Cleveland Clinic
Clinical Rx Forum
From the Department of Pharmacy

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From the Department of Pharmacy
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Comprehensive information about medications, biologics, nutrients, and drug therapy

Updates in Sickle Cell Disease Management

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Background: Sickle cell disease (SCD) is the most common genetic disease identified in the United States.[1] Between 80,000 – 100,000 people have SCD in North America.[2] Many of these patients are of African descent with some being of Mediterranean or Asian ancestry.[2,3] In SCD, a single base pair mutation in the hemoglobin causes red blood cells (RBCs) to become crescent or sickle shaped when deoxygenated.[1-3] The sickle-shaped RBCs cause complications, such as pain crisis, acute chest syndrome (ACS), and stroke.[4] Later in life SCD can cause organ damage through blockage of small blood vessels and tissue damage.[2,4] It may also lead to a poor functioning spleen or asplenia because of the high RBC turnover rate.[2,4]

Updates in Chronic Management: The goals of SCD management include decreasing the likelihood of complications.[2] With universal newborn screening of SCD, disease management can begin at birth.[3] Due to functional or anatomical asplenia, SCD patients are unable to protect themselves from encapsulated bacteria. For this reason it is important that these patients receive pneumococcal vaccination. Pneumococcal vaccination schedule recommendations for sickle cell patients are summarized in Table 1. Treatment options for long term management of SCD are limited to blood transfusions and hydroxyurea. Hydroxyurea is the only available disease-modifying drug for SCD.[5] Its full mechanism is unknown, but it has been shown to reduce sickling of RBCs by increasing the percentage of fetal hemoglobin.[2,5] Infants ≥9 months, no matter the severity of SCD, should be initiated on hydroxyurea therapy because it has demonstrated a decrease in acute and chronic complications.[3] In adults, hydroxyurea is recommended if the patient has ≥3 moderate to severe pain crises, pain interfering with daily activities, history of ACS, or severe symptomatic chronic anemia.

Emerging Therapy: Since approval by the Food and Drug Administration of hydroxyurea in 1998 for the treatment of SCD, there have been no new drugs developed to modify the course of this disease.[5] Recognizing the unmet need for a new agent to target the underlying cause of SCD, the National Institutes of Health collaborated with AesRx to develop Aes-103.[6] The active ingredient in Aes-103 is 5-hydroxymethyl-2-furfural (5-HMF).[7] Aes-103, which is administered as an oral liquid, demonstrated a unique mechanism to decrease sickling of RBCs by binding directly to hemoglobin and changing its structure. A Phase I/IIa study conducted in 2012 – 2013 showed promising results.[8] Eighteen adult subjects received Aes-103 as a single oral dose of 300-, 1000-, 2000-, or 4000-mg, or in a divided regimen of 1000 mg four times daily for one day. The investigators found that there was a greater reduction in pain in patients receiving Aes-103 compared to placebo. Aes-103 was also evaluated in a Phase II placebo-controlled, multicenter, double-blind, prospective clinical trial to determine appropriate dosing based on various safety and efficacy parameters.[9] During phase A of the study, subjects were ran-

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domized to receive 1000 mg of Aes-103 orally four times daily or placebo. In phase B, the dose of Aes-103 or placebo was adjusted based on tolerability and pharmacokinetic parameters and then given once daily or four times daily. Due to unknown factors, this study was terminated in August 2015.

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Table 1: Pneumococcal Vaccination Recommendations for Sickle Cell Patients[10]

Age	Previous Vaccination	Vaccine Formulation	Dose Regimen
6 – 18 years old	Up to date	PPSV23	One dose after 5 years of first PPSV23
19 – 64 years old	Pneumococcal vaccine-naïve	PCV13 & PPSV23	One dose PCV13 Two doses PPSV23 1st - ≥8 weeks after PCV13 2nd -5 years after 1st dose
	No PPSV23 (vaccinated with PCV13)	PPSV23	Two doses PPSV23 1st - ≥8 weeks after PCV13 2nd -5 years later
	One dose PPSV23 (vaccinated with PCV13)	PPSV23	2nd dose after 5 years from 1st PPSV23
	No PCV13 (vaccinated with one dose PPSV23)	PCV13 & PPSV23	One dose PCV13 ≥1 year after PPSV23 2nd PPSV23 ≥8 weeks after PCV13 AND ≥ 5 years from 1st PPSV23
	No PCV13 (vaccinated with two doses PPSV23)	PCV13	One dose PCV13 ≥1 year after last dose of PPSV23

