Requirements for Petitioning to Waive an Advanced Pharmacy Practice Experience (APPE)

The student may elect to waive one (1) of their APPEs if all of the following criteria are met:

1. The student must have at least 6 weeks of work-related experience in the APPE area of specialty. To fulfill this requirement, the student must obtain and mail a signed letter to the ISU College of Pharmacy from the student’s pharmacy supervisor/preceptor and/or peer stating the student has met this requirement.

2. The student must present a portfolio of patient write-ups meeting the following criteria:
   a. A minimum of four (4) patient write-ups in a grand-rounds PHARME or SOAPME format.
   b. Each write-up will be a minimum of twenty-five (25) pages in length.
   c. Each write-up must cover and discuss all drug/health related topics for the patient. The information should not be limited to just the current therapy but also an analysis and discussion of all therapeutic alternatives for each problem listed in the patient write-up. This must include evaluation and comparison of drug side effects, relative efficacy, cost analysis of therapeutic alternatives, and application of treatment guidelines for each problem.
   d. Each write-up must be fully referenced with at least five (5) of the references not older than one (1) year.

3. The portfolio of patient write-ups must cover all the disease states listed for the respective APPE.
   a. A student wishing to waive the Ambulatory Care APPE is responsible for the following disease states and therapies:
      - Diabetes Mellitus
      - Hyperlipidemia
      - Hypertension
      - Peptic Ulcer Disease
      - Arthritis
      - Coronary Artery Disease
      - Thyroid Disease
      - Community Acquired Infections
      - Congestive Heart Failure
      - Reactive and Obstructive Airway Disease
      - Oral Anticoagulant Therapy
      - Pain Management
   
   b. A student wishing to waive the Geriatrics APPE is responsible for the following disease states and therapies:
      - Dementia of the Alzheimer’s Type (DAT)
      - Parkinson’s Disease
      - Insomnia
c. A student wishing to waive the Pediatrics APPE is responsible for the following disease states and therapies:
- Otitis Media/Otitis Externa
- Reactive Airway Disease
- Pediatric and Neonatal Sepsis and Meningitis
- Formulas/Oral Rehydration Solutions/Gastroenteritis
- Immunizations
- Seizure Disorders and Febrile Seizures
- NICU Patient Care (drug administration, drug dosing, pharmacokinetics)
- Attention Deficit Disorder/Hyperactivity
- Type I & II Diabetes
- Bronchiolitis/Croup
- Toxicology (Acetaminophen, ASA, Iron, TCA’s)

d. A student wishing to waive the Medicine APPE is responsible for the following disease states and therapies:
- Central Nervous System
  - Acute Stroke
  - Status Epilepticus
- Cardiovascular Disease
  - Myocardial Infarction
  - Hypertensive Urgency/Emergency
  - Pulmonary Edema/CHF
  - Unstable Angina
  - Antiarrhythmic Agents/ACLS
  - Shock
  - Hypertension
  - Hyperlipidemia
- Endocrinology
  - Diabetic Ketoacidosis
  - Type I & II Diabetes
  - Hypothyroidism/Hyperthyroidism
- Pulmonary Disease
  - Asthma/COPD
- Renal Disease
  - Acute Renal Failure
- Fluid and Electrolyte Management
  - Acid/Base disturbances and electrolyte management
- Gastrointestinal Disease
Liver Disease (cirrhosis, hepatitis)

- Thromboembolic Disease
  - DVT/PE
- Infectious Disease
  - Community-acquired/Nosocomial Pneumonia
  - Pyelonephritis
  - Skin/Soft Bone Tissue Infections
  - Acute Endocarditis
- Nutrition
  - TPN monitoring parameters and limitations

e. A student wishing to waive the Mental Health APPE is responsible for the following disease states and therapies:

- Psychotic Disorders
  - Schizophrenia
  - Delusional disorder
  - Schizoaffective disorder

- Mood Disorders
  - Depression
  - Bipolar-Mania

- Anxiety Disorders
  - Generalized anxiety disorder
  - Panic and phobic disorder
  - Post traumatic stress disorder
  - Obsessive compulsive disorder

- Eating disorders
  - Anorexia Nervosa
  - Bulimia Nervosa
- Substance Abuse/Dependance
- Developmental disorders

4. Completed portfolios should be sent to:
   Beverly Sion
   APPE Office Coordinator
   Nontraditional PharmD Program
   College of Pharmacy
   Idaho State University
   Campus Box 8356
   Pocatello ID  83209-8356
**Patient:** KC 12-year-old female with acute lymphoblastic leukemia (ALL).
CC: KC has been coming to clinic for management of her leukemia in between trips to her cancer clinic in another town. She has been neutropenic for the past few weeks and is here for evaluation.

**Pharmacotherapy List:**

*Current prescription medications:*

Interim maintenance chemotherapy (started 07/15/02)
1. Vincristine 2 mg IV push (1.5 mg/m²; 2 mg maximum dose)
2. Methotrexate 140 mg IV push over 10-15 min (100 mg/m² on day 0; then increase 50 mg/m² on subsequent doses.)
3. PEG-asparaginase 3500 IU IM (2500 IU/m²)
4. Intrathecal methotrexate 12mg IT
5. Anzemet 100 mg po or IV for nausea and vomiting

07/15/02:     Anzemet, Vincristine, methotrexate (IV and IT)
07/16/02:     PEG-asparaginase
07/25/02:     Vincristine, methotrexate (210 IV) – Kytril for emesis
08/05/02:     Vincristine, methotrexate (280mg IV)
08/06/02:     PEG-asparaginase
08/14/02:     Vincristine (_ to 1mg IV, due to T.bili-1.9), methotrexate (355 mg IV; 12 mg IT)
08/23/02:     Vincristine (1 mg IV), methotrexate dose held due to ANC-450 and plt-148.
09/20/02:     PEG-asparaginase
11/07/02:     Vincristine (all doses of chemotherapy were held due to low ANC from 09/20/02-11/07/02.

Diflucan (no dose noted in chart) for thrush (start 6 mg/kg po x 1; the 3 mg/kg po q24h x14 days; start 250 mg, then 150 mg q24h).
MS Contin 15mg for pain qHS (0.3-0.6 mg/kg/dose q24h; 12.3-24.6 mg/dose q24h), started 10/10/02.

*Past prescription medications:*

- Induction chemotherapy (started on 03/13/02) – 35-day therapy
  1. Prednisone 90 mg po QD (30 mg TID); tapered over 10 days at end of cycle.
  2. Vincristine 2 mg IV on days 0, 7, 14, & 21 (only received on days 0&7).
  3. Daunomycin 35 mg IV on days 0, 7, 14, & 21 (only received on days 0&7).
  4. L-asparaginase 8760 IU IM on days 3, 5, 7, 10, 12, 14, 17, 19, & 21 (missed days 5, 14, & 21).
  5. Cytosine arabinoside 70 mg IV on day 0.

Induction therapy ended on 04/22/02 – begin consolidation when ANC >750 and platelets >75,000.

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Example Grand Rounds PHAME Patient Write-up
Consolidation chemotherapy (started 04/22/02)
1. Cyclophosphamide 1430 mg IV on days 0 & 28 (day 28 not given).
2. Cytosine arabinoside 107 mg IV on day 0 (did not receive).
3. Intrathecal methotrexate 12 mg IT on days 0 & 7 (day 7 not given).
4. Vincristine 2 mg IV on day 14.
5. PEG-asparagase 3575 IU IM on day 14.
6. Mercaptopurine 2 tablets po x 3; then _ tablet x4 po on day 0.

- Rocephin 1g IV q24h until ANC are above 500(started 10/14/02, rec’d 11/11/02-11/14/02); was switched over to Suprax on 11/15/02.

