Clinical Care Guidelines and Strategies for Managing the Ketogenic Diet in Pediatric Epilepsy

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The following information being provided is for learning experience only and not as promotional material

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Objectives

1. Review appropriate candidates for the ketogenic diet
2. Identify safety measures to improve the compliance of the diet in the hospital setting
3. Review initiation and weaning protocols
4. Discuss management strategies for potential complications of the ketogenic diet
5. Identify special circumstances on the ketogenic diet and how to effectively manage these situations

Ketogenic Kids: Can celebrate holidays

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Candidates[1]

Table 1. Epilepsy syndromes and conditions in which the KD has been reported as particularly beneficial

Probable benefit (at least two publications)
Glucose transporter protein 1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Myoclonic-astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Infantile spasms
Children receiving only formula (infants or enterally fed patients)
Suggestion of benefit (one case report or series)
Selected mitochondrial disorders
Glycogenosis type V
Landau-Kleffner syndrome
Lafora body disease
Subacute sclerosing panencephalitis (SSPE)

Kossoff et al. *Epilepsia.* 2009;50:304-317.

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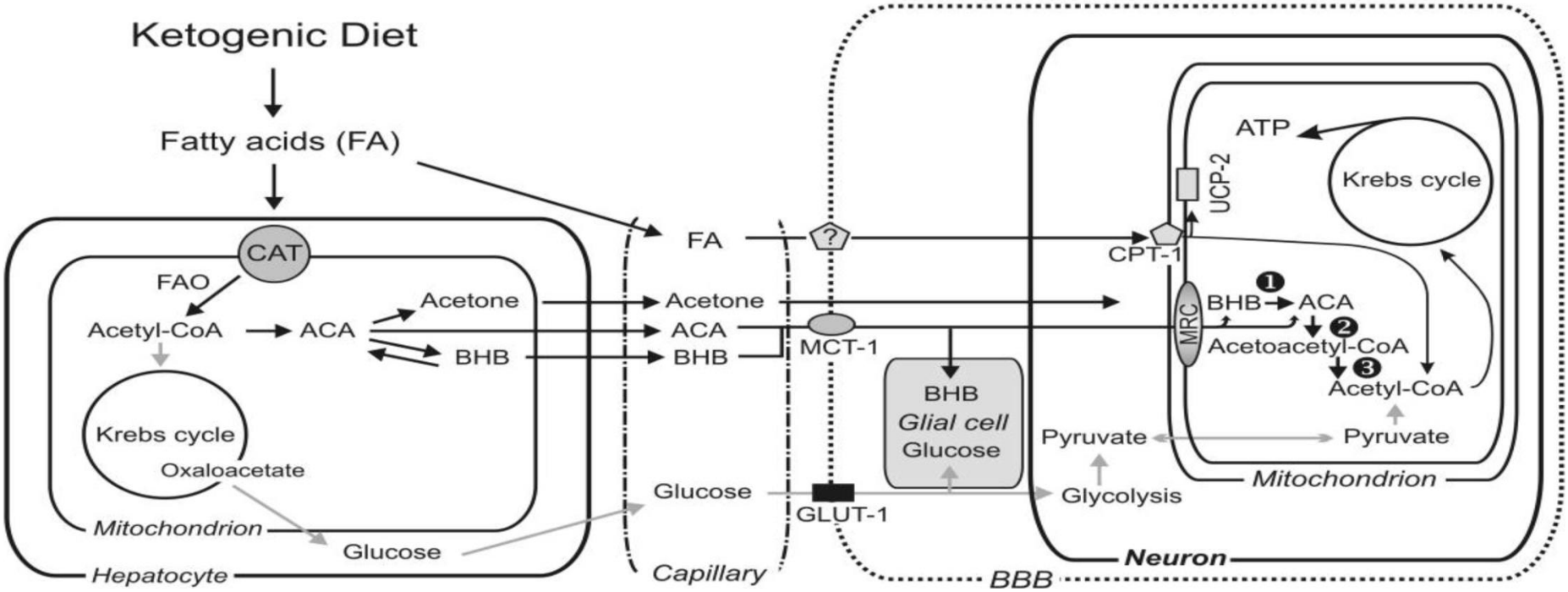

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Contraindications[1]

Table 2. Contraindications to the use of the KD

- Absolute
  - Carnitine deficiency (primary)
  - Carnitine palmitoyltransferase (CPT) I or II deficiency
  - Carnitine translocase deficiency
  - β-oxidation defects
    - Medium-chain acyl dehydrogenase deficiency (MCAD)
    - Long-chain acyl dehydrogenase deficiency (LCAD)
    - Short-chain acyl dehydrogenase deficiency (SCAD)
    - Long-chain 3-hydroxyacyl-CoA deficiency
    - Medium-chain 3-hydroxyacyl-CoA deficiency.
  - Pyruvate carboxylase deficiency
  - Porphyria
- Relative
  - Inability to maintain adequate nutrition
  - Surgical focus identified by neuroimaging and video EEG monitoring
  - Parent or caregiver noncompliance

Kossoff et al. *Epilepsia.* 2009;50:304-317.

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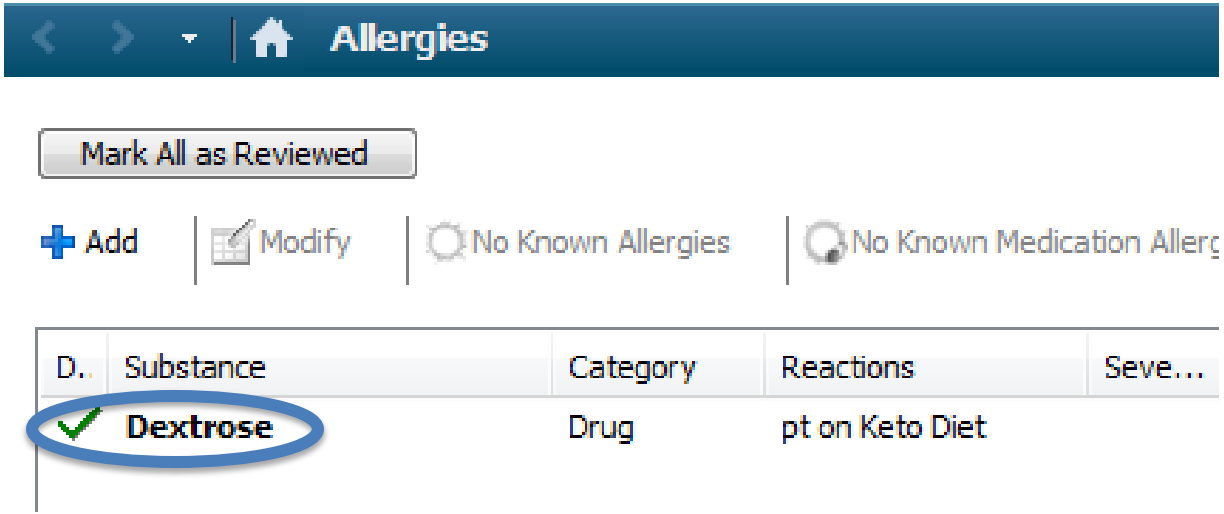
Screening Labs

