PROVINCIAL GUIDELINES FOR THE MANAGEMENT OF MEDICALLY-REFRACTORY EPILEPSY IN ADULTS AND CHILDREN WHO ARE NOT CANDIDATES FOR EPILEPSY SURGERY

Epilepsy Implementation Task Force

Critical Care Services Ontario | March 2016

CCSO Critical Care Services Ontario

These Guidelines are a Product of Critical Care Services Ontario (CCSO)

The *Provincial Guidelines for the Management of Medically-Refractory Epilepsy in Adults and Children Who are not Candidates for Epilepsy Surgery* is the result of a collaborative effort between CCSO, the Epilepsy Implementation Task Force (EITF), and Provincial Neurosurgery Ontario (PNO). The EITF was established in June 2013 to develop and implement a provincial framework to maximize value from the system of epilepsy care in Ontario. To support the flow of patients towards appropriate treatment for epilepsy, this document contains a set of guidelines to help with the diagnosis, treatment and referral practices from the moment of a patient's first seizure. CCSO supports the work of the EITF, a subgroup of PNO, as part of its mandate to support equitable and timely access to neurosurgical care, including epilepsy surgery, and to help maintain the province's neurosurgical capacity.

How to Use This Document

The Guidelines included in this document have been developed by a sub-group of the Epilepsy Implementation Task Force for any health care provider engaged in the care of patients with epilepsy before referral to surgery. The guidelines are based on current processes and represent expectations for the highest standards of epilepsy care.

This document provides recommendations only.

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Disclaimer: *The contents of these Guidelines may change over time. Clinicians and hospital administrators should use sound judgment for individual patient encounters. Critical Care Services Ontario, the Epilepsy Implementation Task Force and Provincial Neurosurgery Ontario strongly recommend evidence-based practices.*

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Please see Appendix 9 for a list of the EITF membership.

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Provincial Guidelines for the Management of Medically-Refractory Epilepsy in Adults and Children Who are not Candidates for Epilepsy Surgery
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Abbreviations

AED	Antiepileptic Drug (also known as Antiseizure or Anticonvulsant drug)
CPSO	College of Physicians and Surgeons of Ontario
CPO	College of Psychologists of Ontario
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
ECG	Electrocardiography
ED	Emergency Department
EEG	Electroencephalography
EMU	Epilepsy Monitoring Unit
EITF	Epilepsy Implementation Task Force
eTNS	External Trigeminal Nerve Stimulation
FHP	First Healthcare Provider
FP	Family Physician
GP	General Practitioner
ILAE	International League Against Epilepsy
LGIT	Low Glycemic Index Therapy
LP	Lumbar Puncture
KD	Ketogenic Diet
MAD	Modified Atkins Diet
MRI	Magnetic Resonance Imaging
NP	Nurse Practitioner
OC	Oral Contraception
OCSWSSW	Ontario College of Social Workers and Social Service Workers
PNES	Psychogenic Nonepileptic Seizures
PNO	Provincial Neurosurgery Ontario
RD	Registered Dietitian
TDM	Therapeutic Drug Monitoring
WWE	Women with Epilepsy
VNS	Vagus Nerve Stimulation
DBS	Deep Brain Stimulation
TMS	Transcranial Magnetic Stimulation

Definitions

Adolescent	A person 13 to 17 years of age.
Adolescent Medicine Specialist	Paediatrician practicing adolescent medicine.
Child	A person less than 18 years of age.
Community Epilepsy Agencies	Community Epilepsy Agencies provide a range of support services to persons with epilepsy and their families. These services include epilepsy information, seizure first aid training, support groups, social opportunities, employment counseling and school advocacy.
Co-morbidity	Co-morbidity refers to the co-occurrence of two conditions with a greater frequency than found in the general population. This does not infer a causal relationship. Co-morbid conditions are common in people with epilepsy. They are found across the lifespan and have important implications for treatment and quality of life.
Epileptologist	**Qualifications and Training:** Clinical fellowship training in epilepsy and video-EEG for at least 12 months in a specialized center in Canada, US or abroad; Recognized as a neurologist by the College of Physicians and Surgeons of Ontario (CPSO); and Certification for EEG reporting (EEG examination by the Canadian Society of Clinical Neurophysiologists or APBN exam in Epilepsy) is mandatory. Neurologists who have/had been reporting Video EEG recordings without supervision in any jurisdiction in Canada or the United States of America anytime in or before 2013 are exempt from EEG/Epilepsy examination.
Epileptic Seizure	An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive and or synchronous neuronal activity in the brain (Fisher et al, 2005).
Epilepsy	Disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (Fisher et al, 2005). In most situations, occurrence of two epileptic seizures is evidence of enduring predisposition to generate epileptic seizures.
Family Physician	A physician recognized by the CPSO as a family physician.
General Practitioner	A physician licensed by the CPSO for general practice.
Internist	A physician recognized by the CPSO as a specialist in internal medicine.
Medically-Refractory Epilepsy	Failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drugs (whether as monotherapy or in combination) to achieve sustained seizure-freedom (Kwan et al. 2010).
Neurologist	A physician recognized by the CPSO as a specialist in Neurology.