- Suprax 200 mg po QD (discontinued on 11/19/02, ANC-310)

- Ceftazidime for three days on 10/31/02 for persistent neutropenia

- Lortab for pain but was discontinued due to neutropenia; because the APAP in the formulation can mask fever caused by an infection.

- Norvasc for hypertension. It is unclear in KC’s medical chart as to whether she has continued taking this medication since March 2002.

**OTC medications:** No OTC medications noted

**Drug allergies:**
1. Penicillin _ rash and hives

**History:**

**HPI:** KC presented with a several month history of hives and a new onset of a cough. She was evaluated by her PMD and given prednisone and Zyrtec for allergies. The hive persisted with some congestion. Earlier in March 2002, she was at a track meet and had some hip pain. She went to emergency room for hip X-rays. Her PMD requested a chest X-ray in order to evaluate the congestion. A mediastinal mass was noted and thought to be lymphoma. She was referred to Primary Children’s Medical Center (PCMC) in Salt Lake City for work-up and management. Evaluation at PCMC in March 2002 stated: KC had no bone pain or bleeding, small amount of weight loss on admission. HEENT was unremarkable. CBC was normal upon admission (she has not had an abnormal blood smear). Blood chemistry revealed evidence of tumor lysis syndrome (Ca: 11.7; uric acid: 14). CT demonstrated a large anterior mediastinal mass and masses on both kidneys and ovaries. She has a diagnostic pleurocentesis and bone marrow aspirate; both showed involvement with lymphoblasts. Flow cytometry demonstrated T-cell acute lymphoblastic leukemia (ALL). Post diagnosis of ALL, KC received induction therapy as outlined above. She continued to have significant tumor lysis syndrome and was treated successfully with fluid hydration and Lasix. Spinal tap showed new evidence of leukemia involvement in the CNS. KC developed mild hypertension while at PCMC, which was treated with Norvasc. She has completed the induction and consolidation phase of chemotherapy; she is currently on interim maintenance therapy. During this time, she has developed long-lasting neutropenia, which has prolonged chemotherapy stages and has resulted in being held from school. On 10/14/02, she presented with neutropenia with fever and was given Rocephin IM every 24 hours for infection prophylaxis; then given 3 days of ceftazidime. On 11/11/02, KC was still very
neutropenic and Rocephin was continued every 24 hours until neutrophil count was above 500. She received Rocephin until 11/15/02, when it was switched to Suprax (cefixime), which was discontinued on 11/19/02. On 10/10/02, KC came to clinic with severe leg and arm pain; she had received doxorubicin and Vincristine two weeks prior. PMD thought the pain was possibly due to decadron and Vincristine. She was on Lortab for pain but was discontinued due to neutropenia and was given MS Contin. Further, KC has had several oral fungal infections is now on prophylaxis therapy with Diflucan.

**PMH:** KC has had an unremarkable medical history outside from current medical problems.

**FMH:** No significant family medical history found in patient’s chart.

**SH:** KC is in 7th grade at Marsh Middle School. She has good family support, likes athletics, and is very talented according to mother. The mother is very supportive, positive, and knowledgeable.

**SurH:** KC has a central-line catheter in place for administration of chemotherapy medications. No other surgeries noted.

**Vitals:** BP-131/87 mm Hg; P-81; T-100F; Wt-41 kg (100 lbs); Ht-160 cm; BSA-1.43 m²; Ht-5’11”

**Labs:**
- Liver function tests (11/19/02): AlkPhos-232 (35-321); ALT-204 (30-65); AST-161 (15-37); Tbilii-0.5 (0.0-0.5); Dbili-0.5 (0.0-0.5); TP-5.0 (6.3-8.6); Alb-2.9 (3.5-5.0); Calc glob- 2.1; A/G ratio 1.4 (1.4-2.6)
- Cr(s): 0.7 mg/dl (0.6-1.0) (11/19/02)
- Glucose: 87 mg/dl (70-110)
- CBC (11/25/02): WBC-2,000; RBC-4.25 (4.2-5.4); Hct- 39.3 (40-50); Hgb-12.6x10⁶ (12.5-16.0); MCV- 92.7 (78-100); MCH-29.7 (27-31); MCHC-32.1; Plt-220x10³ (140-440); RDW-15.6 (11.5-14.0%); Diff.: Lymph-61%; Neut-34%; Baso-0; Mono-5%.

**Assessment and Recommendation:**

1. **Appropriate/Stable Drug Therapy:** Acute lymphoblastic anemia (ALL). ALL is the most common malignancy in children less than 15 years of age, about 60% of all cancers. Males are at a higher risk than females in developing ALL. The etiology of ALL is unknown, but environmental factors have been implicated in causing ALL. It is characterized by the proliferation of immature lymphoblasts. Treatment is divided into four phases: 1) remission induction, 2) CNS prophylaxis, 3) consolidation therapy, and 4) maintenance therapy. KC was diagnosed in March 2002 and she began treatment as outlined above; she is currently in her maintenance phase (with CNS prophylaxis of chemotherapy). Although, KC has had some complications with her chemotherapy regimen, the specific concerns will be addressed as individual problems.

**Pharmacological Recommendations:**
a. Her chemotherapy is set by a treatment protocol that follows a predetermined “road-map”. The road-map outlines which medication they receive on specific days. Her protocol is per the Children’s Oncology Group protocol 1961 as outlined above. However, one therapeutic alternative needs to be addressed.

Alternate/comparative treatment:
b. KC is currently receiving pegaspargase, while in past phases she received L-asparaginase. It is unclear exactly why the switch in agents was made.
   i. L-asparaginase is a bacterial enzyme that is isolated from *E. coli* or *Erwinia* spp. \(^3\)
      1. Asparaginase depletes circulating asparagines, which selectively kills leukocytes since these require external asparagines.
      2. Since asparaginase is a foreign protein, it can induce acute allergic reactions.
      3. Further, clearance is enhanced by the body producing antibodies to the asparaginase.
   ii. Pegaspargase
      1. A polyethylene glycol molecule is attached to naked *E. coli* asparaginase.
      2. The pegylation does not interfere with enzyme affinity for asparagines.
      3. The pegylation increases the half-life 5-fold over unp PegL asparaginase.
      a. This formulation has resulted in less frequent dosing compared to L-asparaginase (Once every 7-14 days in the cycle for PEG-A as compared to three times per week or 9 doses of native asparaginase over two weeks.
      b. In addition, it has resulted in fewer allergic reactions.
   iii. In a randomized comparative study, L-asparaginase (*E. coli*) was compared to pegaspargase in 118 children with newly diagnosed standard-risk ALL. PegasPargase was associated with a more rapid lymphoblast clearance and more asparaginase activity due to lower antibody titer as compared to native asparaginase group. The incidence and type of side effects (infections, adverse reactions, and hospitalization) were comparable between each group. \(^4\)
   iv. PegasPargase has been reported to have a lower risk of side effects and a prolonged effect.
      1. Cost analysis, not available, in this study stated that they are comparable between the two medications and more likely less for pegasPargase, due to less frequency of administration and decreased number of clinic visits in patients receiving pegasPargase. \(^4\)
v. Of note, L-asparaginase administered after methotrexate can stop both the therapeutic and toxic effects of methotrexate. This can be utilized to an advantage in some combination chemotherapy. It is unclear if KC’s current regimen is utilizing this interaction in minimizing the toxicity of methotrexate.3