- Metabolic screening labs:[2]
  - Acylcarnitine profile, serum amino acids, urine organic acids, lactate, ammonia
- Baseline labs:
  - Fasting lipid profile, CBC, CMP, Carnitine free & total, 25(OH)D, AED levels

Ketogenic Kids: Can eat pizza with their family

Flagging Patients



Pharmacy to flag patients on ketogenic diet with Dextrose Allergy

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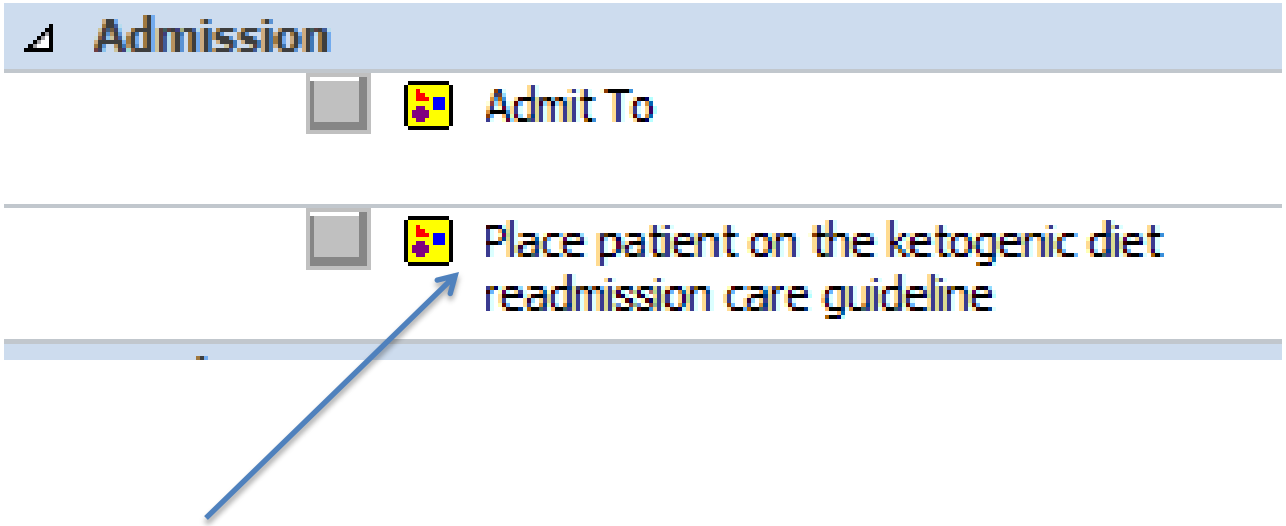
Automatic Notification System



Automatic paging alerts to Keto Pharmacist and RD

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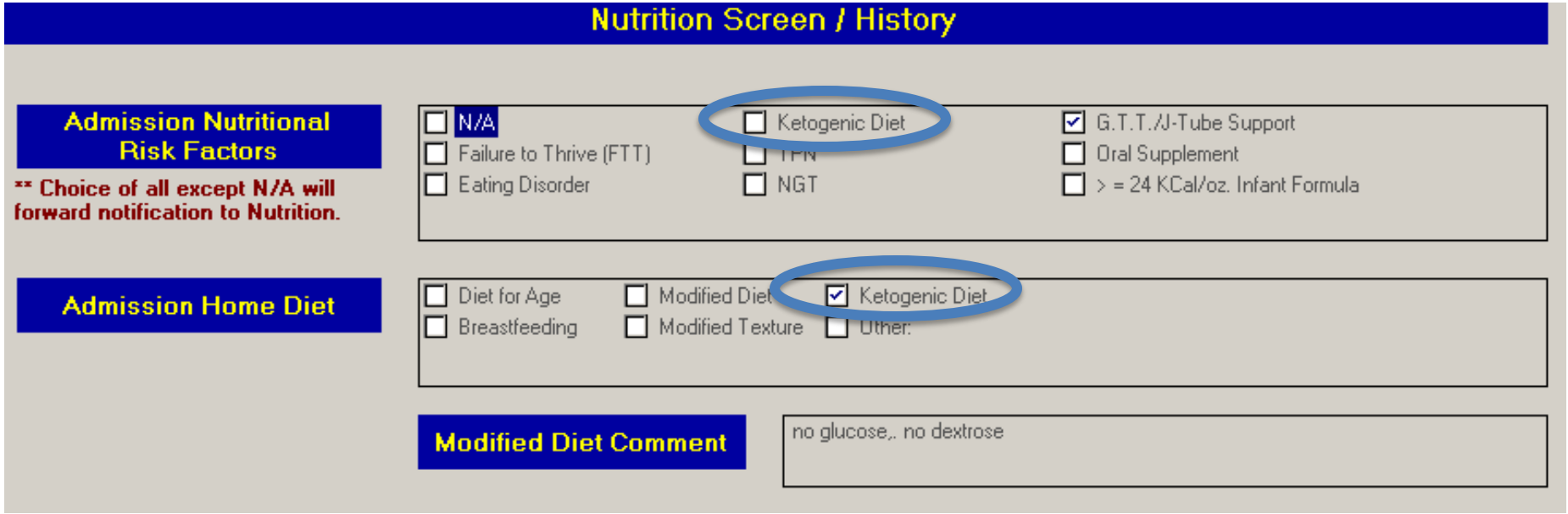
Automatic Notification System



Automatic paging alerts to Keto Pharmacist and RD

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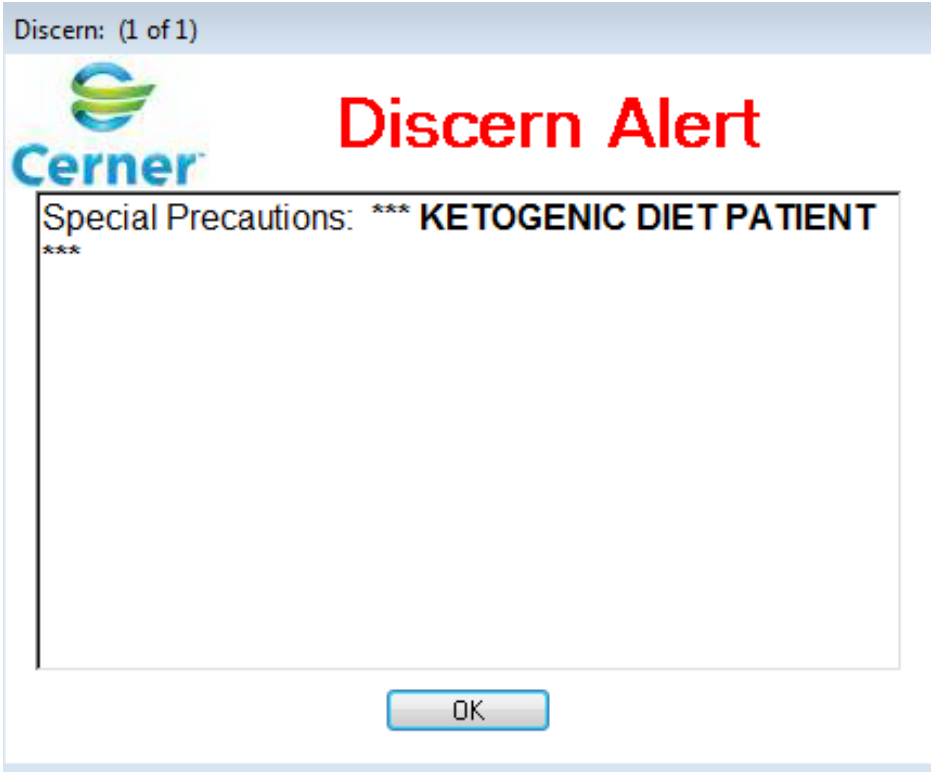
Order Alert