Registered Dietitian	Registered as a dietician with the College of Dietitians of Ontario RDs without previous experience in diet therapies for epilepsy should receive training from a registered dietitian who practices diet therapies for epilepsy.
Nurse Practitioner	Registration in the Extended Class through the College of Nurses of Ontario and experience in epilepsy care.
Social Worker	Registered as a Social Worker with the Ontario College of Social Workers and Social Service Workers (OCSWSSW)
Pharmacist	Registered with the Ontario College of Pharmacists
Child Life Specialist	Baccalaureate degree certification as Certified Child Life Specialist (CCLS) issued by the Child Life Council (CLC)

I. Introduction

Epilepsy affects around 95,000 Ontarians, of whom approximately 80,000 are adults and over 15,000 are children under the age of 18 (Ng et al. 2015). While most individuals with epilepsy can be treated effectively by a primary care physician or general neurologist, an estimated 30% of those diagnosed have medically-refractory epilepsy, experiencing seizures that do not respond to treatment with two or more appropriate antiepileptic drugs (Bowen et al. 2012). These numbers are not static. Each year it is estimated that 6,500 Ontarians will develop epilepsy, and 1,950 of them will have medically-refractory epilepsy (Tellez-Zenteno et al. 2004; Wiebe et al. 1999).

Surgical intervention could be successful in eliminating seizures; there is approximately an 80% chance that an individual will be seizure-free after surgery, resulting in far better outcomes with respect to seizure freedom, improved quality of life, and reduction of psychosocial comorbidities that accompany medically-refractory epilepsy than continued medical treatment (Bowen et al. 2012). However, not all individuals with epilepsy are candidates for surgery – approximately one third of those suffering from medically-refractory epilepsy will not be considered candidates. Despite its effectiveness, surgical treatment is underutilized in Ontario, with only a fraction of the population who may be eligible for surgery assessed every year. A 2012 report by the Expert Panel on a Provincial Strategy for Epilepsy Care (Health Quality Ontario [HQO], 2012) identified that long wait lists at the province's Epilepsy Monitoring Units (EMUs) and low referral rates contributed to the underutilization of surgical treatment. The Panel also noted that awareness of surgical treatment options was low and patients were not diagnosed, treated and referred appropriately. A 2011 estimate determined that less than 2% of potential surgical candidates accessed surgical treatment (HQO, 2011).

The Panel recommended action to improve epilepsy care infrastructure and surgical referral in the Province (HQO, 2012). As a result, the Ministry of Health and Long-Term Care (MOHLTC) made an investment of 21 new Epilepsy Monitoring Unit (EMU) beds in Ontario, bringing the total number of EMU beds to 39 (26 adult and 13 paediatric). The Ministry also resourced additional epilepsy surgery and vagal nerve stimulator capacity through CCSO's Provincial Neurosurgery Strategy and established the Epilepsy Implementation Task Force (EITF) to oversee epilepsy system improvements.

Epilepsy Implementation Task Force

The Epilepsy Implementation Task Force (EITF) was formed in June 2013 to develop and implement a provincial approach to an integrated system for epilepsy care in Ontario. Supported by CCSO, this committee is co-chaired by Dr. Carter Snead, Paediatric Neurologist at the Hospital for Sick Children, and Brenda Flaherty, Executive VP and Chief Operating Officer at Hamilton Health Sciences.

The EITF brings together senior clinical and administrative leaders from the epilepsy community to:

- Improve access along the full continuum of care by coordinating resources and wait lists
- Establish standardized diagnostic and surgical protocols across hospitals with comprehensive epilepsy programs
- Develop supports for primary care providers

CCSO supports the work of the EITF, a subgroup of Provincial Neurosurgery Ontario, as part of its mandate to support equitable and timely access to neurosurgical care, including epilepsy surgery, and to help maintain the province's neurosurgical capacity. CCSO is supported by the Ministry of Health and Long-Term Care, (www.criticalcareontario.ca). For a list of EITF membership, please see Appendix 9.

The creation of the EITF stemmed a report by the Expert Panel on a Provincial Strategy for Epilepsy Care in Ontario, assessing the challenges to access epilepsy care in Ontario (HQO, 2012). The report notes that the community of healthcare providers treating epilepsy needs support with a standardized approach to diagnosis and treatment (such as antiepileptic drugs (AED), electroencephalography (EEG) or neuroimaging), and process for referral to a neurologist or for surgery (if the seizures are determined to be medically-refractory). This document is the outcome of the recommendation to provide province-wide guidelines for first-contact healthcare providers (such as primary care and emergency department physicians) to standardize the diagnosis, treatment and referrals of patients with epilepsy in the province.