PCV13=13-valent pneumococcal conjugate vaccine (Prevnar 13)
PPSV23=23-valent pneumococcal polysaccharide vaccine (Pneumovax 23)

Formulary Update

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Atazanavir/Cobicistat (Evotaz®)	Antiretroviral	Treatment of HIV	N/A
Ceftazidime/Avibactam (Avycaz®)	Antibiotic	Intra-abdominal infections and complicated urinary tract infections.	Restriction: Restricted to the Department of Infectious Diseases
Ceftolozane/Tazobactam (Zerbaxa®)	Antibiotic	Intra-abdominal infections and complicated urinary tract infections	Restriction: Restricted to the Department of Infectious Diseases
Darunavir/Cobicistat (Prezcobix®)	Antiretroviral	Treatment of HIV	N/A
Fluocinolone acetonide ophthalmic implant (Iluvien®)	Corticosteroid	Treatment of DME	Restriction: Restricted for the Department of Ophthalmology for third-line treatment of DME in the outpatient setting
Isavuconazonium (Cresemba®)	Azole Antifungal	Treatment of mucormycosis	Restriction: Restricted to the Department of Infectious Diseases for the treatment of mucormycosis
Lanreotide (Somatuline® Depot Injection)	Somatostatin Analogue	Treatment of NETS	Restriction: Restricted to the Department of Hematology and Medical Oncology in the outpatient setting
Subcutaneous immune globulin/human recombinant hyaluronidase (HyQvia®)	Immune Globulin	Treatment of primary immunodeficiency	Restriction: Restricted to the Department of Allergy and Immunology for the treatment of primary immunodeficiency in the outpatient setting

DME=Diabetic Macular Edema HIV=Human Immunodeficiency Virus N/A=Not applicable
NETS=Neuroendocrine tumors

Medications Removed from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Balsam of peru, trypsin, castor oil (Granulex® Spray)	Topical Skin Protectant	Wound Care	Granulex® is the same product as Vasolex® except in a spray formulation. Since Vasolex® was removed from the Formulary, Granulex® will also be removed. Alternative agents include petrolatum jelly and topical moisturizers
Vitamin K oral 5 mg tablets	Antidote	Treatment of hypoprothrombinemia	Due to the significant increase in cost of Vitamin K 5 mg tablets, as a cost saving initiative, inpatient pharmacies will be preparing a Vitamin K oral suspension (1 mg/mL) from injectable Vitamin K. The only areas that will stock Vitamin K 5 mg tablets are the free-standing emergency rooms, ambulatory pharmacies, and specialty pharmacy.

Therapeutic Interchange Change in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Mesalamine Oral Extended-Release	5-Aminosalicyclic Acid	Inflammatory Bowel Disease	The cost of Apriso® (the prior extended-release product of choice) has significantly increased. Therefore, all mesalamine extended-release orders will be converted to generic balsalazide. The interchange will be as follows: Balsalazide 2.25 grams TID will be automatically substituted for: Apriso® 1.5 grams once daily Asacol® HD 1.6 grams TID Lialda® 2.4 grams once daily Pentasa® 1 gram QID Delzicol® 800 mg TID

