D&T Decisions

… from the Drugs and Therapeutics Committee

Issue #77: April 12, 2024

The information in this newsletter may also be accessed online.
To request a change to the NS Health Hospital Formulary, select & complete the online "Formulary Request Form":
NSH Pharmacy Formulary (nshealth.ca)

Inside this Issue…

The following policies were approved by the Medical Advisory Committee (Dec 23, Feb 24) on the recommendation of the Drugs and Therapeutics Committee (Nov 23, Dec 23, Feb 24).

I. Additions to Hospital Formulary

Posaconazole injection/ *Posanol*®

Oral posaconazole was added to the NS Health Hospital Formulary in 2021 (D&T Decisions #70: Feb. 2, 2021) as a red category systemic antimicrobial formulary agent (i.e., requiring Antimicrobial Stewardship review within 72 hours). Patients with an approved indication to receive oral posaconazole may require an alternative route of administration; therefore, there was a Formulary request to include the injectable formulation.

Posaconazole is a second-generation triazole antifungal indicated for the treatment and prophylaxis of invasive fungal infections (particularly *Aspergillus* sp) in high-risk patients. Posaconazole inhibits the fungal enzyme lanosterol 14-alpha-demethylase preventing the synthesis of ergosterol which in turn disrupts fungal cellular membrane formation and results in growth inhibition or fungal cellular death. Posaconazole has broad antifungal activity against *Candida* spp., *Cryptococcus neoformans, Aspergillus* spp., *Scedosporium apiospermum,* Mucorales, and species of dematiaceous molds.

Options to treat and prevent fungal infections vary depending on patient factors and the cultured species. Posaconazole has the potential for significant drug interactions (e.g., cyclosporine, tacrolimus, sirolimus and other CYP3A4 substrates) and is more expensive than some alternatives. At NS Health, posaconazole is indicated for treatment or prophylaxis of invasive fungal infection in patients with contraindications or intolerance to voriconazole who are at high-risk of infection including allogeneic stem cell transplant recipients, patients with hematological malignancies undergoing chemotherapy, or patients with graft-vs-host disease receiving prednisone. Posaconazole is also a treatment option for invasive fungal infections such as mucormycosis where alternatives are ineffective or not tolerated.

Posaconazole injection has been added to the NS Health Formulary for patients who have an approved indication for posaconazole (as per the defined antimicrobial stewardship red stop light criteria) but are unable to receive it by the oral route. Scenarios when patients may require posaconazole by the IV route include: patients who cannot swallow oral pills due to mucositis; patients who have an altered level of consciousness; patients who have had recent seizures; intubated patients.

Approved Restriction:
Addition to the systemic antimicrobial formulary as a red category agent (i.e., requiring Antimicrobial Stewardship review within 72 hours). Guidelines for use are available on the NS Health Antimicrobial Stewardship website and app.

Ceftobiprole/ *Zevtera*®

Methicillin-resistant *Staphylococcus aureus* (MRSA) has increased in incidence and mortality in the past decade. Ceftobiprole is a fifth-generation cephalosporin that has been studied for over a decade and used to treat several infections caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA.

MRSA infection is associated with significant economic costs to the health care system including increased surveillance, costly MRSA specific therapies, increased hospital stays and the need for patient isolation. Appropriate treatment of MRSA infection has the potential to decrease hospital stay, treatment costs and antimicrobial resistance. Even with the current armamentarium of anti-MRSA antibiotics (e.g., vancomycin, linezolid, daptomycin, tigecycline, dalbavancin), clinicians encounter patients who are not able to be treated with standard therapies due to drug specific limitations or patient specific factors. Ceftobiprole has few drug interactions and is tolerated similarly to 3rd generation cephalosporins with primarily gastrointestinal adverse effects; therefore, it may be an option for patients infected with MRSA who have allergies, intolerances, or contraindications (including drug interactions) to therapy with vancomycin, daptomycin or linezolid.

Despite its broad spectrum and early in vitro data suggesting that ceftobiprole could have a role in treating resistant gram-negative organisms, data to support this has not materialized; therefore, ceftobiprole is not recommended for empiric or directed therapy for extended-spectrum beta-lactamases (ESBL) producing organisms.

Approved Restriction:
Addition to the systemic antimicrobial formulary as a red category agent (i.e., requiring Antimicrobial Stewardship review within 72 hours). Guidelines for use are available on the NS Health Antimicrobial Stewardship website and app.

