D&T Decisions

… from the Drugs and Therapeutics Committee

nova scotia health authority

The information in this newsletter may also be accessed online.
To request a change to the NSHA Hospital Formulary select & complete the online "Drug Request Form":
http://cdhaintra/departmentservices/pharmacy/Formulary/index.cfm

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Inside this Issue…

The following policies were approved by the Medical Advisory Committee (Sep 20, Jan 21) on the recommendation of the Drugs and Therapeutics Committee (Sep 20, Oct 20 via e-mail, Dec 20).

I. Additions to Hospital Formulary

Posaconazole oral/ *Posanol*®

Posaconazole is a second-generation triazole antifungal indicated for the treatment and prophylaxis of invasive fungal infections (particularly *Aspergillus* sp*)* in patients at high risk of developing these infections (such as patients with prolonged neutropenia or hematopoietic stem cell transplant recipients). Available as an IV formulation, delayed-release tablets and oral suspension, posaconazole has broad antifungal activity due to inhibition of the fungal enzyme lanosterol 14-alpha-demethylase. Inhibition of this enzyme results in the prevention of ergosterol synthesis, which in turn disrupts fungal cellular membrane formation and results in growth inhibition or fungal cellular death. Posaconazole has activity against *Candida* spp.*, Cryptococcus neoformans, Aspergillus* spp.*, Scedosporium apiospermum,* Mucorales, and species of dematiaceous molds.

The 2016 Infectious Diseases Society of America guidelines recommend prophylaxis of invasive aspergillosis (IA) with posaconazole (strong recommendation, high-quality evidence), voriconazole (strong recommendation, moderate-quality evidence), or micafungin (weak recommendation, low-quality evidence) during prolonged neutropenia for those at high risk of IA. The guidelines also recommend prophylaxis with posaconazole for allogeneic hematopoietic stem cell transplant (HSCT) recipients with graft-vs-host disease (GVHD) who are at high risk of IA but note that prophylaxis with other mold-active azoles is also effective. These recommendations are based on evidence demonstrating the efficacy of posaconazole prophylaxis in high risk patients [patients with GVHD and neutropenic patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)]. Similarly, the 2018 American Society of Clinical Oncology (ASCO) and IDSA clinical practice guideline update on antimicrobial prophylaxis for adult patients with cancer-related immunosuppression recommend antifungal prophylaxis with an oral triazole or echinocandin (e.g., caspofungin) for patients who are at risk of profound, protracted neutropenia, such as those with AML/MDS or undergoing HSCT (intermediate quality of evidence, moderate strength of recommendation).

Posaconazole has the potential for significant drug interactions (e.g., cyclosporine, tacrolimus, sirolimus and other CYP3A4 substrates) and is more expensive than some alternatives; however, clinical data demonstrates that posaconazole has utility as a prophylaxis agent against *Aspergillus* and other invasive fungal infections among high-risk populations as well as salvage therapy or alternative therapy for the treatment of invasive fungal infections when other antifungal agents are either ineffective, not available, or not tolerated due to adverse effects.

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.

Bictegravir & tenofovir & emtricitabine/ *Biktarvy*®

A new single tablet combination of the integrase inhibitor bictegravir and the nucleos(t)ide reverse transcriptase inhibitors tenofovir alafenamide and emtricitabine is available as Biktarvy®. Biktarvy® is indicated as a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of Biktarvy®.

The Nova Scotia Department of Health and Wellness has approved the addition of Biktarvy® to the Exception Drug Fund formulary for the indication outlined above. The cost of this single tablet regimen is comparable to other first-line treatment options.

Melatonin

Melatonin is a physiological hormone produced by the pineal gland that is involved in the regulation of sleep. Available in Canada as a natural health product, exogenous melatonin has been used to treat primary and secondary sleep disorders due to its sedative properties and effects on the regulation of circadian rhythm. Hospitalized patients may have decreased melatonin secretion due to environmental factors such as noise and artificial light.

Systematic reviews/ meta-analysis have evaluated the use of melatonin in adults with primary sleep disorders as well as individuals admitted to hospital (e.g., critical care). Melatonin has been shown to decrease the time it takes to fall asleep and increase the duration of sleep; however, evidence of efficacy is inconsistent and minimal. Melatonin is inexpensive, associated with relatively few adverse effects (e.g., headache and sedation) and there has been non-formulary usage of melatonin in hospitalized patients throughout NS Health. The melatonin sublingual dosage form may be preferred since at the time of Hospital Formulary approval, the hospital cost of both the 3 mg and 5 mg sublingual tablets was less than that of the 3 mg oral capsule.

