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From the Department of Pharmacy

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Influenza Vaccine Update 2016-2017

By: Ashley Kasper, Pharm.D.

Background: Flu season occurs annually in the United States, with illness peaking between December and February but may arise sometime between October and May.[1] The influenza virus may cause infection without complications in healthy individuals, though other patient populations such as the elderly, very young, pregnant, or immunocompromised are at risk for serious illness or death. Patients should receive an influenza vaccination by October in order to provide adequate immunity during influenza season. In August 2016, new recommendations for the 2016-2017 influenza vaccine were released by the Advisory Committee on Immunization Practices (ACIP) to help guide the use of the various influenza vaccines.

Live-Attenuated Influenza Vaccine: Live-attenuated influenza vaccine (LAIV) (FluMist®) has previously been shown to have similar efficacy as compared to inactivated influenza vaccine (IIV).[2] In 2014, the ACIP recommended that LAIV be administered to children ages 2 to 8 years based on data showing improved immune response in this population.[2,3] However, more recent data suggest that LAIV provides lower immune protection.[4] Therefore, the ACIP recommends against the use of LAIV during the 2016-2017 influenza season due to decreased effectiveness in previous seasons.[1]

Egg Allergy: All of the influenza vaccine formulations are prepared by viral replication in an egg medium except for Flucelvax® and Flublok®.[1,5,6] Flublok® is considered egg-free.[1,5] However Flucelvax®, a cell culture-based vaccine, cannot claim to be egg-free because the manufacturer does not directly measure ovalbumin content. Despite this issue, Flucelvax® can be considered to contain minimal egg content.

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Treatment Update for Stevens-Johnson and TEN Syndromes

By: Kelly Gaffney, Pharm.D.

Background: Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe skin reactions characterized by global mucositis and epidermal loss.[1] Both manifestations are of the same disease state, differing by phenotype within a severity spectrum. Stevens-Johnson syndrome is less severe and affects <10% of the body surface, while TEN affects >30%. This disease state occurs in one to two cases per one million annually and, although rare, has high mortality rates (SJS~1-10%; TEN~30%) and limited treatment options.[1-3] Initially, patients often experience nonspecific prodromal symptoms such as fever, malaise, and cutaneous pain, which later develop into painful lesions that may slough or blister. In severe cases of SJS/TEN, symptoms may spread into oral, ocular, or genital areas and result in multiorgan failure due to necrolysis and hypoperfusion. The most common cause of these mucocutaneous rashes is activated drug-induced cytotoxic T lymphocytes, which release cytolytic proteins

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The ACIP provides the following guidance regarding the influenza vaccine in patients with an egg allergy:

- Patients with an egg allergy only experiencing hives after exposure are recommended to receive an influenza vaccine that is indicated based on age and other health conditions.
- Patients with an egg allergy who experienced angioedema, respiratory distress, lightheadedness, or refractory emesis are recommended to receive an influenza vaccine that is indicated based on age and other health conditions. The vaccine should be administered under the supervision of a healthcare provider who is able to identify and treat severe allergic reactions.
- The influenza vaccine is contraindicated in patients with a history of severe allergic reaction to a previous influenza vaccine.[1]

Trivalent versus Quadrivalent: Influenza vaccines will be available in either the trivalent or quadrivalent formulation during the 2016-2017 season.[1] Human influenza A and B viruses are responsible for causing annual influenza outbreaks. The trivalent vaccine will incorporate hemagglutinin strains from two A-type viruses, A/California/7/2009 (H1N1)-like virus and A/Hong Kong/4801/2014 (H3N2)-like virus, and one B-type virus, B/Brisbane/60/2008-like virus. The quadrivalent vaccine will include the strains in the trivalent formulation in addition to a second B-type virus, B/Phuket/3073/2013-like virus. Data from 2012-2013 indicate that there is no benefit to receiving a quadrivalent vaccine as compared to a trivalent vaccine. According to the ACIP, there are no data to support use of one vaccine formulation over the other.[7]

Standard-dose versus High-dose: All influenza vaccines are standard-dose with one exception, Fluzone® High-Dose.[8] Fluzone® High-Dose is a trivalent influenza vaccine approved in 2009 for use in adults 65 years and older. The high-dose vaccine was designed to contain four times the amount of antigen in order to elicit an adequate immune response.[1] Its efficacy was compared to the standard dose vaccine in adults 65 years and older. The results of an immunogenicity study by Falsey and colleagues showed an increase in immune response in patients who received the high-dose vaccine.[9] It is important to note that patients receiving the high-dose vaccine reported higher rates of injection-site reactions.

