Updates from C&W Pharmacy, Therapeutics & Nutrition (PTN) Committee
Jennifer Kendrick, BScPharm, PharmD

The C&W PTN 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.

**Backorders and Product Changes:**
We are currently facing shortages of many essential medications. The Pharmacy Department continues to monitor supplies and usage. We appreciate all of the assistance in reviewing options to mitigate these shortages.

The epinephrine backorder is now resolved. The shortage gave us an opportunity to review stocking of pre-mixed syringes in the hospital and minimize wastage going forward.

Ranitidine oral products were removed from the market per Health Canada. Famotidine is the alternate H2 receptor antagonist.

**Drug Dosage Handbook**
The following monographs have been updated. Please consider updating your hard copy.

*Cefepime* updated dosing
*Clopidogrel* correction to dosing
* Dexrazoxane added dosing for use with other anthracyclines
* Famotidine new monograph
* Foscarnet new monograph
* Posaconazole new dose for young children and tablet formulation
* Prazosin addition of max ‘mg/kg/day’ dose
* Tacrolimus correction of initial dosing to 0.05-0.2 mg/kg/dose PO Q12H and change in IV:PO conversion for solid organ transplant

**Parenteral Drug Manual**
The following monographs have been updated:

* Alemtuzumab new monograph
* Azacitidine new monograph
* Bevacizumab new monograph
* Bleomycin changed monitoring requirement for subsequent doses
* Brentuximab new monograph
* Carmustine addition of maximum rate of infusion

*Dexmedetomidine* change in restriction to allow oncology physicians to prescribe dexmedetomidine during dinutuximab for cycles 3 onwards
* Etoposide* added maximum rate to intermittent infusion
* Gemtuzumab* new monograph
* Inotuzumab* new monograph
* Levofloxacin* new monograph
* Treosulfan* new monograph
* Vancomycin* addition of reconstitution instructions for 500 mg vial

**Formulary Additions**
*Insulin glargine (Basaglar* brand) was added to formulary. This is the brand of glargine that is covered by Pharmacare.

*Palonosetron* was added to formulary for the treatment of pediatric oncology patients with refractory chemotherapy induced nausea and vomiting despite optimal antiemetic therapy.

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

The following PTN Committee Policies have been renewed with minor changes: **Medication Order Requirements, Patient Specific Authorization for Administration and Temporary Leave of Absence (Pass Medications)**

The following medication administration procedures have been updated with minor changes: **Intranasal Medication Administration, Rectal Medication Administration, Intramuscular Medication Administration, Subcutaneous Medication Administration**

The **Pediatric Asthma Referral Form** and **Pediatric Asthma Education and Discharge Checklist** have been updated. The **Child Health BC Provincial Asthma Guideline Pediatric Asthma – Initial Management Pathway in an Emergency Setting** has been approved for use at BC Children’s Hospital.

The **Pharmacological Treatment Algorithm for the Newborn at Risk for Symptoms of Withdrawal Due to Antenatal Substance Exposure** algorithm has been created to assist with management of withdrawal in newborns at Women’s Hospital.

The **BCCH Refractory Status Epilepticus Practice Guidelines** have been updated with minor changes.

**PediCrisis Guidelines** for use in the OR have been updated with additional guidelines and a separate drug list.

The **BCCH Empiric Antimicrobial Guide** was updated to align with current information about penicillin and beta lactam allergy; new treatment of choice for secondary peritonitis; a new category for health care associate intra-abdominal infections; and new information for osteomyelitis.

The **BCCH Fever and Neutropenia Clinical Practice Guidelines** have been updated to include cefepime as the treatment of choice in stable patients with a penicillin allergy.

The **BCCH Handling Medications in Procedures and Surgical Suites: Authorized Personnel** was approved.

