**Cyclophosphamide Recurring Infusion v4.2**

**Initial Orders**
- Assess pain
- Place IV
- Collect urine output
- Labs: blood, urine, pregnancy test for females ≥ age 10 years

**Therapy**
- **1 hour prior**
  - Bolus NS 25ml/kg over 1 hour
  - Assure urine output adequate* prior to starting cyclophosphamide (see right)
- **30 min prior**
  - (As soon as urine output adequate) Premedications (oral preferred) Ondansetron, diphenhydramine
- **Hour 0**
  - Administer cyclophosphamide IV over 30 minutes
  - Start D5½NS at 2X maintenance (infuse for 4 hours)
- **Hour 2**
  - Optional IV MethylPREDNISolone over 1 hr (if disease management warrants)
- **End of hour 4**
  - Discontinue maintenance fluids

**Monitoring**
- **Urine Output**
  - Strict I&O at presentation and q 2 hours
  - Dipstick all voids; discontinue chemstix if heme +
  - Call provider if urine heme increases 2 grades
  - NS bolus to achieve urine output prior to infusion*
  - Children <40kg: ≥2mL/kg/hr
  - Children ≥40kg: ≥1.5mL/kg/hr
  - Call provider for insufficient urine output over 4 hours:
    - Children <40kg: <1.5mL/kg/hr
    - Children ≥40kg: <1mL/kg/hr
- **Vital signs**
  - Temp, HR, RR, BP q 4 hours
  - Call provider for diastolic BP >90 mmHg during cyclophosphamide
  - During methylprednisolone infusion: blood pressure q 15min (start, during, and at end of infusion); see formulary for methylprednisolone parameters

**Discharge Instructions**
- Labs day 10, 14, and 21*
- Ondansetron for home
- Resume home medications and review steroid taper
- See lab order sheet and steroid template
- Clinic follow-up in 4 weeks (Rheumatology and/or Nephrology)
  - * Skip day 21 if q 2 week dosing
**Cyclophosphamide Impaired Renal Function Infusion v4.2**

**Approval & Citation**
- Start IV Fluids
- Cyclophosphamide IV over
- Optional IV methylPREDNISolone over
- Mesna IV over
- Mesna IV over
- Furosemide IV over
- Mesna IV over
- Pneumocystitis prophylaxis

**Inclusion Criteria**
- Patients with diagnosed disorder initiating treatment with pulse cyclophosphamide (Cytoxan), including lupus nephritis or small vessel vasculitis
- Oliguria or renal insufficiency

**Exclusion Criteria**
- Malignancy, transplant, severe infection, or pregnancy/nursing

**Admit Criteria**
- History of infusion reaction
- Bladder irrigation (Foley catheter)
- Uncontrolled hypertension
- Developmental age requiring toileting assistance
- Other Illness requiring hospital stay
- Concern for ability to safely monitor after discharge

**Summary of Version Changes**
- Prior to Infusion:
  - Confirm impaired renal function and/or urine output

**Prior to Infusion**
- Normal Renal Function
- Impaired Renal Function

**Initial Orders**
- Assess pain
- IV: placement and fluids (per Nephrology orders based on renal function)
- Labs: blood, urine, pregnancy test for females ≥ age 10 years
- Inpatients only: Foley catheter if needed (with bladder irrigation) (for SCH only)
- Maintenance home medications including prednisone taper, calcium, vitamin D, and Pneumocystitis prophylaxis

**Therapy**
- 1 hour prior: Start IV Fluids
- 30 min prior: Premedications (Oral Preferred): Ondansetron, diphenhydramine
- 15 min prior: Mesna IV over 15 minutes
- Hour 0: Cyclophosphamide IV over 30 minutes
- Hour 1.5: Furosemide IV over ~15 minutes (1 hour after end of cyclophosphamide)
- Hour 3.5: Mesna IV over 15 minutes (3 hours after end of cyclophosphamide)
- Hour 4.5: Optional IV methylPREDNISolone over 1 hr (if disease management warrants)
- Hour 6.5: Mesna IV over 15 minutes (6 hours after end of cyclophosphamide)