Norfloxacin

Norfloxacin is a fluoroquinolone antibacterial agent that is Health Canada approved for the treatment of urinary tract infections (uncomplicated and complicated) and gonorrhea. According to the European Association for the Study of the Liver (EASL) Guidelines, norfloxacin is the drug of choice for the prophylaxis of spontaneous bacterial peritonitis (SBP).

SBP is an acute asymptomatic infection of the ascitic fluid in patients with ascites and liver disease that is associated with mortality rates as high as 20% in hospitalized patients. Secondary antimicrobial prophylaxis with norfloxacin is recommended for patients with a history of previous SBP as recurrence rates are estimated to be as high as 68% at one year without prophylaxis. Since norfloxacin has been considered non-formulary (e.g., removed from the QEII Hospital Formulary in 1997), patients admitted on established outpatient norfloxacin SBP prophylaxis are often switched to the Formulary fluoroquinolone ciprofloxacin. Although the current guidelines suggest ciprofloxacin is an acceptable alternative for SBP prophylaxis when norfloxacin is unavailable, adding norfloxacin to the Hospital Formulary will reduce unnecessary use of ciprofloxacin for SBP prophylaxis.

Approved Restriction:
Addition to the systemic antimicrobial formulary as a yellow category agent (i.e., defined criteria for use and/ or important safety considerations). Guidelines for use are available on the NS Health Antimicrobial Stewardship website and app.

Glucagon nasal/ *Baqsimi*®

Baqsimi® is a single use glucagon 3 mg nasal dosing device approved by Health Canada in 2019 for the treatment of severe hypoglycemic reactions that may occur in the management of insulin treated patients with diabetes mellitus, when impaired consciousness precludes oral carbohydrates. Although glucagon is considered a Formulary medication, the nasal formulation has not been listed in the NS Health Hospital Formulary.

Glucagon is a peptide hormone that increases blood glucose by activation of hepatic glucagon receptors resulting in stimulation of glycogen breakdown and release of glucose from the liver. Glucagon also has extrahepatic effects including relaxation of the smooth muscle of the stomach, duodenum, small bowel and colon. Injectable glucagon has been routinely stocked on hospital nursing units to treat patients with hypoglycemia. Injectable glucagon has other indications within the hospital setting including use as an antidote (e.g., second line therapy for beta-adrenergic blocking drug overdose) and as a diagnostic agent (e.g., endocrinology and endoscopy).

The CADTH Canadian Drug Expert Committee (CDEC) recommended that Baqsimi® glucagon nasal powder should be reimbursed for the treatment of severe hypoglycemia reactions and Baqsimi® is listed as a benefit on the NS Provincial Drug Plan Formulary with exception criteria. The CADTH CDEC recommendation was based on a systematic review of four open-label, RCTs of patients with diabetes. Hypoglycemia was induced as part of the RCT study procedures and patients received a single 3 mg intranasal glucagon dose compared to a single 1 mg IM glucagon dose in crossover fashion. The primary outcome of the three adult trials was resolution of low glucose within 30 minutes. Intranasal glucagon demonstrated non-inferiority to IM glucagon based on serum glucose response at 30 minutes.

Since the Canadian market supply of injectable glucagon is uncertain, Baqsimi® glucagon nasal powder has been approved for Formulary inclusion to be stocked on nursing units for the emergency treatment of hypoglycemia. This would reserve the injectable glucagon supply for antidote kits, endoscopy, emergency departments, critical care and other appropriate hospital settings.

II. Non-Formulary

Acetylcysteine oral

Acetylcysteine, a mucolytic and antidote for acetaminophen poisoning, is listed on the NS Health Hospital Formulary as a parenteral formulation that is Health Canada approved as a solution for injection, inhalation or oral administration for various indications including adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in chronic and acute bronchopulmonary diseases; pulmonary complications of cystic fibrosis; post tracheostomy care; pulmonary complications associated with surgery; use during anesthesia; post-traumatic chest conditions; atelectasis due to mucous obstruction; diagnostic bronchial studies. Acetylcysteine solution is also administered orally or intravenously indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.