Famotidine injection

With the removal of ranitidine injection from the Canadian market, famotidine is the only injectable histamine-2 receptor antagonist available in Canada; therefore, it has been used throughout NS Health and has been added to the Hospital Formulary. Famotidine is associated with QT prolongation and should be used with caution when combined with other drugs or conditions associated with QT prolongation.

II. Removal from Hospital Formulary

Ranitidine injection

The only Canadian manufacturer of ranitidine injection has discontinued production; therefore, it is no longer available in Canada and has been removed from the Hospital Formulary.

III. Non-Formulary (Expanded Restrictions)

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

Aprepitant, a neurokinase-1 (NK1) receptor antagonist, is established as part of combination therapy for the prevention of chemotherapy induced nausea and vomiting for high risk patients and is Hospital Formulary approved with restrictions for this indication.

Post-operative nausea and vomiting (PONV) is a common patient complaint and 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. 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. In addition, aprepitant has a long half-life (9-13 hours) and 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 request to expand the aprepitant Hospital Formulary restrictions to include the prevention of PONV was not approved. Formulary restrictions are difficult to maintain in the OR setting; therefore, from a resource perspective, aprepitant was not deemed cost effective for the prevention of PONV at this time.

Aprepitant remains on the Hospital Formulary with restrictions specific to the prevention of chemotherapy induced nausea and vomiting.

IV. Therapeutic Interchange

NS Health Therapeutic Interchange List - Update

Prior to the creation of NS Health, there were eight former therapeutic interchange (TI) lists used throughout hospitals in Nova Scotia. With the creation of the NS Health Hospital Formulary, one approved provincial TI interchange list is required. A NS Health Pharmacy TI Working Group reviewed provincial interchanges and made consensus recommendations (123 TI were reduced to 38). Some TI were not considered by the Working Group (e.g., legacy class TI, non-systemic antimicrobials) as these updates are ongoing. The updated approvals to the NS Health Hospital Formulary TI list may be found as part of the on-line Hospital Formulary:
http://webapp2.cdha.nshealth.ca/formulary/

Famotidine injection

An interim therapeutic interchange has been approved to dispense famotidine injection if ranitidine injection is ordered.

Preparation:	Dispensed As:
ranitidine 50 mg IV (pre-medication regimens)	famotidine 20 mg IV
ranitidine IV (any regimen)	famotidine 20 mg IV q12h (or as appropriate for renal function)

V. New Guidelines

Durvalumab/ *Imfinzi*® *High Alert Medication*

A new guideline has been approved for the role of durvalumab in locally advanced, unresectable stage III non-small cell lung cancer (NSCLC).

Approved Restriction:

For the treatment of patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) following curative intent platinum-based concurrent chemoradiation therapy. Patients must have a good performance status and be deemed fit following curative intent platinum-based concurrent chemoradiation therapy. Treatment should continue until unacceptable toxicity or disease progression to a maximum of 12 months.

Pralatrexate/ *Folotyn*® *High Alert Medication*

A new guideline has been approved for the role of pralatrexate for peripheral T-Cell lymphoma (PTCL).

Approved Restriction:

For the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) who have received previous systemic therapy, none of which include romidepsin. Patients should have a good performance status. Treatment with pralatrexate should continue until disease progression or unacceptable toxicity.

Venetoclax/ *Venclexta*® *High Alert Medication*

A new guideline has been approved for the role of venetoclax with riTUXimab for the treatment of chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL).

Approved Restriction:

In combination with riTUXimab for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) who have received at least one prior therapy, irrespective of their 17p deletion status. Treatment should be continued until disease progression or unacceptable toxicity up to a maximum of two years, whichever comes first.

riTUXimab/ *Ruxience™* *High Alert Medication*

riTUXimab/ *Ruxience* (a biosimilar to Rituxan) was approved for all funded indications in the New Cancer Drug Fund.

Thiotepa/ *Tepadina*® *High Alert Medication*

Thiotepa is a derivative of nitrogen that acts as an alkylating agent and is used as a chemotherapy medication. Central nervous system (CNS) lymphoma is a non-Hodgkin's lymphoma that can occur in the cerebrum, spinal cord, leptomeninges, or orbits and may also present as neurolymphomatosis. Thiotepa works by damaging the DNA in tumor cells, preventing them from undergoing replication and division processes. Due to the location of the lymphoma, and the nature of the blood brain barrier (BBB), delivering a chemotherapy agent at smaller doses to the desired location can be difficult. Thiotepa is lipid soluble and non-polar allowing it to cross the BBB.