New Products: For the 2016-2017 influenza season, there are two new influenza vaccines that will be available, Fluad® and Flucelvax® Quadrivalent.[5,10] In November 2015, Fluad® was FDA-approved for the prevention of influenza in patients 65 years and older. Fluad® is a trivalent vaccine and is the only adjuvanted influenza vaccine available in the United States. Similar to the Fluzone® High-Dose vaccine, Fluad® is used to improve the immune response in the elderly population; however, Fluad® is a standard dose vaccine which contains the MG59-adjuvant. The second new vaccine is Flucelvax® Quadrivalent, which was FDA-approved in May 2016. Similar to the trivalent Flucelvax®, this is a cell-culture based vaccine.[5] Flucelvax® Quadrivalent is indicated for prevention of influenza in patients 4 years and older.

CCHS Influenza Vaccine Availability: Cleveland Clinic Health-System Pharmacies carry various Fluzone® products including Fluzone® Quadrivalent available as a 10 mL multi-dose vial with preservative as well as a single-dose 0.5 mL preservative-free prefilled syringe and a 0.25 mL preservative-free prefilled syringe (to be used primarily for pediatric patients). Fluzone® High-Dose, a trivalent formulation, is also available as a preservative-free 0.5 mL prefilled syringe. It is important to note that the plunger rods for the prefilled syringes of Fluzone® Quadrivalent 0.5 mL and 0.25 mL are clear and pink, respectively, while the plunger rod of the prefilled Fluzone® High-Dose formulation is grey. Because there are multiple Fluzone® formulations, careful selection and verification of these products is recommended.

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such as granulysin.[4] Some medications associated with inducing SJS/TEN include allopurinol, carbamazepine, lamotrigine, nevirapine, oxicam non-steroidal anti-inflammatory drugs (NSAIDs), phenobarbital, phenytoin, sulfa antibiotics, and sulfasalazine.[1]

New Guidelines: Recently, the 2016 United Kingdom guidelines reviewed the treatment of SJS and TEN.[1] The standard of care remains primarily supportive and includes discontinuation of any possible offending agents, fluids and nutrition, wound care, gastric protection, prophylactic anticoagulation, and analgesia.[1] Antimicrobials may be administered if there are signs of infection and topical emollients applied for hydration and re-epithelialization. To date, the only randomized clinical trial involving treatment of SJS/TEN utilized thalidomide, which was associated with an increase in mortality.[5] Other immunomodulating agents such as cyclosporine, systemic corticosteroids, and intravenous immune globulin (IVIG) have also been studied to determine their mortality benefit in SJS/TEN patients.

Cyclosporine: An open pilot study compared 1 month mortality to predicted mortality in 29 SJS/TEN patients.[6] These patients received oral cyclosporine 3 mg/kg daily for 10 days, followed by a taper of 2 mg/kg for 10 days and 1 mg/kg for a final 10 days. Cyclosporine displayed a possible mortality benefit; none of the patients died (2.75 deaths were predicted), but this finding was not statistically significant. Three patients had to discontinue treatment due to the following: severe, acute hallucinations, leukoencephalopathy, or neutropenia attributed to cyclosporine. Other adverse effects included neuropathy, a moderate increase in blood pressure, and a slight decline in renal function. The authors concluded that cyclosporine could possibly increase survival.

Corticosteroids: The use of systemic corticosteroids is controversial since these agents may increase the risk for infection/sepsis and suppress epithelial healing.[1,7] A retrospective case series found a trend towards decreased mortality when patients received a cumulative dose of prednisolone 10-25 mg/kg daily for 7-14 days.[7] Another retrospective case series found patients who received methylprednisolone 1-1.5 mg/kg/day followed by a discontinuation taper at the start of re-epithelialization were 16% more likely to die than those who received supportive care alone; however this result was not statistically significant.[8] Another study found only mild adverse effects were due to corticosteroid use such as hyperglycemia.[9] It is unknown if use of these agents leads to a rise or decline in overall mortality.

IVIG: Some case reports have demonstrated efficacy of IVIG for SJS/TEN, but a meta-analysis of 17 studies found no additional mortality benefit.[10] However, higher doses (≥ 2 g/kg) have exhibited a trend towards reduced mortality. Additional studies have not proven a consistent mortality benefit with dosing regimens ranging from 0.7-4 g/kg over a time period of 2 to 7 days.[11-12] There are some data suggesting a trend in decreased mortality with the combination of IVIG and systemic corticosteroids; however, these findings were not statistically significant.[7,13]