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...update continues on page 2
Pre-printed Orders

The following C&W pre-printed orders have been approved since Mar 2019 and are posted on the C&W Intranet on ePOPs:

**Acute Pain Service**
- P-IVLT Study Morphine

**Biochemical Diseases**
- Cerliponase alfa (Brineura) Infusion

**Cardiology**
- Cardiac Surgery Pre-op Admission

**Emergency Department**
- Asthma ED Order Set
- Heavy Menstrual Bleeding

**Endocrinology**
- Endocrine Growth Hormone Stimulation
- Diabetic Ketoacidosis

**Hematology**
- RBC Administration for Chronically Transfused Patients

**Nephrology**
- Kidney Transplant Admission Pre-Op
- Kidney Transplant Admission Post-Op (PICU)
- Kidney Transplant Admission Post-Op (Inpatient)
- Automated Peritoneal Dialysis
- Continuous Peritoneal Dialysis
- Intermittent Peritoneal Dialysis

**Oncology**
- Chimeric Antigen Receptor (CAR) T cell Infusion Orders – Day 0
- Dexametomidine Infusion for use during Dinutuximab Administration
- Fever and Neutropenia (Stable)

**Ophthalmology**
- Ophthalmology Eye Drop Administration

**Orthopedics**
- Musculoskeletal Tumour Post-Op Admission
- Post-op Spinal Surgery Inpatient

**PICU**
- CRRT
- SHIPPS Study

**Rheumatology**
- Rheumatology Standard Infliximab Infusion
- Rheumatology Rapid Infliximab Infusion
- Rheumatology IV Cyclophosphamide Administration (non-Oncology)

**Other**
- DNAR
- Pediatric Asthma Admission

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**All Things Sepsis - from an Emergency Department Perspective**

By: Kendra Sih, PharmD and Dr. Vik Sabhaney
Reviewed by: Dr. Ashley Roberts

Sepsis and septic shock can have devastating outcomes if not detected early and treated appropriately.[1-4] The Surviving Sepsis guidelines represent landmark documents over the most recent several decades, and pediatric recommendations were buried amongst adult care therapy. In the last few years, additional neonate and pediatric specific literature has emerged.[2-3] In collaboration with BCCH Infectious Disease stakeholders, it was decided some changes were required in the BCCH Emergency Department’s (ED) approach to sepsis and septic shock.

The first stage of the change was to re-invent the scope of the previous order set from “Fever in less than 60 days of age” to “Rule out serious bacterial infection in neonates (less than 30 days)”. The rationale for this change is:

1. patients less than 30 days of life represent a more vulnerable population with different treatment guidelines, and
2. that neonates can often present hypothermic and not febrile. Diagnostically, the new BCCH algorithm emphasizes the need for a lumbar puncture in this population, unless they are clinically unstable.[4]

In terms of treatment management, it remains that the most common pathogens for neonatal sepsis are group B streptococcus, *e. coli*, streptococcus viridans and enterococcus while concern for *listeria monocytogenes* must be considered in empiric therapy.[4-5] In light of needing antibiotics to cover these organisms, it was decided to simplify and standardize the order set to make them more user friendly for ED clinicians and align with continued management upon admission.

Therefore, the order set only recommends combination ampicillin and cefotaxime as antibacterial agents, knowing that resistance to cefotaxime is low in infants and it has the ability to cross the blood brain barrier in case of meningitis. Another important shift in this version has been to give all neonates antiviral empiric therapy. A Canadian review found that herpes simplex virus (HSV) meningitis predominantly affected those less than 16 days of life, and had up to 13% mortality rates and severe...
Opioid-induced neonatal abstinence syndrome (NAS) is a withdrawal syndrome in the neonate secondary to maternal opioid use during pregnancy.[1] Incidence of NAS is growing, and estimated at 0.51% of all infants born in Canada.[1] Presentation of NAS varies, with the central nervous system (e.g. irritability, high-pitched crying, tremors, seizures), metabolic (e.g. febrile), respiratory (e.g. tachypnea), and gastrointestinal (e.g. poor feeding, poor weight gain, diarrhea, emesis) systems affected.[2] BC Women’s Hospital is introducing the “Eat, Sleep, Console” model, a new standardized treatment protocol using morphine (when pharmacotherapy indicated; first-line treatment is non-pharmacological) as a first-line option for opioid-induced NAS.[3] The Canadian Pediatric Society (CPS) does not provide specific recommendations for NAS management but notes morphine is the most common first-line treatment option.[1] A review of NAS drug therapy alternatives is presented in Table 1. This review excludes articles published before 2000 and articles using paregoric or diluted tincture of opium (DTO), as these do not reflect current practice. Table 2 summarizes included head-to-head comparisons.