Formulary Update

Changes in Restrictions in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Ambrisentan (Letairis®)	Endothelin Receptor Antagonist	Treatment of Pulmonary Hypertension	Pharmacists are allowed to verify and dispense one dose ordered by a non-certified REMS prescriber for continuation of therapy during off-hours. The primary service will need to consult a REMS certified prescriber (e.g., Respiratory Institute) the next day for approval of continuation of therapy.
Bosentan (Tracleer®)	Endothelin Receptor Antagonist	Treatment of Pulmonary Hypertension	Pharmacists are allowed to verify and dispense one dose ordered by a non-certified REMS prescriber for continuation of therapy during off-hours. The primary service will need to consult a REMS certified prescriber (e.g., Respiratory Institute) the next day for approval of continuation of therapy.
Rocuronium (Zemuron®)	Neuromuscular Blocking Agent	Neuromusclar Blockade	Restriction Modification: Use of rocuronium is restricted to : 1) Anesthesia, Critical Care, and Emergency Medicine providers with training in airway management 2) For use in patients who are already intubated.
Tocilizumab (Actemra®)	Monoclonal Antibody	Severe CRS	Restriction Modification: Restricted to Department of Hematology and Medical Oncology for the management of CRS following CART or blinatumomab.

CART=chimeric antigen receptor-modified T-cell therapy CRS= cytokine-release syndrome
REMS=Risk Evaluation Mitigation Strategies

Formulary Update

Additions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Ceftazidime/Avibactam (Avycaz®)	Antibiotic	Intra-abdominal infections and complicated urinary tract infections.	Restriction: Restricted to the Department of Infectious Diseases
Ceftolozane/ Tazobactam (Zerbaxa®)	Antibiotic	Intra-abdominal infections and complicated urinary tract infections	Restriction: Restricted to the Department of Infectious Diseases
Fosaprepitant (Emend®)	Neurokinin 1 Receptor Antagonist	Prevention of CINV	Restriction: Restricted to the Department of Pediatric Hematology/Oncology for the prevention of CINV from highly– and moderately-emetogenic chemotherapy
Isavuconazonium (Cresemba®)	Azole Antifungal	Treatment of mucormycosis	Restriction: Restricted to the Department of Infectious Diseases for the treatment of mucormycosis
Phytonadione (Vitamin K) 1 mg/mL Extemporaneously Compounded Oral Suspension	Antidote	Treatment of hypoprothrombinemia	Due to the significant increase in cost of Vitamin K 5 mg tablets, as a cost saving initiative, inpatient pharmacies will be preparing a Vitamin K oral suspension (1 mg/mL) from injectable Vitamin K. The only areas that will stock Vitamin K 5 mg tablets are the free-standing emergency rooms, ambulatory pharmacies, and specialty pharmacy.
Plerixafor (Mobozil®)	Hematopoietic Agent	Peripheral Stem Cell Mobilization	Restriction: Restricted to Pediatric Bone Marrow Transplant
Poractant alfa (Curosurf®)	Surfactant	Neonatal Respiratory Distress Syndrome	N/A

CINV=Chemo-induced nausea and vomiting FDA=Food and Drug Administration N/A=Not applicable

Formulary Update

Medications Removed from the Pediatric CCHS Formulary and Therapeutic Conversion			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Calfactant (Infasurf®)	Surfactant	RDS	Poractant alfa (Curosurf®) will be the new surfactant on the CCHS Formulary for the treatment of RDS in premature infants.
Intranasal Corticosteroids (All)	Corticosteroid	Rhinitis	As a cost saving initiative, all intranasal steroids have been removed from the Pediatric CCHS Formulary. Patients are allowed to bring in their own intranasal steroid product from home.
Sotalol Oral Solution (Sotylize®)	Antiarrhythmic	Life-threatening VA	Sotylize 5 mg/mL oral solution was FDA-approved in October 2014. It will replace the extemporaneously compounded sotalol oral suspension for pediatric patients. It is grape flavored and sugar-free.
Trypsin/balsam peru/castor oil (Granulex®)	Topical Protectant	Mucocutaneous infections	Granulex® is the same product as Vasolex® except in a spray formulation. Since Vasolex® was removed from the Formulary, Granulex® will also be removed. Alternative agents include petrolatum jelly and topical moisturizers.

FDA=Food and Drug Administration RDS=Respiratory Distress Syndrome VA=Ventricular Arrhythmia