**Monitoring**
- **Urinary Output**
  - Strict I&O at presentation and q 2 hours
  - Dipstick all voids; discontinue chemstix if heme +
  - Call provider if urine heme increases 2 grades
  - Call provider for insufficient urine output over 4 hours:
    - Children <40kg: <1.5mL/kg/hr
    - Children ≥40kg: <1mL/kg/hr

- **Vital signs**
  - Temp, HR, RR, BP q 4 hours
  - Call provider for diastolic BP >90 mmHg during cyclophosphamide
  - During methylprednisolone infusion: blood pressure q 15min (start, during, and at end of infusion); see formula for methylprednisolone parameters

**Discharge Criteria**
- Finished with infusion and hydration
- Tolerating oral fluids
- Controlled nausea/vomiting

**Discharge Instructions**
- Labs day 10, 14, and 21*
- Ondansetron for home
- Resume home medications and review steroid taper
- See lab order sheet and steroid template
- Clinic follow-up in 4 weeks (Rheumatology and/or Nephrology)

* Skip day 21 if q 2 week dosing

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For questions concerning this pathway, contact: cyclophosphamide@seattlechildrens.org

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Last Updated: May 2018
Next Expected Review: February 2023
Cyclophosphamide IV dosing

Recommendations:

Initiate cyclophosphamide at 750mg/m2 (initial dose range 500-1000mg/m2) every 4 weeks for a total of 6 cycles.

Alternate dosing:

Euro-Lupus protocol for lupus nephritis: cyclophosphamide 500mg IV every 2 weeks for 6 doses

CYCLOPS protocol for ANCA Vasculitis: may use cyclophosphamide IV 15mg/kg (max 1.2g) every 2 weeks x 3 then every 3 weeks until remission, then for another 3 months following remission

[LOE: Moderate Quality (Ntatsaki 2014, Walters 2015)]

IV Cyclophosphamide dose adjustments

Recommendation:

- *When using monthly dosing*, titrate subsequent doses based on total White Blood Cell count (WBC) and Absolute Neutrophil Count (ANC) nadir (lowest of d10, d14, d21 labs)

**GOAL: WBC 3-4K, ANC: 1500-3000**

- For WBC >4K, increase by 10%.
- IF WBC 2-3K or ANC < 1500, reduce by 20%.
- IF Total WBC<2K, reduce by 40%.

[LOE: Local Expert Opinion (Degroot 2009; Guillemin 1, 1997)]

IV Cyclophosphamide dose adjustment: Renal Failure

For dose adjustment in patients with diminished renal function (Glomerular Filtration Rate [GFR]<10) or oligoanuric, consult nephrology.

Use IV mesna and bladder protection for GFR <60 ml/min per 1.73m2

[LOE: Local Expert Opinion]
Warning Signs: Hemorrhagic Cystitis

Hemorrhagic cystitis:
• Rare but serious complication of cyclophosphamide infusion
• Drug metabolites can cause bladder irritation
• May lead to increased later risk of bladder cancer

Symptoms:
• Frank blood clots in urine
• Extremely painful urination

Prevention:
• Hyperhydration
  • For patients with impaired renal function or decreased urine output, use mesna to bind toxic metabolites

Monitoring:
• Many patients with SLE or vasculitis have baseline asymptomatic hematuria which should not be cause for alarm
• Dipstick all voids; discontinue if initial chemstix are heme positive
• Call provider if urine heme increases 2 grades or becomes painful, grossly bloody
Warning Signs: Cardiovascular Instability

Patients receiving cyclophosphamide have multiple reasons to develop elevated blood pressures:

- Kidney involvement from underlying disease
- Chronic steroid administration
- Hyperhydration/fluid retention
- IV Methylprednisone infusion