**Network Meta-Analysis**
The different pharmacological treatments for NAS were compared in a network meta-analysis.[4] Only randomized controlled trials (RCTs) were analyzed, and older trials using DTO were also included.[4] Of the different pharmacological agents available, buprenorphine had the greatest median rank for the outcomes of length of stay and treatment.[4] Several issues hamper interpretation of these results, including imprecision with large credible intervals, inter-trial heterogeneity with treatment protocols and patient populations, and an incomplete network for meta-analysis.

### Table 1: Pharmacological agents for the treatment of NAS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Pharmacokinetics</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Morphine [23]</td>
<td>µ-opioid receptor agonist</td>
<td>Bioavailability: 20-40% Half-life: 2-9 h</td>
<td>Current 1st-line treatment alternative at BCWH</td>
</tr>
<tr>
<td>Methadone [1,24,25]</td>
<td>Long-acting synthetic opioid, µ-opioid receptor agonist, and NMDA receptor antagonist</td>
<td>Bioavailability: 50% Half-life: 16-25 h high interpatient variability in pharmacokinetics</td>
<td>Prescribers require authorization from the Methadone Maintenance Program, (including NAS)</td>
</tr>
<tr>
<td>Buprenorphine [1,26]</td>
<td>Partial µ-opioid receptor agonist, and κ-opioid receptor antagonist</td>
<td>Bioavailability: 7% Half-life: 11 h</td>
<td>Formulations for the treatment of NAS are not available in Canada</td>
</tr>
<tr>
<td>Clonidine [27,28]</td>
<td>Centrally-acting alpha-2-adrenergic agonist</td>
<td>Bioavailability: 50% Half-life: 44-72 h</td>
<td>Primarily used as adjunctive treatment at BCWH</td>
</tr>
<tr>
<td>Phenobarbital [1,29]</td>
<td>GABA receptor agonist</td>
<td>Bioavailability: &gt;90% Half-life: 74 – 150 h</td>
<td>Primarily used as adjunctive treatment at BCWH</td>
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</tbody>
</table>

**Methadone vs Morphine**
Two RCTs and 3 retrospective cohort trials assessed the differences between morphine and methadone for NAS.[5,6] The RCTs examine similar maternal and infant patient populations, and use a modified Finnegan score to determine treatment initiation, titration, and weaning.[5,6] Both RCTs found methadone superior to morphine in reducing length of hospital stay (LOH) and length of drug treatment (LOD).[5,6] There were no differences in adjunctive treatments.[5,6]

The 3 retrospective cohort trials had variable results: one showing statistical superiority, one showing no difference, and one showing inferiority of methadone to morphine.[7-9] Interpretation of these results are limited due to the lack of a standardized treatment protocol between sites, and significant differences in inter- and intra-trial baseline characteristics.

**Clonidine vs Morphine**
In 1 RCT, clonidine was superior to morphine in reducing LOD, outpatient treatment duration, and LOH.[10] The trial also assessed patients using the NICU Network Neurobehavioral Scale (NNNS) at 5 to 7 days after the start of treatment and again at 40 to 44 weeks postmenstrual age.[10] No clinically significant differences were seen between groups.[10] One retrospective trial comparing continuous infusions of morphine and clonidine found similar results in LOH and LOD.[10]

**Clonidine as adjunct (Morphine vs Morphine and Clonidine)**
One retrospective cohort trial found no differences between morphine monotherapy and concomitant morphine and clonidine therapy for LOH.[12] However, morphine monotherapy was statistically superior for length of morphine treatment and total LOD.[12] Significant differences in baseline characteristics confound interpretation of these results.