Epilepsy Care in Ontario

In order to maximize value and ensure that patients are receiving timely, high quality care, it is crucial to clarify system capacity and referral paths. This will help set clear expectations for planning, coordination and performance for all hospitals with specialty epilepsy care programs.

The EITF has developed a definition of a Comprehensive Epilepsy Program (CEP) and established a planning and integration framework for epilepsy care in Ontario:

> A CEP is an integrated care model for the management of individuals with epilepsy within a multidisciplinary team. A CEP covers various aspects of care including medical, psychosocial, and nutritional management, appropriate neurodiagnostic investigations, a mandatory EMU, capability for pre-surgical diagnostic evaluation, and established links to Community Epilepsy Agencies.

Hospitals with CEPs are divided into two categories based on the level of services they provide:

1. A District Epilepsy Centre (DEC) houses a comprehensive epilepsy program that provides all appropriate epilepsy related clinical services except epilepsy surgery. A DEC should provide basic investigations necessary to determine candidacy for epilepsy surgery including assessment by an Epileptologist, and full EMU service including neuropsychological evaluations.

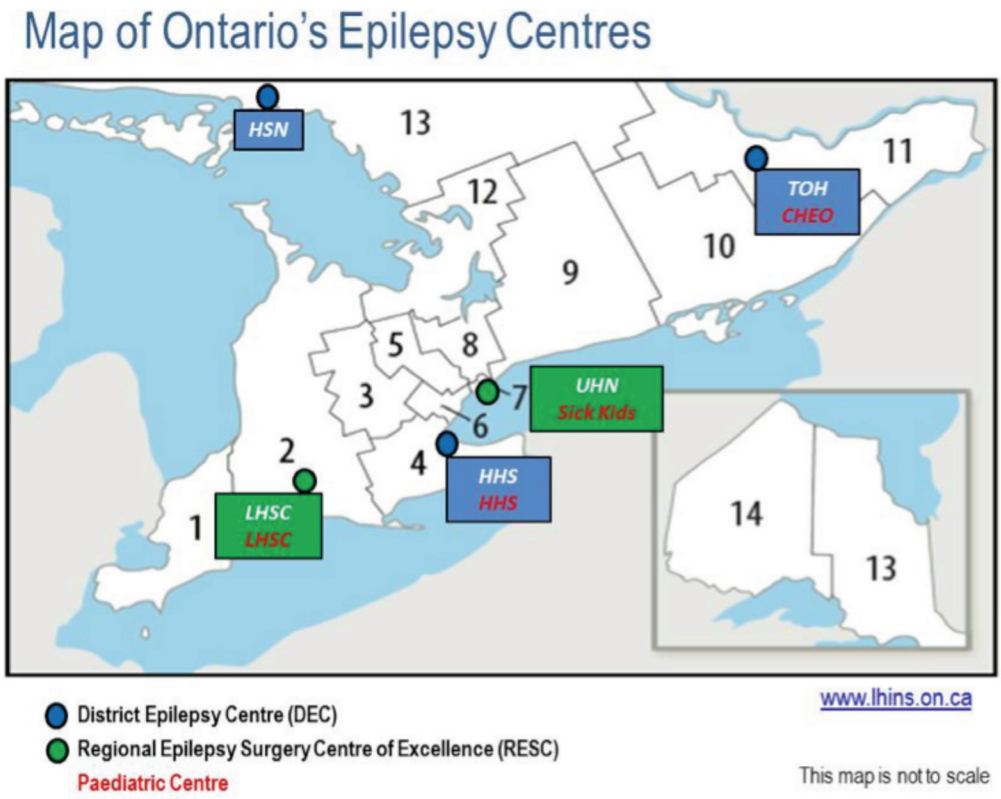
The following hospitals are classified as District Epilepsy Centres:

Hospital	Adult EMU Beds	Paediatric EMU Beds
Health Sciences North (operational 2015)	1	-
Hamilton Health Sciences	3	2
The Ottawa Hospital	2	-
Children's Hospital of Eastern Ontario	-	2

2. A Regional Epilepsy Surgery Centre (RESC) is a facility with a comprehensive epilepsy program that provides all the services available in a DEC, and in addition, epilepsy surgery including facility for intracranial monitoring. An RESC is also a DEC for its catchment area.

