The C&W PT&N Committee serves as the Pediatric subcommittee to the Provincial Pharmacy and Therapeutics Committee. We continue to have representation from other Health Authorities, in addition to our membership from C&W.

**Policies & Procedures**

The following new or updated policies & procedures have been approved and are posted on the C&W Intranet on ePOPS:

**The Procedural Sedation: Non Critical Care Areas** policy (formerly Procedural Sedation and Analgesia Standards and Guidelines) have been updated. Monitoring respiratory rate is no longer required for oral or intranasal sedation. The Sedation Record has also been updated.

The updated **Empiric Antimicrobial Guidelines** were approved.

The following **PT&N Policies** have been updated:

- Dose Administration by a Nurse or Prescriber, Medication Handling in the Procedure Suites, Nutrition Orders by Dietitians
- **Drug Dosage Handbook Updates**
  - Epinephrine – The ratios were removed and replaced by the strength in mg/mL, as recommended by ISMP Canada. There is a reference to the ratio conversion to mg/mL, as some products may have both listed until manufacturers switch their labelling.
  - Gentamicin and Tobramycin (neonatal) monographs were updated with the new extended interval dosing and monitoring guidelines. See the article in this edition for further information.

**Pre-printed Orders**

The following C&W pre-printed orders have been approved since September 2016 and are posted on the C&W Intranet on ePOPS:

**Blood Product Administration**
- Red Blood Cells
- Platelets
- Plasma and Cryoprecipitate

**Emergency Department**
- Outpatient IV Antibiotics
- Status Epilepticus
- Trauma Team Activation

**Pain**
- Analgesic, Antiemetic, Antipruritic Agents for patients greater than 3 months
- APS, PICU and Oncology Hydromorphone Infusion (2):
  - regular and overweight
- Fentanyl Infusion – Acute Pain Service (APS) and PICU Only Hydromorphone PCA For Acute Pain Service (APS) Only (2):
  - regular and overweight
- Intermittent Morphine for patients greater than 3 months
- Morphine Infusion (2):
  - Greater than 3 months and overweight
  - Morphine Infusion Weaning
- Morphine PCA for APS:
  - regular and overweight
- Oncology Peripheral Blood Progenitor Cell Collection (2):
  - weight less than 25 kg and weight greater than or equal to 25 kg

**PICU**
- PICU Admission (Neonate)
- PICU ECLS Circuit Priming

**Oncology**
- Plasma Exchange Standard Apheresis Orders (2):
- TTP and Coagulation Disorders and Other
- Red Blood Cell Exchange
- White Blood Cell Depletion

**Other**
- High Flow Humidified Nasal Prong Oxygen Therapy
- Intranasal Medication for Procedural Sedation
- Pre-Op Surgical Daycare
- Spinal Surgery Postoperative

**NICU**
- NICU Inborn Admission
- NICU Discharge
- NICU Pre-Operative/Pre Interventional Radiology
- NICU Post-Operative/Post Interventional Radiology

**Women’s Hospital**
- WH Adult IVIG
- WH Newborn Admission
Aminoglycosides are commonly used in the treatment of neonatal sepsis. [1] Traditional dosing (TD) of aminoglycosides involves smaller doses given more frequently while extended interval dosing (EID) involves larger doses given less frequently. EID of aminoglycosides is based upon certain pharmacokinetic (PK) and pharmacodynamic (PD) drug properties including concentration dependent bactericidal activity and an extended post-antibiotic effect. [2,3] Achieving early high peak concentrations has been associated with improved clinical outcomes and lower trough concentrations may be associated with reduced nephrotoxicity. [4,5] Other proposed advantages of EID include convenience with administration of fewer daily doses and the potential for decreased therapeutic drug monitoring resulting in reduced blood loss.

EID of aminoglycosides has been used extensively in the adult and older pediatric population. Overall, TD and EID of aminoglycosides in these populations have comparable efficacy. [6-8] Decreased nephrotoxicity reported with EID mostly comes from animal model data as meta-analyses of human data show no significant difference. Also, to date, there is no evidence to suggest any differences in ototoxicity between the two dosing schemes. [6-9]

Neonates, until more recently, had largely been excluded from EID protocols due to variability in pharmacokinetics of aminoglycosides in this population and limited published literature.

