

Supplement 1: Summary of major changes to the 2005 Recommendations for Ancillary and Supportive Care

COMPLICATION MONITORING UPDATES: Minimum monitoring frequencies during systemic immunosuppressive therapy are suggested and thereafter, referral to existing late effects consensus guidelines is advised (Table 2).

ORGAN SYSTEM UPDATES:

Skin:

- a. Quarterly monitoring for new malignancy during immunosuppressive therapy with referral to Dermatology for evaluation of suspicious abnormalities (Table 2)
- b. Addition of “Avoidance of photosensitizing agents” to highlight the potential risks of voriconazole toxicity (also in Table 3).
- c. Hyperlink to systemic therapy for patients with steroid-refractory skin GVHD.
- d. Endorsed urea or glycerol containing topical preparations as good skin hydrators although these should be avoided in young children due to increased potential for skin disruption and irritation.
- e. Clarified that standard doses of antihistamines rarely alleviate severe pruritus and that refractory symptoms might benefit from gabapentin. Doxepin was deleted from the recommendations.

Mouth and Oral cavity:

- a. Extensive reorganization of text and Table 4 for greater clarity.
- b. Aphthous-like ulcers due to sirolimus and fibrovascular ulcers due to calcineurin inhibitors are added as an important toxicity consideration.
- c. Clarified the use of topical steroid gels versus solutions for oral mucosa.
- d. Removed the statement that Vaseline-based ointments such as topical tacrolimus are generally less effective in the mouth than alcohol-based corticosteroids.
- e. Suggest topical tacrolimus ointment to treat GVHD of the lips rather than high-potency steroids that may cause irreversible atrophy.
- f. Emphasis added to counsel patients adequately on how to self-administer oral rinse formulations (follow the published instructions for each preparation (Supplement 3), then spit out, then avoid oral intake for 30 minutes).
- g. Azathioprine rinses have been removed, since they are rarely recommended and supportive data are lacking. Systemic azathioprine removed because it is not ancillary therapy.
- h. Noted that a small amount of viscous lidocaine may make oral rinses more tolerable for patients who experience burning discomfort.
- i. Suggested the use of intralesional steroids and physical therapy for the treatment of focal intraoral mucosal sclerosis.
- j. Patients should receive routine professional dental care including professional scaling and oral hygiene instructions
- k. Pediatric considerations are clarified and expanded (Table 4).

Eyes:

- a. Greater emphasis and detail added regarding the use of scleral lenses for severe KCS.
- b. Evidence for use of PROSE and BSCL lenses is stronger than for moisture chamber glasses or goggles.

Genitalia:

- a. Added brief section to recognize chronic GVHD of the male genitalia.
- b. Clarified higher incidence of female genital chronic GVHD based on newer literature.
- c. Added that mild to very active chronic GVHD can be asymptomatic
- d. Added new section to highlight the importance of “Routine surveillance”.
- e. Re-titled section on “Symptomatic low estrogen states” as “Vulvar and vaginal atrophy”.
- f. Added that clindamycin added to topical steroids has benefit in vaginal GVHD.

Gastrointestinal and Liver:

- a. Toxicities of commonly used drugs are noted to be possible causes of nausea / weight loss.
- b. Clarifications and additions to Table 7: “topical” gastrointestinal steroids, bile acid binding resins, and anti-viral therapy for hepatitis B and C.

Lungs:

- a. Extensive rewrite and deletion of Figure 1 to improve clarity.
- b. Greater emphasis to encourage regular PFT monitoring for airflow obstruction.
- c. Addition of fluticasone, azithromycin and montelukast (“FAM”) as initial therapy for BOS.
- d. New paragraph on potential role of lung transplantation for end-stage BOS.

Neurologic:

- a. Mentioned utility of EMG and nerve conduction studies to assess neuropathies and myopathies.
- b. Called attention to prevention of falls among patients with myopathies and neuropathies
- c. Called attention to easily unrecognized extremity ulcers in patients with distal insensitivity in the extremities.
- d. Called attention to entrapment mononeuropathies in sclerotic phenotype GVHD and possible treatment with bracing, splinting, off-loading or surgical release.
- e. Added reminder that maintaining muscle strength requires strength training, not just cardiovascular fitness.
- f. Added a section on “Muscle cramps” as well as relevant additions to Table 10.

