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Cleveland Clinic

Clinical Rx Forum

From the Department of Pharmacy

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The Transition from Combivent® MDI to Combivent® Respimat®

By: Gabrielle Gibson, Pharm.D.

Introduction: Based on the Montreal Protocol, an international treaty developed to protect the ozone layer, products that contain chlorofluorocarbons (CFCs) must be phased out of production.^{1,2} Most inhalers that contain CFCs as propellants are no longer available. Combivent® MDI (ipratropium/albuterol), one of the few remaining CFC-containing inhalers, is currently discontinued and will no longer be on the market after December 2013. Combivent® Respimat®, a CFC-free product, approved by the Food and Drug Administration (FDA) in October 2011 will replace Combivent® MDI.

Product Similarities: It is important to note some of the major similarities of the different Combivent® formulations.

- Both are indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regu-

lar aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.^{3,4}

- Combivent® Respimat® was shown to be clinically comparable in terms of forced expiratory volume in one second (FEV₁) and safety to Combivent® MDI in clinical trials.^{3,5}
- Combivent® MDI and Combivent® Respimat® are contraindicated in patients hypersensitive to any of the ingredients of the drug product or to atropine or its derivatives.^{3,4}

Advantages of Respimat®: There are unique features of the Combivent® Respimat® that set it apart from the Combivent® MDI. It is important to highlight these, as they are essential when educating patients.

(Continued on page 2)

A Review of “Tech-Check-Tech”

By: Ashley Overy, Pharm.D.

Introduction: The American Society of Health-System Pharmacists’ (ASHP) Pharmacy Practice Model Initiative (PPMI) emphasizes expanding individual pharmacy services to all patients, 24/7 in all clinical practice settings.¹ Healthcare providers are challenged with providing expanded clinical services promoted by the 2010 Patient Protection and Affordable Care Act (PPACA) in midst of budgetary constraints. So, how can this be accomplished? One of the proposed methods is through an initiative called “tech-check-tech” (TCT).² According to ASHP, TCT is the checking of a technician’s

order-filling accuracy by another technician instead of a pharmacist.² This initiative alleviates portions of the pharmacist’s burden on dispensing and allows qualified pharmacy technicians to expand their roles within the institution.

Clinical Role Expansion: In 2009, pharmacists spent 55% of their workday focusing on distribution of medications to patients and 16% of their day performing direct patient care services.² With advanced training, such as a Doctorate of Pharmacy and an ASHP

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These advantages are as follows:

- Unlike the Combivent® MDI, which requires two puffs four times daily, Combivent® Respimat® requires only one puff four times daily.^{3,4}
- Combivent® Respimat® has a dose counter to inform patients how much medicine is left. When the dose pointer enters the red area of the counter, there is enough medicine remaining for 7 days, which alerts patients to refill their medication. The device locks when all of the medication has been used.³
- The cost of the Combivent® Respimat® is slightly more than Combivent® MDI. However, each Respimat® provides a 30-day supply compared to a 25-day supply in each Combivent® MDI, so Respimat® patients may require two less inhalers over the course of a year.^{3,4}
- Combivent® Respimat® does not contain soy lecithin. Unlike the MDI product, Combivent® Respimat® is not contraindicated in patients with a peanut or soybean allergy.³

Disadvantages of Respimat®: While there are many advantages of the Respimat® formulation, it is important to be aware of certain disadvantages when recommending this product and providing patient education.

- The Combivent® Respimat® has a relatively complicated process for preparation before first use and priming compared to the Combivent® MDI.³
 - ◇ When using the Respimat® for the first time, the inhaler should be actuated toward the ground until an aerosol cloud is visible; the process should be repeated three more times. The unit is then considered ready for use.
 - ◇ If not used for more than 3 days, the inhaler should be actuated once to prepare the inhaler for use, unlike Combivent® MDI which doesn't require priming if not used for 3 days.
 - ◇ If not used for more than 21 days, the inhaler should be actuated until an aerosol cloud is visible; the process should be repeated three more times to prepare the inhaler for use.