The following hospitals are classified as Regional Epilepsy Surgery Centres:

Hospital	Adult EMU Beds	Paediatric EMU Beds
London Health Sciences Centre	10	2
Hospital for Sick Children (SickKids)	-	7
University Health Network (Toronto Western Hospital)	10	-



The following flow chart is a high-level depiction of the process each provider should follow in order to appropriately diagnose and manage a patient with epilepsy:

Epilepsy Patient Flow by Provider

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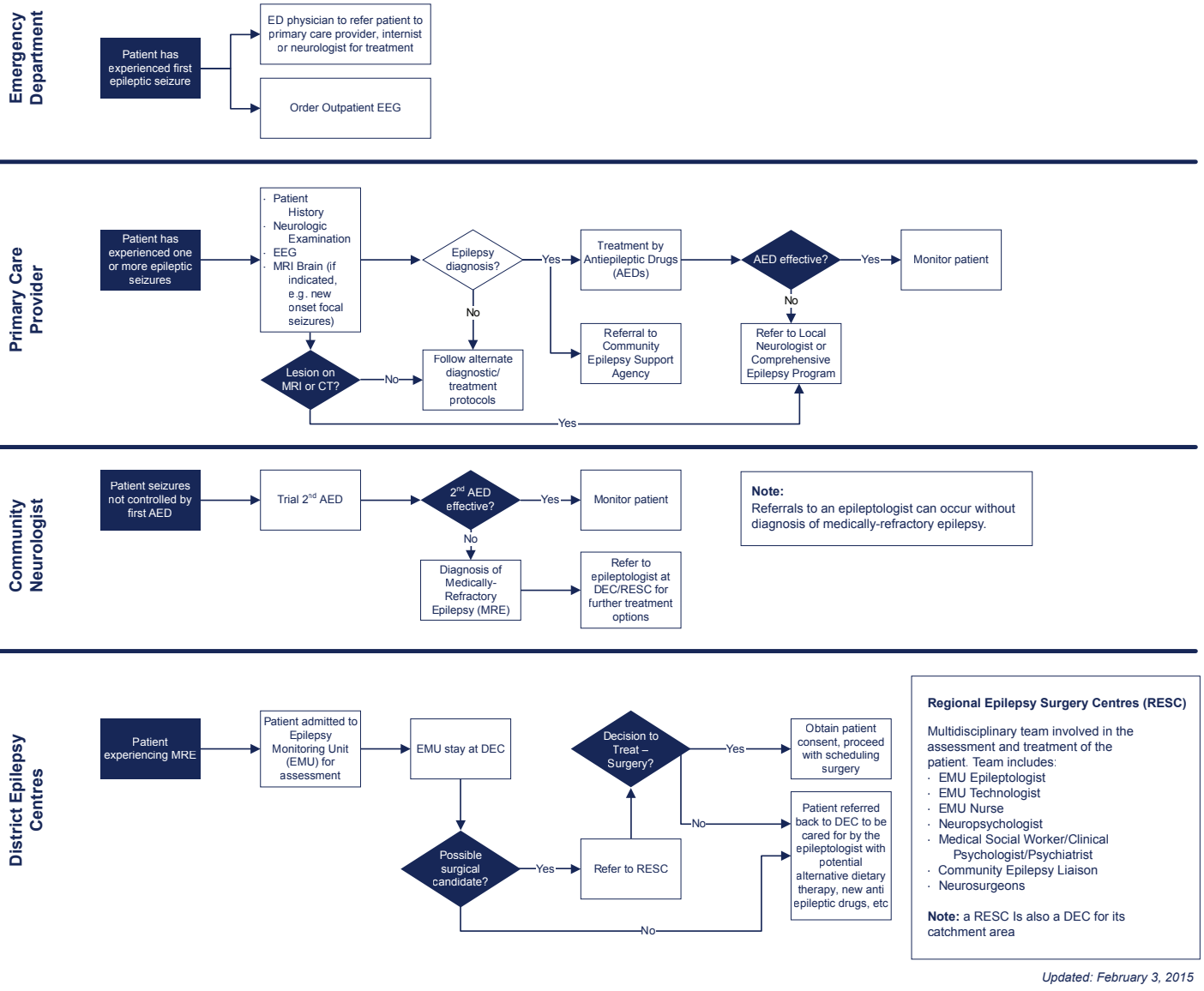

Updated: February 3, 2015

About this Document

The EITF has developed this document in an effort to provide guidelines for evidence-based practice for all healthcare providers in Ontario who provide care for patients with epilepsy. This document is a continuum of the previous guidelines of management of epilepsy in adults and children. As it addresses refractory epilepsy it is expected that these patients will be referred to neurologists with appropriate expertise in epilepsy.

Target Audience

The intended target audience of these guidelines is mainly Epileptologists but includes Neurologists, Family Physicians (FP), Nurse Practitioners (NP), Registered Dietitians, Paediatricians, Internists, Emergency Physicians and Community Epilepsy Agencies. The guidelines should be shared with anyone involved in the care of patients with epilepsy.