### Monitoring and Education

ALL

1. Monitor for side effects of therapeutic agents as listed in chart below:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
<th>Labs</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>Neurotoxicity (dose-limiting); alopecia; extravasation reaction; hypertension; constipation; N/V</td>
<td>Serum electrolytes; LFTs; CBC; uric acid</td>
<td>Reflexes, neurological, HR, BP</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Myelosuppression (high dose), leukopenia, anemia, thrombocytopenia (O: 7days; nadir: 10 days; R: 21days); mucositis; nephrotoxicity; N/V; alopecia</td>
<td>Methotrexate levels; CBC with differential; LFTs; Chem panel</td>
<td>CXR to rule out third compartment spacing, typically pleural effusions.</td>
</tr>
<tr>
<td>PEG-asparaginase</td>
<td>Myelosuppression (dose-limiting), leukopenia, anemia, thrombocytopenia (O: 7days; nadir: 14 days; R: 21days); allergic reactions; weakness; N/V; edema, hyperglycemia (due to decrease in insulin secretion).</td>
<td>LFTs (due to hepatotoxicity), Chem panel, urine analysis for glucose, and blood glucose</td>
<td>Allergic reactions, vital signs during administration</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>Arachnoiditis; seizures; motor paralysis</td>
<td>Neurological and rigidity in extremities</td>
<td></td>
</tr>
<tr>
<td>Anzemet</td>
<td>Headache; diarrhea</td>
<td>LFTs; chem panel</td>
<td>BP, HR, and EKG in patients with CVD.</td>
</tr>
</tbody>
</table>

2. Instruct the patient to maintain adequate hydration (2-3 L/day) and to have small frequent meals. Alopecia will resolve when chemotherapy is discontinued. Report any fever or signs of infection immediately during therapy. Avoid crowded places due to increased susceptibility to infections. Other specific precautions will be addressed below.

### Assessment and Recommendation:

2. **Untreated Chemotherapy Induced Problem: Fever with neutropenia.** KC had recurrent fever and neutropenia for over one month. Although no lab reports contained any blood cultures, KC was considered low risk for her neutropenia due
to ANC >100/mm$^3$ and fever. KC had received ceftazidime, ceftriaxone, and cefixime as outpatient prophylaxis therapy. The antibiotic prophylaxis was discontinued when her ANC reached 310/mm$^3$. Ceftriaxone was a good choice due to cost and frequency of administration, however discontinuation of antibiotic should have been done when ANC was >500/mm$^3$.

**Recommendation:** KC should be closely watched for infections and fever. If she becomes neutropenic (ANC <500) or febrile (T >101.3F on a single reading or >100.4F) in future, antibiotic prophylaxis with ceftriaxone 2g IV q24h (recommended 1-2g q12-24 hours) should be initiated empirically. Consider oral cefixime in future if KC after 3 days treatment of IV antibiotics and she has no other signs of infection except for fever.

**Pharmacological Recommendation/Evaluation:**

a. Bacterial infection is a major risk factor in patients with neutropenia secondary to chemotherapy. They have a 10-fold increase risk of infection with declining neutrophils, especially <500/mm$^3$. Due to the severity of neutropenia and that organisms are identified in 20-30% of these patients, empiric therapy must be initiated before an organism can be identified. In the past, empiric therapy consisted of a β-lactam antibiotic.$^5,6,7$

b. In patients with neutropenia, gram-negative bacteria were major players of infection in the past. *E. coli*, *K. pneumonia*, and *P. aeruginosa* account for a majority of gram-negative infections in cancer patients. However, the gram-positive bacteria, *S. aureus* and staphylococci species, are of increasing concern and have supplanted gram-negatives in causing the majority of infections in cancer patients (60-70%). The choice of empiric antibiotic therapy should cover these organisms.$^5,6$

   a. Empiric antibiotic options include: third-generation cephalosporins, carbapenems with an aminoglycoside, extended-spectrum penicillins with aminoglycoside and/or third-generation cephalosporin, monobactams with vancomycin, quinolones, and vancomycin.$^5,6,7$

   b. Most of these regimens require IV delivery, which requires inpatient management. Outpatient therapy with injectable and oral third-generation cephalosporins has shown great benefit not only in positive therapeutic outcomes but also in cost savings.

   c. The third-generation cephalsporins that can be used IV in neutropenic patients are cefotaxime, ceftizoxime, cefoperazone, and ceftriaxone.

      i. All have good coverage for gram-negative bacteria, especially *E. coli*, *K. pneumonia*, and *P. aeruginosa* but have variable coverage of gram-positive bacteria, *S. aureus* and staphylococci species.$^8$

      ii. Ceftriaxone does have a slight pharmacokinetic advantage over the other injectable third generations through its long half-life and once daily dosing.
iii. There is no significant difference in efficacy between these agents except for cost. Although the drug costs favor ceftizoxime, indirect costs should favor ceftriaxone.

1. In a study using ceftriaxone (80mg/kg; max 2g) monotherapy as an outpatient treatment in neutropenic pediatric cancer patients, 18/19 patients were treated for neutropenia without complications. The study also evaluated the cost between inpatient and outpatient management. The investigators reported a 88% cost savings in outpatient management with an average savings of $5600 dollars to patient and/or third-party payers.9

2. In another study evaluating ceftriaxone as first-line therapy in 828 pediatric patients with neutropenia (mean ANC: 423/mm³). The study compared 376 patients treated with ceftriaxone (80mg/kg/dose; max 2g/day) alone with 525 patients treated with ceftriaxone combined with another agent. An overall response rate in children treated with ceftriaxone alone was 70.8%. Children with leukemia (n=158), 69 were treated with ceftriaxone and 63.8% had a definite response. These results were similar as compared to combination therapy.10

iv. Cefepime is an extended spectrum fourth generation cephalosporin with good activity against Gram-positive organisms, including methicillin-susceptible S. aureus, α-hemolytic streptococci and some S. epidermidis. It also has good activity against gram-negative organisms including P. aeruginosa, E. coli, Enterobacter spp., and Klebsiella spp. Recent studies have compared the efficacy of cefepime to ceftazidime in neutropenic pediatric patients who became febrile. The results of two studies showed that cefepime was just as safe and effective as ceftazidime.11,12

1. Recent clinical guidelines have placed cefepime as a first line in the treatment of neutropenia along with third generation cephalosporins.6

2. Cefepime is theoretically a better choice for empiric therapy of neutropenia in patients over the third-generation cephalosporins, due to its broader coverage of gram-positives. However, comparative studies have not shown superiority to the third-generation cephalosporins. Therefore, the decision will come down to cost of administration.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended dosing</th>
<th>Available formulations</th>
<th>Cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>1-2 mg/dose q12-24h (max. 4mg/day)</td>
<td>Powder for INJ: 250, 500mg; 1g, 2g, 10g; Infusion (premixed, frozen): 1g in D3.8W (50mL), 2g D2.3W(50mL)</td>
<td>$68.83</td>
</tr>
<tr>
<td>Ceftizoxime</td>
<td>50mg/kg IV q6-8h (max. 200 mg/kg/day or 12 g/day)</td>
<td>Infusion, as sodium (premixed, frozen): 1g or 2g (50mL); Powder for INJ: 500mg; 1, 2, 10g</td>
<td>$49.28</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1-2g q6-8h (upto 12 g/day)</td>
<td>Infusion, as sodium (premixed, frozen) 1g or 2g (50mL); Powder for INJ: 500mg; 1, 2, 10g</td>
<td>$66.00</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>1-2 mg/dose q12h(max.12-16mg/day)</td>
<td>Infusion, as sodium (premixed, frozen) 1g or 2g (50mL); Powder for INJ: 1, 2</td>
<td>$71.90</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>500 mg - 2 g q8-12</td>
<td>Infusion, (premixed, frozen): 1, 2 g (50mL);Powder for INJ: 500mg, 1, 2, 6 g</td>
<td>$86.64</td>
</tr>
<tr>
<td>Cefepime (4th gen.)</td>
<td>50 mg/kg q 8h for 7-10 days</td>
<td>Infusion: piggyback: 1, 2g (100 mL), ADD-vantage: 1g; Injection: 500mg; 1, 2g</td>
<td>$98.25</td>
</tr>
</tbody>
</table>

d. Oral antibiotics can be considered in patients who have no identifiable signs of infection other than fever. Oral third-generation cephalosporins, such as cefixime, are a viable option for treatment.