- Combivent® Respimat® delivers a slow-moving mist that does not feel as powerful as the dose delivered by the Combivent® MDI.³
- Combivent® Respimat®, unlike Combivent® MDI, is not recommended for use with a spacer as it was not studied in this manner, and there is concern about patients receiving subtherapeutic doses when used with a spacer.⁶
- Combivent® Respimat® has not been evaluated in mechanically ventilated patients. There are only in-vitro data evaluating efficacy of the Respimat® in these patients, thus its use in this patient population cannot be recommended at this time.^{6,7} The albuterol and ipratropium products for nebulized use may be recommended for these patients.

Conclusion: Combivent® Respimat® is similar to Combivent® MDI in that it carries the same FDA-approved indication and has similar efficacy and safety profiles. Combivent® Respimat® does have a different look, feel, and dosing regimen than Combivent® MDI. The Cleveland Clinic Health System is currently making the transition from Combivent® MDI to Combivent® Respimat®.

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accredited pharmacy practice residency, many pharmacists would like to have a greater role in direct patient care. Current pharmacy practice models create a disparity within the workforce when pharmacists focus solely on distributive activities instead of counseling patients and educating medical staff. “Tech-check-tech” allows pharmacists to shift their workload to be able to perform more direct patient care activities.

TCT Studies: Studies have demonstrated the safety and effectiveness of TCT over the past 30 years. A review of 11 studies published in the American Journal of Health-System Pharmacy (AJHP) demonstrated that technicians and pharmacists have an overall similar final dispensing check accuracy rate of 99.6% ± 0.55% versus 99.3% ± 0.68% (mean ± S.D.), respectively.² Six out of these eleven studies have provided statistically significant (p<0.05) results that favor technician checking accuracy over pharmacists.² Prior to participation in TCT, technicians in these studies were required to complete training and validation procedures.² It is important to note that the technicians only provided a second validation for medications as part of cart fill or medication station refills, not first doses or intravenous compounding.²

Safety Concerns with TCT: “Tech-check-tech” does not come without criticism. Most of the published studies were performed in a controlled environment where technicians knew they were being studied.² Regardless of the literature, many pharmacists voice concerns about actual safety and error rate. On the other hand, working together as a team along with new bar code technology may be the best solution for preventing medication errors. System analyses have shown that most medication errors occur in the prescribing and administration stage (up to 77%) compared to pharmacy dispensing stage (11%).³ The “tech-check-tech” model may allow pharmacists more time to intercept prescribing errors and help improve patient outcomes. Additionally, bedside barcode medication administration (BCMA) has shown to decrease medication administration errors by up to 75.5% after implementation.⁴

Conclusion: “Tech-check-tech” is currently authorized in twelve states (See Table 1). A formal technician education process is required in each of these state programs.² Published evidence demonstrates that pharmacy technicians were able to perform a final dispensing check as accurately as pharmacists.² However there are still some safety concerns. “Tech-check-tech” discussions with legislators are underway in Ohio, with specific guidelines to be created in the future.

Table 1: States that Allow “Tech-Check-Tech”^{2,5}

State	Hospital/ Institutional Pharmacy	Community Practice
California	Yes	No
Colorado	Yes	Yes
Idaho	Yes	No
Iowa	Yes	No
Kansas	Yes	No
Kentucky	Yes	No
Minnesota	Yes	No
Montana	Yes	No
North Carolina	Yes	No
North Dakota	Yes	No
Oregon	Yes	No
South Carolina	Yes	No

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Ceftaroline – A Novel Cephalosporin Antibiotic

By: Collin Verheyden, Pharm.D.