The EITF Guidelines Series

The EITF is developing a series of guidelines intended to support primary care providers, community neurologists, and District and Regional Epilepsy Centres. These guidelines aim to increase the awareness of, and referrals to, appropriate diagnostic assessment and surgical care of patients in Ontario.

For Primary Care Providers

1. *Provincial Guidelines for the Management of Epilepsy in Adults and Children (January 2015)*
   To support the flow of patients towards appropriate treatment for epilepsy, this document contains a set of guidelines to help with the diagnosis, treatment and referral practices from the moment of a patient's first seizure.

2. *Provincial Guidelines for Epilepsy Surgery Referrals in Ontario (February 2016)*
   This document provides an approach to referral of medically-refractory epilepsy patients by defining evidence-based indications for epilepsy surgery, with careful consideration given to the paediatric population.

3. *Provincial Guidelines for the Management of Medically-Refractory Epilepsy in Adults and Children who are not Candidates for Epilepsy Surgery*
   This guideline will provide an approach to the management of the patient with medically-refractory epilepsy in whom surgical treatment is not an option. It will include the use of antiepileptic medications and non-antiepileptic therapy such as dietary management and neurostimulation.

4. *Provincial Guidelines for Transitional Care of Paediatric Epilepsy Programs to Adult (to be released April 2016)*
   To ensure uninterrupted quality medical care for adolescent patients with chronic disorders, this document provides guidelines for paediatric and adult practitioners to assist in the seamless transition of epilepsy care for adolescents who are departing the paediatric system and entering the adult health care network.

For Providers and Administrators in District and Regional Epilepsy Centres:

5. *Provincial Epilepsy Monitoring Unit (EMU) Guidelines for Ontario (January 2014)*
   This document outlines protocols and provides guidelines for EMUs for diagnostic evaluation for epilepsy. It can be used as a guide for neurosurgical centres with EMU beds.

6. *Provincial Guidelines for Regional Epilepsy Surgical Centres (to be released April 2016)*
   This document presents guidelines that set out accountabilities for hospitals and their collaborative interdisciplinary teams that provide care for patients at Regional Epilepsy Surgical Centres. It also presents best practices as a recommended, but not mandatory, program model.

II. Incidence and Demographics

In this document the term 'medically-refractory epilepsy' refers to those epilepsies where there has been a failure of two antiepileptic drugs.

The term 'drug resistant epilepsy' has been preferred to 'refractory epilepsy' by some authors and is used by the International League Against Epilepsy (ILAE); defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al. 2010). The term 'intractable epilepsy' has also been used as a synonym for medically-refractory epilepsy.

There is little evidence-based data on the management of medically-refractory epilepsy. Effectiveness (seizure control and lack of side effects) of an antiepileptic drug (AED) is more important than efficacy (seizure control alone). Side effects of AEDs are an important reason why treatment is changed. 37% of patients with epilepsy develop medically-refractory epilepsy (Kwan and Brodie 2000). 82% of patients with idiopathic generalized epilepsy became seizure free but only about 26% of those with symptomatic or cryptogenic epilepsy (Semah et al. 1998). In children, 55% with symptomatic generalized epilepsy are refractory (Berg 2001). A number of factors may be used to predict whether epilepsy will be refractory including type of epilepsy, underlying syndrome, etiology, seizure frequency, density and clustering, environmental factors and genetic factors affecting anticonvulsant pharmacodynamics (French 2007; Mohanraj and Brodie 2006).

The management of medically-refractory epilepsy includes:

1. Review of the diagnosis of episodic paroxysmal events that are not epilepsy
    - Psychogenic non epileptic seizures (PNES): 30% of patients with presumed 'refractory epilepsy' had psychogenic seizures (Mohanraj and Brodie 2006). Particular difficulty arises when a patient has both epilepsy and PNES.
    - Cardiogenic (arrhythmias) and vasovagal events (syncope)
    - Parasomnias
    - Movement disorders (paroxysmal dyskinesias, cataplexy)

2. Drug related problems
    - Therapy non-compliance
    - Enzyme induction, especially if more than one AED or other medication is used
    - Inadequate anticonvulsant therapy

3. Consideration of further investigations as outlined below
    - Carefully review clinical history (including family history, health history) and seizure semiology (current and past), lifestyle (recreational drug use, alcohol abuse, sleep-deprivation), seizures triggers, post-ictal state
    - Review response to current AEDs and previous AEDs including doses to assess if appropriate/ adequate dosing

- Repeat EMU admission or video EEG monitoring to characterize seizures
- Lumbar puncture of infectious process suspected
- Repeat or obtain brain imaging with 3T MRI, epilepsy protocol (if proper neuroimaging has not been done) to rule out potential lesion (e.g. hamartoma, mesial temporal sclerosis, cortical dysplasia, low-grade glioma) or if no neuroimaging was done at the time of diagnosis
- Review previous investigations – screening metabolic studies, genetic epilepsy panel

III. Management of Refractory Epilepsy (in patients who are not candidates for Surgery)

This section is intended to follow from the discussion on the management of epilepsy detailed in *Provincial Guidelines for the Management of Epilepsy in Adults and Children* (Pg. 24-25)

Key areas of focus in managing medically-refractory epilepsy patients who are not candidates for surgical interventions include antiepileptic drugs, immunotherapy, diet, neurostimulation and non-pharmacological considerations. These are discussed in the following sections and may be considered for use in combination and under the care of a multidisciplinary care team.

