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 NS Health 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 (Oct 21, Nov 21, Jan 22) on the recommendation of the Drugs and Therapeutics Committee (Sep 21, Oct 21, Dec 21).

I. Additions to Hospital Formulary

Sucroferric oxyhydroxide/ *Velphoro*®

Sucroferric oxyhydroxide (Velphoro) is an iron-based phosphate binder indicated for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis.

Hyperphosphatemia is common in end stage renal disease as a result of accumulation of dietary phosphorous and decreasing ability to excrete it in the urine. Management through dialysis and diet modification are often insufficient requiring patients to use oral phosphate binder medications. Calcium based phosphate binders (e.g., calcium carbonate/ *Tums*) are moderately effective, inexpensive and well tolerated; however, hypercalcemia and vascular calcification complications may occur. Non-calcium based phosphate binders (e.g., sevelamer HCL/ *Renagel*, sevelamer carbonate/ *Renvela, generics* and lanthanum/ *Fosrenol*) may be associated with poor patient adherence due to the large size of the tablets, high pill burden and GI effects.

Sucroferric oxyhydroxide (a flavoured tablet that must be chewed or crushed) works by binding dietary phosphorous throughout the physiological pH range of the GI tract via ligand exchange with hydroxyl groups and/or water. It is practically insoluble, not systemically absorbed or metabolized and is excreted as unbound phosphate in the feces. Although there are no studies directly comparing sucroferric oxyhydroxide to calcium-based phosphate binders, studies have demonstrated non-inferiority to both sevelamer carbonate and sevelamer hydrochloride. The frequency of reported adverse effects were not substantially different between treatment and control groups; however, overall treatment emergent adverse effects were high in both groups. Diarrhea, discoloured stools and hyperphosphatemia were reported more frequently with sucroferric oxyhydroxide whereas constipation and nausea were more frequently reported with sevelamer. Sucroferric oxyhydroxide is potentially more costly than other phosphate binders.

Approved Restriction:
Treatment of patients with hyperphosphatemia who have:
- Inadequate control of phosphate levels on a calcium-based phosphate binder, OR
- Hypercalcemia (corrected for albumin), OR
- Calciphylaxis (calcific arteriolopathy)

Dapagliflozin/ *Forxiga*®

Sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g., dapagliflozin, canagliflozin, empagliflozin) are medications for the treatment of Type 2 Diabetes Mellitus that reduce glucose levels by inhibiting the reabsorption of glucose in the kidneys; therefore, increasing the urinary excretion of glucose. These medications pose a low risk of hypoglycemia and have blood pressure lowering effects; however, SGLT2 inhibitors are associated with an increased risk of genital and urinary tract infections, volume depletion-related adverse effects and diabetic ketoacidosis.

There has been an increased interest in the use of SGLT2 inhibitors due to evidence of cardiovascular safety (assessed for dapagliflozin in the DECLARE-TIMI trial). Dapagliflozin is also indicated as an adjunct to standard of care therapy, for the treatment of heart failure with reduced ejection fraction to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit (based on the DAPA-HF trial). More recently, dapagliflozin has been approved to reduce the risk of sustained eGFR decline, end-stage kidney disease, and cardiovascular and renal death in adults with chronic kidney disease.

Tetracaine gel/ *Ametop*

Tetracaine gel/ *Ametop* has been added to the NS Health Hospital Formulary based on the IWK Health Formulary status.

Lidocaine and prilocaine cream/ *EMLA*®

Lidocaine and prilocaine cream/ *EMLA*® has been added to the NS Health Hospital Formulary based on the IWK Health Formulary status.

Amoxicillin and clavulanate injection

Although oral formulations of amoxicillin (a beta-lactam antibiotic) and clavulanate (a beta-lactamase inhibitor) have been available on the Hospital Formulary for many years, the IV formulation has only recently been approved by Health Canada. Amoxicillin is a semisynthetic penicillin that binds to penicillin binding proteins used by bacteria in the biosynthesis of peptidoglycan (an integral structural component in bacterial cell walls). The inhibition of this process in susceptible microorganisms weakens the cell wall leading to cell lysis and death. Microorganisms may be resistant to amoxicillin by producing beta-lactamase enzymes that cleave the beta-lactam ring structure of amoxicillin. This resistance can be overcome by pairing amoxicillin with clavulanic acid. In doing so, it protects amoxicillin cleavage by beta-lactamases and broadens the spectrum in which amoxicillin is effective. Amoxicillin and clavulanic acid have demonstrated efficacy against both Gram-positive and Gram-negative microorganisms. It is active against MSSA (methicillin susceptible *Staphylococcus aureus*), beta-hemolytic *Streptococcus sp*., *Enterococcus faecalis*, *Bacteroides sp*., *Haemophilus influenzae*, penicillin susceptible *Streptococcus pneumoniae,* and some activity against *Escherichia coli*, and little to no activity against *Pseudomonas spp.* and *Enterococcus faecium*.