Introduction: Bacterial resistance has been prevalent since the beginning of the antibiotic era and is a growing concern in the hospital setting.¹ One bacteria that exhibits resistance is methicillin-resistant *Staphylococcus aureus* (MRSA). While some reports indicate MRSA rates are declining, this infection is still a major health care concern both in the hospital and in the community causing significant morbidity and mortality.^{2,3} Some current agents with activity against MRSA include daptomycin (Cubicin®; Cubist Pharmaceuticals), linezolid (Zyvox®; Pfizer Inc.), and vancomycin, but due to increasing resistance as well as treatment-associated toxicities, new agents are needed. Forest Pharmaceuticals has responded, releasing the novel cephalosporin ceftaroline fosamil (Teflaro®). This unique antibiotic is a broad-spectrum cephalosporin with activity against many Gram negative pathogens as well as Gram positive cocci, including MRSA and penicillin-resistant *Streptococcus pneumoniae*.⁴

Usage: Approved by the Food and Drug Administration (FDA) in October 2010 based on several multicenter randomized phase III trials, ceftaroline is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) including those caused by MRSA and community-acquired bacterial pneumonia (CABP).⁵⁻⁹ Additionally, there are case reports of it being used off-label for MRSA bacteremia, endocarditis, and osteomyelitis, but these indications have not been studied in well-designed trials at this time.^{10,11}

Mechanism of Action: Ceftaroline fosamil is a pro-drug that is converted to ceftaroline in the plasma and inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBP) 1-3.⁵ Ceftaroline has a strong affinity for PBP2a in MRSA, and PBP2x in *S. pneumoniae*, contributing to its activity against these bacteria. This mechanism differs from other cephalosporins in that ceftaroline induces a conformational change in PBP2a rendering the binding site susceptible to the activity of the beta-lactam ring.⁴

Dosing and Adverse Effects: The usual dose of ceftaroline for patients ≥ 18 years of age is 600 mg every 12 hours administered intravenously over 1 hour. It is not currently available as an oral formulation. Renal adjustment is required (See Table 1); in contrast to other beta-lactam antibiotics the dosing interval stays the same, but the dose is adjusted for the level of renal impairment.¹² More severe infections, however, may require shorter dosing intervals such as every 8 hours.^{10,11} Adverse effects of ceftaroline are

similar to other cephalosporins and include positive Coombs' test without hemolysis, rash, and nausea and vomiting.^{12,13}

Formulary Status and Cost: Ceftaroline is restricted to the Department of Infectious Diseases. In relative terms, it is more expensive than vancomycin but significantly less expensive than either daptomycin or linezolid.¹⁴ Drug level monitoring is not required with ceftaroline as it frequently is with vancomycin. This factor may make the cost comparison more favorable between these two agents.

Conclusion: Ceftaroline is a novel broad-spectrum cephalosporin that is FDA-approved for the treatment of CABP and ABSSSI including those infections caused by MRSA. It is adjusted for progressive renal dysfunction and is only available as an intravenous formulation. It has the advantage of not requiring drug level monitoring and is less expensive than either daptomycin or linezolid. It may represent a possible alternative agent for the treatment of infections such as bacteremia and endocarditis, but it is not approved for these indications. Further study is required before ceftaroline can be recommended as first-line therapy.

Table 1: Renal Dosage Adjustment¹²

Estimated CrCl* (mL/min)	Recommended Dosage Regimen for Ceftaroline†
> 50	No dosage adjustment
> 30 to ≤ 50	400 mg IV every 12 hours
≥ 15 to ≤ 30	300 mg IV every 12 hours
End-stage renal disease, including hemodialysis‡	200 mg IV every 12 hours

* Creatinine clearance (CrCl) estimated using the Cockcroft-Gault formula.

† All doses are administered over 1 hour.

‡ End-stage renal disease is defined as CrCl < 15mL/min.