Antiepileptic Drug (AED) Therapy

There are at least 21 antiepileptic drugs (AEDs) available today, 15 of which have been recently released. Given that there are few robust randomized controlled trials or comparative studies, determining which AED to use can be challenging (Glauser et al. 2006; Glauser et al. 2013). The following general principles can be applied. If the trial of two AEDs is found to be ineffective by a Neurologist, patients should be referred to an Epileptologist as per the *Provincial Guidelines for the Management of Epilepsy in Adults and Children* (Pg. 33-34).

Practice recommendations for AED trial:

1. Optimise the dose of each AED by increasing the dose incrementally. If the maximum dose is ineffective, introduce a second AED while continuing on the first. If seizure control is achieved, consider tapering the first AED. The advice to "start low and go slow" is appropriate (French 2004).
2. If one or two AEDs are ineffective, rational polytherapy should be explored. There is little systematic study of rational polytherapy. Considerations include a higher incidence of side effects when multiple AEDs are used.
3. Consider using AEDs with different mechanisms of action (see discussion on following page). However, although mechanisms of action have been described for a number of AEDs, it is not certain that these are their only mechanisms of action or even the most important. For example, Levetiracetam (LEV) affects the SV2a receptor on the synaptic vesicle but also has calcium channel modulating effects and GABAergic properties.
4. Avoid using an AED that may worsen or provoke seizures. Carbamazepine (CBZ), Oxcarbazepine (OXC), Phenytoin (PHT), Vigabatrin (VGB) and Tiagabine (TGB) may worsen myoclonus and absence seizures. Gabapentin (GBP) and Lamotrigine (LTG) may worsen myoclonus (Ben-Menachem 2014). Benzodiazepines given intravenously may worsen tonic seizures but may be very useful in treating Lennox-Gastaut and does not contraindicate their use (Somerville 2009).

Recent literature has concentrated on the most recently introduced AEDs. There have been few class 1 studies and no comparative studies done on these new AEDs (French 2004; Glauser 2013). The most recently available AEDs are Rufinamide (RUF), Lacosamide (LCM), Perampanel (PER), Eslicarbazepine ESL) and Retigabine (ezogabine). As per literature its use is limited because of the long term effect of developing a blue hue to the skin and retina (Ben-Menachem 2014).

Despite the agreed need for consideration of many factors in deciding which AED to use, the most important consideration is still the type of seizure. Greater precision can be applied when a particular epilepsy syndrome is identified (e.g. childhood absence epilepsy, juvenile myoclonic epilepsy) but many patients do not have an easily identifiable syndrome. Using a broad-spectrum anticonvulsant may be an efficient approach for the large number of children who do not have a defined epilepsy syndrome. These broad spectrum anticonvulsants are:

- Valproate
- Levetiracetam (Doumbia-Ouattara et al. 2011)
- Lamotrigine
- Topiramate
- Clobazam (Canadian Study Group for Childhood Epilepsy 1998)

Options for AED use are set out in the *Provincial Guidelines for the Management of Epilepsy in Adults and Children* (Pg. 25)

Clobazam is safe and effective for seizures associated with Lennox-Gastaut syndrome (Ng et al. 2011; Wheless and Phelps 2013), focal epilepsy in tuberous sclerosis complex (Jennesson et al. 2012) and other refractory epilepsies in childhood (Kalra et al. 2010). There is no data to recommend one of these AEDs over another and the age of patient, concomitant medications, potential side effects, ease of use and cost to the patient are important considerations when data on efficacy and effectiveness are lacking.

Newer AEDs have a better side effect profile, better tolerability and pharmacokinetic profile. A list of the known actions of currently available AEDs is shown below (Bialer 2010; Löscher 2012) and several authors (Kwan and Brodie 2006; French and Fraught 2009; Brodie and Sills 2011; Brigo et al. 2013) have advocated using AEDs based on their mechanisms of action in refractory epilepsy cases. This approach is relatively new and a significant criticism is that knowledge of the mechanisms of action of individual AEDs is incomplete. Some AEDs are known to have multiple mechanisms (see table below on Proposed Pharmacological Targets for AEDs (St. Louis 2009)). This approach has not been tested in any rigorous clinical trial given the potential for an enormous number of combinations (McCabe 2015).