Immunologic and Infectious Diseases:

- a. Encapsulated organism prophylaxis more definitively stated as necessary but choice of antibiotic should consider patterns of pneumococcal resistance with more options provided in Table 11.
- b. Vaccinations against encapsulated organisms may begin earlier (3-6 months posttransplant) reflecting newer recommendations by ASBMT/IDSA and other groups.
- c. Antifungal prophylaxis updated to consider primary prophylaxis with posaconazole or voriconazole for high-risk patients and secondary prophylaxis based on history of prior specific pathogen.
- d. Stronger emphasis on cotrimoxazole (if tolerated) over alternative forms of PJP prophylaxis.
- e. Added option of CMV prophylaxis with valganciclovir (or high dose valacyclovir) for CMV-seropositive cord blood recipients during 1st year after transplantation.
- f. Pediatric considerations (Table 11) explain the more liberal use of IVIG in children treated for primary immunodeficiency diseases.

Musculoskeletal:

- a. Added information about avascular necrosis to text and Table 12.
- b. Added hyperlinks the online 10-year fracture risk calculators that are available to guide anti-resorptive therapy in adults: FRAX (<http://www.shef.ac.uk/FRAX/tool.aspx>), FORE (<https://risk.calculator.fore.org/default.aspx>).
- c. Brief mention is made regarding the use of teriparatide and denosumab for osteoporosis.
- d. Emphasis on preferred use of hormone replacement (HRT) for osteoporosis in patients who are hypogonadal and of an age where HRT is not contraindicated.
- e. Added section on weight bearing exercise and management of vertebral compression fractures.
- f. Clarified the definition of osteoporosis in pediatrics and the generally higher threshold for bisphosphonate therapy.

Psychosocial:

- a. Extensive rewrite of the four sections with expansion of the “Fatigue” section to include “Musculoskeletal Symptoms” (non-overlapping with #9 above) and a new section on “Behavioral Interventions” that is introduced by first acknowledging the often under-recognized psychological, functional or adjustment difficulties among HCT survivors.
- b. New data highlight the importance of suicide being 3-fold higher than the HCT population in general, which in turn is higher than the general population – strengthening the recommendation to screen for depression.
- c. New data about the natural history of sexual dysfunction among post-HCT survivors are incorporated including management suggestions.
- d. New data are included with hyperlink to NCCN Guidelines to address fatigue and its management with exercise and cognitive behavioral interventions.
- e. More aggressive neuropsychological screening is proposed for children and, more controversially, for adults given the under-recognition of cognitive problems after transplantation.

Supplement 2 - Specific Dispensary Directions for Skin and Appendages

In general, topical steroids should not be used continuously for more than 14-21 days in order to avoid tachyphylaxis. After the 14-21 day burst, application should be decreased to twice daily on weekends. Bursts may be repeated every 4-6 weeks as needed (twice daily for 2 weeks).

Steroid Formulation Considerations:

Ointment	<ul style="list-style-type: none"> • Generally more potent due to occlusive nature • Most lubricating, but greasy • Limited use in intertriginous areas • Generally least acceptable preparation by patients
Cream	<ul style="list-style-type: none"> • May contain preservatives that can cause further irritation • Can be used in intertriginous areas • May have drying effect • Quick absorbing and better tolerated by patients
Lotion	<ul style="list-style-type: none"> • May contain alcohol which can cause further irritation • May be used in scalp or other hair covered areas • Typically has drying effect
Gel, solutions, spray, foam	<ul style="list-style-type: none"> • Dry and absorb quickly • Useful in scalp and other hair covered areas • Often contain alcohol or propylene glycol which can be irritating • Most drying formulations

Steroid Potency Considerations:

Potency of steroid preparation is generally determined by vasoconstrictor assay¹.

Super high and high potency	<ul style="list-style-type: none"> • Max dose 50 gm/wk • Cautious use in both children and elderly patients • Better for hyperkeratotic and lichenoid skin changes as well as thickened skin areas such as palms and soles • Avoid use on face or intertriginous areas
Medium and low potency	<ul style="list-style-type: none"> • Continuous use of low potency preparations is generally safe • Daily use of medium potency preparations for ~ 3 months is