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Fecal Microbiota Transplantation for *Clostridium difficile* Infections

By: Kelly Rudd, Pharm.D. Candidate

Introduction: *Clostridium difficile* infection (CDI) has become a significant economic burden to U.S. health care systems as the number of recurrent episodes continues to increase and the effectiveness of antibiotics continues to decrease.^{1,2} In 2008, acute care facilities may have experienced up to \$4.8 billion in excess healthcare costs, solely associated with CDI.¹ Treatment guidelines were released in 2010 (See Figure 1); however, these guidelines do not address fidaxomicin or fecal microbiota transplantation (FMT).³

Emergence of Fecal Microbiota Transplantation: Fecal microbiota transplantation is the transfer of stool from a healthy donor to an ill recipient.⁴ Transfaunation has been a common practice for centuries in veterinary medicine for equine diarrhea and ruminant gastrointestinal disorders.^{4,5} However, the first case reported to use FMT in humans was not done until 1958.^{2,5} It was not until 1983 that the first documented case of confirmed CDI treated with FMT occurred and remained successful at the 9 month follow-up. Administration of FMT has occurred several ways since its

inception: duodenal tube, rectal tube, colonoscopy, nasogastric (NG) tube, or enemas administered at home.⁵

The first randomized, controlled trial with FMT was published in January 2013, and the results demonstrated significantly higher success rates with FMT administered via nasoduodenal tube compared to vancomycin and vancomycin plus bowel lavage.⁶ Due to the relapse rates in the control groups, the trial was terminated after the efficacy interim analysis. Therefore, only 42 patients were analyzed. The FMT group (n=16) had a cure rate of 94% while each control arm, vancomycin monotherapy (n=13) and vancomycin plus bowel lavage (n=13), had rates of 31% and 23%, respectively (p<0.001). Thirty-five days after therapy initiation, 6% (n=1) of the FMT group, 62% (n=8) of the vancomycin group, and 54% (n=7) of the vancomycin plus bowel lavage group had CDI recurrence.

Donor Selection and Stool Preparation: While there has been no consensus on the optimal donor for FMT, arguments have been made for a spouse or significant

other, a household family member, or any healthy donor as the top three choices.^{5,7} The following donor exclusion criteria have been suggested:

- Risk of infectious agent
- Gastrointestinal comorbidities
- Various factors affecting intestinal microbiota
 - ◊ Previous antimicrobial use within 3 months
 - ◊ Immunosuppressive/antineoplastic agents
 - ◊ Recent ingestion of recipient allergen

Despite no established protocol, the instructions found in Table 1 regarding donor, recipient, and sample preparation have been compiled to serve as a guide for providers and institutions pursuing FMT treatment.^{5,7} Some of the instructions are dependent upon whether the FMT is administered via the upper-GI route (e.g., NG tube, nasoduodenal tube) or the lower-GI route (e.g., retention enema).

FDA’s Role Still Evolving: In late April 2013, the FDA announced that all FMT procedures and clinical trials would require an Investigational New Drug (IND) application approval to proceed since FMT is not approved for any therapeutic uses.^{8,9} The FDA states that fecal microbiota is within the definition of a biologic product and drug when it is used to “prevent, treat, or cure a disease or condition” or is “intended to affect

the structure or any function of the body of man.”