Guidelines for chronic obstructive pulmonary disease (COPD) highlight that oral acetylcysteine (also referred to as n-acetylcysteine, NAC) should be added to therapy to prevent exacerbations for patients not stabilized while on triple inhaler therapy (e.g., 2023 Canadian Thoracic Society Guideline). The mechanism of action for which oral acetylcysteine prevents COPD exacerbations is not well known, but a few mechanisms have been proposed including that acetylcysteine acts as a mucolytic in the respiratory tract to reduce the viscosity of secretions which promotes secretion elimination. It is also suggested that acetylcysteine has antioxidant and anti-inflammatory effects.

In Canada, oral acetylcysteine formulations are available as natural health products [i.e., licensed with a natural product number (NPN) rather than a drug identification number (DIN)]; therefore, oral acetylcysteine is not available through routine hospital pharmacy procurement strategies. The Formulary parenteral acetylcysteine solution may be administered orally to hospitalized patients; however, the taste is reported as less than desirable and administration with fluids may improve palatability.

There is variability in the available oral acetylcysteine natural health product formulations, strengths and costs. A NS Health Natural Health Products Policy and Procedure provides guidelines to support patients who wish to continue their own supply. Therefore, oral formulations of acetylcysteine were not added to the NS Health Hospital Formulary.

III. Expanded Restrictions

Aprepitant/ *Emend*® - Anesthesia (Post-operative Nausea and Vomiting Prevention)

Aprepitant is a neurokinase-1 (NK1) receptor antagonist that is an established part of combination therapy for the prevention of chemotherapy induced nausea and vomiting for high-risk patients; therefore, aprepitant is included in the NS Health Hospital Formulary with restrictions for this indication. The original request to expand the aprepitant Hospital Formulary restrictions to include the prevention of post-operative nausea and vomiting (PONV) was reviewed in 2021 but not approved (D&T Decisions #70: Feb. 2, 2021); therefore, an appeal was received from the Dept. of Anesthesia, Pain Management and Perioperative Medicine for reconsideration.

PONV is a common patient complaint that is generally defined as nausea and/ or vomiting either in the post-anesthesia care unit (PACU) or within 24 hours post-operation. PONV may result in patient complications including reopening of surgical incisions, esophageal rupture, aspiration, dehydration, electrolyte abnormalities, pneumothorax, increased intracranial pressure, longer length of hospital stay and overall increased health care costs. Despite significant efforts in preventing this outcome, PONV continues to be extremely prevalent. Thirty percent of patients will experience PONV, and this number is as high as 80% in patients deemed to be high-risk.

The mechanism of aprepitant is unique among antiemetic medications used for PONV (e.g., antihistamines, steroids, serotonin receptor antagonists). Patients at moderate to high-risk are typically provided with a multi-modal approach to PONV prevention and there is evidence as well as guideline support for the use of aprepitant. Advantages of aprepitant include oral administration, a low incidence of adverse effects and a half-life (i.e., 9-13 hours) that results in a long duration of action (up to 72 hours or more). However, aprepitant is relatively more expensive than other antiemetic medications and is not Health Canada approved for the prevention of PONV. The Hospital Formulary restrictions for aprepitant have been expanded to include criteria for the prevention of PONV in high-risk patients.

Approved Restriction:
For the prevention of postoperative nausea and vomiting (PONV) for patients who meet one of the following criteria:

- history of being refractory to antiemetic therapy **AND** at high-risk for PONV (i.e., presence of at least 3 of the following: female gender, history of PONV, non-smoker, postoperative use of opioids)

  OR
- cases where PONV would have significant impact on patient recovery (e.g., gastric surgery, neurosurgery, surgery that requires jaw wiring).

Tocilizumab/ *Actemra*®

Tocilizumab was added to the NS Health Hospital Formulary in 2022 with restrictions for the management of severe or life-threatening chimeric antigen receptor (CAR) T-cell related toxicities of cytokine release syndrome (CRS) +/- concurrent neurotoxicity.

Since Hospital Formulary approval, several other immune effector cell therapies, including bi-specific T-cell engagers (BiTEs), have come onto the Canadian market, carrying a similar significant CRS risk. The protocols of the pivotal trials for these agents included tocilizumab for managing CRS, and the product monographs emphasize the importance of having tocilizumab available if sites are administering these therapies. An additional need has also been identified for patients receiving haploidentical hematopoietic cell transplantation (haploHCT) induced CRS. Although uncommon, prompt treatment of CRS in these patients may reduce the risk of non-relapse mortality and improve overall survival.