i. A study examined the effectiveness of switching pediatric cancer patients who were neutropenic currently receiving IV therapy (vancomycin plus tobramycin/ticarcillin or ceftazidime) for 48-72 hours to oral cefepime. Rates of treatment failure where the between IV and oral therapy were identical 27 vs. 28 (p=1.0). Efficacy between the two groups were similar 73(IV) vs. 72(oral) (p=1.0). The authors concluded that by switching patients over to oral therapy, they could then be managed as an outpatient, thus reducing the overall hospital costs.13

ii. No other oral third-generation antibiotic (ceftibuten, cefpodoxime proxetil, and cefdinir) besides cefixime has been evaluated for outpatient treatment in neutropenic patients. So the use of oral cephalosporins should be limited to cefixime.

c. Empiric use of quinolones as outpatient therapy has never been promoted due to concerns of selecting for resistant bacteria and conflicting results from studies. A study compared ciprofloxacin and cefixime as outpatient therapy in low-risk neutropenic children who received ceftriaxone with amikacin. Ciprofloxacin was just as effective as cefixime; however this
study had several weaknesses, including: duration of initial therapy differences between groups and duration of outpatient therapy differences between the groups. Other studies have shown unfavorable results.\(^5,6,7,14\)

d. Anaerobes account for relatively few infections in patients with neutropenia. Therefore, the use of metronidazole and clindamycin has a minor role in empiric treatment. There is no current literature of use of these agents in neutropenic patients. These agents should not be used empirically but should be considered if anaerobic bacteria are isolated or suspected in order to minimize the development of resistant bacteria.

e. Mycobacteria have not been a major cause of infections in neutropenic patients. So the use of macrolide antibiotics has limited or no use as empiric therapy; they should be reserved for when atypical bacteria have been isolated.\(^5\)

**Monitoring and Education:**

KC should report any fever above 100F. After each chemotherapy treatment, her CBC should be monitored for neutropenia, anemia, and thrombocytopenia every week until resolution of nadir. Also, CBC should be done everyday during treatment of neutropenia until ANC >500/mm\(^3\). Avoidance of large crowds and sick people should be practiced at all times, especially during neutropenic episodes. KC should be educated that extended therapy with cephalosporins can cause diarrhea, rash, and pain at injection site. Monitor for signs of allergic reaction to cephalosporin therapy since she is allergic to penicillins. Instruct her to finish all oral medication unless otherwise instructed by MD. KC should be instructed to abstain from taking NSAIDs or acetaminophen during neutropenia episodes, since these medications can mask a fever and prevent detection of worsening neutropenia.

**Assessment and Recommendation:**

3. **Likely Chemotherapy Induced Problem:** Myelosuppression manifested as neutropenia, anemia, or thrombocytopenia. KC has frequent neutropenia due to her chemotherapeutic regimen. The major player is

a. **Neutropenia:** KC has a history of neutropenia caused by chemotherapy. Her last episode was one month ago lasting one month. KC’s beginning ANC was 100 and one month later after antibiotic prophylaxis, her ANC was 680.

b. **Anemia:** KC does not have anemia at this time based on her current CBC values.

c. **Thrombocytopenia:** KC does not have sign or symptoms of thrombocytopenia at this time; platelets are 295,000.

d. KC chart does not have a current management plan for the above problems and since her current chemotherapy regimen can precipitate the above problems, it warrants a discussion below.

**Pharmacological Recommendation:**

a. **Neutropenia:** As outlined above KC is currently being treated for neutropenia with antibiotic prophylaxis. Since antibiotics have shown to decrease mortality due to neutropenic infections, antibiotic prophylaxis is
the current standard of treatment in patients with neutropenia. However, other option are available for treating neutropenia.\textsuperscript{15}

i. The routine use of granulocyte transfusions have been investigated but are generally not advocated due to the lack of efficacy.

ii. Granulocyte colony-stimulating factor (G-CSF) can be used in patients with neutropenia. However, their use is limited and not recommend in acute neutropenia unless neutropenia continues or other comorbid diseases are present such as, pneumonia, hypotensive episodes, severe sinusitis, systemic fungal infections, and complications due to sepsis. G-CSF should also be considered in patients that have persisting neutropenia or infections refractory to appropriate antimicrobial therapy. In addition, data is limited in the pediatric population but the recommendations in adults can be applied to this population.\textsuperscript{6,7,16,17} There is some concern of use of these agents in leukemia patients due to in vitro proliferation of myeloid leukemia blasts, because these are the progenitor cells for the cancerous cells. In addition, the use of GM-CSF is contraindicated in patients with excessive myeloid leukemia blasts; and its use has been limited to patients that have received bone marrow transplants. However, clinical data has not supported this finding.

1. Available agents include:
   a. G-CSF: filgrastim (Neupogen), pegfilgrastim (Neulasta)
   b. GM-CSF: sargramostim (Leukine)

2. Comparison of agents:
   a. GM-CSF and G-CSF have similar activity in stimulating, but GM-CSF toxicities are considerably higher (low grade fevers, myalgias, bone pains, abdominal pains). Due to this and lack of clinical evidence of effectiveness (survival advantage) in leukemia patients, GM-CSF should not be recommended but should be reserved for patient undergoing bone marrow transplant and stem-cell transplant.
   b. G-CSF has shown to be beneficial in reducing neutropenia related complications associated with chemotherapy in non-hematologic malignancies. However, G-CSF is not effective once neutropenia is established or in patients with an active infection.\textsuperscript{15,16}

iii. \textbf{Recommendation:} KC is not a candidate for G-CSF due to lack of beneficial studies in leukemia and pediatric patients. For cases of neutropenia prophylaxis with antibiotics should be initiated when ANC <500/mm\textsuperscript{3}. 


b. **Anemia:** Anemia often occurs in patients on chemotherapy. It usually manifests as low red blood cell count and hematocrit. Treatment options include the use of epoetin, transfusion of red blood cells, and iron supplementation in iron deficiency anemia.

i. The use of red blood cells is still recommended as first line treatment in patients with hematologic malignancies. However, there are concerns due to the risk of blood borne infections.

ii. The use of epoetin alpha (Procrit) is recombinant human erythropoietin that stimulates the bone marrow stem cells to produce red blood cells. Epoetin is recommended as a treatment in patients that have anemia secondary to chemotherapy and a hemoglobin that has declined to <10 mg/dL; but it is not recommended in acute anemic situations. Further, epoetin is not recommended in patients with hematologic malignancies, but rather conventional therapy (blood transfusion and iron supplementation) should be initiated.¹⁹

iii. Epoetin has been used for over 10 years in treating patients with chemotherapy-induced anemia. Most of the clinical studies have examined the use of epoetin in non-hematological cancers; limited data exists for epoetin use in the pediatric population. Epoetin alpha is administered in pediatric patients at 150 IU/kg SC three times week; up to a maximum of 1200 IU/kg/week. There is evidence of once weekly dosing (40,000 IU/wk) but it is based on common clinical practice.¹⁹,²⁰ Preliminary studies have suggested a beneficial effect of epoetin alpha in the treatment of anemia in children with cancer. There are large-multicenter studies currently underway to determine the efficacy and a safety of epoetin alpha in anemic pediatric patients with cancer.²¹

iv. There are many factors that can influence the efficacy of epoetin. Factors that affect hemoglobin production have the greatest impact on efficacy of epoetin (iron deficiency, folic acid/B12 deficiency).