The pharmacokinetics of drugs in neonates are variable and influenced by gestational age, postnatal age, and weight. The neonatal population has a higher volume of distribution (Vd) due to an increased extracellular fluid compartment and decreased renal clearance compared to adults. [10-12] As a result, larger milligram per kilogram doses are often required to overcome the larger Vd and extended dosing intervals are often required to accommodate the reduced glomerular filtration rate. [13] These pharmacokinetic differences make EID of aminoglycosides a viable and potentially favorable option in this population. [14]

There is an increasing amount of published literature surrounding the use of extended interval gentamicin, particularly in the late preterm and term neonatal population and EID dosing protocols are now being used in neonatal intensive care units (NICU) worldwide. [13,15-26]

Two meta-analyses have been published reviewing EID of aminoglycosides in neonates. [15,17] Overall, EID of gentamicin results in a higher percentage of neonates within target peak and trough concentrations compared to TD. In neonates, target peak concentrations are most common defined as 5 to 12 mg/L and target trough concentrations are defined as <2 mg/L for both TD and EID regimens. Both studies concluded that there was no difference in nephrotoxicity or ototoxicity between the two regimens. There have also been no reported differences in treatment failures; however, there were a low number of neonates with culture proven sepsis in the included studies. [15,17]

Based on the above summarized literature and proposed advantages of EID of aminoglycosides in neonates, the NICU at BC Women’s Hospital developed and implemented EID protocols in May 2017 in place of the previous TD protocols. The variations in EID protocols for neonates published in tertiary references (including NeoFax and the Redbook) reflect the variability of EID protocols used in the literature. Development of the new dosing protocols at our center was undertaken as a joint effort between the NICU, antimicrobial stewardship, infectious diseases, and pharmacy. They can be found online at Pedmed in the Neonatal Drug Dosing Guidelines. (BCCH intranet)

At this time, EID of aminoglycosides can be used in neonates at BC Children’s Hospital and at BC Women’s Hospital in the Intermediate Nursery and NICU only. For those neonates admitted to any of the postpartum units at BC Women’s Hospital the TD aminoglycoside protocol will continue to be used. Aminoglycosides on the postpartum units are currently given IV push. The larger doses used in the EID protocol cannot currently be given safely by this method and need to be given via IV intermittent infusion over 30 minutes. Please refer to the BC Women’s Hospital policy and procedure on antibiotic administration in the newborn which can be found on ePOPS.

References
Prescription of long-acting injectable antipsychotics (LAIA) in adolescents appears to be increasing, despite a lack of published randomized controlled trials demonstrating efficacy and safety in adolescents. [1-5] Among contemporary antipsychotics with available LAIA formulations, only oral aripiprazole currently has Health Canada approval for use in adolescents (age 13 and up in bipolar disorder, and age 15 and up in schizophrenia).[6]

**Potential benefits of LAIAs**

Adherence to a medication regimen can be challenging for adolescents, particularly in those with severe mental illness and a lack of insight. LAIAs virtually guarantee medication adherence if they are administered at appropriate intervals. Child and adolescent psychiatrists may be leaning towards LAIA prescribing as they become aware of literature showing improved symptom control and significantly reduced relapse rates in adults receiving LAIAs.[7]

**Potential barriers to LAIA use**

Potential barriers to LAIA use include patient fear of injection-related pain, high acquisition cost and restricted drug benefit plan coverage. There are also logistical challenges since many adolescents do not have a consistent primary care provider to administer the injections. Unfortunately, despite extensive uptake of injection training certification programs, pharmacists in British Columbia are currently not permitted to administer LAIAs.

**Specific LAIA formulations**

LAIAs may be administered via deltoid or gluteal injections (exception: loading doses of paliperidone (Sustenna)) must be given into the deltoid.[8] Current BCCH policy limits deltoid site injection volume in children to 1 mL, which may influence LAIA usage.

**Risperidone** (Consta) was the first LAIA available in Canada. Challenges with using this product in adolescents include an every-two-week injection frequency, the need for overlap with oral risperidone for three weeks after the first injection, the need for product refrigeration if dispensed more than seven days before the scheduled injection date, and administration delays due to reconstitution procedures.[9] When possible, arranging for scheduled ordering, prescription processing and direct delivery of the Consta formulation by the community pharmacy to the administering provider reduces the risk of treatment delay and drug wastage due to improper storage. For all LAIAs, this also reduces the risk of late or missed doses.