The MATRIX Regimen (methotrexate-cytarabine-ritTUXimab-thiotepa) was studied in an open label, randomised, phase 2 trial of patients (aged 18-70) who had been diagnosed with B-cell non-Hodgkin lymphoma that was localised in the CNS, cranial nerves, and/or eyes. This trial consisted of two phases and patients who received the MATRIX regimen followed by consolidation therapy showed a 4-year overall survival of 85% in the whole brain radiation group and 83% in the autologous stem cell transplant group.

A meta-analysis revealed that 75.9% of patients with CNS lymphoma that are given regimens that include thiotepa followed by hematopoietic stem cell transplant achieve a complete remission, and 61.7% have a progression free survival for up to 125 months post treatment.

New guidelines have been approved for the role of thiotepa for primary or secondary CNS lymphoma.

Approved Restriction:

For the treatment of primary CNS lymphoma, in combination with high-dose methotrexate, cytarabine and riTUXimab (MATRIX regimen).

As part of an approved conditioning regimen prior to autologous hematopoietic stem cell transplantation for primary or secondary CNS lymphoma.

VI. Revised Guidelines

Azacitidine/ *Vidaza*® *High Alert Medication*

The guidelines for the role of azacitidine for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been revised.

Approved Restriction:

For the treatment of patients with intermediate-2 and high risk myelodysplastic syndrome (MDS) based on the IPSS classification.

For the treatment of patients with acute myeloid leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, or with blasts greater than 30% in the presence of either poor risk cytogenetics or AML with myelodysplasia-related changes, and who are not suitable for intensive chemotherapy.

VII. Expanded Guidelines

riTUXimab subcut, *Rituxan*® *SC* *High Alert Medication*

New guidelines have been approved for the role of riTUXimab subcut in chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL).

Approved Restriction:

In combination with fludarabine and cyclophosphamide (FC) in previously untreated symptomatic patients with documented evidence of CD20 + CLL (including SLL) with ECOG PS 0-2 or patients previously treated with chemotherapy but not exposed to a riTUXimab-based regimen.

In combination with idelalisib for patients with relapsed CLL or SLL.

In combination with bendamustine as a first line therapy for CLL/SLL, WHOPS ≤2 and not medically fit to tolerate fludarabine based regimens.

In combination with venetoclax for the treatment of adult patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) who have received at least one prior therapy, irrespective of their 17p deletion status.

Trastuzumab/ *Trazimera*® *High Alert Medication*

A new guideline has been approved for the role trastuzumab for HER-2 positive locally-advanced or metastatic gastro-esophageal adenocarcinoma.

Approved Restriction:

In combination with chemotherapy for the treatment of patients with HER2-positive locally advanced or metastatic gastro-esophageal adenocarcinoma who have not received prior treatment for their metastatic disease. Following combination treatment, trastuzumab may be continued as a single-agent until disease progression.

VIII. Medication Policies

The following hospital policies have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee.

PH-HP-015 Immunization

IX. Order Sets

The following order sets have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee.

NS_OSCFAO Cystic Fibrosis Admission Orders (CZ)
NS_OSEPIM Ectopic Pregnancy Single Dose Intramuscular Methotrexate (WZ)
NS_OSEMUAO Epilepsy Monitoring Unit Admission Orders (CZ)
NS_OSHSMTO Hospitalist Medicine Service (HSM) Transfer Orders (CZ)
NS_OSICUMB ICU Major Burn Admission Orders (CZ)
NS_OSIFDSBI Intrauterine Fetal Death and Still Birth Investigations (NS)
PPO0439MR Withdrawal Management Unit Admission Orders (CZ)

X. IV Manual

Since the last D&T Decisions, three NSHA IV Drug Therapy Manual and/or smart pump updates have occurred (refer to list and links below). These memos are distributed to physicians, Health Service Managers and Nurse Educators in each zone via Executive Directors of Operations and Medicine. If you believe you should be receiving these memos but are not email theresa.hurley@nshealth.ca to obtain the name of your contact.

September 25, 2020
http://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20200925.pdf

November 27, 2020
http://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20201127.pdf

January 18, 2021
http://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20210118%20SP%20Library.pdf

These may also be accessed on the NSHA IV Manual website under "Update Memos" http://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/SitePages/Home.aspx

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