Monitor BP closely throughout infusion:

- Call provider for diastolic BP > 90 or
- Symptomatic hypertension for age
Recommendation:

Initial steroid dose at diagnosis:

- Methylprednisolone  IV 30mg/kg/dose (max 1000mg) daily, x 3 doses if inpatient

[LOE: Expert opinion, Mina 2012]
Calcium/Vitamin D Supplementation

Recommendation:

Supplemental Ca/Vitamin D for patients on chronic steroids:

Calcium

- Age ≥4 yrs: Elemental calcium 1000mg daily
  (=2500mg calcium carbonate) in divided doses

Vitamin D

- Age 4 yr-adult: Vitamin D 600 IU daily
- Suspected vitamin D deficiency, check baseline levels

If vitamin D deficient, may need higher dosing

[LOE: ☀️☀️ Very low quality (Muske 2017, Buckley 2017)]
**Recommendation:**

Prophylaxis for Pneumocystis infection for all patients on Recurring Cyclophosphamide Infusion Pathway:

**Bactrim 2.5 mg TMP/kg twice daily (max 160mg TMP)**

- 2 days/week (usually Monday, Tuesday)

- If contraindicated alternative agents:
  - Atovaquone
  - Dapsone
  - Pentamidine

# VALUE ANALYSIS TOOL

<table>
<thead>
<tr>
<th>DIMENSION</th>
<th>CARE OPTION A</th>
<th>CARE OPTION B</th>
<th>PREFERRED</th>
<th>ASSUMPTIONS MADE</th>
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<tbody>
<tr>
<td>DESCRIPTION OF CARE TREATMENT OPTION</td>
<td>Inpatient admission for cyclophosphamide infusion</td>
<td>ANI setting for cyclophosphamide infusion</td>
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<td></td>
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<tr>
<td>OPERATIONAL FACTORS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Percent adherence to care (goal 80%)</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Care delivery team effects</td>
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<tr>
<td>BENEFITS / HARDS (QUALITY/OUTCOME)</td>
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<td></td>
<td></td>
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<tr>
<td>Degree of recovery at discharge</td>
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<td>n/a</td>
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<td>Effects on natural history of the disease over equivalent time</td>
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<tr>
<td>Potential to cause harm</td>
<td>some harm potentially due to hospitalization related infections?</td>
<td>currently no mechanism to pair patient visit with medication administration; may result in prolonged steroid taper, less oversight of cyclophosphamide dosing</td>
<td>OPTION A</td>
<td>no changes to existing ANI clinic flow</td>
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<tr>
<td>Palatability to patient/family</td>
<td>HIGH - convenience; avoids missed work/school; combines clinic visit with medication administration</td>
<td>LOW - extra clinic visit required; need to arrive early for ANI appt so must either live close or leave the night prior</td>
<td>OPTION A</td>
<td>no access to weekend ANI hours for outpatient cyclophosphamide</td>
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<tr>
<td>Population-related benefits</td>
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<td>improved access to hospital beds for sicker patients</td>
<td>OPTION B</td>
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<td>Threshold for population-related benefits reached</td>
<td>n/a</td>
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<td>COST (Arisng from Options A or B) - express as cost per day</td>
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<tr>
<td>“ROOM RATE” ($ or time to recovery)</td>
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<tr>
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## VALUE ANALYSIS GRID

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<tr>
<th>BENEFIT (QUALITY &amp; OUTCOMES)</th>
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<th>A = B</th>
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<tr>
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<tr>
<td>A costs more than B</td>
<td>Make value judgement</td>
<td>B</td>
<td>B</td>
<td>Do B and PDSA in 1 year</td>
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<tr>
<td>A and B costs are the same</td>
<td>A</td>
<td>A or B, operational factors may influence choice</td>
<td>B</td>
<td>A or B, operational factors may influence choice, PDSA in 1 year</td>
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<tr>
<td>B costs more than A</td>
<td>A</td>
<td>A</td>
<td>Make value judgement</td>
<td>Do A and PDSA in 1 year</td>
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</tbody>
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## VALUE STATEMENT