1. Blocking excitatory channels
   a) Presynaptic voltage-gated Na+ channel
      - Phenytoin
      - Carbamazepine
      - Oxcarbazepine
      - Eslicarbazepine
      - Lamotrigine
      - Lacosamide
      - Zonisamide
   b) Presynaptic vesicle membrane receptor (SV2A)
      - Levetiracetam

c) Postsynaptic AMPA receptor (Na+)(antiglutamatergic)
- Perampanel

d) Postsynaptic KCNQ (K+) channel
- Retigabine (first in class potassium channel opener (Kristian et al. 2013)

e) Postsynaptic T-type Ca 2+ channel
- Ethosuximide

2. Enhancing inhibitory channels
   a) Presynaptic KCNQ K+ channel
   - Retigabine

   b) Presynaptic Ca2+ channel
   - Gabapentin
   - Pregabalin

   c) Presynaptic GAT-1 channel
   - Tiagabine

   d) Postsynaptic GABAA receptor (Cl-)
   - Benzodiazepines
   - Barbiturates

3. Other mechanisms
   a) Vigabatrin inhibits GABA metabolism
   b) Valproate increases GABA turnover and blockade of voltage dependent Na+ channels and reduces NMDA receptors
   c) Topiramate blocks voltage dependent Na+ channels, decreases AMPA/kainate receptors and potentiates activity of GABAA receptors
   d) Felbamate decreases Na+ channels, increases GABAA receptors and reduces NMDA receptors

Ideal AED polytherapy would combine supra-additive (synergistic) efficacy with infra-additive toxicity. The following list of anticonvulsants classified by mechanism of action is intended to encourage the use of AEDs with different mechanisms of action rather than combining AEDs with the same mechanism of action. Limited data has suggested the following combinations (Brigo 2013).

- Ethosuximide-Valproate
- Lacosamide-Levetiracetam
- Stiripentol-Clobazam
- Lamotrigine-Valproate

N.B.: This combination has the best human evidence for synergy especially for focal seizures. The question whether the addition of VPA causes apparent synergy by inhibiting lamotrigine metabolism and increasing lamotrigine levels has been studied and the limited data does not show this. Nonetheless, because of the recognised effect of VPA on lamotrigine, the latter drug should be introduced very cautiously in patients on VPA. Current practice would be to use doses of lamotrigine that are 25% of usual introductory doses and in children a maximum dose of 5 mg/kg/day is suggested. However, the introduction of valproate in someone

who is already on lamotrigine is said not to cause any risk for sensitivity reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

AED Interactions and Interactions between AEDs and Other Drugs

This is a potentially complex component of polytherapy (Zaccara and Perucca 2014)

Drug Level Monitoring

Please see the discussion in the *Provincial Guidelines for the Management of Epilepsy in Adults and Children* (Pg. 26).

For new anticonvulsants, routine drug-level monitoring has not been demonstrated to be of any value. In selected patients, drug-level monitoring may be of value. Examples include renal failure, dialysis, to assess compliance and in patients who are pregnant (Striano et al. 2008).

Proposed Pharmacological Targets for AEDs (St. Louis, E.K, 2009):

Drug	Sodium Channels	Calcium Channels/ Currents	GABA Receptors	GABA Synapse	Glutamate Receptors	Other
Older AED's						
Benzodiazepines			+++			Abuse potential may limit use
Carbamazepine	+++	+	+			Modulates brain adenosine
Phenobarbital/ Primidone			+++			Abuse potential may limit use
Ethosuximide		+++ (Modulates Ttype Currents)				Inhibits NADPH-linked aldehyde reductase (necessary for gammahydroxybutyrate (GHB) synthesis; GHB can induce absences)
Phenytoin	+++					
Valproate	+++	+ (Modulates T-type)		+		
Newer AEDs						
Felbamate	++	++		++	++	Idiosyncratic Toxicity limits use
Gabapentin	+	++		+		
Lacosamide						Binds CRMP-2 receptor
Lamotrigine	+++	+				
Levetiracetam						Modulates presynaptic neurotransmitter release by SV2A receptor binding.

Oxcarbazepine	+++	+				
Pregabalin		++				
Rufinamide	++					+?
Tiagabine				+++		
Topiramate	++	++	++	+	++	+weak carbonic anhydrase inhibtion
Zoisamide	+++	++ (Modulates T-type Currents)				++facilitates catecholaminergic and dopaminergic neurotransmission; +weak carbonic anhydrase inhibition;

+++ Primary target; ++ Probable target; + Possible target.
Modified from: Kwan and Brodie 2006

For the common medical refractory childhood epilepsy syndromes the following suggestions are made (Hussain and Sankar 2011):

