D&T Decisions

… from the Drugs and Therapeutics Committee

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

Issue #71: June 14, 2021

Inside this Issue…

The following policies were approved by the Medical Advisory Committee (Mar 21, Apr 21) on the recommendation of the Drugs and Therapeutics Committee (Feb 21, Mar 21, Apr 21).

I. Additions to Hospital Formulary

Magnesium oxide

The Hospital Formulary lists magnesium glucoheptonate 100 mg/ mL oral solution (equivalent to elemental magnesium 5 mg/ mL) as the oral magnesium supplement; however, magnesium oxide 420 mg oral tablets (equivalent to elemental magnesium 252 mg per tablet) have been stocked and utilized as the standard of care for QEII oncology/ hematology patients for decades.

Hypomagnesemia is often asymptomatic and may be caused by deficient dietary intake, decreased intestinal absorption, internal redistribution, increased GI losses, renal losses or medications (e.g., diuretics, aminoglycosides, cisplatin, digoxin, hormones, cyclosporine). Hypomagnesemia most often affects the neuromuscular and cardiovascular systems and if untreated, may cause symptoms such as tetany, twitching, tremor, generalized convulsions and heart arrhythmias. Magnesium supplementation may be given by the oral, IM and IV route with the goals of treating symptoms and correcting magnesium serum levels.

Asymptomatic patients and those with mild hypomagnesemia (i.e., 0.55-0.7 mmol/L) may be treated with oral supplementation. Oral magnesium salts differ in the content of elemental magnesium and have limited oral bioavailability. Diarrhea is the most common dose limiting side effect of oral magnesium supplementation.

For various clinical reasons, patients requiring oral magnesium supplementation may not be able to tolerate the volume of magnesium glucoheptonate oral solution required for an adequate dose; therefore, magnesium oxide tablets have been added to the Hospital Formulary.

Rifaximin/ *Zaxine*

Rifaximin is a non-absorbable oral antibiotic that is Health Canada approved for reduction in the risk of overt hepatic encephalopathy (HE) recurrence in adult patients. HE is a complication of liver dysfunction that presents as a range of potentially reversible brain abnormalities. The pathophysiology is multifactorial. Ammonia (NH_3) is a nitrogenous toxin in the gut that is metabolized by the liver and cleared from the body by the kidneys. In patients with cirrhosis, there is impairment in the hepatic metabolism of NH_3. Additionally, portal hypertension leads to shunting of NH_3 rich blood into the systemic circulation without detoxification. NH_3 crosses the blood brain barrier where it is converted to glutamine in astrocytes. Accumulation of glutamine causes an osmotic gradient resulting in swelling of the astrocytes and a cascade of events including the formation of reactive oxygen species and inflammatory cytokines that increase the permeability of the blood brain barrier. The result is the cerebral dysfunction that is seen in HE (e.g., confusion, drowsiness, stupor, coma).

The main goal for the management and prevention of HE is to reduce the nitrogenous load in the gut. The current standard of therapy is lactulose, a non-absorbable synthetic disaccharide. For patients who cannot tolerate lactulose due to its gastrointestinal side effects or who are suffering from refractory HE, rifaximin can be added to or used in place of lactulose therapy. The non-absorbable rifaximin inhibits bacterial RNA synthesis by binding to RNA polymerase. It targets colonic bacteria responsible for producing nitrogenous compounds; therefore, rifaximin reduces the nitrogenous waste in the gut.

In a randomized, double blind, placebo-controlled trial, rifaximin significantly reduced the time to first breakthrough episode of HE. There were less hospitalizations at six months for patients who

received rifaximin compared to those who received placebo and the adverse effect rates were similar in both groups. A meta-analysis of eight randomized controlled trials found that rifaximin was at least as effective as non-absorbable disaccharides for the treatment of HE and that rifaximin was less likely to cause diarrhea and abdominal pain.

Approved Restriction:
Treatment of hepatic encephalopathy (HE) when:
- Patients are unable to achieve adequate control of HE recurrence with lactulose alone
- Used in combination with a maximal tolerated dose of lactulose

II. Removal from Hospital Formulary

Codeine injection

Codeine, considered a "mild" or "weak" opioid analgesic, has historically been part of the WHO analgesic ladder "second step" for mild to moderate pain when therapy with acetaminophen or a NSAID is inadequate. Codeine is metabolized by the liver enzyme cytochrome P450 (CYP) 2D6 to morphine, its active metabolite. Since codeine itself has poor infinity for the mu receptor, it is generally considered a prodrug with a mechanism of action attributed to its conversion to morphine.