v. **Recommendation:** Since KC is not anemic at this point, it is best to monitor her hemoglobin and hematocrit during her chemotherapy cycle. Due to the lack of clinical evidence in children with leukemia, epoetin should not be used in KC to manage future anemia. However, the use of red blood cell transfusion and iron supplementation should be the first line of therapy. Iron dose for KC should be based on severity of anemia. Prophylaxis iron should be initiated with iron sulfate 324 mg po QD (20 mg elemental iron; recommended 1-2 mg/kg/day).

c. **Thrombocytopenia:** Along with neutropenia and anemia, thrombocytopenia is also of concern in patients who receive myelosuppressive chemotherapy. Thrombocytopenia occurs when platelet level drop <100,000/mm³.

i. The use of platelet infusion is the standard of care in treating acute thrombocytopenia. However, infusion of platelets is costly due to hospitalization and preparation costs.²² Also, there is a great
concern with blood borne infections and allergic reactions associated with platelet transfusions.

ii. Oprelvekin (Neumega) or IL-11 is used for the prevention of thrombocytopenia. Oprelvekin simulates megakaryocyte growth and production. It is indicated for patients who required platelet transfusions during previous chemotherapy cycle.

   1. Adult dosing 50 mcg/kg/day SC injection.
   2. A safe and effective dose of oprelvekin in children has not been established. Therefore it should not be administered to pediatric patients, particularly under the age of 12 years. In a preliminary safety and pharmacokinetic trial, 25% of children who received doses of 100 mcg/kg/day developed papilledema. Further, these children did not achieve effective serum levels when administered doses of 50 mcg/kg/day. Side effects seen in children were higher incidences of papilledema (14%), tachycardia (46%), and conjunctival injection (50%).

   3. Use of oprelvekin should be limited to adult patients, until more clinical-data is gathered in the pediatric population.

iii. Other agents that have been investigated include: thrombopoietin, stem-cell factor, IL-1, IL-3, IL-6, and GM-CSF. They all stimulate megakaryocyte growth and production as well. However, these agents have failed to produce significant clinical effects. This could be due to the complexity of platelet production. Also, these agents in clinical trials have been fraught with severe toxicities, such as fever, fatigue, hyperbilirubinemia, rapid induction of anemia, and development of neutralizing antibodies.

iv. **Recommendation:** Monitor KC platelet counts with every cycle of chemotherapy. If KC needs medical intervention, consider platelet infusion; but platelet levels should recover after 21 days of chemotherapy cycle.

   *Note:* If myelosuppression is of great concern, dose reduction on subsequent cycles of chemotherapy can minimize suppression. However, this needs to be balanced with the largest possible dose needed to obtain maximal tumor effect.

**Monitoring and Education:**

   a. **Neutropenia:** Monitor as above in fever with neutropenia.
   b. **Anemia:** Baseline and periodic monitoring of iron, TIBC, transferrin, or ferritin levels, CBC at baseline of chemotherapy cycle, day 7, day 10, and day 28. Then CBC every month. Educate KC that iron needs to be taken every day and taking it with a glass of orange juice in order to increase absorption of iron from the GI tract. The iron should be taken 30 minutes before a meal. Inform KC that her stools could turn dark brown or black due to the iron supplement. The iron supplement can cause constipation, so maintain adequate fluid intake ~2-3 L/day along with plenty of food high in fiber.
c. **Thrombocytopenia:** Monitor platelets, bleeding complications: i.e. bruising, bleeding from gums, blood in stools. KC should avoid taking NSAIDs and aspirin since they inhibit platelet activity in clotting.

**Assessment and Recommendation:**

4. **Likely Chemotherapy Induced Problem/Sub-optimal Therapy: Nausea and vomiting.** KC is currently receiving Anzemet (dolasetron) for prophylaxis of acute onset during chemotherapy treatment, but it is unclear whether she is receiving Anzemet before chemotherapy and what medications she is using for treatment of delayed or breakthrough emesis. KC did receive Kytril (granisetron) once for prophylaxis of emesis. Since, KC is receiving intermediate-high dose methotrexate(>200/mm$^3$), this classifies her as receiving a Level 3 emetic agent (30-60% frequency). According to the ASHP(American Society of Heath-systems Pharmacist) guidelines for N/V, KC should receive a corticosteroid plus a 5-HT$_3$ receptor antagonist for prophylaxis of acute N/V. Further, there is no mention in KC medical chart on management of delayed onset or breakthrough N/V.

**Pharmacological Recommendation:**

a. Nausea and vomiting (N/V) is a common consequence of chemotherapy. Uncontrolled N/V can lead to severe complications such as anorexia, weight loss, dehydration, electrolyte imbalances, and aspiration pneumonia.

b. There are three distinct categories of chemotherapy-induced emesis and each has different recommendations for management.$^{18}$

   i. Anticipatory N/V occurs before drug administration. This learned response is usually triggered by smell, tastes, anxiety, or thoughts of chemotherapy. Anticipatory N/V is typically refractory to antiemetic therapy and usually requires behavior modification therapy.$^{18}$

   ii. Acute-onset N/V occurs within 24-hours of chemotherapy; but this time range is variable depending on the chemotherapeutic agent used it can vary between 4-24 hours. Since KC is young and female, she is at a higher risk for developing acute emesis, so proper management is essential.

   1. According to the ASHP guidelines$^{18}$, patients who are receiving chemotherapy agents classified Level 2 through Level 5 should receive antiemetic agents. Each level has appropriate standard of care; in treating patients receiving Level 3 emetic agents, the standard recommendation is the use of a corticosteroid (dexamethasone or methylprednisone) in combination with a 5-HT$_3$ receptor antagonist (ondansetron, granisetron, or dolasetron).

   2. Clinical studies have shown equivalent safety, tolerability, and therapeutic effects among the 5-HT$_3$ receptor
antagonists in the treatment of acute-onset N/V. Therefore, decision of drug choice is dependant on drug cost.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended dosing</th>
<th>Available formulations</th>
<th>Cost per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>&gt;11 y.o.: 8mg orally 30 min. before and 4 and 8 hours after chemotherapy; may also be given as a single 12-mg dose 30 min before chemotherapy; IV: 0.15 mg/kg IV 30 min before and 4 and 8 hours after chemotherapy.</td>
<td>4, 8, 24 mg tablets</td>
<td>PO: $25.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4mg/5mL solution</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2mg/mL IV solution (2mL; 20 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>32 mg (single dose packs)</td>
<td></td>
</tr>
<tr>
<td>Granisetron</td>
<td>&gt;2 y.o.; 20 - 40 mcg/kg IV 30 min before chemotherapy</td>
<td>1 mg tablets</td>
<td>PO: $47.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1mg/mL IV solution (1 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1mg/mL IV solution (4mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4, 8 mg ODT</td>
<td></td>
</tr>
<tr>
<td>Dolasetron</td>
<td>1.8 mg/kg po or IV 30 min before chemotherapy</td>
<td>50, 100 mg tablet</td>
<td>PO: $68.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20mg/mL (0.625 mL; 5mL)</td>
<td></td>
</tr>
</tbody>
</table>

3. Based on cost comparison, ondansetron would be a better choice for preventing acute onset emesis due to cost benefit. Further, ondansetron is the only one available as an oral solution. The dosing is varied based on clinical studies. In general, there was no advantage of using higher doses (32 and 24 mg) of ondansetron compared to lower doses (8mg). In comparing IV (8 mg) versus oral (24 mg) administration of ondansetron, control of emesis was 90% and 89% respectively. Both doses were administered with dexamethasone. Just a note on clinical studies in antiemetics. The majority of studies were conducted in adult patients receiving highly emetic chemotherapy agents.

