires maintenance of drug level above minimum inhibitory concentration throughout the dosing interval. Vancomycin trough concentrations of >1-2 mcg/ml is necessary to treat most susceptible organisms. However, based on the fact that vancomycin is 50% protein bound and the assumption that only free or unbound drug is capable of interacting with bacteria, vancomycin trough levels of 2-4 mcg/ml are necessary. Many experts do not recommend monitoring levels in adults with normal renal function because empirical dosing methods provide trough levels that equal or exceed these levels. Since pediatric patients often exhibit high clearances, monitoring trough level will ensure that concentrations are within the recommended range.

Why peak? In 1958, Geraci and colleagues¹ reported ototoxicity in 2 of 6 patients with vancomycin levels ranging from 80-100 mcg/ml. They suggested that serum vancomycin concentrations >50 mcg/ml be avoided in all patients in order to reduce the risk of ototoxicity. It had then become the accepted clinical practice to measure trough and peak concentrations at steady state in the same way that aminoglycoside levels were measured. However, with the current dosing recommendation and the maintenance of trough level 5-10 mcg/ml, it is almost impossible to achieve those high vancomycin peak levels that were associated with ototoxicity. In addition to the fact that effective killing appears to be independent of peak level, the routine monitoring of vancomycin peak levels is therefore in question.

Do vancomycin levels correlate with toxicity?

Ototoxicity- Most animal studies show lack of ototoxic potential associated with vancomycin. Although reports of either tinnitus or hearing loss have appeared in the literature, it remains difficult to demonstrate a cause-and-effect relationship. As in some cases, other proven ototoxic drugs were given with or just before vancomycin. Some patients were also being treated for pneumococcal meningitis, a condition that can potentially cause hearing loss. As mentioned above, ototoxicity associated with vancomycin level >80 mcg/ml has been suggested. However, the occurrence of ototoxicity remains extremely rare and vancomycin-induced ototoxicity has never been well proven.

Nephrotoxicity-The incidence of vancomycin-related nephrotoxicity is 5-7% in trials that were controlled for potentially confounding factors.¹ In combination with other nephrotoxic agents, the incidence may rise to 35%.² Some reported an association of vancomycin >10 mcg/ml with nephrotoxicity, but it is unclear whether these levels actually contribute to renal insult. Evidence of preventing nephrotoxicity by maintaining vancomycin level within a certain range is also lacking. In conclusion, the correlation of vancomycin levels with toxicity is inadequately documented. Routine monitoring of peak and trough vancomycin levels in order to prevent toxicity is therefore poorly justified.

New recommendation for vancomycin monitoring

- Monitoring of peak level is no longer recommended
- Monitoring of trough serum vancomycin levels is indicated for all patients with planned treatment course > 3 days. Trough level can be drawn with the third to fifth dose. Draw immediately prior to the next dose
- Acceptable trough level is 5-10 mcg/ml
- Before starting therapy, **all patients draw a baseline BUN and Cr.**
- If the trough level is within the therapeutic level, further monitoring of troughs is no longer necessary for a 7-10 day course of treatment
- Repeat trough levels are indicated under the following circumstances:
 - a. Sub-therapeutic or supra-therapeutic troughs levels
 - b. Course is anticipated to exceed 10 days
 - c. Fluctuating renal function or pre-existing renal insufficiency
 - d. Patients who are on concomitant aminoglycoside therapy or other nephrotoxic drugs
- To monitor for nephrotoxicity:
 - a. A baseline Cr and BUN is recommended for all patients
 - b. If there is evidence or suspicion of renal insufficiency or changing renal function, check Cr every 3 days
 - c. Monitor Cr weekly if administering other nephrotoxic drugs or anticipated course of therapy is > 10 days

Note: The vancomycin order set will be revised to eliminate peak vancomycin levels on or around February 9, 2004.

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