The role of parenteral codeine has been questioned in the literature for decades and it is now recognized that the pharmacogenetics of codeine's metabolism to morphine is complex. Individuals who lack or have a deficiency of CYP2D6 will have inadequate analgesia. Other individuals may express extensive or rapid CYP2D6 metabolism resulting in higher than expected morphine levels and symptoms of opioid toxicity. CYP2D6 may also be induced or inhibited by medications and environmental factors; therefore, even individuals without a genetic variation in CYP2D6 may have an unpredictable dose response to codeine due to drug interactions and other factors.

Parenteral codeine has not been purchased for NSH hospital use for several years and is not listed on the IWK or NS Provincial Drug Plan Formularies. Due to safety concerns, codeine injection has been removed from the Hospital Formulary.

Lactobacillus spp/ *Bacid, others*

Due to a lack of efficacy demonstrated in the largest randomized controlled trial of Lactobacillus acidophilus, the use of probiotics is not recommended for the prophylaxis or treatment of antibiotic associated diarrhea or *C. difficile* diarrhea. Lactobacillus spp, including Bacid, have been removed from the NSH Hospital Formulary.

III. Revised Restrictions

DexmedeTOMidine/ *Precedex*® *High Alert Medication*

DexmedeTOMidine [Health Canada approved for conscious sedation and intensive care unit (ICU) sedation] has NSH Hospital Formulary restrictions specific to the operating room, acute pain service and ICU. The previously approved ICU restrictions reserved dexmedeTOMidine for intubated patients who had contraindications/ were intolerant to propofol or intubated patients with agitated delirium refractory to trials with other agents (e.g., antipsychotics). New Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult Patients in the ICU (2018) recommend a more prominent role for the use of dexmedeTOMidine for ICU sedation. The Guidelines suggest that either propofol or dexmedeTOMidine is favored compared to benzodiazepines for sedation in critically ill, mechanically ventilated adults. Additionally, the guidelines recommend against the use of antipsychotics to treat patients with delirium.

DexmedeTOMidine is a sedative that has been shown to achieve ICU sedation goals in a similar manner to alternative sedatives, provides an opioid and sedative sparing effect, is associated with less restraint use, and allows patients to mobilize sooner. DexmedeTOMidine has a neutral effect on the patient's respiratory status, whereas other agents such as propofol and benzodiazepines suppress the respiratory drive; therefore, dexmedeTOMidine has an advantage over other sedatives for patients with an agitated delirium requiring sedation that is precluding them from being weaned from the ventilator and subsequently extubated and discharged from the ICU.

A meta-analysis of randomized controlled trials comparing dexmedeTOMidine to lorazepam, midazolam and propofol found that dexmedeTOMidine was associated with statistically significant decreases in ICU length of stay, duration of mechanical ventilation and the incidence of delirium.

Propofol is still the most common and preferred first line agent for ICU sedation; however, there are situations where dexmedeTOMidine may be an appropriate alternative sedative. These situations include: when patients are not reaching sedation goals, are experiencing or are at risk of adverse effects from propofol, alternative sedatives (e.g. midazolam) are not felt to be the most appropriate option, and/or the patient is requiring sedation for an agitated delirium that is precluding weaning from the ventilator. The dexmedeTOMidine ICU restrictions have been revised to reflect these clinical situations.

Approved Restriction:
Intensive Care Unit (ICU):
- In mechanically ventilated patients where sedation with other sedatives (e.g. propofol, midazolam etc.) is contraindicated or deemed not be the most appropriate option.
- In mechanically ventilated patients where sedation is required for agitation and is precluding weaning from the ventilator.
    - Note: agitation defined as RASS > +1 where patients are a danger to themselves or staff OR their agitation is precluding medically necessary care.

IV. New Guidelines

Gemtuzumab ozogamicin/ *Mylotarg*®

High Alert Medication

A new guideline has been approved for the role of gemtuzumab ozogamicin in previously untreated de-novo CD-33 positive acute

myeloid leukemia (AML).

Approved Restriction:

In combination with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia (APL).

Patients should have a good performance status and favourable, intermediate, or unknown cytogenetics* (using the European LeukemiaNet [ELN] 2017 risk classification). Should a patient's unknown cytogenetic status become known as adverse, treatment with gemtuzumab ozogamicin should be discontinued.

Gemtuzumab ozogamicin in combination with daunorubicin (or idarubicin) and cytarabine should consist of one induction cycle; if a second induction cycle is required, gemtuzumab ozogamicin should not be administered during the second induction cycle. For patients with complete remission following induction, gemtuzumab ozogamicin in combination with standard cytarabine consolidation** or cytarabine and daunorubicin consolidation for up to two cycles is permitted.

*unknown cytogenetics because the test was unsuccessful or because cytogenetic results are not yet available.