The injectable formulation of amoxicillin and clavulanate has been added to the Hospital Formulary to address clinical indications and patient scenarios when oral administration would not be appropriate or feasible (e.g., severe intra-abdominal infection). Intravenous amoxicillin and clavulanate has a role in the treatment of polymicrobial infections that are proven or strongly suspected to be caused by susceptible bacteria, particularly those in which anaerobic and *Enterococcus sp*. coverage is required but where coverage of *Pseudomonas sp.* is not required, and the enteral route is not appropriate or available. The availability of IV amoxicillin and clavulanate will allow it to be appropriately used instead of other broader spectrum antibiotics including piperacillin-tazobactam or carbapenems for polymicrobial infections. Assessment of patients' clinical status and stability will facilitate appropriate step down to oral therapy, including oral amoxicillin-clavulanic acid.

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.

Aminolevulinic acid/ *Gleolan*

Aminolevulinic acid (5-ALA)/ Gleolan is an oral imaging agent indicated for patients with glioma World Health Organization (WHO) Grades III or IV (suspected on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery. Gleolan should only be used by neurosurgeons who have completed a training program on use of fluorescence in surgery.

5-ALA is a naturally occurring biochemical involved in the hemoglobin synthesis pathway. Endogenous synthesis of 5-ALA is regulated by a feedback mechanism based on the concentration of free heme; however, the administration of excess exogenous 5-ALA bypasses the feedback control and results in intracellular accumulation of its photoactive metabolite protoporphyrin IX (PpIX) in certain cells and tissues. When aminolevulinic acid is administered orally (e.g., Gleolan), it selectively accumulates in neoplastic brain tissue where it is metabolized into fluorescent PpIX that can be stimulated by blue light using special filters on a surgical microscope resulting in intraoperative visualization of the tumor which glows pink or red while healthy brain tissue appears blue. With conventional white light microscopy, it can be difficult to distinguish viable tumor from normal adjacent brain at the tumor margin; therefore, fluorescent visualization with 5-ALA during resection surgery provides a potential advantage.

In March 2020, Ontario Health published a Health Technology Assessment of 5-ALA-guided surgical resection of high-grade gliomas that included an evaluation of effectiveness, safety, the budget impact of publicly funding 5-ALA and patient preferences/ values. This assessment concluded that there is low grade evidence that 5-ALA guided surgical resection appears to improve the extent of resection compared with standard white-light microscopy and that for individuals diagnosed with high-grade gliomas, 5-ALA is seen positively as a useful imaging tool for surgical resection.

Patiromer/ *Veltassa*®

Patiromer is an oral powder cation exchange polymer indicated for the treatment of hyperkalemia in adults with chronic kidney disease. Similar to polystyrene sulfonate (sodium/ Kayexalate and calcium/ Resonium Calcium), patiromer is a non-absorbed resin that binds potassium in the gastrointestinal tract and facilitates fecal potassium removal. Patiromer contains a calcium sorbitol complex that exchanges calcium ions for potassium.

Studies to date compare the potassium lowering effects of patiromer to placebo; therefore, there is a lack of comparative evidence. The OPAL-HK trial evaluated the potassium lowering effect of patiromer in outpatients with chronic kidney disease receiving a stable dose of renin-angiotensin-aldosterone system (RAAS) inhibitor who were experiencing hyperkalemia. The initial 4 week treatment phase consisted of patiromer twice daily (dose adjusted to maintain a target serum potassium) followed by an 8 week treatment withdrawal phase where patients with normokalemia were randomized to continue patiromer or switch to placebo. At the end of the 4 week initial phase, 76% of patients achieved the target serum potassium range. In the treatment withdrawal phase, significantly more patients in the placebo group than the patiromer group experienced potassium levels of 5.5 mmol/L or higher.

The acute use of patiromer has been well tolerated; however, comparative and long term safety evidence is lacking. GI disturbances (i.e., constipation, diarrhea, nausea) were common adverse events in the OPAL-HK trial. Other adverse events reported included hypomagnesemia and anemia.

Due to a delayed onset of action, patiromer should not be used in the emergency treatment of life threatening hyperkalemia; however, it is a newly available alternative for the treatment of acute hyperkalemia and maintenance therapy for chronic hyperkalemia.

Approved Restriction:
Patients with hyperkalemia in the setting of chronic kidney disease.

II. Non-Formulary

Sodium zirconium cyclosilicate/ *Lokelma*®

Similar to patiromer, sodium zirconium cyclosilicate is a cation exchange polymer recently approved by Health Canada for the treatment of hyperkalemia in adult patients. There was a request to evaluate both sodium zirconium cyclosilicate (SZC) and patiromer for NS Health Hospital Formulary inclusion. SZC is an orally administered non-absorbed powder resin that facilitates fecal potassium removal by using hydrogen and sodium ions to exchange for potassium. As per patiromer, SZC has a delayed onset of action and should not be used in the emergency treatment of life threatening hyperkalemia.