4. Other alternatives to 5-HT₃ receptor antagonists include:
   a. Antihistamines such as promethazine, prochlorperazine, and chlorpromazine. These agents are typically reserved for breakthrough and delayed onset emesis due to 5-HT₃ receptor antagonists effectiveness in controlling acute onset emesis.
   b. Metoclopramide was once the drug of choice for acute emesis prophylaxis. At low doses, metoclopramide has little affinity/action at the 5-HT₃ receptor, but at high doses, it was found to function as a 5-HT₃ receptor antagonists. 5-HT₃ receptor antagonists were serendipitously formulated after studies of high dose metoclopramide for emesis revealed the mechanism of blocking the 5-HT₃ receptor. Clinical studies
show that 5-HT<sub>3</sub> receptor antagonists are superior to metoclopramide in preventing acute emesis after chemotherapy. Further, patients experience more significant side effects with high doses of metoclopramide as compared to 5-HT<sub>3</sub> receptor antagonists, particularly extrapyramidmal effects, drowsiness, and diarrhea.<sup>12,14</sup>

5. KC should also receive a corticosteroid in addition to ondansetron. Typically, patients receive a corticosteroid as part of their chemotherapy regimen; so, the use of a corticosteroid for emesis is usually not warranted in these patients. Since KC’s regimen at this time does not include a corticosteroid and she is receiving a Level 3 emetic agent, she could possibly benefit from the addition of a corticosteroid administered prior to chemotherapy.
   a. The evidence of using corticosteroids in combination with 5-HT<sub>3</sub> receptor antagonists is positive.
      i. In a clinical study of combining dexamethasone with ondansetron and granisetron was more efficacious than either agent alone.
      ii. In a study comparing ondansetron 8 mg IV with either placebo or dexamethasone 8 mg IV 15 minutes before chemotherapy, the combination of dexamethasone and ondansetron was superior to placebo and ondansetron group (81% versus 64%; p = 0.04).
      iii. In pediatric patients, adding dexamethasone to ondansetron showed a higher complete control of emesis when compared to placebo.
      iv. Similar results have been observed with dexamethasone when used in combination with other 5-HT<sub>3</sub> receptor antagonists.
   b. The two most widely used corticosteroids used for emesis is dexamethasone and methylprednisolone.
   c. The bulk of medical literature supports the addition of dexamethasone over methylprednisolone. However, either can be used in pediatric populations. Methylprednisolone has a lower risk of perineal irritation.
### Medication | Recommended dosing | Available formulations | Cost per dose
--- | --- | --- | ---
Dexamethasone | 10-14 mg/m² po or IV in single or divided doses 30 minutes prior to chemotherapy | Various oral formulations: elixir(5mg/5mL), oral solution (5mg/5mL; 5mg/0.5mL) | $1.06
| | Tablets: 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 mg | 8mg/mL INJ solution (5mL vial); 16mg/mL (1mL; 5mL vial) | $4.41
| | INJ powder for IV solution as succinate (this is the only formulation methpred. that can be given IV): 40mg (1, 3mL vials); 125 mg (2, 5mL vials); 500 mg(1, 4, 8, 20 mL vials); 1000 mg (1,8,50 mL vials) 2000 mg (30.6 mL) | $13.60
| | Tablets: 2,4, 8, 16, 24, 32 mg | $0.94

6. **Recommendation for acute emesis prophylaxis** based on cost comparison and clinical evidence:
   a. Ondansetron 8mg IV through central catheter 30 min prior to chemotherapy regimen.
   b. Dexamethasone 16 mg (10-14 mg/m²; 14-20 mg/dose) IV or po with ondansetron 30 minutes prior to chemotherapy.

iii. Break-through emesis
   1. All patients receiving chemotherapy should receive breakthrough antiemetic medications as needed for nausea and vomiting. The ASHP guidelines recommend in pediatric patients: chlorpromazine, lorazepam, or methylprednisone or dexamethasone.
   2. All of these agents have low cost when used in recommended range.
   3. The efficacy of haloperidol, dronabinal, prochlorperazine and promethazine as rescue medications has not been well documented in the medical literature.
   4. Metoclopramide has been studied but is generally not used due to cost and frequent adverse events seen in children.
   5. The 5-HT₃ receptor antagonists have been investigated as well. Due to their high cost and lack of superiority over the other recommended treatments; they are not recommended for rescue therapy. But results from studies indicate that ondansetron and granisetron are effective in treating emesis refractory to standard therapy.¹⁸
<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended dosing</th>
<th>Available formulations</th>
<th>Cost per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>0.5-1 mg/kg po or IV q 4-6h prn; 1 mg/kg pr q6-8h prn; alt: 10 mg every 6 hours</td>
<td>Tablet: 10, 25, 50, 100, 200 mg; Syrup: 10mg/5mL (120mL). Oral conc. 30mg/mL and 100 mg/mL; Suppository (rectal): 25, 100mg</td>
<td>PO: $0.52; PR: $3.78</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.04-0.08 mg/kg/dose (max. 4mg) po or IV q6h prn</td>
<td>Oral solution: 2 mg/mL (30mL); Tablets 0.5, 1, 2 mg; IV: 2mg/mL (1, 10 mL vials); 4 mg/mL (1, 10 mL)</td>
<td>PO: $0.57</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>0.5-1 mg/kg po or IV q12h prn</td>
<td>INJ powder for IV solution as succinate (this is the only formulation methpred. that can be given IV): 40mg (1, 3mL vials); 125 mg (2, 5mL vials); 500 mg(1, 4, 8, 20 mL vials); 1000 mg (1,8,50 mL vials) 2000 mg (30.6 mL)</td>
<td>PO: $0.94</td>
</tr>
<tr>
<td>Dexamethazone</td>
<td>5-10 mg/m² po or IV q12h prn</td>
<td>Various oral formulations: elixir(5mg/5mL), oral solution (5mg/5mL; 5mg/0.5mL)</td>
<td>PO: $0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablets: 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8mg/mL INJ solution (5mL vial); 16mg/mL (1mL; 5mL vial)</td>
<td></td>
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</tbody>
</table>

6. **Recommend for break-through emesis**: chlorpromazine 20mg po q 4-6h prn nausea and vomiting. Chlorpromazine makes a good choice for rescue due to affordability and the various available formulations allows flexibility for routes of administration.

iv. Delayed onset emesis

1. Delayed onset occurs after the first 24 hours post-chemotherapy. Typically, delayed onset emesis occurs with Level 4 and 5 emetic medications, especially cisplatin and cyclophosphamide. Since KC is receiving a Level 3 emetic (high dose emetic), the chance of delayed onset is minimal. Usually, the onset of N/V with methotrexate will occur between 4-12 hours and last 3-12 hours. If KC is managed properly at the beginning, the need for antiemetics later is small.

2. However, it is good medical practice to establish a plan of action if delayed emesis occurs. For pediatric patients, the recommended agents for prevention of delayed onset is chlorpromazine, lorazepam, or a 5-HT₃ receptor antagonists used in combination with corticosteroid.¹⁸

3. **Recommendation for delayed emesis**: considering that KC is receiving a Level 3 emetic and her other chemotherapeutic agents cause minimal N/V, the best
treatment strategy is to evaluate KC emetic episode patterns and initiate chlorpromazine 20mg po q 4-6h prn and dexamethasone 8 mg po q12 h prn to prevent delayed emesis if it is warranted.

Monitoring and Education:
Monitor KC for frequency and duration of N/V during and after a chemotherapy treatment. This is key to optimizing antiemetic treatment in cancer patients. Also, monitor for frequency of use of rescue medications. Serum electrolytes should be monitored regularly and more frequently during severe emesis. Ondansetron: Monitor LFTs at baseline, cardiac side effects: tachycardia, bradycardia, angina; this medication can cause constipation and/or diarrhea. Dexamethasone: Monitor: Hemoglobin, blood pressure, serum potassium and glucose. Instruct KC not to discontinue medication abruptly if she is taking it for a long time. Chlorpromazine: Monitor eyes periodically, BP, and CBC. Educate patient that this medication can cause drowsiness and use in combination with pain medications can enhance the drowsiness. Have her report any abnormal shaking in hands and extremities.