**standard cytarabine consolidation is also known as single agent high-dose cytarabine.

Atezolizumab/ *Tecentriq*® *High Alert Medication*

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

Approved Restriction:

As a single agent for the treatment of locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) in patients who have disease progression on or after cytotoxic chemotherapy. Patients with genomic tumor driver aberrations, [e.g. epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)] should first be treated with targeted agents followed by cytotoxic chemotherapy prior to receiving atezolizumab. Treatment should be discontinued upon loss of clinical benefit or unacceptable toxicity.

Filgrastim/ *Nivestym™*

Nivestym™ (a biosimilar to the reference drug Neupogen®) will be the brand of filgrastim supplied and dispensed by NSH hospital pharmacies for both inpatient and outpatient use. Filgrastim brands Neupogen® and Gastrofil® are removed from the Hospital Formulary.

V. Expanded Guidelines

Pembrolizumab/ *Keytruda*® *High Alert Medication*

A new guideline has been approved for the role of pembrolizumab in combination with axitinib for advanced renal cell carcinoma (RCC).

Approved Restriction:

In combination with axitinib for the treatment of patients with advanced renal cell carcinoma (RCC) as first-line treatment. Eligible patients should be previously untreated in the advanced

or metastatic setting and have a good performance status.

Treatment with pembrolizumab should continue until confirmed disease progression or unacceptable toxicity or to a maximum of 35 cycles or 2 years of treatment, whichever comes first.

Treatment with axitinib should continue until disease progression or unacceptable toxicity.

Brentuximab vedotin/ *Adcetris*® *High Alert Medication*

A new guideline has been approved for the role of brentuximab vedotin for previously untreated peripheral T-cell lymphoma (PTCL).

Approved Restriction:

For the treatment of previously untreated adult patients with systemic anaplastic large-cell lymphoma (sALCL), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), or angioimmunoblastic T-cell lymphoma (AITL), whose tumors express CD30, plus cyclophosphamide, doxorubicin, and prednisone (CHP).

Patients with anaplastic lymphoma kinase (ALK) positive sALCL should have an International Prognostic Index (IPI) score of ≥ 2.

Treatment should be continued for six to eight cycles, until disease progression or unacceptable toxicity, whichever comes first.

VI. Medication Policies

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

MM-SR-030 Medication Reconciliation

VII. Order Sets

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

NS_OSBCCBMT Blood Cell Collection – Bone Marrow Transplant Program (NS)
NS_OSBRCNSR Bevacizumab – Recurrent CNS (NS)
NS_OSCDPG Carboplatin Desensitization Protocol – Gyne Oncology (NS)
NS_OSCRRTCA Continuous Renal Replacement Therapy (CRRT) – Citrate Anticoagulation (CZ)
NS_OSCRRTNA Continuous Renal Replacement Therapy (CRRT) – No Anticoagulation (CZ)
NS_OSCSAGR Carboplatin Single Agent – Gyne Oncology (NS)
NS_OSCSARGR Cisplatin Single Agent with Radiation – Gyne Oncology (NS)
NS_OSDSPOA Day Surgery – Post-operative Anesthesia Orders (CZ)
NS_OSDSPRA Day Surgery – Pre-operative Anesthesia Orders (CZ)
NS_OSIPCT Immediate Pre-operative Cardiac Transplantation

(CZ)
NS_OSISIV Iron Sucrose IV (NS)
NS_OSMAIDIVI Medical Assistance in Dying – IV Protocol – Inpatient (NS)
NS_OSMAIDIVO Medical Assistance in Dying – IV Protocol – Outpatient Prescription (NS)
NS_OSNANYR Neuraxial Analgesia – Non-Obstetrical – Yarmouth Regional Hospital (WZ)
NS_OSOHDCF Outpatient High-Dose CycloPHOSPHAMIDE with Filgrastim − Stem Cell Mobilization (NS)
NS_OSPDKA Pediatric Diabetic Ketoacidosis (NS)
NS_OSWPCR Weekly PACLitaxel / CARBOplatin (with radiation) – Locally Advanced Non-Small Cell Lung Cancer (NS)
NS_OSZA Zoledronic Acid (NS)
NS_PPOFIL Filgrastim (NS)
NS_PPOEMPAPD Empiric Management of Peritonitis Associated with Peritoneal Dialysis (NS)
NS_PPOMCPP Management of Confirmed Pathogen Peritonitis Associated with Peritoneal Dialysis (NS)

VIII. IV Manual

Since the last D&T Decisions, one NS Health IV Drug Therapy Manual and/or smart pump update has occurred; refer to link 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.

April 13, 2021
https://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20210413.pdf

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

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