	<p>generally safe.</p> <ul style="list-style-type: none"> • OK to use on large body surface area • Preferred for face and intertriginous areas • Preferred for children and the elderly
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Drug Name	Strength	Formulation	Special considerations
Super High Potency			
Clobetasol propionate	0.05%	Cream, foam, gel, lotion, ointment, shampoo, spray	Avoid axilla, groin & face Use for no more than 14 days
Flucinonide	0.1%	Cream	
Halobetasol propionate	0.05%	Cream, ointment	
High Potency			
Flucinonide	0.05%	Cream, gel, ointment, solution	Avoid axilla, groin & face Use for no more than 14 days
Triamcinolone acetonide	0.5%	Ointment	
Medium-High Potency			
Betamethasone valerate	0.12%	Foam	
Fluocinolone acetonide	0.025%	Ointment	
Fluocinolone acetonide	0.2%	Cream	
Medium-Low Potency			
Desonide	0.05%	Lotion, ointment	
Fluocinolone acetonide	0.025%	Cream	
Hydrocortisone butyrate	0.1%	Cream	

Hydrocortisone valerate	0.2%	Cream	
Triamcinolone acetonide	0.1%	Lotion	
Low Potency			
Desonide	0.05%	Cream	
Fluocinolone acetonide	0.01%	Cream, oil, shampoo, solution	Helpful for scalp lesions
Hydrocortisone (OTC)	1%	Cream, lotion	
Triamcinolone acetonide	0.1%	Cream	

Additional Topical Therapy for Consideration:

Topical Calcineurin inhibitors:

Tacrolimus (0.03%, 0.1% cream/ointment): Apply to affected area two times a day. Consider 0.03% strength in pediatric patients only.

Pimecrolimus (1% cream): Apply to affected area two times a day.

Antipruritic agents:

Hydrocortisone acetate (1.0% or 2.5%)/Pramoxine HCL (1.0% lotion/cream/ointment): Apply to pruritic areas two times a day.

Pramoxine HCL (1.0% cream/liquid/lotion/ointment): Apply two times a day to pruritic areas

Camphor/Menthol (0.5%/0.5% lotion): Apply as needed to pruritic areas.

Supplement 3 - Specific Dispensary Directions for Chronic GVHD of the Mouth and Oral Tissues

Generalized sensitivity or mucosal erosions/ulcers: Steroids solutions – for most of the steroid or calcineurin inhibitor solutions (see Table) the instructions are to swish with 5 ml for 4-6 minutes and spit out up to 6 times a day. For budesonide the published duration of rinse is up to 10-15 minutes. Food or drink should be avoided for 30 minutes afterwards. Patients should be advised about the increased risk of oral candidiasis, and may consider co-treatment with nystatin for prevention.

Table: Examples for common topical preparations for oral cGVHD

Preparation	Family	Drug	Concentration	Daily dose	Available commercially in the US
Solutions	Steroids	Dexamethasone	0.1 mg/mL (0.01%)	10 mL x3-6/d	Yes
		Dexamethasone	0.4 mg/mL (0.04%) ¹	10 mL x3-6/d	No
		Prednisolone	3 mg/mL (0.3%)	5 mL x3-6/d	Yes
		Budesonide	0.3 mg/mL (0.03%)	10 mL x2-4/d	No
		Clobetasol	0.5 mg/mL (0.05%)	5 mL x3/d	No
		Triamcinolone	1 mg/mL (0.1%)	x10/d	Yes
		Triamcinolone	10 mg/mL (1%)	5 mL x3-6/d	No
		Betamethasone ¹	0.02 mg/mL (0.002%)	10 mL x3-4/d	No
	calcineurin inhibitor	Tacrolimus (oral solution)	0.1mg/mL (0.01%)	5 mL x3/d	No
Creams/gels /ointments	Steroids	Clobetasol cream/gel	0.05%	x2/d	Yes
		Triamcinolone cream ¹	0.1%	x2/d	Yes
		Triamcinolone cream ¹	0.5%	x2/d	Yes
		Halobetasol cream ¹	0.05%	x2/d	Yes
		Betamethasone cream/ointment/gel ¹	0.05%	x2/d	Yes
		Betamethasone cream/ointment ¹	0.1%	x2/d	Yes
		Betamethasone ointment ¹	0.05%	x2/d	Yes
		Fluocinonide gel	0.05%	x2/d	Yes
	Other immuno-modulators	Tacrolimus ointment	0.1%	x3/d	Yes

¹Preparations that are in use for oral vesiculobulbous diseases and were suggested in the literature specifically for oral cGVHD.

