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Shands at the University of Florida

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Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 20, 2012. 4 products were added in the *Formulary* and no drugs were deleted or designated nonformulary and not available. 1 drug was evaluated, but not added into the *Formulary*, while criteria for use changes were adopted for 5 drugs.

◆ ADDED

Acetylcysteine Capsules [Dietary Supplement]*

**Added temporarily during the inhaled acetylcysteine shortage*

Alvimopan (Entereg®)†

†*Restricted: Labeled indication*

Baclofen Injection (Gablofen®)†

†*Restricted: Emergency refills and other emergencies*

Ketamine, Oral [Extemporaneous]†

†*Restricted: PACU, ICU, ED, and approval of Palliative Care or Pain Services*

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

None

◆ EVALUATED, BUT NOT ADDED

Hyaluronidase, Human Recombinant (Hylenex®)

◆ CRITERIA FOR USE CHANGES

Codeine (Generic)†

†*Restricted: Removed from all EPIC order sets*

Dexmedetomidine (Precedex®)†

†*Restriction Modified: Use in the OR for pain approved*

Palivizumab (Synagis®)†

†*Restriction Modified: American Academy of Pediatrics guidelines*

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PRESCRIBING

Why we still use animal products

If recombinant human products are available, why do we still use animal products? There are 3 factors to consider: efficacy, safety (risk of infection and allergic reactions), and cost.

From the standpoint of efficacy, the assessment must be done on an individual basis. Take bovine and human thrombin for instance. These products have to be compared using head-to-head trials to know if efficacy truly differs. Studies have not shown them to be different.[1] Recombinant human (Hylenex®) and purified ovine (Vitrase®) hyaluronidase also have similar efficacy profiles (see *Formulary Update*). If products are similar in terms of efficacy, then relative safety is considered.

Assessing the safety of human and animal formulations considers the risk of infection and allergic reactions of the products. Proponents for human recombinant formulations argue there is less chance of transmitting infections compared to animal-derived formulations. Bovine-derived products raise concern about Bovine Spongiform Encephalopathy (BSE or "mad cow disease") for some products.[2] Ovine-derived products have a similar concern for scrapie (a disease similar to BSE that occurs in sheep, but not known to affect humans). For some human-derived and bovine products, there remain concerns for transmitting variant Creutzfeldt-Jakob disease (vCJD), a fatal brain disease to humans that first appeared in mid-1990s because of BSE epidemic in the United Kingdom. However, no cases of vCJD have been linked to medicinal products.

The World Health Organization (WHO) suggests that an ideal strategy would be to avoid the use of ruminant materials in the manufacture of pharmaceutical products. However, the WHO guidelines also recommend that a risk assessment should take into account the source of the starting materials, the manufacturing process, and the clinical use of the final product. Evaluating the starting material refers to the part of the animal a product is derived from. For instance, bovine blood poses a higher risk of transmission of infection compared to bovine muscle. To evaluate manufacturing processes, recombinant products pose less risk of infection compared to plasma-derived formulations. Recombinant processes apply virus testing to minimize viral contamination risks.[3]

Plasma-derived products must be tested for viral contamination, and donors must be screened for possible infections. Applying this approach to plasma-derived factor products plays a huge role in minimizing the transmission of infections between humans.

In March 1999, the Food and Drug Administration (FDA) released a statement to explain the shortage of Abbokinase® (urokinase), a thrombolytic agent made from human neonatal kidney cells *in vitro*.[4] Three lots, which were not manufactured into finished Abbokinase®, were found to contain reovirus, an agent that should not have been present at any step in the production process. The FDA was not aware of any cases of infectious diseases that were caused by Abbokinase®. The FDA described Current Good Manufacturing Practice deficiencies during inspections of the manufacturer. The deficiencies could have increased the risk of transmitting infectious agents. Abbokinase® is no longer marketed. This reinforced the importance of proper manufacturing processes to minimize the potential transmission of infections for products using tissue cultures.

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◆ INSIDE THIS ISSUE

Formulary update, *from page 1*

◆ CRITERIA-FOR-USE CHANGES

Regorafenib (Stivarga®)†
†Added in the Chemotherapy Policy; Nonformulary Drug

Vancomycin, Oral
[Extemporaneous]†
†Restriction: 1st-line for severe or fulminant C. difficile infections

Acetylcysteine or N-acetylcysteine (NAC) is the N-acetyl derivative of L-cysteine. It is marketed in a sterile inhaled form as a mucolytic and as an IV form for use in acetaminophen overdoses. The inhaled liquid is taken orally for acetaminophen overdoses and for the prevention of radiocontrast-induced nephropathy (RCIN).