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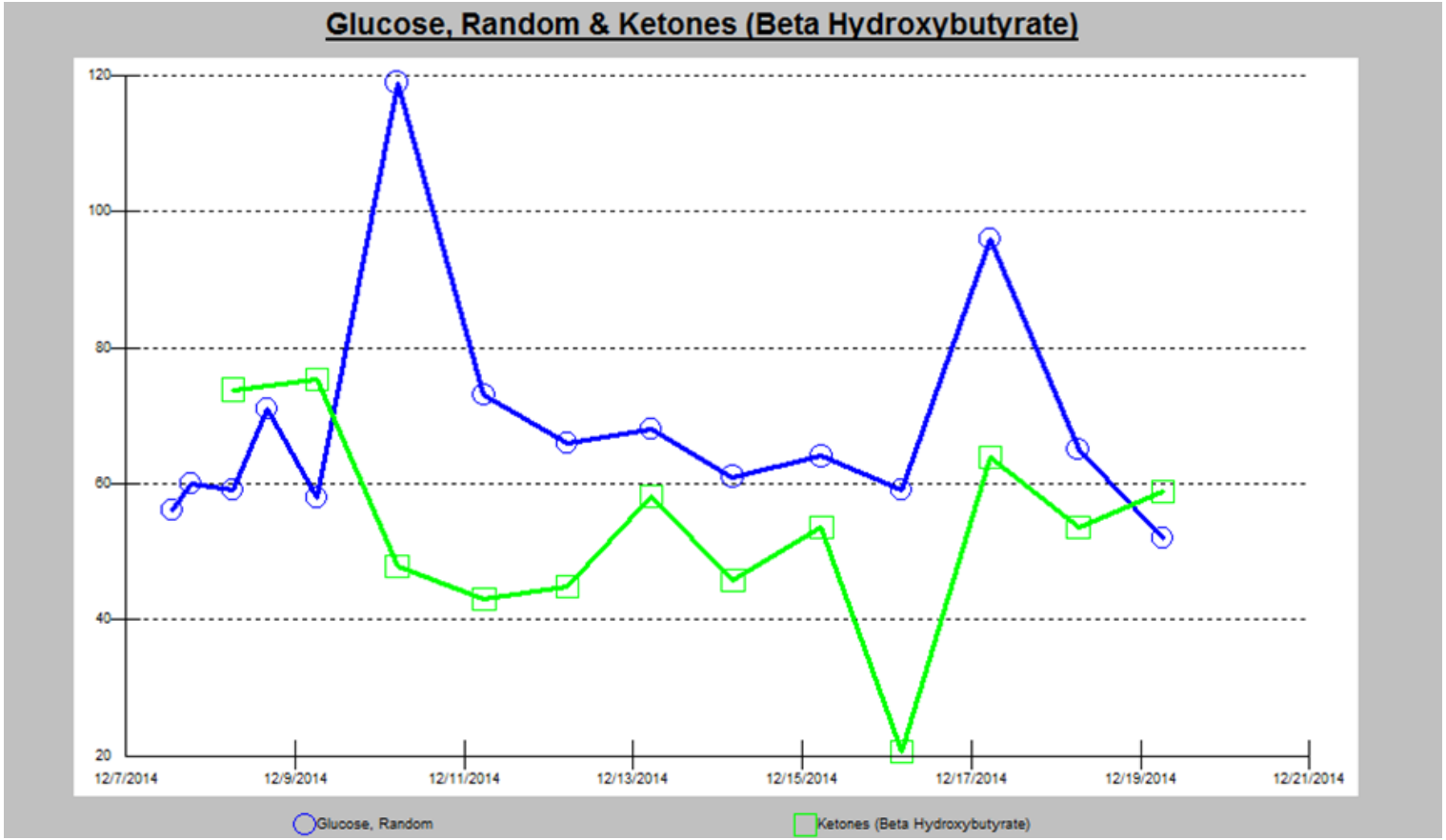
Carbohydrate from Medications



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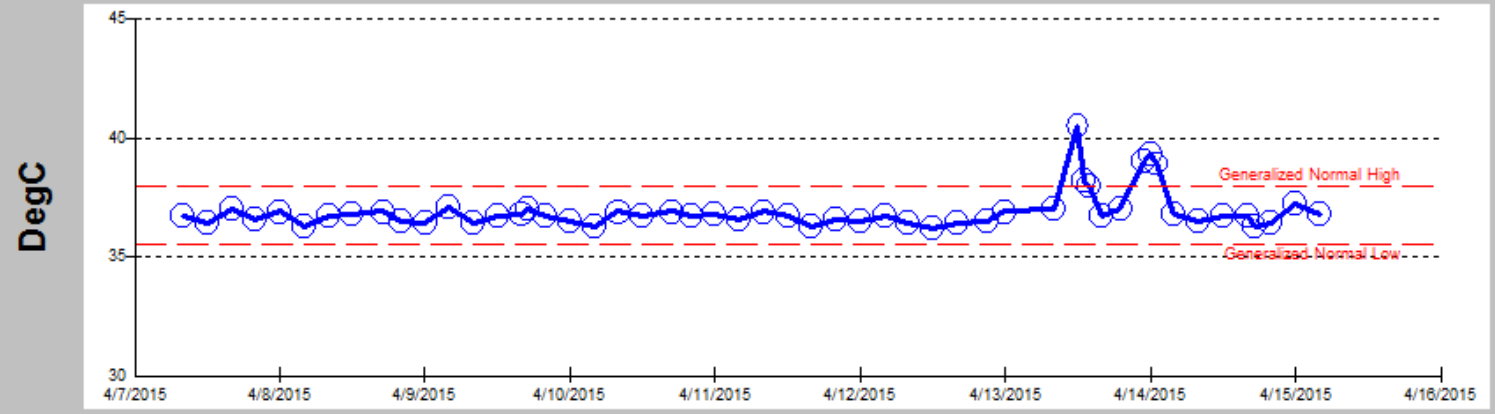
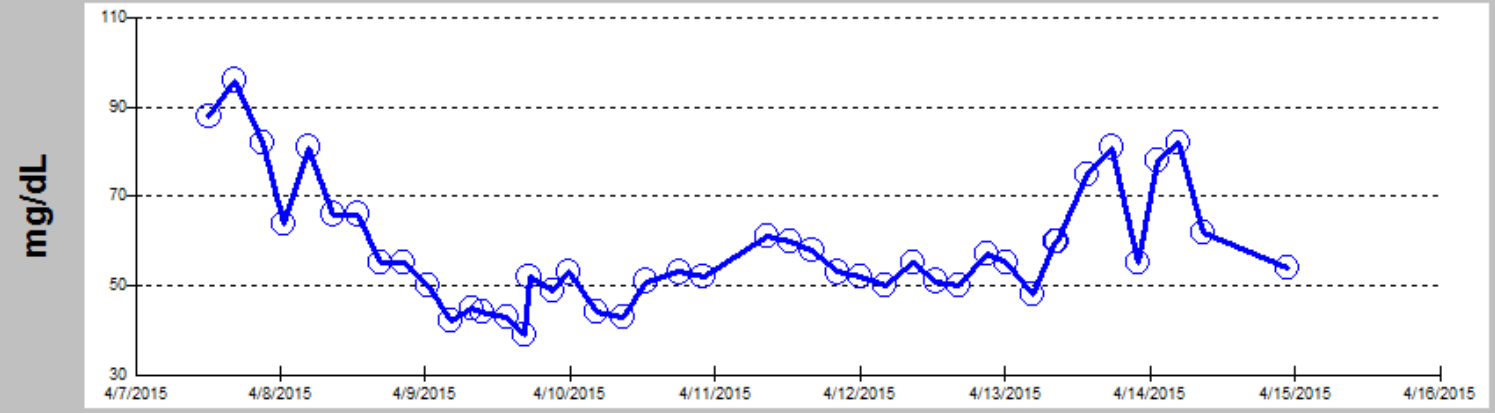
Intravenous Products[3]