**Buprenorphine vs Methadone**
Two retrospective cohort trials compared buprenorphine and methadone.[13,14] In both trials, buprenorphine was superior for reducing LOH and length of treatment.[13,14] Several limitations impact interpretation of the results, including confounding of the methadone arm by allowing patients to be on morphine instead, exclusion of patients from the buprenorphine treatment arm based on maternal methadone exposure, and potential treatment site differences. ...article continues on page 4
Phenobarbital vs Morphine
Two RCTs comparing phenobarbital and morphine monotherapy found differing results. One RCT found that the morphine monotherapy group had a statistically significant lower LOD, and lower admission to the Special Care Baby Unit.[15] One prospective pre-post cohort trial found similar results for LOD with similar limitations.[16] The other RCT demonstrated a nearly identical LOH and LOD.[17] These results may be accounted for by several significant differences, including prevalence of maternal methadone use, phenobarbital and morphine dosing, and maternal exposure to alternative drugs, such as benzodiazepines.

Buprenorphine vs Morphine
Three sequentially published RCTs, culminating in the BBORN trial, compared the use of buprenorphine to morphine, and all found that the LOD and LOH were reduced in the buprenorphine group.[18-20] One of the RCTs did not find statistical significance, but the trial was underpowered. Results appear clinically significant and consistent with other RCTs.[18]

Morphine and Phenobarbital vs Morphine and Clonidine
One RCT compared the adjunctive use of phenobarbital and clonidine with morphine. The RCT initiated either phenobarbital or clonidine at the same time as morphine, and not sequentially after trialing morphine as is typically done at BCWH.[21] In this context, phenobarbital was superior to clonidine in the average time taken to wean off morphine and the total morphine dose given.[21] Unfortunately, these positive findings in the phenobarbital group are limited due to the much extended duration of outpatient phenobarbital use, 3.8 months (range 1-8 months), compared to clonidine which was, according to protocol, weaned off completely within 48 hours of morphine discontinuation. One retrospective pre-post cohort trial found conflicting results, in that the total length of treatment and length of hospitalization was reduced in the adjunctive clonidine group.[22] In this retrospective trial, phenobarbital and clonidine were sequentially added to morphine therapy, and morphine was up-titrated more rapidly than the phenobarbital group, potentially confounding the results in favour of the clonidine group.[22]

Conclusions
Current literature does not state a superior pharmacological option for treatment of NAS. No significant adverse events were observed in any of the included trials. A recent network meta-analysis found buprenorphine is likely superior to other options, but limitations impact indirect comparisons. Logistical issues prevent use of buprenorphine and methadone at BCWH. While phenobarbital remains a viable treatment option for NAS, morphine and clonidine appear superior.

Table 2: Evidence summary of NAS head-to-head comparison trials

<table>
<thead>
<tr>
<th>First Author (Publication year)</th>
<th>Study design (Total N)</th>
<th>Patient population</th>
<th>LOH (d)</th>
<th>LOD (d)</th>
<th>Use of any adjunct/rescue</th>
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<tbody>
<tr>
<td>Methadone vs Morphine</td>
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<tr>
<td>Davis (2018) [5]</td>
<td>R, DB, AC (N = 116)</td>
<td>Term infants, maternal treatment with methadone or buprenorphine</td>
<td>Mean: 21.8±15 vs 23.2±8.8, adjusted p=0.046</td>
<td>Mean: 14.7±8.0 vs 16.6±6.9; adjusted p=0.02</td>
<td>17.2% vs 29.3%; adjusted p=0.07</td>
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<tr>
<td>Brown (2015) [6]</td>
<td>R, DB, AC (N = 31)</td>
<td>Term infants, maternal treatment with methadone or buprenorphine, no maternal benzodiazepine exposure</td>
<td>Mean: 14 vs 21; p=0.008</td>
<td>Mean: 14.5 vs 25; p=0.004</td>
<td>40% vs 56%; p=0.64</td>
</tr>
<tr>
<td>Lainwala (2005) [7]</td>
<td>Retrospective cohort (N = 46)</td>
<td>Term infants, maternal exposure to any opioid</td>
<td>Median: 40 (IQR 30-51) vs 36 (IQR 33-39); p=0.142</td>
<td>Not assessed</td>
<td>Not assessed</td>
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<tr>
<td>Tolia (2018) [8]</td>
<td>Retrospective cohort (N = 7667)</td>
<td>Term infants, diagnosed with NAS, received morphine or methadone first prior to any other drug therapy for NAS</td>
<td>Median: 18 (IQR 11-30) vs 23 (IQR 16-33); p&lt;0.001, adjusted for confounders methadone was still superior</td>
<td>Not assessed</td>
<td>17% vs 26%; p&lt;0.001</td>
</tr>
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<td>Young (2015) [9]</td>
<td>Retrospective cohort (N = 26)</td>
<td>Preterm and term infants, maternal exposure to any opioid</td>
<td>Mean: 44.23±27.95 vs 12.08±4.63; p&lt;0.001</td>
<td>Mean: 38.08±27.38 vs 7.46±4.88; p=0.001</td>
<td>46% vs 23%; p=0.216</td>
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</table>