The P&T Committee has restricted the use of the inhaled dosage form of NAC because of a nationwide shortage. Its use has been restricted to oral use for the prevention of RCIN. This decision was based on weak evidence of its effectiveness as a inhaled mucolytic. Because of insufficient supplies of inhaled NAC, its use has not been permitted as a mucolytic. It is anticipated that the shortage of NAC will not resolve until sometime in 2013.

Since the limited supplies of inhaled NAC are almost exhausted, the P&T Committee considered the use of an oral dietary supplement capsule as an alternative for the prevention of RCIN. Before allowing the use of a dietary supplement, issues of quality and safety were considered.

The United States Pharmacopeia (USP) has a voluntary testing and auditing program that allows manufacturers to gain the USP-verified mark for dietary supplements. This is a way to assure consumers of product quality. If products meet the stringent criteria, consumers can be assured that the supplements contain the ingredients listed on labels in the stated amounts and potencies. This also indicates that the drug will break down in the body within a specified amount of time, does not contain contaminants, and has been made according to the FDA's Good Manufacturing Practices (GMP).

Without this verified mark, there is no reliable method to determine the content and quality of a dietary supplement. Supplements do not have to gain FDA approval before coming to market. Currently, there are no commercially available NAC dietary supplements with the USP-verified certification.

In the face of the current shortage, the use of a NAC dietary supplement for prevention of RCIN was a pragmatic decision balancing the potential risks versus benefits. A product that uses USP-quality ingredients, but that is that is not a USP-verified finished product was identified. Therefore, a 600-mg acetylcysteine dietary supplement capsule is temporarily available for oral use for the prevention of RCIN during the shortage. Our limited supplies of inhaled NAC are so low, this will not allow modification of the restriction on the use of inhaled NAC as a mucolytic.

Alvimopan is a peripherally acting mu-opioid receptor antagonist approved in 2008 to accelerate time to upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection with primary anastomosis.

Alvimopan reverses the peripheral effects of mu-opioid receptor agonists, but not the central pain relieving effects. It is poorly absorbed from the GI tract and is eliminated primarily through biliary secretions. The dose is 12 mg administered 30 minutes to 5 hours before surgery, followed by 12 mg twice daily for up to 7 days or until discharge. When a patient tolerates solid foods, has a bowel movement, or experiences flatus, alvimopan should be stopped. Alvimopan is not recommended in severe hepatic dysfunction or end-stage renal disease and is contraindicated when therapeutic doses of opioids have been used for more than 7 consecutive days before starting therapy.

Alvimopan appears efficacious with short-term safety in preventing postoperative ileus (POI). A large matched-cohort study affirmed possible associations with reductions in hospital morbidity, costs, and postoperative length of stay (LOS). The reduction in LOS was 1.1 days, which is similar to phase III trials (ie, 20 hours). Original studies were conducted in open laparotomies. In the matched-cohort study, its effectiveness in laparoscopic surgeries was less than for laparotomies (LOS reduction of 0.8 days vs 1.8 days).

Alvimopan is only available for short-term use in patients admitted to hospitals enrolled in the ENTEREG Access Support & Education (E.A.S.E.) program. Patients should not receive more than 15 doses of alvimopan. This limitation stems from concerns of increase myocardial infarctions seen in a long-term study.

The average wholesale price of alvimopan is $100.97 for each capsule. A manufacturer program offers incentive to evaluate alvimopan. Shands UF will receive a rebate for a percentage of drug acquisition costs if postoperative LOS is not improved by 1 or more days compared to a historical control. The 6-month period before adding alvimopan in the *Formulary* defines the control group. The rebate period is up to 12 months after starting date, in which an equivalent or greater number of patients must be given alvimopan by the same surgeons as the control group (minimum 50).

Alvimopan was added in the *Formulary* for a 1-year evaluation to determine its effect on LOS and total costs for the labeled indication. It will be restricted to the labeled indication and duration of therapy using an EPIC order set. If off-labeled use is detected, the P&T Committee will consider stopping the evaluation early and removing alvimopan from the *Formulary*.