Administering cyclophosphamide in the infusion center versus overnight hospital admission reduces the cost per infusion by $2300 and offers some population related benefits; however this option places undue burdens on certain families and is associated with some potential for harm due to lack of existing structure to fully support this model. Given this, the choice of setting should be open to family preference until such time as institutional ability to facilitate enhanced access options and structural support for outpatient infusions. A cost-minimization approach was applied.
This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94.):

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Guideline – Recommendation is from a published guideline that used methodology deemed acceptable by the team.

Expert Opinion – Our expert opinion is based on available evidence that does not meet GRADE criteria (for example, case-control studies).

**Quality of Evidence:**
- 🌟🌟🌟🌟 High quality
- 🌟🌟🌟 Moderate quality
- 🌟🌟 Low quality
- 🌟 O Very low quality

Guideline
Expert Opinion
Approved by the Cyclophosphamide Recurring Infusion Clinical Standard Work (CSW) Team for February 13, 2018 go live

Cyclophosphamide Recurring Infusion CSW Team:

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Medical Clinical Nurse Specialist: Rebecca Engberg, BSN, RN, CPN
Clinical Pharmacist: Dominique Mark, PharmD, BCPS, BCPPS
Pharmacy Informatics: Rebecca Ford, PharmD

Clinical Effectiveness Team:

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CE Analyst: Susan Stanford, MPH, MSW
CIS Informatician: Carlos Villavicencio, MD
CIS Analyst: Maria Jerome
Librarian: Jackie Morton, MLS
Program Coordinator: Kristyn Simmons

Executive Approval:

Sr. VP, Chief Medical Officer Mark Del Beccaro, MD
Sr. VP, Chief Nursing Officer Madlyn Murrey, RN, MN
Surgeon-in-Chief Bob Sawin, MD

Retrieval Website: http://www.seattlechildrens.org/pdf/cyclophosphamide-pathway.pdf

Please cite as:
Summary of Version Changes

- Version 1.0 (4/30/2012): Go live
- Version 1.1 (5/29/2012): Clarified timing for cyclophosphamide pre-medications
- Version 1.2 (9/10/2013): Updated charting instructions for steroid taper
- Version 1.3 (2/25/2014): Added requirement for pregnancy testing
- Version 2.0 (12/19/2014): Removed maximum on initial cyclophosphamide dose
- Version 3.0 (1/25/2016): CSW Value Analysis completed, changes include recommending ambulatory infusion when patient meets criteria
- Version 3.1 (11/1/2016): Changed next revision date to April 2017 (5 years from go-live)
- Version 4.0 (2/13/2018): Removed mesna and increased hydration for patients with normal renal function
Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.
Search Methods

Studies were identified by searching electronic databases using search strategies developed and executed by a medical librarian, Jackie Morton. Searches were performed in May, 2017. The following databases were searched – Ovid Medline; Cochrane Library; Embase; National Guideline Clearinghouse; TRIP; and Cincinnati Children’s Evidence-Based Recommendations. In Medline and Embase, appropriate Medical Subject Headings (MeSH) and Emtree headings were used respectively, along with text words, and the search strategy was adapted for other databases using text words. Concepts searched were dosing of cyclophosphamide in glomerulonephritis, lupus nephritis, or systemic lupus erythematosus. Dosing of calcium and vitamin D in patients receiving cyclophosphamide concurrent with steroids and dosing of cyclophosphamide with plasmapheresis. Retrieval was limited to 2007 to current, humans, pediatrics, English language and to certain evidence categories, such as relevant publication types, index terms for study types and other similar limits.

February 12, 2018

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</table>

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535


Bibliography: from 2012 Initial Pathway