CRS is an acute systemic inflammatory syndrome associated with significant toxicities; therefore, patients receiving potential CRS inducing therapies must be closely monitored for early signs and symptoms indicative of CRS. Access to treatments (including tocilizumab) for CRS is crucial, as CRS can progress to severe life-threatening complications such as hypoxia and hypotension requiring pressor or ventilatory support, multi-organ failure, or death.

Tocilizumab is a humanized anti-human IL-6 antibody immunosuppressant that binds specifically to both soluble and membrane-bound IL-6 receptors and inhibits IL-6 mediated signaling through these receptors. IL-6 is believed to be the principal mediator of toxicity in CRS, making tocilizumab a highly effective first-line treatment option for patients with high-grade CRS.

Approved Restriction:
Management of patients with cytokine release syndrome (CRS) related to systemic therapy for cancer.

IV. Therapeutic Interchange Revision

Fenofibrate

There are four formulations of fenofibrate available on the market: regular, micronized, microcoated and nanocrystals. The approved NS Health therapeutic interchange to dispense the micronized fenofibrate formulation has been revised to provide guidance for correct renal dosage adjustment.

Preparation:	Dispensed as:
Fenofibrate 100mg (standard, non-micronized)	Fenofibrate micronized 67 mg
Fenofibrate microcoated 100 mg	
Fenofibrate nanocrystals 48 mg	
Fenofibrate microcoated 160 mg	Fenofibrate micronized 200 mg
Fenofibrate nanocrystals 145 mg	

Trastuzumab deruxtecan/ *Enhertu™*

A new guideline has been approved for the role of trastuzumab deruxtecan for the treatment of unresectable or metastatic HER2-positive breast cancer.

Approved Restriction:

For the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant/adjuvant setting. If prior anti-HER2 treatment was given in the early-stage setting, patients must have experienced disease progression within six months of completing neoadjuvant/adjuvant treatment.

Treatment should continue until disease progression or unacceptable toxicity.

Crisantaspase recombinant/ *Rylaze™*

A new guideline has been approved for the role of crisantaspase recombinant in the treatment of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL).

Approved Restriction:

For the treatment of pediatric and adult patients who have acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) with documented hypersensitivity to or silent inactivation of an E. coli-derived asparaginase as part of a multi-agent chemotherapeutic regimen.

V. New Guidelines

Enfortumab vedotin/ *Padcev®*

A new guideline has been approved for the role of enfortumab vedotin for the treatment of unresectable, locally advanced, or metastatic urothelial carcinoma.

Approved Restriction:

As monotherapy for the treatment of adult patients with unresectable, locally advanced, or metastatic urothelial carcinoma who have previously received platinum-based chemotherapy (in any setting), and a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting.

Patients should have a good performance status and may continue to receive enfortumab vedotin until confirmed disease progression or unacceptable toxicity, whichever occurs first.

Isatuximab/ *Sarclisa®*

New guidelines have been approved for the role of isatuximab for the treatment of relapsed or refractory multiple myeloma.

Approved Restriction:

1. Relapsed or Refractory Multiple Myeloma

For the treatment of adult patients with relapsed or refractory multiple myeloma, in combination with carfilzomib and dexamethasone (IsaKd), who have received at least one prior line of therapy.

2. Relapsed or Refractory Multiple Myeloma

For the treatment of adult patients with relapsed or refractory multiple myeloma, in combination with pomalidomide and dexamethasone (IsaPd), who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

VI. Expanded Guidelines

Pembrolizumab/ *Keytruda®*

Five new guidelines have been approved for pembrolizumab.

A new guideline has been approved for the role of pembrolizumab for the treatment of advanced and metastatic cervical cancer.

Approved Restriction:

For the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer that express PD-L1 (combined positive score [CPS] ≥1 as determined by a validated test) in combination with platinum-based chemotherapy, with or without the addition of bevacizumab.

Treatment should continue until disease progression, unacceptable toxicity, or a maximum of 24 months of therapy, whichever occurs first.

A new guideline has been approved for the role of pembrolizumab for adjuvant treatment of melanoma.