Baclofen is a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA) that is used orally as a skeletal relaxant and by the intrathecal (IT) route for spasticity. When baclofen injection is given IT, it is administered by an implantable pump. The implantable pump kit contains Lioresal® brand baclofen IT. When the pump needs to be refilled, Lioresal® or Gablofen® can be used. Refills are generally done in the outpatient setting. In January 2011, Gablofen® was designated nonformulary and not available, because it was assumed that refills in the inpatient setting were unnecessary, and their availability could be used to "top up the pump" before discharge. Because of the expense of baclofen IT, this practice would not be covered adequately by fixed-reimbursements.

There are rare circumstances when refills for baclofen pumps are reasonable in the inpatient setting (ie, the implanted pump is empty). There are even more rare situations when an intrathecal infusion of baclofen may be needed for patients without pump access with severe spasticity.

Therefore, baclofen intrathecal refills were added in the *Formulary*, but restricted to refractory dystonias and for the refill of baclofen pumps in an emergent situation. The use of baclofen must be approved by the adult critical care or pediatric on-call

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Formulary update, *from page 2*

pharmacist. Appeals will be referred to the pharmacy administrator on-call.

Ketamine is a dissociative anesthetic with sedative and analgesic effects. Ketamine targets a wide range of receptors both centrally and peripherally and consequently evokes a wide range of effects. Ketamine for oral use is currently not FDA approved.

Ketamine is a schedule III controlled substance and only has a labeled indication for parenteral use as an anesthetic, but the IV dosage form has been used for pain at Shands UF. The effects of ketamine appear to be dose dependent, and at low doses, analgesia can be achieved without anesthesia.

Oral formulations of ketamine have 16-20% bioavailability and undergo extensive first-pass metabolism to norketamine. Norketamine exhibits a 20-30% analgesic effect compared with ketamine, but has a much longer half-life (12 hours compared with ketamine at 2-3 hours). The exact mechanism that ketamine uses to elicit analgesia is unknown; it is also not known if norketamine has the same mechanism of action.

Clinical trials, case series, and case reports suggest that oral ketamine can reduce hyperalgesia in some individuals with opioid-resistant neuropathic pain. However, this promising effect exhibits variability as different studies required different dosages to produce analgesia, and many studies specifically screened for patients who responded to intravenous ketamine.

Oral ketamine for analgesia shows a low incidence of adverse effects. At analgesic doses, the drug appears to be well tolerated with few psychotomimetic effects (hallucination, confusion, etc.), some anticholinergic effects (blurred vision, dizziness), and a few other minor effects such as somnolence, headache, and nausea. Adverse effects (especially psychotomimetic effects) appear to be dose related. None of the adverse effects noted in the literature were life threatening or serious adverse effects.

Since an oral formulation is not approved by the FDA, the Pharmacy Department will dispense individual doses of the injectable form in an oral syringe rather than compound an extemporaneous oral liquid. Oral syringes containing 10 mg or 20 mg of ketamine will be used to achieve all ordered doses. The oral syringe will be diluted in juice or cola immediately prior to use. Doses given down a tube can be given undiluted.

Oral ketamine is restricted to use in patients in intensive care units (ICUs), the Emergency Department (ED), or the Post-Anesthesia Care Unit (PACU) without any approval, but use on general wards require a Palliative Care or Pain Service consult to approve its use. The dosage will be limited to 60 mg 3 times a day up to a total daily dose of 180 mg.

Human hyaluronidase injection was considered for use to facilitate subcutaneous fluid administration, to increase the dispersion and absorption of other injected drugs in patients with difficult IV access, and in those requiring fluid hydration. These are labeled indications for human hyaluronidase. This is also a labeled indication for ovine hyaluronidase (Vitrase®), which is listed in the *Formulary*.

Vitrase® was added in the *Formulary* in May 2010 when bovine hyaluronidase (Amphadase®) was discontinued by its manufacturer. At that time, the Florida Surgical Center was the primary user of Amphadase®. Ophthalmologists use hyaluronidase as a dispersing agent for local anesthetics during ophthalmologic surgeries. It is also used in extravasation kits. At that time, recombinant hyaluronidase was twice the cost of ovine hyaluronidase.