Assessment and Recommendation:
5. **Suboptimal Therapy**: High-dose methotrexate without leucovorin rescue. KC is receiving high dose methotrexate, 194mg/m$^2$ (which is >100 mg/m$^2$) and her records did not state as to whether she is receiving leucovorin rescue therapy or preventative therapy during methotrexate treatments. Toxic levels of methotrexate can have detrimental effects on blood marrow, GI mucosa, and the kidneys.

Pharmacological Recommendation:
   a. Methotrexate is primarily eliminated by the kidneys (80% unchanged). Since methotrexate is a weak acid, it can precipitate in the renal tubules after large doses and cause acute tubular necrosis.
      i. Patients receiving high-dose methotrexate need to maintain adequate fluid intake and output. Optimal urine outflow in children should be 0.1-1.8 mL/m$^2$ per minute to ensure adequate methotrexate clearance.$^{24}$
      ii. The urine must be maintained at an alkaline pH ≥7.0. Lower pH levels increase the risk of renal tubular necrosis, due to precipitation of methotrexate in acidic urine. Alkalization of the urine can be accomplished by the administration of oral sodium bicarbonate. This method was effective in maintaining the urine pH ≥7.0.$^{24}$
         1. The recommended dose of sodium bicarbonate for the alkalization of urine in children is 1-10 mEq (84-840 mg)/kg/day in divided doses; dose should be titrated to desired urine pH.
b. Methotrexate does not require leucovorin rescue in doses from 30-40 mg/m$^2$ but Leucovorin is required in doses >100mg/m$^2$.

i. Leucovorin helps minimize toxicity and counteract the effects of impaired methotrexate elimination. It helps rescue normal cells from cytotoxic effects of methotrexate.

ii. Dosing of leucovorin is dependant on the blood levels of methotrexate. This is best illustrated by the following graph:

![Graph showing leucovorin rescue](image)

Figure 1. Leucovorin Rescue. adapted from Ref. 25

1. Leucovorin rescue dose: IV: 10mg/m$^2$ to start then 10 mg/m$^2$ every 6 hours orally for 72 hours; increase dose if serum creatinine is elevated ≥50% 24 hours after methotrexate or serum methotrexate is >5.0x10$^{-6}$M, increase leucovorin dose to 100mg/m$^2$/dose every 3 hours until methotrexate levels are <1.0x10$^{-7}$M.

c. Leucovorin comes in two forms for injection: solution 3mg/mL(1mL); 10 mg/mL (30mL, 50mL); powder for injection: 50mg, 100mg, 200mg, 350mg; and as tablet: 5 mg, 15 mg, 25 mg.

d. **Recommendation**: KC should receive Leucovorin 15 mg IV initial; then 15mg tab po q6h (10mg/m$^2$ IV to start; then 10mg/m$^2$ po q6h for 72h until MTX <1x10$^{-7}$) rescue therapy and sodium bicarbonate 600 mg 2 tabs po TID (1-10 mEq (8-84mg)/kg/day; 40-400 mEq (328-3444 mg)/day) for urine alkalinization for each methotrexate dose >100mg/m$^2$.

**Monitoring and Education:**

Monitor CBC with differential and platelet count should be done at baseline, 7, 10, and 21 days post admission, creatinine clearance, serum creatinine, BUN, LFTs, serum electrolytes, UA for urine pH. Methotrexate levels daily until they drop below 1x10$^{-7}$ M. Educate KC on the importance of drinking plenty of fluids; this will help minimize renal toxicity of methotrexate.

Sodium bicarbonate: Monitor serum electrolytes and urine pH.

Leucovorin: Monitor methotrexate as above. Leucovorin can be taken without regard to food. Educate KC to maintain adequate hydration (2-3L of water/day) while taking leucovorin. Report any burning, itching, lethargy, and respiratory difficulty.
Assessment and Recommendation:

6. **Possible Chemotherapy Induced Problem: CNS toxicities from intrathecal methotrexate.** KC is on intrathecal methotrexate to prevent invasion of leukemia cells into the CNS. Her current records do not have an action plan for treatment of toxicities that can arise with this treatment. As long as KC receives her prescribed dose of intrathecal methotrexate 12 mg, her chance of neurotoxicity is minimal. However, a protocol of management needs to be defined.

Pharmacological Recommendation:

a. Acute lymphoblastic leukemia has a high propensity of relapse in to the CNS. Before CNS prophylaxis treatment was established, 50-75% of leukemias in children relapsed in the CNS. Due to the blood-brain barrier, treatment of leukemia in the CNS is difficult via systemic routes. Strategies of prophylaxis include: a) intrathecal therapy with methotrexate, cytarabine (Ara-C), or steroids, b) cranial irradiation, c) systemic dexamethasone, d) high-dose systemic chemotherapy with methotrexate or Ara-C.

b. Common side effects of intrathecal methotrexate are mainly localized to the CNS, but some systemic manifestations are present due to CNS toxicity.

i. Acute chemical arachnoiditis can occur within several hours to 1 or 2 days after dose and occurs in 5-40% of patients receiving intrathecal methotrexate. This side effect is characterized by headache, nuchal rigidity, vomiting, fever, and CSF pleocytosis.

ii. Encephalopathy, which may be irreversible, can present with weakness of limbs, cranial nerve palsies, ataxia, visual impairment, seizures and coma. This usually manifests within a few days to a week or more after starting a course of therapy.

iii. Severe and fatal reactions can occur from inadvertent administration of excessive doses of methotrexate or the administration of the wrong agent.

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c. Medical literature on the management of toxicity due to intrathecal methotrexate is very limited. Mainly articles found were case reports of treatment.

i. In general prompt measures are critical in the removal of intrathecal methotrexate in achieving favorable outcomes in toxic patients.

ii. One report by Addiego et al., documented the removal of cerebral spinal fluid in order to minimize methotrexate toxicity in two patients that received 50 mg methotrexate intrathecally. 28% and 20% of the initial dose was effectively removed via lumbar drainage within two hours post dose. The authors went on to illustrate that the total dose, the time post dose and volume of CSF removed was detrimental in reducing methotrexate levels in the CSF; thus reducing the effects of toxicity. CSF fluid was replaced.
with an equal amounts of Elliot’s B solution in both case patient. Their guidelines are listed in the Table 1 below.

Table 1. Amount (%) of methotrexate predicted to be recovered by CSF removal

<table>
<thead>
<tr>
<th>Volume CSF removed (ml)</th>
<th>Time after methotrexate injection (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>40</td>
<td>94</td>
</tr>
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</table>

*Assuming 10 ml of methotrexate-containing fluid was injected. Other assumptions are described in the text.

Table 1 adapted from ref. 28.

iii. The successful use of carboxypetidase G₂ was reported in another case report of 6-year-old boy who received an overdose of 600 mg methotrexate intrathecally instead of the typical 12 mg dose. Carboxypetidase G₂ is an enzyme that inactivates methotrexate.