Conclusion: Despite the new 2016 guidelines, the available data do not demonstrate any existing systemic treatment option that offers an unequivocal survival benefit. Providers should continue to evaluate patients on a case-by-case basis and decide if additional therapy is needed to supplement standard supportive care.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions**
Antihemophilic Factor (Recombinant), Porcine Sequence (Obizur®)	Blood Factor	Treatment of bleeding episodes in adults with acquired hemophilia A	Restricted to the Department of Hematology and Medical Oncology
Diatrizoate Meglumine and Diatrizoate Sodium (Gastrografin®)	Iodinated Contrast Media	Distal Intestinal Obstructive Syndrome in cystic fibrosis patients	Restricted to Pulmonary and Critical Care Medicine
Hydromorphone Extended-Release Tablets (Exalgo®)	Opioid Analgesic	Management of moderate-to-severe chronic pain in opioid tolerant patients	Restricted to Palliative Medicine and the Department of Hematology and Medical Oncology
Hydroxyprogesterone caproate (Makena®)	Progestin	Reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth	Restricted to continuation of therapy for inpatient use No restrictions for outpatient use
Olaratumab (Lartruvo®)	Antineoplastic Agent	Treatment of soft tissue sarcoma in combination with doxorubicin	Restricted to the Department of Hematology and Medical Oncology for outpatient use only

Changes to Restrictions in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction**
Inhaled epoprostenol (Veletri®)	Prostaglandin	Pulmonary Hypertension	Modify restrictions to allow prescribing by: 1) CT Surgery Fellows to continue inhaled epoprostenol when originally ordered by Anesthesia in the OR upon transfer from OR to ICU 2) Critical Care Transport Nurse Practitioners or Physician Assistants for the following: a) To initiate inhaled epoprostenol in consultation with the prescriber during transport b) To continue and titrate inhaled epoprostenol per protocol during transport

CT=Cardiothoracic ICU=Intensive Care Unit OR=Operating Room

Formulary Denial for the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Denial/Comments**
Patiromer (Veltassa®)	Antidote	Treatment of Hyperkalemia	Patiromer was not added to Formulary because other medications cannot be administered within a 12-hour window. Also, there are more cost-effective therapies on Formulary. Patiromer binds to many orally administered medications, decreasing absorption and reducing efficacy. Oral medications need to be administered at least 6 hours before or 6 hours after patiromer. It cannot be taken concomitantly with continuous-release medications.

Change of Formulary Products on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Product/ Comments**
Calcium Acetate Tablets (Calphron®)	Phosphate Binder	Reduction of hyperphosphatemia in end-stage renal disease	As a cost-savings initiative, calcium acetate tablets (Calphron®) will replace calcium acetate capsules (Phoslo®). The calcium acetate tablets contain the same amount of active ingredient (667 mg) as the capsules, and contain approximately 169 mg of elemental calcium. The tablets are not film-coated and dissolve readily in water for enteral tube feed administration.
Lidocaine HCl Jelly 2% (Glydo®)	Mucosal Anesthetic Lubricant	Reduce pain in urological procedures	As a cost savings initiative, Glydo® will replace Urojet® on the Formulary as a mucosal anesthetic lubricant for painful urological procedures. Glydo® is available as 6 mL and 11 mL single-use pre-filled syringes, compared to Urojet® which is available as 5 mL and 10 mL single-use vials packaged with injectors.

Therapeutic Interchange in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange/ Comments**
Sumatripan (Imitrex®)	Antimigraine Agent	Treatment of Migraine Headache	Pharmacists will be able to switch any home triptan to sumatriptan. The recommended conversion from any dose of another triptan is sumatriptan 100 mg orally. However, the drug file will allow physicians to select a lower dose if preferred. Patients with chronic migraines who prefer their home therapy will be able to use their home medication per the home medication policy. If a patient fails two doses of sumatriptan, rizatriptan 10 mg will be available as a second-line therapy. Patients on concomitant propranolol should use rizatriptan 5 mg.

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions**
Diatrizoate Meglumine and Diatrizoate Sodium (Gastrografin®)	Iodinated Contrast Media	Distal Intestinal Obstructive Syndrome in cystic fibrosis patients	Restricted to Pediatric Pulmonary Medicine and Pediatric Critical Care Medicine
Lipid Injectable Emulsion 20% (Smoflipid®)	Caloric Agent	Limited to patients with short bowel syndrome and/or TPN cholestasis	Restricted to Pediatric Gastroenterology

TPN= Total Parenteral Nutrition

Denial to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Rationale**
Melphalan (Evomela®)	Antineoplastic Agent	High-dose conditioning treatment prior to hematopoietic stem cell transplantation for patients with multiple myeloma or palliative treatment of patient with multiple myeloma	Pediatric patients were not included in the Evomela® clinical trials. Evomela® has not been studied for intraocular use and because of differences in preservatives and vehicles, intraocular Evomela® is not recommended at this time.