Vitrase® remains a fraction of the cost of Hylenex®. A thorough review of the literature could find no data that support superior efficacy of either product for this labeled indication. Further, no data could be located that demonstrated superior safety for either product. *(see Why we still use animal products on page 1)*

Human hyaluronidase is 82 times more expensive than ovine hyaluronidase. The rationale for the selection of human hyaluronidase would be a theoretical advantage in the antigenicity of human versus ovine hyaluronidase and the possible risk of ovine-associated diseases. There are no data to support these concerns.

Therefore, human hyaluronidase was not added in the *Formulary*.

Codeine was approved by the FDA in 1939. It has been widely used for its pain relieving abilities, usually in combination with acetaminophen, or for it antitussive effects, usually in combination with guaifenesin. The use of codeine has gradually decreased, and it is anticipated that the most recent warnings from the FDA will decrease its use further.

Codeine is an opioid prodrug, which is converted to morphine to provide analgesia. Codeine alone does not provide pain relief. The metabolic conversion by CYP2D6 of codeine to morphine is what led to the recent FDA warnings about its use. Some patients are "ultra-rapid" metabolizers of codeine and form more morphine than would normally be expected. Excessive morphine exposure in ultra-rapid metabolizers can cause respiratory depression and even death. This has occurred in children who receive acetaminophen with codeine for post tonsillectomy pain and in the children of breastfeeding women who are ultra-metabolizers.

The Medication Safety Subcommittee recommended that codeine be removed from all order sets. The P&T Committee passed this restriction effective December 1, 2012.

An article was published in the November-December 2012 issue of the *Drugs & Therapy Bulletin* asking for input on a proposal to delete codeine from the *Formulary* and designate it not available for use.

When Pediatric ENT was approached to discuss the risk of codeine use in children post tonsillectomy and the possible use of pharmacogenetic information to guide therapy, they chose, instead, to use other options for pain control. Other services that have used codeine have made the same decision. Codeine, however, is a difficult drug to assess for complete removal from the *Formulary*. It is used, albeit infrequently, by several services and providers.

The pain services have already expressed support for this proposal. Not only are some patients at risk for excessive effects, but slow metabolizers do not achieve adequate pain relief or cough suppression with codeine. Other services have already switched to alternatives for pain (eg, nonsteroidal anti-inflammatory drugs or oxycodone). Dextromethorphan is listed in the *Formulary* as an alternative for suppressing a cough.

Dexmedetomidine was reviewed by the P&T Committee for addition in the *Formulary* in 2002, 2004, 2008, and for use in pediatrics in 2010. The P&T Committee voted to designate dexmedetomidine nonformulary and not available in 2002 and 2004 based on unimpressive results presented in the clinical trials. The literature at the time of review failed to demonstrate superiority of dex-

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Formulary update, *from page 3*

medetomidine to midazolam and propofol, despite costing 28 and 10 times more, respectively.

Dexmedetomidine was finally added in the *Formulary* in 2008 based on new evidence with restrictions for use in awake craniotomy, awake intubation, ventriculostomy placement for non-intubated patients, and transition to extubation for agitated patients who are difficult to wean from the ventilator and who met specific criteria. In 2010, dexmedetomidine was approved for use in pediatrics with restrictions outlined in the Pediatric Dexmedetomidine Order Form. A medication-use evaluation in 2009 revealed modest use of dexmedetomidine at Shands, primarily for awake intubation.

Dexmedetomidine was re-evaluated for use for 4 possible uses: (1) opioid sparing or opioid adjunctive effects in hospitalized non-OR patients (ICU, burn, sickle cell, chronic pain, GI/Crohns diseases, etc); (2) opioid sparing/opioid adjunctive effects in OR patients receiving opioid analgesics with less than desirable results or increased adverse effects; (3) opioid sparing/opioid adjunctive effects in post-surgical patients receiving opioid analgesics with less than desirable results or increased adverse effects; or, (4) primary analgesia in OR patients on buprenorphine in whom opioids are less effective and are unpredictable or contraindicated because of their addiction history.

The evidence for the use of dexmedetomidine for pain is limited. A thorough review of the literature did not find any evidence to support the 4 indications requested. It remains an expensive alternative, although the patent is scheduled to expire in the summer of 2013.