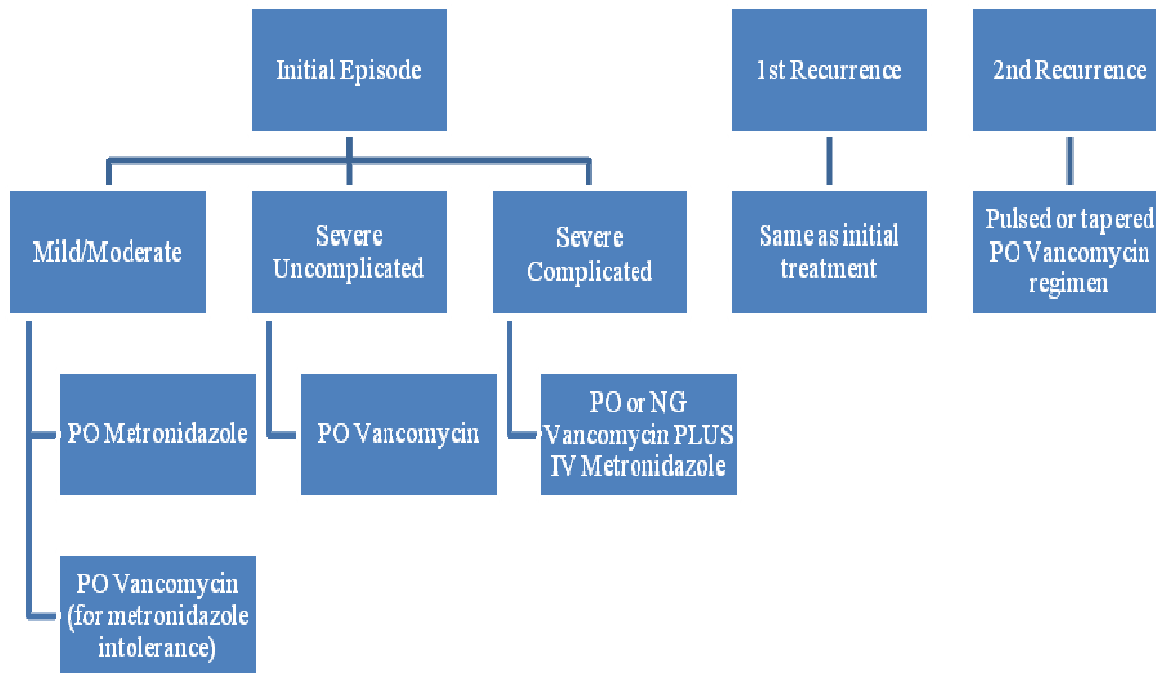
As of June 17, 2013, the FDA announced that after hosting the public workshop to further discuss FMT, it has decided to “exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies.”¹⁰ In other words, if the physician obtains appropriate informed consent from the patient or legal representative, an IND will not be required. The informed consent is expected to contain at a minimum:

- Declaration that the procedure is investigational
- Discussion of potential risks

This enforcement discretion is designed to be temporary while the FDA develops more appropriate policies concerning the study and use of FMT in clinical practice.⁹ However, the FDA still strongly encourages following the IND regulations.

Cleveland Clinic and FMT: Currently, a process for FMT has not been developed in the Cleveland Clinic Health System (CCHS) and has not yet been reviewed by the CCHS Medical Pharmacy and Therapeutics Committee.

Figure 1: Current Infectious Diseases Society of America Treatment Algorithm for CDI*³



*CDI=*Clostridium difficile* Infection

Table 1: Suggested Preparation of Donor, Recipient, and Stool^{5,7}

Donor	Recipient	Stool Preparation
<ul style="list-style-type: none"> • Avoid intake of substances that may cause allergies to recipient • Report any signs/symptoms of infection • Take osmotic laxative (milk of magnesia, lactulose) the night before transplant 	<ul style="list-style-type: none"> • Stop PO vancomycin and metronidazole 3 days before transplant • Bowel prep with polyethylene glycol the night before transplant • Take proton pump inhibitor the evening before and morning of transplant (if by upper-GI route) • Take loperamide on day of transplant (if by lower-GI route or colonoscopy) 	<ul style="list-style-type: none"> • Universal precautions/use a hood if possible to prepare stool • Collect fresh stool sample and use within 6 hours • Homogenize sample with normal saline or 4% milk in a blender • Filter with gauze pads, coffee filters, or urine stone strainers • Prepare 25 to 50 mL of stool suspension (upper-GI) or 250 to 500 mL (lower-GI)