...table continues on page 5
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<thead>
<tr>
<th>First Author (Publication year)</th>
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<th>LOH (d)</th>
<th>LOD (d)</th>
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<tr>
<td><strong>Clonidine vs Morphine</strong></td>
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<tr>
<td>Bada (2015) [10]</td>
<td>R, DB, AC (N = 31)</td>
<td>Term infants, maternal exposure to any opioid</td>
<td>Mean: 14.9±6 vs 21±12.3; p&gt;0.05</td>
<td>Mean: 32±20.4 vs 42.9±17.8; p=0.02</td>
<td>Not assessed</td>
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<tr>
<td><strong>Morphine vs Morphine plus Clonidine</strong></td>
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<tr>
<td>Gullickson (2018) [12]</td>
<td>Retrospective cohort (N = 122)</td>
<td>Late preterm and term infants, diagnosed with NAS</td>
<td>Median: 22.5 (IQR 14-33) vs 21 (IQR 15-33); p=0.6</td>
<td>All treatment, mean: 11.3±7.6 vs 19.7±12.9; p&lt;0.01</td>
<td>Not assessed</td>
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<td><strong>Buprenorphine vs Methadone</strong></td>
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<tr>
<td>Hall (2016) [13]</td>
<td>Retrospective cohort (N = 201)</td>
<td>Term infants, maternal opioid exposure, patients with antenatal methadone exposure were not given buprenorphine</td>
<td>Mean: 16.3 (95% CI 13.7-18.9) vs 20.7 (95% CI 19.1-22.2); p&lt;0.001</td>
<td>Mean: 9.4 (95% CI 7.1-11.7) vs 14 (95% CI 12.6-15.4); p&lt;0.001</td>
<td>23.7 vs 25.8%; p=0.79</td>
</tr>
<tr>
<td>Hall (2017) [14]</td>
<td>Retrospective cohort (N = 360)</td>
<td>Term infants, any infant treated for NAS with an opioid (buprenorphine, morphine, or methadone)</td>
<td>Mean: 12.4 (95% CI 11.3-13.6) vs 15.2 (95% CI 14.1-16.4); p&lt;0.001</td>
<td>Mean: 7.4 (95% CI 6.3-8.5) vs 10.4 (95% CI 9.3-11.5); p&lt;0.001</td>
<td>52.3 vs 46.2%; p=0.3</td>
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<tr>
<td><strong>Phenobarbital vs Morphine</strong></td>
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<tr>
<td>Jackson (2004) [15]</td>
<td>R, DB, AC (N = 75)</td>
<td>Preterm and term infants, maternal methadone exposure</td>
<td>Not assessed</td>
<td>Mean: 12 vs 8; p=0.02</td>
<td>47 vs 35%; p=0.11</td>
</tr>
<tr>
<td>Nayeri (2015) [17]</td>
<td>R, OL, AC (N = 60)</td>
<td>Term infants, maternal exposure to any addictive drugs, no benzodiazepine exposure</td>