The criteria for dexmedetomidine were expanded to include opioid sparing/opioid adjunctive effects in OR patients receiving opioid analgesics with less than desirable results or increased adverse effects, and primary analgesia in OR patients on buprenorphine in whom opioids are less effective and are unpredictable or contraindicated because of their addiction history.

Palivizumab is a composite monoclonal antibody with an FDA-labeled indication for prevention of respiratory syncytial virus (RSV) in pediatric patients at high risk of severe disease. It targets the "F" glycoprotein on the surface of RSV, which is responsible for viral fusion to the cytoplasmic membrane of the host. By targeting this protein, it exhibits neutralizing and fusion-inhibitory activity against RSV.

The current criteria for palivizumab at Shands UF include its use for respiratory syncytial virus (RSV) prophylaxis in high-risk children. The Anti-infective Subcommittee recommended clarification of these "high-risk" criteria. The P&T Committee adopted the following American Academy of Pediatrics (AAP) recommendations.

The following patients may receive up to 5 doses of palivizumab during RSV season (September 1 through March 31): (1) infants and children 24 months of age or younger with chronic lung disease of immaturity (CLD) who receive medical therapy (supplemental oxygen, bronchodilators, diuretics, or chronic corticosteroid therapy) for CLD within 6 months before the start of RSV season; (2) infants and children 24 months of age or younger with hemodynamically significant cyanotic or acyanotic congenital heart disease (CHD) (to include a post-op dose following cardiopulmonary bypass); (3) infants born at 28 weeks gestation or earlier and are less than 12 months of age; (4) infants born at 29 to 32 weeks gestation and are less than 6 months of age at the start of RSV season; (5) infants and young children who are less than 12 months of age **AND** have either significant congenital abnormalities of the airway **OR** a neuromuscular condition that compromises handling of airway secretions; and, (6) infants and children 24 months of age or younger with severe immunodeficiency (eg, AIDS or severe combined immunodeficiency).

Infants born at 32 to 35 weeks gestation who are born less than 3 months before the onset or during RSV season **AND** the child attends child care **OR** lives with 1 or more children younger than 5 years of age may receive up to 3 doses during RSV season.

Regorafenib is an oral multi-kinase inhibitor with a labeled indication for the treatment of metastatic colorectal cancer who have been treated previously with fluoropyrimidine-, oxaliplatin-, or irinotectan-based chemotherapy, an anti-VEGF (vascular endothelial growth factor) therapy, and, if KRAS (Kirsten rat sarcoma viral oncogene homolog) wild type, and anti-EGFR (epidermal growth factor receptor) therapy.

Because regorafenib was approved under FDA's priority review process, there are limited data on its efficacy and its place in therapy is not clear. Regorafenib is very expensive and current studies showed a median of 1.4 months greater survival than patients who received placebo.

Regorafenib has a boxed warning in the labeling warning prescribers that severe and fatal hepatotoxicity occurred in clinical trials. The most common adverse effects include weakness or fatigue, loss of appetite, hand-foot syndrome (palmar-plantar erythrodysesthesia), diarrhea, mucositis, weight loss, infection, high blood pressure, and dysphonia.

Regorafenib remains nonformulary but was added in the Chemotherapy Policy. It must be ordered on a chemotherapy order form in the inpatient setting.

Oral vancomycin is only used to treat *Clostridium difficile* infections (CDI). The P&T endorsed a new treatment algorithm for CDI (See New *C. difficile* treatment algorithm article on page 5 of this issue of the *Bulletin*). In addition to better defining the various levels of CDI, it restricts ALL antibiotics when a patient has a CDI diagnosis. It also liberalizes the use of oral vancomycin for severe and fulminant CDIs.

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.

PRESCRIBING

New C. difficile treatment algorithm endorsed

The Anti-Infective Subcommittee proposed a new *Clostridium difficile* Infection (CDI) Algorithm based on a review of past CDIs. Continuation of concomitant antimicrobial therapy (beyond 72 hours of CDI diagnosis) resulted in higher failure/relapse rates exceeding 30% of patients with CDI. When concomitant antimicrobial therapy was discontinued, only 15% of patients failed or relapsed.

Infectious Diseases and General Surgery often were consulted late in the disease process. This limits the opportunity to minimize concomitant antimicrobial therapy and the ability to assess the need for early surgical intervention. Early surgical intervention with a temporary loop ileostomy instead of colectomy usually leads to better outcomes.