Pain Management:

Artificial saliva and oral lubricants can be prescribed to improve oral comfort (examples include but are not limited to: Oral Balance gel, Stoppers 4 Dry Mouth Spray, Oasis, Salivart, Xerolube). Patient should be advised to use bland toothpaste (ex. children's toothpaste) and alcohol free mouthwashes to minimize irritation to the oral mucosa. Viscous Lidocaine (2% solution) individually, or mixed with Kaolin/Pectin or aluminium hydroxide -magnesium hydroxide (Maalox)-and diphenhydramine (1:1:1) may provide some pain relief. Patients may swish with 5 mL for 5 minutes and spit, preferably not more than 5 times daily to limit possible lidocaine systemic absorption.

Dental Decay Prevention:

High sugar diet should be avoided. Daily neutral 1.1% NaF application – gel or toothpaste can be used for prevention of further dental decay. Neutral pH fluorides or non-mint flavored fluoride products are available and may be better tolerated when oral sensitivity exists. May consider adding chlorhexidine mouth rinse (prefer alcohol-free) in caries-active patients (rinse up to twice daily) for limited durations since it may cause taste loss and tissue discoloration. Patients may chew sugar free gum, either one that contains xylitol or Calcium Phosphate to stimulate saliva flow and prevent caries.

Excessive Oral Dryness:

Artificial saliva and lubricants as recommended above. In addition, systemic sialogogues can be prescribed: Cevimeline (30mg oral capsules): 30 mg orally 3 times daily; or Pilocarpine (5 mg tablets): 5-10 mg orally 3 times daily. Commercial lip-coating/moisturizers may relieve the lip dryness. Lip-coating agents with SPF ratings >30 are preferred to minimize the risk for lip cancer.

Gastric Reflux: if gastroesophageal reflux is present and there is reduced saliva (and hence reduced salivary bicarbonate), patients may benefit from proton pump inhibitors and anti-reflux measures to minimize oral mucosal symptoms as a result of unopposed gastric acid.

Supplement 4 - Specific Dispensary Directions for Eyes:

Topical agents to potentially decrease ocular surface inflammation:

Cyclosporine (ophthalmic emulsion 0.05%): Apply one drop in both eyes twice a day.

Prednisolone (1.0% ophthalmic solution, e.g. Pred Forte®) one drop in both eyes 2-4 times daily.

Fluorometholone (0.1/0.25% ophthalmic suspension) one drop in both eyes 2-4 times daily.

Loteprednol etabonate (0.5% ophthalmic suspension) 1-2 drops in both eyes 4 times daily.

Topical agents to support ocular lubrication: Patients who depend on the use of artificial tears more than 4 times a day should use preservative-free artificial tears which are gentler for the ocular surface. The preservative-free artificial tears may be used as often as every 30 minutes, if needed. Patients should be counseled that one brand may work better than others for them.

- Examples of some available brands are Refresh®, Refresh Endure®, Refresh Plus®, Systane®, Bion Tears®, TheraTears®, GenTeal PF®.
- Hydroxypropyl cellulose (i.e. Lacrisert® 5 mg ophthalmic insert). Place into the cul-de-sac of the eye daily as an alternative
- Autologous serum eye drops can be considered, but have limited availability
- Thicker formulations maybe helpful for patients requiring frequent use of artificial tears, and are most appropriately recommended at bedtime, such as Celluvisc®, and Genteal Gel ®, Lacrilube®, Hypotears® ointment

Systemic medications that may increase tear production:

Cevimeline (30mg oral capsules): 30 mg orally three times daily

Pilocarpine (5 mg tablets): 5-10 mg orally 3 times daily

Supplement 5 – Routine Gynecological Health and Specific Dispensary Directions for Vulva and Vagina

General hygiene: Irrespective of the underlying cause, the following hygiene measures are recommended for the prevention or alleviation of vulvar or vaginal symptoms.

- Mechanical and chemical irritants should be avoided.
- The genital area is best cleansed with warm water rather than soap or feminine wash products. The area may be air-dried and patients should be counseled to wipe in a front to back direction.
- A small amount of emollients or Lanolin Cream applied to the external genitalia, and not into the vagina, may provide relief from itching and irritation, provided that abnormal discharge (infection) is not also present.
- Replens or other bacteriostatic gels may be used in the vagina for comfort. Replens adheres to the vaginal wall and is intended to have a longer lasting effect than bacteriostatic water-soluble gels.