LAIA formulations of **paliperidone** monthly (Sustenna) and every three months (Trinza) offer several advantages over risperidone (Consta), including no required oral paliperidone overlap after the first loading dose, and availability as a pre-loaded syringe that does not require reconstitution or refrigeration.[8,10] Longer intervals between injections and leeway in dose timing (up to 7 days [Sustenna] or 14 days [Trinza] earlier or later than the scheduled date is allowed for maintenance doses) offer flexibility for scheduling appointments.[8,10] However, a reduced frequency of office visits for injections means fewer opportunities for providers to meet with adolescents to observe and discuss their functioning and provide psychosocial support.

**Aripiprazole** (Maintena) is administered monthly and a 2-week overlap with oral aripiprazole is recommended after the first injection. It does not require refrigeration, but must be reconstituted before administration.[11] The recommended monthly dose of Maintena is 400 mg daily for adults, except in patients taking strong CYP2D6 or CYP3A4 inhibitors concurrently for more than two weeks, who require a reduced dose.[11] The 400 mg monthly dosage is potentially problematic in adolescents, since this dose was designed to achieve serum levels comparable to oral aripiprazole 20 mg daily, which is higher than the approved adolescent aripiprazole dose of 10 mg daily.[6,11]

Prescribers and pharmacists should verify patient tolerance of the corresponding oral antipsychotic formulation before dispensing/administering the first dose of a LAIA. Following administration, LAIA effects may persist for several months and can’t be “taken back” if severe adverse effects develop. At present there are no LAIA dosing guidelines for children & adolescents. Cautious dosing is particularly warranted in adolescents with low deltoid or gluteal muscle mass, and in those who vigorously exercise injection-site muscle groups, since exercise can lead to faster drug absorption, increased adverse effects, and shorter duration of action or symptom relapse before the next scheduled injection.[12]

Drug absorption rate from the injection site is the main determinant of LAIA duration of action, not elimination half-life.[13,14] When initiating treatment, many prescribers follow the manufacturer’s adult dosage guidelines and may “overshoot” the required dosage, or underestimate the time required to reach steady-state levels. This can result in higher than anticipated serum levels and delayed adverse effects, including severe extrapyramidal symptoms (EPS), akathisia and dystonia.[14-17] If an oral anticholinergic such as benztropine is not prescribed concurrently with the LAIA, prescribers and pharmacists should educate patients that oral (nonprescription) diphenhydramine is available over the counter and 25 mg taken as needed can treat mild to moderate EPS symptoms.[18] For more severe EPS, such as dystonia or oculogyric crisis, oral diphenhydramine is likely to be inadequate, and patients should be educated regarding when to contact emergency health services.

As with use of oral antipsychotics, appropriate Canadian monitoring guidelines for antipsychotic treatment, including periodic blood testing for monitoring metabolic complications should be followed.[19] (see http://camesaguideline.org/) At a cost of up to $5000/year, most families cannot afford to pay for LAIA treatment. BC Pharmacare special authority coverage for LAIAs is available when special authority criteria (usually, when the treatment is for a psychotic disorder, and there is evidence of repeated hospitalizations due to non-adherence to oral medication) are met. A special authority approval application should be completed before LAIA treatment starts. Prescribers can also assist families to apply for coverage via the BC Pharmacare Plan G no-charge psychiatric medication program if the net annual family income is below $30,000/year, plus an additional $3,000 per dependent. Continued on page 5.
After an annual review of available evidence and guidelines, the Antimicrobial Stewardship Program has updated the BC Children’s Hospital Empiric Antimicrobial Guidelines. Please refer to the full version posted on ePOPS for details. Therapeutic updates in this version include:

- **Mastoiditis:** Empiric therapy has been changed from cefotaxime* + vancomycin to cefotaxime ± metronidazole. The most common pathogens implicated are Staphylococcus pneumoniae, Streptococcus pyogenes, and Staphylococcus aureus.[1] Although no published guidelines for the treatment of mastoiditis exist, the consensus from a meeting involving ENT, ID, CTU and AMS is that MRSA is an uncommon etiologic pathogen, thus vancomycin should be reserved for patients with colonization or a history of MRSA infection.[2] Empiric anaerobic coverage should be considered in severe cases with evidence/suspicion of abscess. An antipseudomonal agent may be added if *P. aeruginosa* infection is suspected based on a patient history of recurrent mastoiditis or after tympanostomy tube insertion.[3,4]