<td>Mean: 12.5±5.3 vs 12.6±5.6; NSS</td>
<td>Mean: 8.5±4 vs 8.5; NSS</td>
<td>6.6 vs 3.3%; NSS</td>
</tr>
<tr>
<td>Ebner (2007) [16]</td>
<td>Prospective, pre-post (N = 32)</td>
<td>Term infants, maternal exposure to an opioid maintenance program, no illicit polysubstance abuse permitted, no benzodiazepine exposure</td>
<td>Not assessed</td>
<td>Mean: 17.7±10.1 vs 9.9±8.2; p=0.021</td>
<td>Not assessed</td>
</tr>
<tr>
<td>First Author (Publication year)</td>
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<tr>
<td><strong>Buprenorphine vs Morphine</strong></td>
<td>R, OL, AC (N = 26)</td>
<td>Term infants, maternal exposure to any opioid, no benzodiazepine exposure</td>
<td>Mean: 27±11 vs 38±16; p = 0.068</td>
<td>Mean: 22±11 vs 32±16; p = 0.077</td>
<td>23.1% vs 7.7%; p &gt; 0.05</td>
</tr>
<tr>
<td>Kraft (2008) [18]</td>
<td>R, OL, AC (N = 24)</td>
<td>Term infants, maternal exposure to any opioid, no benzodiazepine exposure</td>
<td>Mean: 32±24 vs 42±13; p = 0.05</td>
<td>Mean: 23±12 vs 38±14; p = 0.01</td>
<td>25% vs 8.3%; p &gt; 0.05</td>
</tr>
<tr>
<td>Kraft (2017) [20]</td>
<td>R, DB, AC (N = 63)</td>
<td>Term infants, maternal exposure to any opioid, no benzodiazepine exposure</td>
<td>Median: 21 (range 7-71) vs 33 (18-70); p &lt; 0.001</td>
<td>Median: 15 (range 3-67) vs 28 (range 13-67); p &lt; 0.001</td>
<td>15% vs 23%; p = 0.36</td>
</tr>
<tr>
<td><strong>Morphine and Phenobarbital vs Morphine and Clonidine</strong></td>
<td>R, OL, AC (N = 68)</td>
<td>Term infants, maternal exposure to any opioid, no benzodiazepine exposure</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Morphine treatment time: 12.4 (95% CI 10.1-14.7) vs 19.5 (95% CI 15.7-23.2); p = 0.001</td>
</tr>
<tr>
<td>Surran (2013) [21]</td>
<td>R, OL, AC (N = 68)</td>
<td>Term infants, maternal exposure to any opioid, no benzodiazepine exposure</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Morphine treatment time: 12.4 (95% CI 10.1-14.7) vs 19.5 (95% CI 15.7-23.2); p = 0.001</td>
</tr>
<tr>
<td>Devlin (2017) [22]</td>
<td>Retrospective, pre-post cohort</td>
<td>Term infants, diagnosed with NAS</td>
<td>Mean: 42 vs 33; p &lt; 0.001</td>
<td>Mean: 35 vs 26.5; p &lt; 0.001</td>
<td>63% vs 39%; p = 0.004</td>
</tr>
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AC = active-comparator; DB = double-blind; IQR = interquartile range; NSS = not statistically significant; OL = open-label; R = randomized