Routine surveillance: Recent prospective studies support routine gynecologic evaluations prior to HCT and beginning 100 days post HCT to ensure appropriate patient education about sexual and gynecologic dysfunctions common after HCT as well as early identification and treatment of CGVHD²⁻⁴. Self-examination and use of vaginal dilators within 3 months post-HCT is recommended to ensure maintenance of a patent vaginal canal. With the use of routine surveillance and early intervention, the late sclerotic features of vulvovaginal GVHD become less likely.

Vulvar and vaginal atrophy: Vulvar and vaginal atrophy occurs commonly after HCT, either due to ovarian failure that follows cancer therapies or natural menopause. Because estrogen supports the barrier and repair functions of vulvar and vaginal epithelia, estrogen replacement is generally offered whenever there is vaginal mucositis, symptomatic atrophy (e.g. dryness, pain with sexual activity) or signs of vulvar or vaginal GVHD. The decision to prescribe estrogen topically to the vulva, intravaginally, or systemically by oral or transdermal routes, should be made in consultation with a gynecologist or other physician with experience in ovarian hormone therapy. Topical and intravaginally applied estrogen leads to limited systemic exposure which is an advantage for patients in whom systemic hormone replacement is contraindicated or otherwise undesirable. Systemic estrogen therapy is associated with specific risks. If systemic

estrogen is used in a woman who has a uterus, a progestin needs to be included as additional therapy to prevent endometrial neoplasia. While there is anecdotal evidence that estrogen replacement (systemic or topical) is an effective adjunctive therapy for vulvar or vaginal GVHD, prospective controlled studies are needed.

Topical Therapy for Vulvar GVHD:

Mild GVHD: Triamcinolone acetonide (0.1-0.5% ointment). Apply topically twice daily as needed to control symptoms. Gynecological evaluation should be considered at 6-8 weeks intervals.

Moderate GVHD: Betamethasone dipropionate (0.05% gel or ointment). Apply topically to the vulva every 12-24 hours for up to 12 weeks. Gynecological evaluation should be considered at 4-6 week intervals during treatment, or sooner if new or worsening symptoms.

Severe GVHD: Clobetasol (0.05% ointment). Apply topically to the vulva twice daily up to 8 weeks. Gynecological evaluation should be considered at 4-6 week intervals during treatment, or sooner if new or worsening symptoms

Vulvar GVHD unresponsive to topical corticosteroids: Tacrolimus (0.1% ointment). Topical application once or twice daily to severe vulvar lesions under the direction of a gynecologist with experience in managing chronic GVHD or lichen planus.

Intravaginal therapy for vaginal GVHD

Betamethasone dipropionate (0.05% gel or ointment). Apply 1gm intravaginal (using vaginal estrogen cream calibrated applicator) every 12-24 hours for up to 12 weeks. Gynecological evaluation should be performed at 4-6 week intervals during treatment, or sooner if new or worsening symptoms.

Hydrocortisone (10%) in 2% clindamycin base. Apply 5 g with vaginal applicator every other night for 4 weeks. May repeat course based on response that is evaluated after 4-6 weeks.

Tacrolimus vaginal suppositories 0.1% (2 mg tacrolimus per 2 gram suppository). May be used nightly for 2 months, evaluate response after 4-6 weeks.

Supplement 6 - Dispensary directions for GI and Liver:

Chronic Diarrhea: If infectious etiology has been ruled out, judicious use of anti-diarrheal agents may be appropriate. There have been no studies assessing the safety and efficacy of Probiotics.

Loperamide (oral tablet or capsule 2 mg; oral solution 1 mg/7.5 ml, 1 mg/5ml): Adults: 2-4 mg po prn loose stools, max daily dose of 16 mg. Children: 0.08 to 0.24 milligram/kilogram/day in 2 to 3 divided doses can be used. Taking loperamide at regular intervals is often more effective for patients with chronic diarrhea than as needed dosing.

Diphenoxylate/Atropine (Lomotil) (based on diphenoxylate component – oral tablet 2.5 mg; oral solution 2.5 mg/5ml): Adults: 2 tabs up to four times daily (20 mg/d of diphenoxylate). Children (2yr and older): 0.3-0.4 mg/kg/day of diphenoxylate (max 20 mg/d) divided four times per day. Note that atropine in Lomotil tablets may lead to intestinal pseudoobstruction, especially if non-agonist opioids are given concomitantly.