Intravenous Product	Strength	Carbohydrate	Fat	Alcohol
Phenobarbital	130 mg/mL	Propylene glycol 702 mg	-	79mg
Diazepam	5 mg/mL	Propylene glycol 414 mg	-	79mg
Lorazepam	2 mg/mL	Propylene glycol 753 mg	-	-
Phenytoin	50 mg/mL	Propylene glycol 414 mg	-	79mg
Pentobarbital	50 mg/mL	Propylene glycol 414 mg	-	79 mg
Famotidine	10 mg/mL	Mannitol 20 mg	-	-
Propofol	10 mg/mL	22.5 mg Glycerol	100 mg Soybean oil 12 mg Egg lecithin	-

Temperature, Axillary



Glucose, Blood (POC)



Ketogenic Diet Initiation Care Guideline

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Inclusion Criteria: a patient who is deemed a candidate by a child neurologist and the multidisciplinary team in the Ketogenic Diet Clinic and who have met the following:
- Failed 2 or more appropriately chosen antiepileptic medications
- Compliant with antiepileptic drug regimen
- Completed screening labs
- Parental consent and interest/motivation

Exclusion Criteria: malnourished, non-compliance with antiepileptic drug regimen, defect in fatty acid oxidation

Assessment
- Vital signs q 4 hrs until tolerating diet (without emesis or hypoglycemia), then q shift
- Daily weights

Interventions
- Seizure precautions
- Continue prescribed antiepileptic drugs
- Lab: Panel 18 on admit, Panel 9 daily, serum Ketones daily beginning on day 2
- Accuchecks q 2 hrs if < 1yr, after 24 hrs q 4hrs if no hypoglycemia
- Accuchecks q 4 hrs if > 1yr
- If blood glucose < 40 mg/dL or patient symptomatic, give 15 mL juice & recheck in ½ hr (repeat as necessary until > 50 mg/dL). If NPO, give 0.25 gm/kg D10W. Notify MD.
- If intractable hypoglycemia (3 episodes of BG <40 mg/dL within 24 hrs), consider D2.5W-D5W continuous infusion to maintain blood glucose 50-80mg/dL.
- Urine ketones, ~~and~~ specific gravity, and pH q void; if specific gravity > 1.030 consider IV fluid bolus (no dextrose)
- Ketogenic diet – PO or Enteral (see p. 2)
- Fluids – maintenance divided throughout the day (caffeine & calorie free). If NPO, provide maintenance IVF (no dextrose)
- Consults: Nutrition, Psychology, Social Service, Child Life

Goals
- Urine ketones: 80-160 mg/dL
- Serum ketones: 40-100 mg/dL
- Beta-hydroxybutyrate (BOHB): 4-10 mmol/L
- Urine specific gravity (USG): 1.010-1.025
- Blood glucose (BG) (non-fasting): 50-80 mg/dL
- Urine pH: 6-8

Discharge Criteria
- Consumed and tolerated 3 full strength keto meals or feedings
- Normoglycemic (>50 mg/dl) for previous 12 hrs
- Ketones in urine are moderate to large.
- Parents have all necessary supplies (gram scale, formula, medications, urine dipsticks)
- Parental education complete; successful return demonstration

Recommendations/Considerations/ Information
- The ketogenic diet is a high fat, low carbohydrate diet that has been employed as a treatment for medically refractory epilepsy since the 1920s.
- The ketogenic diet reduces seizures in up to two-thirds of children refractory to anticonvulsant drugs.
- The diet mimics the biochemical changes associated with starvation and induces, among other changes, production of ketone bodies (mainly beta hydroxybutyrate, and to lesser extent, acetoacetate and acetone), which has been implicated in the mechanisms of seizure control.
- The ketogenic diet is strictly calculated requiring family to weigh all food consumed. The family and social structure of the patien is critical to its success. If the family cannot help maintain complete compliance, ketosis cannot be achieved.
- Patients are scheduled for a 3-4 day admission for ketogenic diet initiation.

Patient/Family Education

Education by RN
Day 1
- Urine ketone testing
- Urine specific gravity testing

Education by RD
Day 1
- Ketogenic Diet: Parents' Guide
- Meal plan and vitamins and minerals
- Fluids

Day 2
- Ketogenic food prep
- Reading labels

Day 3
- Monitoring and sick day

- Refer to CharlieFoundation.org

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Ketogenic Kids: Can consume fat in creative ways

Ketogenic Diet Initiation Protocol[4]

		Day 1	Day 2	Day 3	Day 4
Ratio	FAST-KD	0	4:1	4:1	4:1
	GRAD-KD	1:1	2:1	3:1	4:1
% Goal calories	FAST-KD	0%	33%	67%	100%
	GRAD-KD	100%	100%	100%	100%

Bergqvist et al. *Epilepsia.* 2005;46:1810-1819.