Approved Restriction:

For the adjuvant treatment of patients with cutaneous melanoma with completely resected Stage IIB, IIC, and IIIA (limited to lymph node metastases of ≥ 1 mm) to Stage IV (8th edition of the American Joint Committee on Cancer [AJCC] melanoma staging system), regardless of BRAF status. Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients should have a good performance status and brain metastases, if present, must be completely resected (or definitively treated with stereotactic radiation). Eligible patients should continue treatment until disease progression or a maximum of 1 year, whichever comes first.

A new guideline has been approved for the role of pembrolizumab for the treatment of advanced and metastatic endometrial cancer.

Approved Restriction:

As monotherapy for the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial carcinoma whose tumors have progressed on prior therapy.

Treatment should continue until disease progression, unacceptable toxicity, or a maximum of 24 months of therapy, whichever occurs first.

A new guideline has been approved for the role of pembrolizumab in combination with lenvatinib for the treatment of advanced or metastatic renal cell carcinoma.

Approved Restriction:

In combination with lenvatinib for the treatment of adult patients with advanced or metastatic RCC who have not had prior systemic therapy for metastatic disease.

Treatment with pembrolizumab should continue until disease progression, unacceptable toxicity, or to a maximum of 24 months of therapy, whichever occurs first.

A new guideline has been approved for the role of pembrolizumab in combination with lenvatinib for the treatment of advanced endometrial cancer.

Approved Restriction:

In combination with lenvatinib for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression following prior platinum-based systemic therapy and are not candidates for curative surgery or radiation.

Treatment should continue until disease progression, unacceptable toxicity, or to a maximum of 2 years of therapy, whichever occurs first.

Nivolumab/ *Opdivo*®

Two new guidelines have been approved for nivolumab.

A new guideline has been approved for the role of nivolumab for the adjuvant treatment of urothelial carcinoma.

Approved Restriction:

As monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at a high risk of recurrence following radical resection of muscle invasive UC.

Treatment with nivolumab should be initiated within 120 days after completion of local therapy and continued for a maximum treatment duration of 1 year, or until confirmed disease progression or unacceptable toxicity whichever occurs first.

A new guideline has been approved for the role of nivolumab for the treatment of neoadjuvant non-small cell lung cancer. (NSCLC).

Approved Restriction:

In combination with platinum-doublet chemotherapy for the neoadjuvant treatment of adult patients with resectable NSCLC for tumors that are ≥ 4cm or node positive.

Treatment should continue until disease progression, unacceptable toxicity, or completion of 3 cycles of neoadjuvant therapy.

Atezolizumab/ *Tecentriq*®

Two new guidelines have been approved for atezolizumab.

A new guideline has been approved for the role of atezolizumab for the treatment of extensive stage small cell lung cancer .

Approved Restriction:

For the first line treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) in combination with etoposide and platinum chemotherapy. Treatment should continue until disease progression or unacceptable toxicity.

A new guideline has been approved for the role of atezolizumab for the adjuvant treatment of non-small cell lung cancer (NSCLC).

Approved Restriction:

For the treatment of adult patients with fully resected non-small cell lung cancer (NSCLC) as adjuvant treatment following surgery who meet the following criteria:

1) No progression after platinum-based adjuvant chemotherapy
2) Lymph node positive OR primary tumour size > 5 cm
3) Tumors express PD-L1 on at least 50% of tumor cells
4) No EGFR or ALK mutations

Treatment should continue until disease progression, unacceptable toxicity, or maximum of 16 cycles or 1 year of therapy, whichever occurs first.

VII. Other

Parenteral Nutrition/ *SMOFKabiven Peripheral with electrolytes*

SMOFKabiven® Peripheral with electrolytes (1.9 L bag) is approved as the NS Health Hospital Formulary 3-in-1 choice for peripheral parenteral nutrition (PPN). PPN has been standardized across the province to address safety concerns, inconsistent practices and challenges with provincial PPN patient access.

The SMOFKabiven® Peripheral mixture contains all the nutritional components in one bag including the fat (lipid) emulsion. The pharmacy will add daily multivitamins and trace elements, but no other additions will be made. The 1.9 L bag is intended to be administered at 80 mL/hour; therefore, the bag and administration set only need to be changed once every 24 hours. To prevent complications such as thrombophlebitis, the product meets the ASPEN parenteral nutrition clinical guideline PPN osmolarity recommendation of <900 mOsm/L. The simplicity of ordering and administration also adds to the safety of using this product for PPN.

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