Irritable Bowel Type Symptoms:

Nortriptyline (10, 25, 50, 75 mg tablets; oral solution 10 mg/5ml): 25-125 mg po daily may be helpful for patient with symptoms similar to irritable bowel syndrome.⁵ Anticholinergic effects may lead to pseudo-obstruction.

Dicyclomine (10 mg capsule; 20 mg tablet; oral solution 10 mg/5ml): Adults: 20 mg orally four times a day. Safety and efficacy has not been established in pediatric patients. Anticholinergic effects may lead to pseudo-obstruction.

Malabsorption:

Pancreatic enzyme replacement: Different formulations are not interchangeable, but in general should be dosed prior to each meal, and ½ dose with snacks. These may be helpful for patients whose fat malabsorption is causing diarrhea and weight loss. Various brand names include: Creon®, Zenpep®, Pancreaze®, Ultresa®, Viokace®, Pertye®. Usually prescribed along with a proton pump inhibitor to avoid inactivation of lipase enzymes in the stomach.

Abnormal liver tests:

Ursodeoxycholic acid (300 mg capsules, 250 mg tablets or 25 mg/mL suspension compounded by pharmacy.) Adults: 250-300 mg orally 3-4 times daily, Children: 10-15 mg/kg daily divided

three times a day or alternatively < 15 kg – 150 mg po daily, 15-29 kg - 300 mg po daily, > 30 kg – 300 mg po BID.

Supplement 7 - Specific Dispensary Directions for Lung:

Consideration should be given to adding a spacer for both adult and pediatric patients when an inhaler is being prescribed.

Albuterol (multiple formulations of inhalation aerosols and solutions): Adults: 1-2 puffs every 4-6 hr as needed or nebulized 2.5 mg 3-4 times daily, Children: 4 years and older, 1-2 puffs every 4-6 hr. Age 2 to 12 years, nebulized 1.25 or 0.63 mg 3-4 times daily.

Beclomethasone (multiple formulations of inhalation aerosols and solutions): Adults (12 years and older): Oral inhalation, 2 puffs (42 mcg each) 3-4 times daily or double strength 2 puffs (84 mcg each) twice daily; maximum 840 mcg/day. Pediatric: Safety and efficacy not established in children under age 5 or 168 mcg twice daily; maximum 420 mcg/day.

Fluticasone (multiple formulations and combinations, Flovent® used here as an example): Adults (12 years and older): Oral inhalation, 2 puffs (110-220 mcg each) twice daily.

There is some evidence that combination therapy with Fluticasone, montelukast and azithromycin may be helpful in stabilizing the manifestations of BOS⁶.

Montelukast: (Tablet 10 mg; Chewable tablet 4, 5 mg; Oral packet 4 mg/packet): Adults (15 years and older): 10 mg po daily. Children ages 12 mo to 5 years 4 mg daily (granules or chewable tablets available); children 6-14 years 5 mg po daily (chewable tablets).

Azithromycin: (Tablet 250 mg; oral suspension 100 mg/5 ml, 200 mg/5 ml): Adults and children 6 years and older: 250 mg po three times per week

Supplement 8 - Specific Dispensary Directions for Neurologic System

Neuropathy:

Amitriptyline (Tablets: 10, 25, 50, 75, 100, 150 mg) Adults: start at 25 mg orally at bedtime and increase dose by 25mg weekly to effect or maximum of 150 mg daily.

Paroxetine (Oral Suspension: 10 mg/5 ml, Oral Tablet: 10, 20, 30, 40 mg): Adults start at 10 mg orally daily and increase by 10 mg weekly to effect or maximum dose of 50 mg daily. Safety and efficacy has not been established in children.

Gabapentin (Oral Capsule: 100, 300, 400 mg, Oral tablet: 100, 300, 400, 600, 800 mg, Oral Solution: 250 mg/5 ml) Adults or children > 12 years, initiate therapy with 300 mg orally daily on day 1 then 300 mg orally twice a day on day 2 and then 300 mg orally 3 times daily on day 3. Then titrate dose up to effect or maximum daily dose of 3600 mg.

Pregabalin (Oral Capsule: 25, 50, 75, 100 mg, Oral Solution: 20 mg/ml): 50 mg orally three times a day (150 mg/day) and may be increased to MAX dose 100 mg orally three times a day (300 mg/day) within 1 week based on efficacy and tolerability. The safety and efficacy of pregabalin has not been established in pediatric patients, but doses of 5-15 mg/kg/day have been used in epilepsy trials⁷.