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Ketogenic Diet Weaning Protocol: Enteral Diet[1]

1. Reduce ratio q 2-4wks from 4:1 to 3:1 to 2:1 to 1:1 (ratio reduction may also be completed as 4:1 to 3.5:1 to 3:1, etc.)
2. Continue stepwise advancement by making the following changes q 1-3days
   a) Mix new formula 1/3, 2/3, FS

Ketogenic Diet Weaning Protocol: Oral Diet

2. Continue stepwise advancement by making the following changes q 2-3days
   a) Double the fruit/veggie portion of each meal
   b) Replace heavy cream with WCM (60gm/meal)
   c) Add ¼ cup potatoes, pasta, rice, beans; or ½ slice bread; or ½ cup dry cereal at each meal
   d) Once ketones measure trace/negative DFA can be resumed
   e) Introduce fluid milk stepwise to avoid any GI complications
   f) Avoid introducing sweets for at least 1mo
   g) Continue MVI until age-appropriate diet well established

Ketogenic Kids: Can go to McDonald's

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Managing Potential Side Effects: Constipation[5]

Prevention

- Prepare meals with Group A vegetables
- Incorporate MCT oil into meals (5-30gm/meal)
- Incorporate Avocado into diet (15-30gm/day)
- Add Flax or Chia seeds (5-10gm/meal)
- Flaxseed Porridge or Chia seed pudding
- Adequate fluids (Holiday-Segar)
- Increase fluids by 100-150cc/day

Treatment

- Miralax or Milk of Magnesia
- Glycerin suppository

Goal

- BM q 2-4 days

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Managing Potential Side Effects: Hypoglycemia[2]

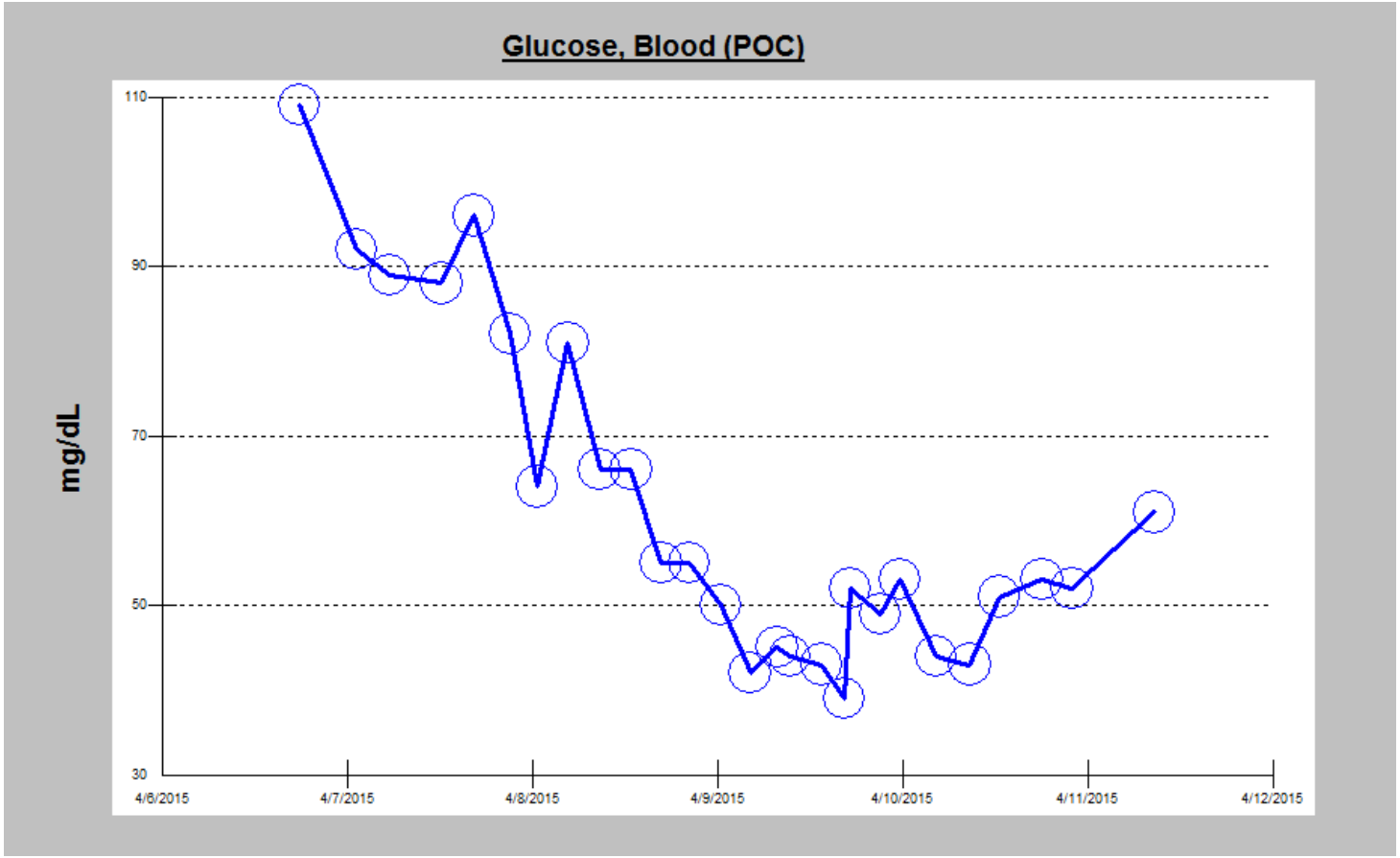
Hypoglycemia BG <40 mg/dL or symptomatic

s/s may include diaphoresis, lethargy, altered mental status, tachycardia, tachypnea

- If NPO give 0.25 g/kg dextrose as D10W bolus
- If PO give 15 mL juice
- Recheck in 30 min
- Repeat as necessary until BG >50 mg/dL
- If intractable hypoglycemia (3 episodes of BG <40 mg/dL w/in 24hr), consider D2.5W-D5W continuous infusion at maintenance

Goal BG 50-80 mg/dL

Blood Glucose during KD initiation



Managing Potential Side Effects: Acidosis[1,2,6,7]

Acidosis CO_2 <20 mmol/L; Anion gap >15 mmol/L

s/s may include lethargy, loss of appetite, dehydration, & emesis

- Evaluate for excessive serum ketones (>80 mg/dL)
- Maintain BG >50mg/dL (D10W bolus, D2.5W IVFs, 15 mL juice, Pedialyte)
- Ensure adequate hydration
- Close monitoring on topiramate & zonisamide
- Ensure adequate Phosphorus – not included in most MVI supplements
- Initiate $NaHCO_3$ or citrates at 1-2 mEq/kg/day divided 2-3x daily
- Consider Decr KD ratio if persistent

Supplement Considerations

Supplement	Bicarbonate (mEq)
Baking soda, ¼ tsp	13.7
Sodium Bicarbonate, 650 mg Tab	7.6
Cytra-K Crystals, packet	30

- Note: Folic acid absorption may be reduced in an alkaline environment
  - Monitor for megaloblastic anemia[1]