1. The authors drained 15 mL of CSF via lumbar puncture 2 hours after administration of methotrexate. This resulted in the removal of 32% (192 mg) of methotrexate. Lumbar and ventricular catheters were inserted and 240mL of a warmed preservative-free isotonic saline solution was pumped through the ventricular catheter and while the CSF was removed from the lumbar catheter. This procedure removed 90% of the remaining methotrexate (367 mg). Administration 2000 U of carboxypetidase G₂ intrathecally after these procedures resulted in a 150-fold reduction in methotrexate concentrations. The authors concluded that major overdoses of methotrexate may benefit from carboxypetidase G₂ treatment. The authors went on to state that a clinical trial is underway to further evaluate the efficacy of carboxypetidase G₂.²⁹

d. Recommendation: Due to the limited evidence in the medical literature it is difficult to make recommendation. However, based on case reports, CSF removal and replacement with preservative-free isotonic saline is effective in reducing methotrexate levels in CSF early on in toxicity. In addition, ventriculolumbar perfusion was shown to be effective in removing methotrexate from CSF. Both of these measures should be considered in patients that receive toxic doses of methotrexate. Hopefully results of the carboxypetidase G₂ trial will establish this agent as a treatment in methotrexate toxicity. Careful dose preparation and administration is the most important factor in preventing toxicity.
**Monitoring and Education:** Educate KC on recognizing early signs of CNS methotrexate toxicity: headache, altered vision, rigidity of neck and extremities. The onset of these side effects is variable from hours to days after treatment. Inform KC to seek medical attention immediately if signs of toxicity occur. If methotrexate toxicity is suspected, CSF and serum levels of methotrexate should be determined.

**Assessment and Recommendation:**

7. **Stable Drug Therapy: Oral thrush and systemic fungal infection prophylaxis.**
   KC is currently taking fluconazole for oral thrush and since KC is neutropenic, for prevention of systemic fungal infection.

**Pharmacological Recommendation:**

a. Fungal infections are common in patients receiving chemotherapy, especially patients with persistent neutropenia are prone to invasive fungal infections. The most likely organism is *Candida albicans*, however other fungal species can cause infections in cancer patients (*Aspergillus* spp. and *Trichosporon* spp.). For outpatient treatment, oral antifungal agents are the best choice.

b. Although KC has oral candidiasis, a non-systemic oral agents such as nystatin and clotrimazole are not a good choice for treatment. Since neutropenia patients have a high risk for systemic infections, oral nystatin and clotrimazole will not effectively treat systemic fungal infections due to is lack of being absorbed systemically.

c. Both fluconazole and itraconazole are systemically absorbed and have shown to be effective prophylaxis antifungal treatment in patients with ALL. Little or no evidence is available for other systemically absorbed antifungals (ketoconazole and terbinafine) in prophylaxis treatment in neutropenic patients.

   a. Although itraconazole has shown to be effective in prophylaxis treatment, it can increase neurotoxicity in patients receiving vincristine. Since KC is receiving vincristine, itraconazole should not be recommended as treatment for her.

   b. On the other hand, fluconazole does not exacerbate neurotoxicity secondary to vincristine.

   d. Fluconazole is the drug of choice for the treatment of fungal disease and for prophylaxis treatment in neutropenic cancer patients. Further, fluconazole has shown to be effective in treating and preventing fungal infection in ALL patients with neutropenia.

   a. In a placebo-controlled study, 266 patients were randomized to receive fluconazole 400 mg or placebo. Fluconazole markedly reduced oropharyngeal, rectal and urinary fungal infections. A larger percentage of patients receiving fluconazole remained free of fungal colonization during prophylaxis as compared to placebo (47% v. 24% respectively; p<0.001).

   e. **Recommendation:** Continue fluconazole 150 mg po QD until resolution of oral thrush; also, consider prophylaxis fluconazole if she becomes neutropenic in the future.
Monitoring and Education:
Monitor LFTs and renal function, if KC will be on therapy for long duration. Evaluate KC at each visit for recurrent or resistant fungal infections. Instruct KC to report any suspected fungal infection immediately to her PMD. KC needs to understand that this medication needs to be taken everyday and complete full course of therapy. Fluconazole can be taken with a meal; common side effects include: headache, rash, N/V, and diarrhea.

Assessment and Recommendation:
8. Cost Ineffective Therapy/Stable Drug Therapy: Pain. KC has severe pain in her arm and legs that can be due to chemotherapy. KC is currently treated with MS-Contin. She was switched from Lortab since the acetaminophen can mask fever during neutropenia. Oral morphine is the treatment of choice in cancer patients with pain. This is due to familiarity and cost effectiveness of treating cancer pain with morphine. However, newer longer acting formulations of morphine have supplanted short-acting morphine in the treatment of pain in cancer patients due to decrease in dosing frequency.32,33 These newer controlled-release (CR) formulations cost more when compared to immediate-release (IR) morphine.

Pharmacological Recommendation:
a. Morphine is the drug of choice for the management of pain in cancer patients. It is the gold standard to which all analgesics are compared.
b. CR was formulated to make dosing and administration easier.
   a. Clinical studies have shown CR morphine administered every 12 hours to be just as effective as IR morphine administered every 4 hours.33
   b. Since these two formulations of morphine are comparable in pain management, cost will be the deciding factor as to choice of agent.
c. Methadone is another alternative to morphine for pain in cancer patients. However, it is considered a second- or third-line opioid.
   a. Methadone has long been used for the treatment of opioid addiction. New interest has developed recently in using methadone in treating patients with pain.
   b. Methadone is a synthetic opioid agonist which has several unique characteristics:
      i. such as excellent oral and rectal absorption,
      ii. no known active metabolites,
      iii. long duration of action resulting in longer dosing intervals up to every 12 hrs,
      iv. lower cost than other opioids.35
      v. it has shown encouraging results in controlling pain that is refractory to morphine, fentanyl, and hydromorphone.
c. However, methadone does have some down sides:
i. long and unpredictable half-life, which can complicate proper dosing and will require careful and extensive assessment. The half life for methadone in children is 19 hours (range: 4-62 hours),

ii. variable duration of effect: 6-8 hours; after repeated doses it can increase to 22-48 hours.\textsuperscript{25,33,35}

iii. unfamiliarity of clinicians on how to use methadone correctly.

iv. Initial clinical studies were impressive and new clinical studies are underway to further evaluate methadone’s ability to manage pain in cancer patients.\textsuperscript{33}

d. Just considering cost, methadone is the best choice. As to methadone efficacy compared to morphine is unclear.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended dosing</th>
<th>Available oral formulations</th>
<th>Cost per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine IR</td>
<td>0.2-0.5 mg/kg/dose q4-6h prn</td>
<td>Tablet: 15, 30 mg; oral solution 10mg/5mL; 20mg/5mL</td>
<td>PO: $0.18</td>
</tr>
<tr>
<td>Morphine CR</td>
<td>0.3-0.6 mg/kg/dose q12h</td>
<td>Tablet: 15, 30, 60, 100, 200 mg</td>
<td>PO: $0.94</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.1 mg/kg/dose q4h for 2-3 doses, then every 6-12h prn (max. dose: 10mg/dose)</td>
<td>Tablet: 5 and 10 mg; Oral solution: 5mg/5mL; 10mg/5mL; Oral conc.: 10mg/mL</td>
<td>PO: $0.09</td>
</tr>
</tbody>
</table>

d. Recommendation: Recommend to switch KC from MSContin to morphine IR 15 mg po q4-6h prn pain; due to less cost and no difference in efficacy between CR and IR morphine, IR morphine should be used in this patient.

Monitoring and Education: Monitor KC level and tolerance of sedation. Routinely check KC pain relief/control at each visit and phone calls for the first few days of starting IR morphine and then one week later. Check heart rate and respiratory status at each visit. Instruct KC to call or come into clinic if pain becomes unmanageable. Use of this medication and the other medications for N/V can cause enhance sedation; which can interfere with activities that require concentration and coordination. In addition morphine can cause constipation, so diets high in fiber with plenty of fluids should help minimize the constipation.
References

18. ASHP Reports. ASHP Therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Heath-Syst Pharm 1999;56:729-764.