Most patients at SUF received metronidazole for mild or moderate and severe CDI. Response rates were approximately 80% in both arms, but the Anti-Infective Subcommittee determined an evaluation by Infectious Disease or Antimicrobial Management Program (AMP) should be used to better triage who would benefit from oral vancomycin. Further, better definitions of criteria for using oral vancomycin for CDIs were established.

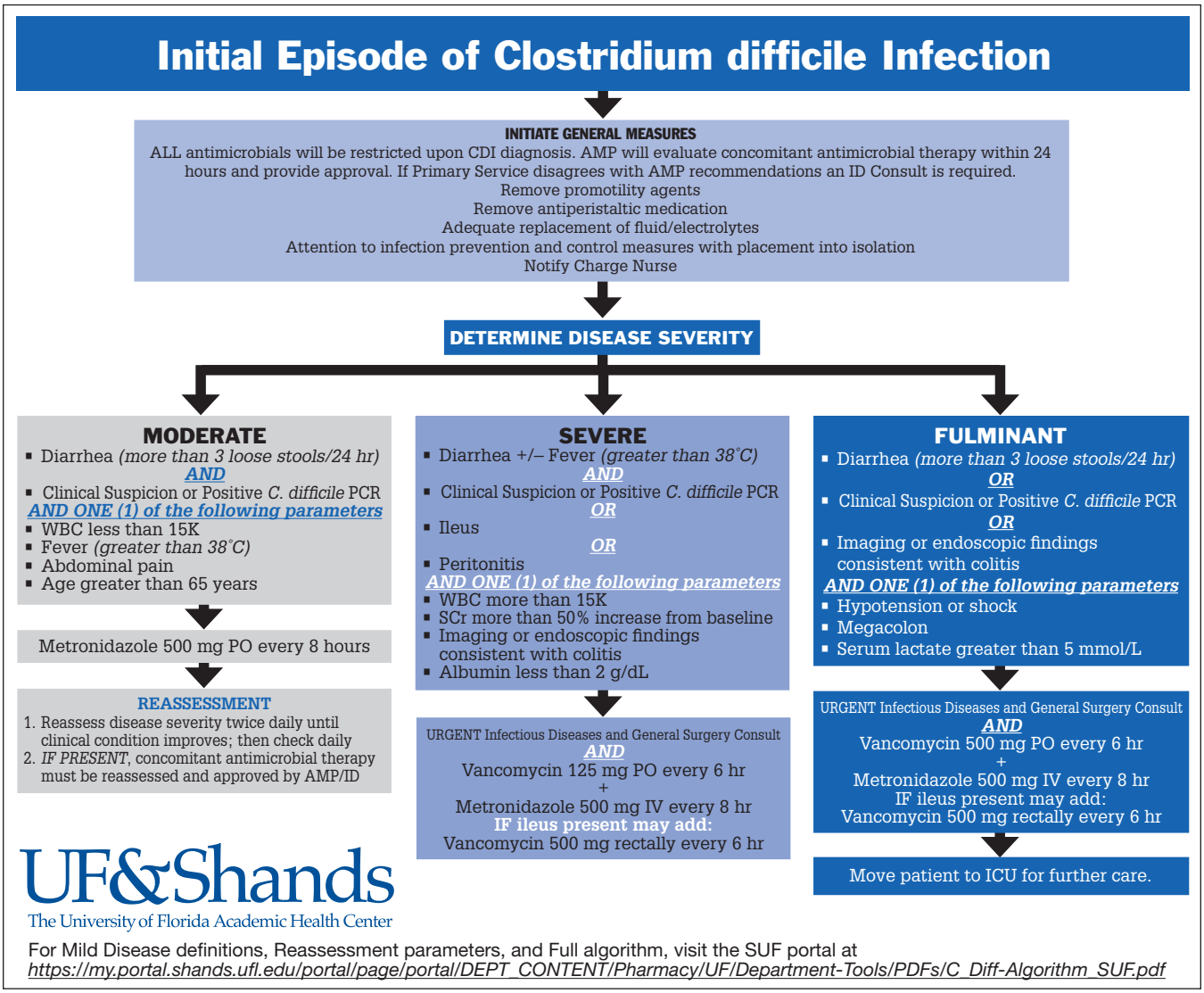
Continuation of concomitant antimicrobial therapy (beyond 72 hours of CDI diagnosis) resulted in higher failure/relapse rates exceeding 30% of patients with CDI.