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Formulary Update

Restriction Changes to Adult CCHS Formulary			
Drug	Pharmacologic Class	Formulary Use	Restriction/Comments
Anti-inhibitor coagulant complex (FEIBA®)	Antihemophilic Agent	Hemophilia management; Anticoagulant reversal	<p>Original restrictions: The Departments of Hematology/Oncology and Vascular Medicine for hemophilia management</p> <p>The Department of Hematology for anticoagulant reversal (protocol is contained within C-CAMP guidelines)</p> <p>Change in restriction: The restriction to Hematology for select anticoagulant reversal for initial dosing will be eliminated; however, C-CAMP guidelines must be followed for the initial dose and a Hematology consult is needed for repeat doses</p>
Inhaled epoprostenol (Flolan®)	Prostaglandin	Pulmonary Hypertension	<p>Original restriction: Restricted to the adult ICUs and must be ordered by an ICU physician</p> <p>Restriction expanded to include: Prescribing/ordering by CT Anesthesia Staff Physicians and Fellows at Main Campus in the J4 ORs according to a specific protocol</p> <p>Prescribing/ordering by Medical ICU Staff and Fellows according to the MICU protocol</p>
Levofloxacin (Levaquin®)	Fluoroquinolone Antibiotic	Pneumonia and other infections	<p>Original restriction: Treatment of CAP or early-onset ventilator associated pneumonia in patients with a beta-lactam allergy</p> <p>Restriction was eliminated</p>
Liposomal doxorubicin (Doxil®)	Antineoplastic Agent	Kaposi's sarcoma and other malignancies	<p>Original restriction: Treatment of Kaposi's sarcoma within specified protocols</p> <p>New restriction: Restricted to Hematology/Oncology for outpatient use only</p>

CAP=Community Acquired Pneumonia C-CAMP=Cleveland Clinic Anticoagulation Management Program CT=Cardiothoracic ICU=Intensive Care Unit MICU=Medical Intensive Care Unit ORs=Operating Rooms

Formulary Update

Additions to Adult CCHS Formulary			
Drug	Pharmacologic Class	Formulary Use	Restriction/Comments
Ceftaroline (Teflaro®)	Broad-spectrum cephalosporin	Treatment of gram-positive infections, especially MRSA in persons with vancomycin intolerance or failure	Restricted to the Department of Infectious Diseases
Gablofen® (branded-generic intrathecal baclofen)	Skeletal Muscle Relaxant	Spasticity Control	Gablofen® may be used for new patients; Lioresal® may be continued for current patients
Lactobacillus GG (Culturelle®)	Probiotic	Digestive Health	Should not be used to treat <i>Clostridium difficile</i> infections
Levonorgestrel IUS (Skyla®)	Contraceptive	Contraception	Restricted to outpatient use only
Omacetaxine mepesuccinate (Synribo®)	Antineoplastic Agent	Treatment of chronic or advanced phase CML with resistance and/or tolerance to two or more TKIs	Restricted to Hematology/Oncology for outpatient use only
Taliglucerase alfa (Elelyso®)	Enzyme	Treatment of Type I Gaucher disease	Restricted to Hematology/Oncology for outpatient use only

CML=Chronic Myeloid Leukemia MRSA=Methicillin Resistant *Staphylococcus Aureus* IUS=Intrauterine System
 TKIs=Tyrosine Kinase Inhibitors

Additions to Pediatric CCHS Formulary			
Drug	Pharmacologic Class	Formulary Use	Restriction/Comments
Bumetanide (Bumex®)	Loop Diuretic	Diuresis in patients refractory to other diuretic therapies	Restricted to Pediatric Intensive Care and Pediatric Cardiac Step-Down
Guanfacine extended-release tablets (Intuniv®)	CNS Agent	Attention Deficit Hyperactivity Disorder	Restricted to continuation of therapy Exception: Restricted to Pediatric and Psychiatry Service at Fairview Hospital for initiation and continuation of therapy
Lactobacillus GG (Culturelle®)	Probiotic	Digestive Health	Should not be used to treat <i>Clostridium difficile</i> infections
Restriction Change to Pediatric CCHS Formulary			
Intravenous Acetaminophen (Ofirmev™)	Analgesic	Pain Management	Restriction was expanded to include patients ≥ 2 years of age