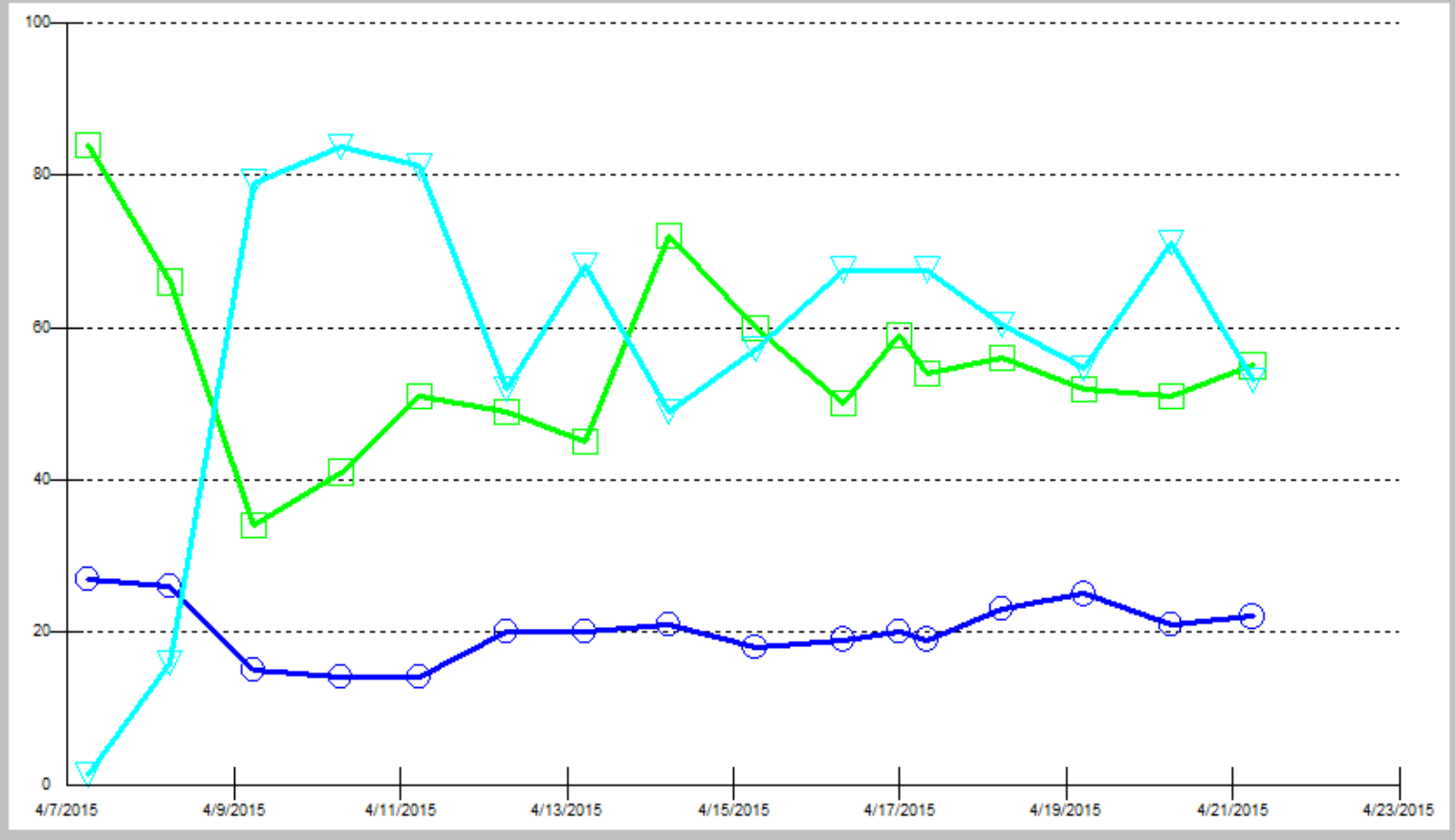
Managing Potential Side Effects: Acidosis

- If 1-2mEq/kg/day does not provide repletion
  - $CO_2 \leq 20$ mmol/L &/or pt symptomatic
  - Incr supplementation starting at 50% of calculated deficit

$HCO_3^-(mEq) = 0.3 \times weight\ (kg) \times base\ deficit\ (mEq/L)$

- Provide as $NaHCO_3$ oral supplementation
- Advance to NaAc continuous parenteral infusion if low CO_2 persists
  - May add up to 150 mEq of NaAc in 1 L solution, titrate rate to desired bicarbonate goal
  - If solution also contains NaCl, total Na content should not exceed 154 mEq/L

CO2 Level, Glucose, Random, & Ketones (Beta Hydroxybutyrate)



Managing Potential Side Effects: Emesis and Lethargy

Emesis

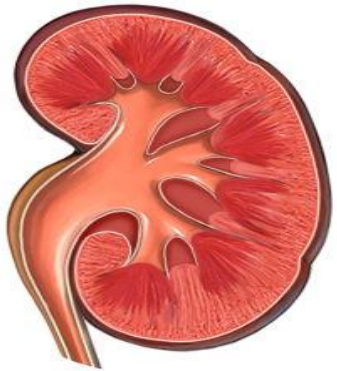
- Evaluate for excessive BOHB &/or acidosis
- Hold feeds or trial ½ volume meals
- Powerade zero
- Allow Pedialyte after 12-24 hrs
- Consult GI for reflux management
- Consider Blenderized Ketogenic formula (gtube)

Lethargy[7]

- Ensure adequate calories and protein
- Evaluate for Carnitine deficiency
- Evaluate for drug toxicity
- Evaluate for acidosis or hypoglycemia
- Evaluate for excessive ketosis (>80 mg/dL)
- Check ammonia level

Managing Potential Side Effects: Kidney Stones[1,8-12]

Kidney Stones



s/s include hematuria, “gritty” urine, flank pain, dysuria, Incr sz’s, nonspecific illness, fever, decr appetite, abd pain

- Adequate fluid intake – maintain USG 1.010-1.020
- Close monitoring on topiramate & zonisamide
- Monitor for acidosis – CO2 >20 mmol/L; urine pH 6-8
- Early detection – Hematest q 1-2 wks
- Consult Nephrology
- Check urine for Ca^{++}/Cr ratio, if >0.2 &/or urine remains positive for blood, start oral citrates at 2 mEq/kg/day divided BID (30 mEq/pckt)

Note: Some citrate products contain 30 mEq/pckt of K^{+} (may need to adjust lite salt)

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Managing Potential Side Effects: Hyperlipidemia[7,13-15]

Hyperlipidemia

Abnormal Values:
Total Cholesterol ≥200 mg/dL
LDL Cholesterol ≥130 mg/dL
HDL Cholesterol <40 mg/dL
Triglycerides ≥200 mg/dL

- Verify if obtained after 12 hr fast
- Consider decrease calories or ratio
- Add omega-3 fatty acids to Decr TG
- Increase PUFA/MUFA for SFA
- Substitute MCT oil for SFA
- Carnitine supplementation to Decr TG
- Add soluble fiber to Decr Total Chol & LDL:
  Age (yrs) + 5-10 g/day
  up to 25 gm at 15 yo

Managing Potential Side Effects: Hypocarnitinemia[1,6,7,16]

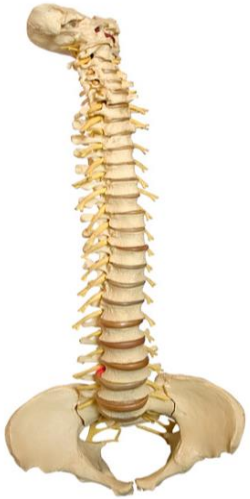
Hyocarnitinemia Free carnitine <20 uMol/L

s/s include generalized weakness, excessive fatigue, decreased muscle strength, elevated TG, hyperammonemia, elevated LFT's, & FTT