The HARMONIZE randomized placebo controlled trial evaluated the potassium lowering effect of SZC in patients with hyperkalemia. Patients received SZC for 48 hours in the initial open-label acute correction phase and within 24 hours 84% of patients achieved normokalemia compared to 98% achieving normokalemia within 48 hours. Following the acute correction phase, patients were randomized to receive SZC or placebo once daily for 28 days. A higher proportion of patients taking SZC maintained normokalemia at the end of this phase compared to placebo. Edema and gastrointestinal disturbances were reported in all patient groups.

The CADTH Canadian Drug Expert Committee (CDEC) Common Drug Review concluded that due to a lack of comparative trials, there is insufficient evidence that SZC addresses any of the clinical needs of patients with hyperkalemia that are not already met by other reimbursed treatments (e.g., sodium polystyrene sulfonate/ Kayexalate). Limitations in the evidence prevented CDEC from identifying subpopulations in whom SZC may provide addition benefit. Therefore, SZC is not a benefit with NS Pharmacare and remains non-formulary at NS Health hospitals.

III. Therapeutic Interchange

Macrolide antibiotics

The NS Health approved Hospital Formulary macrolide antibiotics for systemic use are erythromycin, clarithromycin and azithromycin. The role of erythromycin should be limited to the promotion of gastric motility. Clarithromycin and azithromycin are both indicated to treat adult infections (primarily respiratory). At NS Health hospitals, azithromycin is more commonly prescribed than clarithromycin, in part due to its lower propensity for drug-drug interactions and a shorter treatment course. Apart from a few exceptions, azithromycin can appropriately substitute the prescribing of clarithromycin.

A 2019 NS Health point-prevalence survey of antimicrobial prescribing identified community-acquired pneumonia (CAP) as a top infection for which antimicrobials were prescribed inappropriately and this often involved macrolide treatment. A lack of documented stop date and inappropriately prolonged treatment durations were other prescribing trends for macrolides. In an effort to address these priority areas and to help simplify prescribing practices, an expanded macrolide therapeutic interchange has been approved that includes the automatic substitution of clarithromycin with azithromycin and a three-day stop date. Specific exceptions are defined:

Antimicrobial Order	Dispensed as
Erythromycin IV (all regimens)	Azithromycin 500 mg IV daily x 3 days **Exceptions:** erythromycin IV used as motility agent, preterm premature ruptures of membranes (pPROM)
Erythromycins, oral: Base (enteric/particle - coated tab) 250 mg, 333 mg, estolate 250 mg, ethylsuccinate 400 mg	Azithromycin 500 mg PO daily x 3 days **Exceptions**: erythromycin po used as motility agent, (i.e. one dose prior to endoscopic procedure) in which case interchange to erythromycin base 250-500 mg at ordered frequency, preterm premature rupture of membranes (pPROM)
Clarithromycin, oral: for solution, suspension, tablet; any dose	Azithromycin 500 mg PO daily x 3 days **Exceptions:** treatment or prophylaxis of non-tuberculosis mycobacterial infection, treatment of *H. pylori*, skin and soft tissue infections where a beta-lactam cannot be used and there are no suitable alternative oral agents
Azithromycin, oral: any dose/duration OR no duration specified	Azithromycin 500 mg PO daily x 3 days **Exceptions:** patients admitted to ICU and receiving empiric or definitive *Legionella* pneumonia treatment, treatment of chlamydia infection with single 1 g dose, treatment or prophylaxis of non-tuberculosis mycobacterial infection, when used for prophylaxis of exacerbations in underlying lung disease or lung transplant recipients
Azithromycin, IV: any dose/duration OR no duration specified	Azithromycin 500 mg IV daily x 3 days **Exceptions:** patients admitted to ICU and receiving empiric or definitive *Legionella* pneumonia treatment, treatment of chlamydia infection with single 1 g dose, treatment or prophylaxis of non-tuberculosis mycobacterial infection *Note: IV to PO policy may be implemented in patients appropriate for PO administration*

IV. Medication Policies

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

MM-MS-005	Natural Health Products
CL-EC-090	Preparing Approximate IV Solutions for Pediatric Patients with Metabolic Disorders

V. IV Manual

Since the last D&T Decisions, three NS Health IV Drug Therapy Manual and/or smart pump updates have occurred; refer to 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 local contact.

July 21, 2021
https://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20210721.pdf

November 9, 2021
https://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20211109.pdf

January 31, 2022
https://intra.nshealth.ca/clinical-resources/infusiontherapy/IV%20Drug%20THerapy%20Manual/Update%20Memos/IV%20Manual%20Update%20220131.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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