Muscle Cramps:

Baclofen (Oral Tablet: 10 mg) Adults 5-10 mg orally three times a day as needed for cramps. Children 12 years and older 10-15 mg per day in 2-3 divided doses as needed.

Clonazepam (Oral Tablet: 0.5, 1, 2 mg, Oral Tablet, Disintegrating: 0.125, 0.25, 0.5, 1, 2 mg): 0.25 – 1 mg orally at bedtime.

Diazepam (Oral Tablet: 2, 5, 10 mg; Oral solution 5 mg/5ml, 5 mg/ml): Adults 2-10 mg orally at bedtime; Children 1-2.5 mg orally at bedtime.

Cyclobenzaprine (Oral Capsule, Extended Release: 15, 30 mg, Oral Tablet: 5, 7.5, 10 mg): Approved for muscle spasms in patients 15 years and older. Extended release 15 mg oral daily, immediate release 5 mg orally up to three times per day. Should only be used for 2-3 weeks.

Ropinirole (Oral Tablet: 0.25, 0.5, 1, 2, 3, 4, 5 mg): For patients whose muscle cramps are worst at night. Initial dose is 0.25 mg orally 1 to 3 hours prior to bedtime; may begin to up titrate after 2 days: 0.5 mg/day on days 3 to 7; 1 mg/day on week 2; 1.5 mg/day on week 3; 2 mg/day on week 4; 2.5 mg/day on week 5; 3 mg/day on week 6; 4 mg/day on week 7; MAX dose, 4 mg/day.

Vitamin B complex (including fursulthiamine 50 mg, hydroxocobalamin 250 µg, pyridoxal phosphate 30 mg, and riboflavin 5 mg) can be taken three times per day.

Supplement 9 - Specific Dispensary Directions for Infectious Disease

PCP prophylaxis:

Sulfamethoxazole – Trimethoprim (400 mg-80 mg, 800 mg-160 mg; single or double strength tablets): Adults: a minimum of 6 single strength equivalents per week, which can be administered in a variety of ways, e.g.: one double strength tablet twice daily for 2 days per week, one double strength tablet daily three days per week or one single strength tablet every day of the week.

Children (Oral suspension 200 mg/5 ml-40 mg/5 ml): < 20 kg, 5 mg/kg/day TMP component in 2 divided doses for two days per week. For children 20-40 kg, 1 single-strength tablet twice daily 2 days per week. For children > 40 kg follow adult dosing.

Dapsone (Oral tablet 25, 100 mg): Adults: 50 mg orally twice daily or 100 mg once daily.

Children: 1 mg/kg/day orally in 2 divided doses (up to 100 mg/day).

- G6PD screening should be performed for African Americans, Indians and those of Mediterranean decent.
- Contraindicated in patients allergic to sulfa
- Monitor for the development of methemoglobinemia (periodic pulse oximetry)

Pentamidine (300 mg inhalation powder for solution): Adults and children > 5 years: 300 mg inhaled every 4 weeks. May also be given IV 4 mg/kg every 14-21 days.

Atovaquone (Oral Suspension: 750 mg/5 ml): Adults and children > 13 years: 1500 mg orally daily with a meal. Children 1-3 mo and > 24 months 30 mg/kg/day, 4-24 mo 45 mg/kg/day.

Encapsulated Organism prophylaxis:

TMP/SMX (use based on local antibiotic sensitivities): The following regimen covers both PCP and encapsulated organisms.

Adults: 1 double strength tablet orally daily.

Children: < 20 kg, 2.5 mg/kg/day TMP component once a day, > 20 kg, 1 single-strength tablet orally daily. Patients > 40 kg, follow adult dosing.

If local antibiotic sensitivities do not support the use of TMP/SMX for encapsulated organisms:

Penicillin VK (Oral Tablet: 250 mg, 500 mg; Oral Suspension: 125 mg/5 ml, 250 mg/5 ml):
Adults: 750 mg orally twice daily (weight > 60 kg), 500 mg orally twice daily (weight < 60 kg).
Children: 250 mg orally twice daily (weight 20-40 kg), 125 mg orally twice daily (weight < 20 kg)

VZV prophylaxis:

Acyclovir: (Oral capsule: 200 mg; Oral tablet 400 mg, 800 mg; Oral suspension 200 mg/5 ml):
Adults: 400 mg orally twice daily, children < 6 yo 200 mg orally twice daily.
Valacyclovir (500 mg and 1 g oral tablets): Adults: 500 mg orally once to twice daily.
Children and adults < 40 kg: 250 mg orally twice daily

Fungal Prophylaxis: For those considered at high risk for mold infections, generally on > 0.5 mg/kg of prednisone.