- KD &/or VPA may lead to decrease carnitine levels
- Initiate supplementation at 30-50 mg/kg/day divided 2-3x/day
- Hold L-carnitine AM dose to obtain trough levels with lab

Managing Potential Side Effects: Osteoporosis[7,17,18]

Osteoporosis



- Prevent/correct acidosis
- Ensure adequate Ca^{++}, Vitamin D, Phos, Mg^{++}
- Prophylactic Vitamin D supplementation for pts on AEDs:
  400-2000 IU/day
- Monitor 25(OH)D q 3 months
- If Vitamin D insufficient/deficient:
  2000 IU/day x 6 wks

Pts on AEDs may require 2-3x ↑ dose for deficiency & maintenance

Goal: >30 ng/mL

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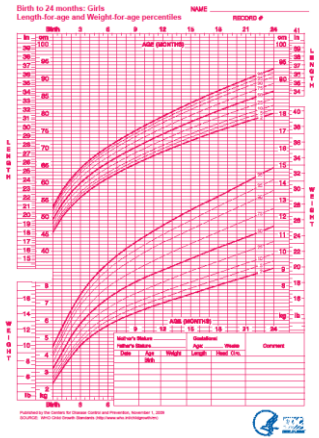
Managing Potential Side Effects: Decreased Growth[7,11,19]

Decreased Growth



- Ensure 100% of diet consumed
- Incr Kcal &/or Protein intake (evaluate for HBV)
- Evaluate zinc intake/status (Alk phos vs serum Zn)
- Consider Decr ratio
- Evaluate/correct for acidosis

- IGF-1 may be suppressed by the KD, leading to Decr linear growth velocity

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Sick Day Guidelines

Fluids

- May take Powerade Zero ad lib
- If feeding intolerance prolonged (12-24 hours) provide Pedialyte
- Add grams CHO + Pro from KD Rx to establish goal allotment of Pedialyte per 24 hrs
  - Pedialyte is 2.5% dextrose solution
  - (CHO + Pro Rx)/0.025 = mL of Pedialyte/day
- Provide remainder of hydration requirements as water

Home Oral Electrolyte Solution

Recipe:

½ tsp Lite salt

½ tsp Baking soda

2 TBS Sugar

1 L Water

Per 1 L solution	Home Recipe	Pedialyte	Enfalyte
Sodium, mEq	52	45	50
Potassium, mEq	18	20	25
Chloride, mEq	42	35	45
CHO, gm	25	25	32
HCO_3, mEq	27	-	33

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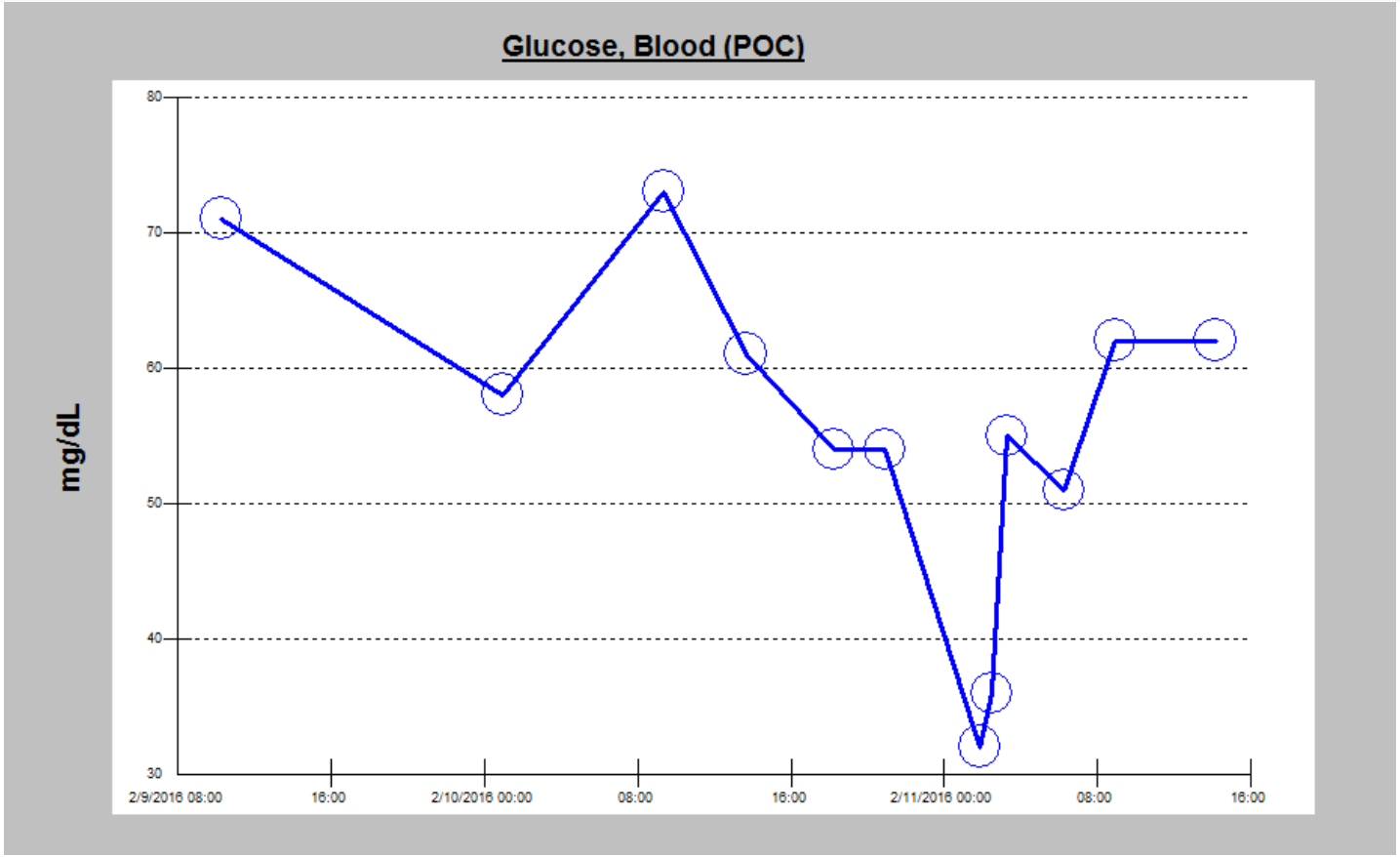
NPO Care Guidelines[2]

Patients on the ketogenic diet should be able to fast the same as other children…

- NPO
  - Maintenance IVF (without Dextrose)
  - Monitor blood glucose q 4hrs
  - Obtain BMP and BOHB daily
  - If NPO >3-5 days, consider starting TPN
  - Start trophic ketogenic formula feeds as soon as able
  - Consider MCT oil EN
    - 2.5-5 mL q 4 hr and increase stepwise per tolerance

NPO Blood Glucose Curve



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Ketogenic TPN Guidelines[20-22]