### References - Opioid-induced Neonatal Abstinence Syndrome


### Awards and Recognition

- Pharmacy Informer Editorial Board

**Dean Elbe, BScPharm, PharmD, BCPP (Editor)**
**Vanessa Paquette, BScPharm, PharmD (Editor)**
**Jason Tan, BScPharm, PharmD (Editor)**
**Jennifer Kendrick, BScPharm, PharmD (PTN Liaison)**
**Roxane Carr, BScPharm, PharmD, BCPS, FCSHP (Clinical Coordinator)**
The use of balanced crystalloids is becoming increasingly popular in both critical care and other settings. The rationale for their use is that their composition more closely resembles the composition of plasma when compared to normal saline. Specifically, balanced crystalloids contain less chloride as well as additional anions such as lactate, or gluconate and acetate that are metabolized by the liver to carbon dioxide and water which consumes hydrogen cations and produces a metabolic alkalinizing effect. This could possibly reduce the development of a hyperchloremic metabolic acidosis, especially in patients requiring large volumes of intravenous fluid. The balanced crystalloids most commonly used at BCCH are Plasma-Lyte and Ringer’s Lactate.

The development of a metabolic acidosis can be undesirable in critically ill patients, as is the development of hyperchloremia itself. Hyperchloremia has been associated with development of acute kidney injury (AKI); while the exact mechanism of hyperchloremia associated AKI is unclear, it is thought to be related to renal vasoconstriction mediated by tubuloglomerular feedback. Whether the use of balanced crystalloids reduces AKI or other morbidities compared to normal saline has been debated in the literature. The SPLIT trial, a large randomized controlled trial (RCT) that included ICU patients receiving saline or a balanced crystalloid found no difference in mortality, development of AKI, or need for renal replacement therapy (RRT). A more recent meta-analysis found decreased mortality at 28 or 30 days in groups that received balanced crystalloids compared to normal saline (RR: 0.86, 95% CI: 0.75-0.99), however this was powered by observational studies and the effect was not significant among the subgroup of RCTs. Additionally, there was a significant reduction in the incidence of AKI (RR: 0.91, 95% CI: 0.85-0.98), however the difference in progression to RRT was not statistically significant (RR: 0.91, 95% CI: 0.79-1.04). Two large recently published RCTs comparing the use of saline to balanced crystalloids, the SALT-ED study, conducted in critically ill patients, and the SMART study conducted in non-critically ill patients, both found significant reductions in major adverse kidney events, but did not find significant reductions in mortality or other morbidities.

Despite the theoretical advantages to balanced crystalloids and possible benefits in reducing adverse outcomes, there are potential limitations to their widespread use. Ringer’s lactate has a sodium concentration of 130 mmol/L, and could increase the risk of hyponatremia. The incidence of hyponatremia was higher in ICUs that used more Ringer’s lactate compared to saline. This is not normally an issue for Plasma-Lyte, unless dextrose is added, which is commonly done in an attempt to reduce the risk of hypoglycemia. As dextrose is added to a bag of Plasma-Lyte, its contents become more dilute, making it a more hypotonic solution (Table 1). Additionally, there is less data regarding intravenous compatibility of medications with balanced crystalloids, particularly Plasma-Lyte. Of note, Plasma-Lyte has been reported to be incompatible with propofol and with certain concentrations of midazolam. Lastly, balanced crystalloids tend to be more expensive; while the cost of obtaining a 1 liter bag of Ringer’s Lactate is only 20% higher than saline, a 1 liter bag of Plasma-Lyte is 2.5 times the cost of saline.

Recent studies have served to spur further debate regarding the use of balanced crystalloids. Pharmacists play a role in the management of intravenous fluids and determination of compatibilities with other medications and therefore should be familiar with the literature pertaining to balanced crystalloids as well as the practicalities regarding their use.

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<thead>
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<th>Table 1. Balanced Crystalloid Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Na</strong></td>
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</tr>
<tr>
<td>Ringers Lactate**</td>
</tr>
<tr>
<td>Plasma-Lyte***</td>
</tr>
<tr>
<td>D5-Plasma-Lyte</td>
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<tr>
<td>D10-Plasma-Lyte</td>
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</tbody>
</table>

**Ringer’s lactate also contains 28 mmol/L of lactate**

***Plasma-Lyte also contains 27 mmol/L of acetate and 23 mmol/L of gluconate

All Things Sepsis continued from page 2

eurodevelopmental morbidity. With this in mind, the new algorithm recommends all neonates receive acyclovir until lumbar punctures rules out the possibility of neonatal HSV.

These changes prompted the creation of an additional order set that addressed ED management of sepsis and septic shock in pediatric patients greater than 30 days of life to adolescence. The need for this order set was to create concise information that aligns with early goal-directed therapy from landmark guidelines such as the Surviving Sepsis Campaign as well as antibiotic therapy guided by the BCCH Empiric Guide. The order set provides conservative guidelines in which antibiotics, fluids and if needed, vasopressors, should be initiated in a timely manner.

Both “ED Rule Out Serious Infections in Neonates less than 30 Days of Age” and “ED Suspected Sepsis and Septic Shock (greater than 30 days of age)” can be found on ePOPs.

**References**