Voriconazole (Oral Tablet: 50 mg, 200 mg; Oral Suspension: 40 mg/ml): Adults: 200 mg orally twice daily. Children: 4 mg/kg/day in twice daily divided doses. In order to avoid toxicity and to ensure appropriate dosing, recommend monitoring levels after 5 days of dosing with goal trough level of between 2-6.

Posaconazole (Oral Tablet: 100 mg; Oral suspension 40 mg/ml). Of note, due to the inconsistent absorption of the suspension, it is not generally recommended. The following dose is based on the tablet. Adult: 300 mg oral daily.

- For 13 years and older a tablet dose of 300 mg daily has been established. Standard dosing with tablets for younger patients has not been established, but based on bioavailability the following weight based dosing could be considered: 10-20 kg: 100 mg daily, 20-40 kg: 200 mg daily and >40 kg 300 mg daily
- For pediatric patients unable to take tablets the following doses of suspension have been used in pediatric clinical trials for fever and neutropenia⁸, post-allogeneic HCT⁹ as well as the chronic granulomatous disease population¹⁰ with acceptable trough levels and safety profile.
 - BID dosing: up to 25 kg: 10-15 mg/kg/dose 25-40 kg: 8 mg/kg/dose at 25-40kg
 - TID dosing: 4 mg/kg/dose (max dose 200 mg) for children less than 12 yo

Levels have not been well established for Posaconazole but the general recommendation for prophylaxis based on average levels in prior clinical trials is a trough concentration > 750 mcg/L and < 3000 mcg/L.

Supplement 10 - Specific Dispensary Directions for Musculoskeletal System

Calcium replacement (multiple formulations): 1000-1500 mg of elemental calcium oral daily.

Vitamin D replacement (25000 IU oral capsule, 50,000 IU oral capsule, liquid filled, 8000 IU/ml oral liquid, 400 IU, 50000 IU oral tablet): 400-800 IU orally daily.

Biphosphonates: (e.g. alendronate 5, 10, 35, 40, 70 mg oral tablets and 70 mg/75ml oral solution)

Treatment of osteoporosis= 10 mg orally daily (in corticosteroid-induced osteoporosis, post-menopausal women), 5 mg orally daily (in corticosteroid-induced osteoporosis, males) or 70 mg orally weekly.

Prevention of osteoporosis= 35 mg orally weekly.

Raloxifene (60 mg oral tablet) 60 mg orally daily.

Calcitonin (200 IU/ml injection solution and 200 IU/actuation nasal spray): 100 IU intramuscular/subcutaneous daily or 200 IU intranasally daily.

Supplement 11 - Pediatric Neuropsychiatric Assessments:

The following brief neuropsychological battery closely parallels the ongoing Children's Oncology Group Standard Neuropsychological and Behavioral Battery¹. This brief (60 minute) battery could be implemented by a neuropsychologist at 6 month intervals. If the screening results indicate concern, a more extensive battery could be used to supplement these subtests. All the tests listed have age-based versions.

To estimate intellectual functioning, Wechsler Intelligence Scales: Block Design, Vocabulary subtests (15 minutes). To estimate working memory/processing speed, Wechsler Intelligence Scales: Digit span, Coding, Symbol Search subtests (15 minutes). To estimate memory, Children's Memory Scale: Stories, Faces, Dots subtests (15 minutes) plus California Verbal Learning Test (15 minutes). In addition, parent report measures could be used as screeners for behavior/emotion/social problems (Behavior Assessment System for Children – 2nd Edition; 20 minutes), executive functioning (Behavior Rating Inventory of Executive Function; 5 minutes)

¹Children's Oncology Group, ALTE07C1 Neuropsychological, Social, Emotional, and Behavioral Outcomes in Children with Cancer

<https://kidscancer.uchicago.edu/sites/pedscancer.uchicago.edu/files/uploads/ALTE07C1DOC.pdf>

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