- Difficult to maximize ketogenic ratio with TPN
- Start IL at 2-3g/kg/d, advance 0.5g/kg/d as tolerated
  - Max lipid infusion 0.15-0.25 g/kg/hr
  - 20% IL contains **glycerol** (CHO), 22.5g/L
  - Obtain TG daily (goal <300 mg/dL; some centers allow 1,000 mg/dL)
  - Consider adding carnitine (10-20 mg/kg/day) to TPN
  - Run over 24 hours
- ~1g/kg/d protein to maximize ratio
- Limit dextrose as low as institution allows (2.5% CHOC Pharm limits)
  - Cycle TPN over 12-16 hrs to limit dextrose infusion
  - Provide additional fluid with ½ NS or NS

Ketogenic Kids: Can eat grab-n-go foods

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Vitamin/Mineral Supplementation[23]

- The KD is deficient in many known micronutrients
  - 4:1 ketogenic ratio has been shown to meet only 3 of the 28 DRI's
  - 1:1 ketogenic ratio has been shown to meet only 12 of the 28 DRI's
- General supplementation:
  - MVI and mineral supplement
  - Calcium and Vitamin D
  - Phosphorus and potassium

Zupec-Kania and Zupanc, Epilepsia. 2008;49:23-26

Supplementation Considerations[23-27]

- Limit Ca^{++} intake to ≤ 500mg per dose
- Consider Ca^{++} citrate if on PPI/Histamine H_2 Antagonist
  - Citrate form is better absorbed with Decr gastric acid secretion
- Provide Ca^{++} separately from $NaHCO_3$
- Ensure meeting EFA with oil choices
  - Olive oil and coconut oil are suboptimal sources of EFA
- Supplementing 100% DRI of K^+ may lead to elevated serum levels
  - Recommend 2 mEq/kg/day
- Many MVI supplements do not contain Phosphorus
  - Administer Phosphorus separately from Ca^{++}

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How to Manage: Swallow Studies and UGI

1. For UGI may be NPO for 6 hrs…may be okay without a CHO adjustment
   a) Standard order - “dose up to 350 mL” = 5.6 gm CHO
   b) Known KD patient – “dose up to 30 mL” = 480 mg CHO
2. Make changes after swallow study – as pt may not participate
3. Ensure feeding therapist, parent or Radiology tech quantifies volume consumed

Product	CHO (mg/mL)
E-Z Paque	16
Readi-Cat	33
Optiray	-

How to Manage: Swallow Studies & Feeding Therapy

- Choose foods that do not require weighing
  - Liquids: formula or heavy cream
  - Soft solids & purees: avocado or sour cream
- Free foods extended version for feeding therapy
  - Use these foods to practice oral motor skills and texture advancement

Extended Free Food List

Food Item	Serving	Food Item	Serving
Iceburg Lettuce	25 grams	Ore-Ida French Fries	½ fry
Black Olives	3 small	Dill Pickles	1 baby dill
Cheerios	8 Cheerios	Jicama – raw	2 slices (12 grams)
Rice Chex	2 Chex	Tofu Shirataki Noodles	¼ cup
Corn Chex	2 Chex	Firm Tofu	½ Tablespoon
Gerber Graduate Fruit Puffs	8 puffs	Sugar Free (SF) Jell-O	1/3 container
Pepperidge Farm Goldfish	1 cracker	Imitation or Pure Extracts	15 drops

How to Manage: Sneaking Food or Medications

1. Sneaking food
   a) Remove CHO portion from next meal
   b) Provide fat bolus (MCT oil, fat bomb, etc)
2. Medications (i.e. abx)
   a) Subtract “x” grams of 10% fruit
      - If pt receives 1 gm CHO from medications, subtract 10 gm of 10% fruit from daily recipe
   b) Provide oil to balance ratio
      - If pt on a 4:1 ratio and receives additional 1 gm CHO from medications, can supplement with 4 grams oil

How to Manage: Feeding Issues

1. **Offer choices**. Behavioral refusal is about control. Use the 10% fruit list to allow choice between 2 foods.
2. **Social modeling**. Modeling the appropriate behavior or desired skill will be motivating during mealtimes.
3. **Praise.** Maintaining a positive meal experience is necessary for long-term success. "High-fives" or "great jobs" will help maintain motivation.
4. **Structured mealtimes.** This will allow for the development of hunger/satiety cycles.
5. **All-In-One meals.** This will ensure intake of prescribed ratio.

How to Manage: After Hours or Urgent KD Starts

KETOCAL 4:1 RATIO (30 Cal/oz)

2 boxes Ketocal 4:1 liquid

250 mL sterile water

KETOCAL 3:1 RATIO (30 Cal/oz)

2 boxes Ketocal 4:1 liquid

6 grams cornstarch

250 mL sterile water

RCF 4:1 RATIO (30 Cal/oz)

1 can RCF

1 jar Microlipid

2 grams cornstarch

250 mL sterile water

RCF 3:1 RATIO (30 Cal/oz)

1 can RCF

1 jar Microlipid

9 grams cornstarch

250 mL sterile water

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Ketogenic Kids: Can eat “Carbs”

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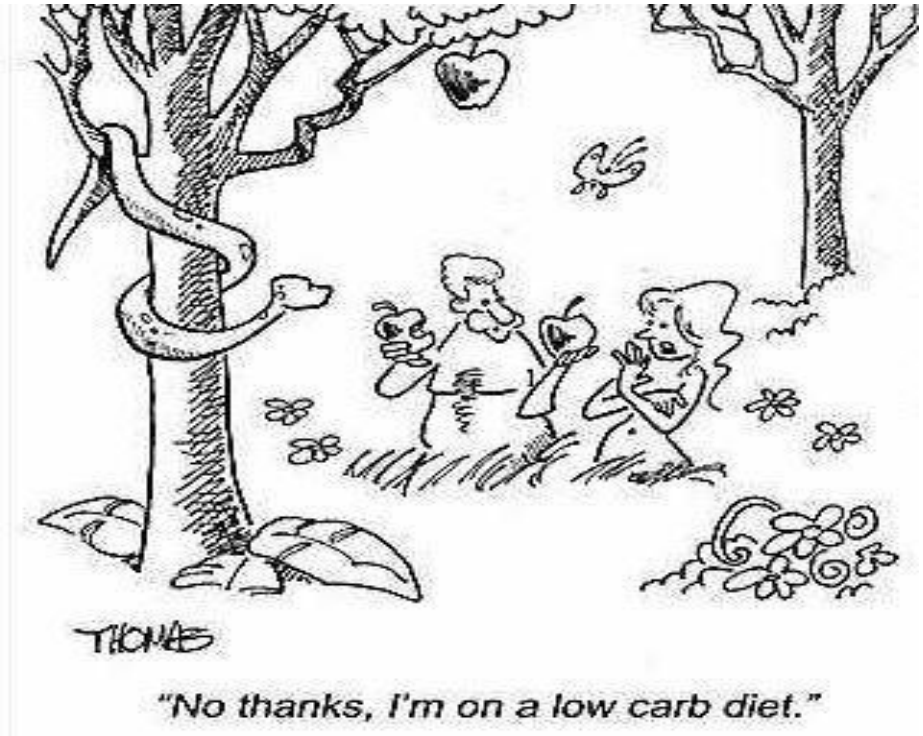
Questions?



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