The P&T Committee passed a policy restricting all antimicrobials upon CDI diagnosis. The AMP will evaluate concomitant antimicrobial therapy within 24 hours of positive CDI results and provide approval status to the medical team. Changes to therapy will be implemented by collaboration between the AMP and the team responsible for the patient's care. If there is disagreement between AMP and the medical team, antibiotic changes will be deferred and a mandatory Infectious Diseases Consult will be ordered. The ID Service will evaluate the patient within 24 hours and make a final determination of which antibiotics will be continued.

The P&T Committee approved new definitions for moderate, severe, and fulminant CDI to highlight differences in disease presentation.

The definition of moderate disease was changed to diarrhea (greater than or equal to 3 loose stools in 24 hours) **AND** clinical suspicion or a positive *C. difficile* PCR **AND** stable renal function **AND** one of the following: (1) WBC of 4,000 to 15,000, (2) fever (greater than 38˚C), (3) abdominal pain, (4) age greater than 65 yrs, or (5) immunocompromised.

The definition of severe disease was changed to diarrhea (greater than or



For Mild Disease definitions, Reassessment parameters, and Full algorithm, visit the SUF portal at *https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Department-Tools/PDFs/C_Diff-Algorithm_SUF.pdf*

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C. difficile treatment, *from page 5*

equal to 3 loose stools in 24hr) and clinical suspicion or *C. difficile* PCR **OR** the presence of an ileus **OR** peritonitis with clinical suspicion or positive *C. difficile* PCR **AND** one of the following: (1) WBC greater than 15,000, (2) acute kidney injury, (3) albumin less than 2 g/dL, or, (4) imaging or endoscopic findings consistent with colitis.

Fulminant was defined as diarrhea (greater than or equal to 3 loose stools in 24 hours) **OR** clinical suspicion or positive *C. difficile* PCR **OR** imaging or endoscopic findings consistent with colitis **AND** one of the following: (1) hypotension or shock, (2) megacolon, or (3) serum lactate greater than 5 mmol/L.

After updating the severe and fulminant CDI categories, oral vancomycin restrictions were modified to reflect the above definitions. It is now recommended that oral vancomycin be used in patients with severe or fulminant CDI as a first-line agent. An abbreviated version of the algorithm is on page 5. The complete algorithm is available as a link in EPIC *(https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Department-Tools/PDFs/C_Diff-Algorithm_SUF.pdf).*

Animal vs Recombinant products, *from page 1*

Assessing the clinical use of the final product refers to the route by which the drug will be given and how many times it will be administered. When comparing the risk of transmittable infections from animal and human pharmaceuticals, this must be done on a case-by-case basis, taking into account the derived source, the manufacturing process, and the clinical application.

The second part of evaluating safety is comparing the risk of allergic reactions. For instance, bovine and human thrombins have not been shown to be clinically significantly different in efficacy and safety profiles. In rare cases, patient may benefit from using human recombinant product if they have developed a reaction to the bovine product. However, a possibility still remains for patients to develop a reaction to the human product as well, and some patients may benefit from the use of an animal-sourced product.

When comparing Hylenex® and Vitrase®, there have been no studies directly comparing both products for safety. However, an indirect comparison of these products showed that there was no clinically significant difference in reported allergic reactions to these agents.[5]

If both human and animal products are similar in terms of efficacy and safety, what is the next step? A cost comparison must be done. Here at Shands, the P&T Committee evaluated whether Hylenex® should replace Vitrase®, which was already listed in the *Formulary*.

Given similar efficacy, a low risk of transmitting infections, and low risk of allergic reactions, the cost differences was considered. Since Hylenex® is 82 times more expensive than Vitrase®, it was not added in the *Formulary*.

However, in September 2012, the P&T Committee added human thrombin in the *Formulary*, while removing bovine thrombin. In this case, the costs were similar. If the costs had been greatly different, the use of human thrombin would have been limited to patients in whom bovine thrombin antibodies could result in differences in efficacy.

By Olusola Apena, Pharm.D.

References available upon request from the Editor.