- **Orbital Cellulitis:** Distinguishing signs may include blurred vision, ophthalmoplegia, proptosis, and chemosis.[5,6] Published treatment guidelines are not available, but ENT, ID, CTU and AMS reviewed available literature and changed recommended empiric therapy from cefotaxime + vancomycin to cefotaxime ± vancomycin ± metronidazole. The most commonly implicated pathogens are similar to those in rhinosinusitis, including *S. pneumoniae*, *S. aureus*, *Streptococcus anginosus*, Staphylococcus epidermidis, *S. pyogenes*, and *Haemophilus influenzae*.[7-9] The infection is often polymicrobial, with anaerobic bacteria generally associated with chronic or inflamed sinuses. Empiric MRSA coverage can be added in cases with evidence of abscess or bone involvement, orbital trauma, recent ophthalmic surgery or severe infection. Empiric anaerobic coverage should be considered in severe cases with evidence/suspicion of abscess. Antibiotics which provide adequate CNS penetration should be used for intra-orbital and/or intracranial complications.

- **Community-acquired pneumonia (CAP) (<1 month of age):** For the unlikely scenario that there are penicillin allergy concerns for a neonate, the empiric regimen has been changed to vancomycin + (cefotaxime or gentamicin). The previous combination of vancomycin + cefotaxime + gentamicin provided an unnecessary gram-negative overlap. Vancomycin replaces ampicillin for *Listeria* in the penicillin-allergic patient as it provides in vitro activity, but should be changed if *Listeria* is confirmed as vancomycin provides sub-optimal clinical activity.[10]

- **Community-acquired pneumonia (CAP) (>3 month of age):** S. pyogenes was added to the list of most likely organisms. Empiric treatment for patients allergic to penicillin was changed to allow optional vancomycin. Cefotaxime provides coverage for the most likely organisms of MSSA, *S. pneumoniae*, *H. influenzae*, and *S. pyogenes*. Vancomycin should be reserved for patients with suspected MRSA infection, as the incidence of resistant *S. pneumoniae* requiring vancomycin for pneumonia has dropped to very low rates approaching 0%.[11]

- **Aspiration Pneumonia:** Aspiration can cause a spectrum of pulmonary syndromes depending on a number of factors including the nature, amount and frequency of aspiration and the patient’s response.[12] Rather than one empiric regimen, treatment has been separated into:
  - **Severe/Hospital-acquired aspiration pneumonia:** Aspiration pneumonia occurring during hospitalization may include mixed bacterial pathogens similar to those implicated in nosocomial infections, and therefore requires broader antimicrobial coverage with the empiric regimen of cefotaxime + metronidazole. Although beta-lactams provide some anaerobic coverage, addition of clindamycin or metronidazole may be necessary for beta-lactamase producing anaerobes as failures have been reported with beta-lactam monotherapy.[13]
  - **Pelvic inflammatory disease:** As per the most recent BCCDC guidelines,[15] azithromycin has been added as an alternative to doxycycline. Treatment regimens cover for both gonorrhea and *Chlamydia* infections, but doxycycline may provide increased effectiveness for the co-treatment of *Chlamydia* over azithromycin.[16]
  - **Severe cellulitis:** when MRSA risk factors are present, vancomycin has replaced clindamycin in this update to target MRSA. With increasing MRSA clindamycin resistance of ~28%,[17] vancomycin is more reliable. For patients without MRSA risk factors, cefazolin remains the first-line empiric option.
  - **Documented Group A Streptococcal (GAS) necrotizing fasciitis:** for penicillin-allergic patients, rather than using cefotaxime as the alternative for penicillin, this has been changed to cefazolin. GAS is generally susceptible to cefazolin, with an MIC90 of 0.12.[18]
Research & Awards
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Empiric Antibiotic Guidelines Update ...continued from page 4

References
17. Division of Medical Microbiology. BC Children’s and Women’s Health Centre Cumulative Antibiotics. 2015 Vancouver; Dec 2016. Link ( intranet)

Research


Book chapter

Awards
Dr. Mary Ensom received the Class of 2017 Master Teacher Award, UBC Faculty of Pharmaceutical Sciences (June, 2017).

Dr. Jennifer Kendrick was awarded the Lower Mainland Pharmacy Services Residency Program Veteran Preceptor of the Year for 2016-17, recognizing her excellence in teaching, precepting, and mentoring residents.

Dr. Katie Haubrich was awarded the Lower Mainland Pharmacy Services Residency Program New Preceptor of the Year for 2016-17, recognizing her excellence in teaching, precepting, and mentoring residents.

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