- Infantile spasms: ACTH, high dose prednisone/prednisolone, vigabatrin,
- Lennox-Gastaut Syndrome: Lamotrigine (LTG), topiramate (TPM). Lamotrigine can exacerbate myoclonic seizures in select patients. Lamotrigine and topiramate appear to have a synergistic effect. Rufinamide and clobazam also have demonstrated effect.
- Severe Myoclonic Epilepsy of Infancy (Dravet syndrome): Because this is a SCN1A-based voltagegated sodium channel disorder, AEDs targeting this should not be used. Recommended treatments are valproate (VPA), clonazepam and clobazam (CLB). The addition of stiripentol to VPA and CLB has been shown to be effective
- Landau-Kleffner Syndrome/Electrical Status Epilepticus in Sleep: High dose roal diazepam at night, valproate, levetiracetam. If AEDs are ineffective, immunomodulatory treatments should be considered including steroids and IVIG.

Immunotherapy

The main treatment options other than antiepileptic drugs include medications used when the immune system is involved.

Evidence that the immune system is involved in the pathogenesis of epilepsy particularly, medically-refractory epilepsy, has given rise to the use of adjunctive immunotherapy to slow or change the epileptogenic process. Medications include immunoglobulins, corticosteroids, plamapharesis and monocloncal antibodies such as rituximab, natalizumab. There is limited data of these treatments outside of specific epileptic encephalopathies such as West syndrome, Rasmussen encephalitis, Landau Kleffner and specific anitbody mediated encephalitis such as anti NMDA encephalitis.

Corticosteroids form one of the main treatment options. Corticosteroids cause immunosuppression by decreasing the function and numbers of lymphocytes, including both B cells and T cells. By inhibiting a critical transcription factor involved in the synthesis of many mediators (i.e., cytokines) and proteins (i.e.,

adhesion proteins) that promote an immune response, they blunt the capacity of the immune system to mount a response.

Corticosteroids have an anti-inflammatory effect by preventing the formation of prostaglandins and leukotrienes, two main factors in inflammation. This is mediated by the release of lipocortin which by inhibition of phospholipase A2 reduces arachidonic acid release.

Corticosteroids have been used as therapy in many epileptic syndromes including infantile spasms, an age-specific epilepsy syndrome associated with epileptic spasms, and in many cases with neurodevelopmental regression and an EEG finding of hypsarrhythmia (West Syndrome).

Low dose ACTH, or vigabatrin should be considered for the treatment of infantile spasms. However hormonal therapy with prednisolone or other steroids have also been used but the review by Go et al. (Go et al. 2012) found there was little evidence to suggest that prednisolone, dexamethasone, and methylprednisolone are as effective as ACTH for short-term treatment of infantile spasms (Level U).

Steroids are also used in Rasmussen's Encephalitis (RE) which is a rare, sporadic but potentially severe immune-mediated brain disorder leading to unilateral hemispheric atrophy, associated progressive neurological dysfunction and poorly controlled seizures.

Prednisolone/prednisone started at a high dose and then slowly tapered down has been reported to have beneficial effects on seizures and neurological functions in several series (Class IV evidence), particularly when started early on in the course (Chinchilla et al. 1994; Hart et al. 1994; Granata et al. 2003). For long-term steroid therapy, it has been recommended to start with boluses of intravenous methylprednisolone [e.g. 400 mg/m2/day (Hart et al. 1994) or, in children, 20 mg/kg/day (Granata et al. 2003)] and then to introduce 1–2 mg/kg/day oral prednisolone or prednisone (Hart et al. 1994; Granata et al. 2003). This dose should be slowly reduced, ideally to a dose below the threshold of Cushing's syndrome.

Bahi-Buisson et al. confirmed steroid treatment can be useful when given early on in the course of Rasmussen encephalitis, but they found that long term relapse can occur among the good responders requiring delayed hemispheric disconnection (Bahi-Buisson et al. 2007).

Immunoglobulins have also been used in Rasmussen's as well immune mediated encephalitis (Garnata et al. 1994; Hart et al. 2003). IVIg is a purified blood product pooled from many human donors composed mainly of IgG and some IgA. The precise mode of action of this product is unclear. Several studies have shown efficacy in treating patients with immunodeficiency. The use in patients with epilepsy has increased given the identification of immune mediated epilepsy but Cochrane reviews show no randomised evidence outside of specific syndromes such as anti NMDA and Landau Kleffner (Geng et al. 2013; Gayatri et al. 2007).

Steroid, immunoglobulins and other anti-inflammatory agent are also increasingly used in immune epilepsy. If these agents are to be used it would be important to Identify potential patients who have an immune basis for their seizures because adjunctive immunotherapy may slow, halt, or even reverse the epileptogenic process.

Zuliani and Suleiman (Zuliani et al. 2012; Suleiman et al. 2013) have proposed guidelines for recognition of these patients in adults and children respectively. Clinical features suggestive of an autoimmune pathogenesis include patients with recent onset epilepsy (< 2 years), early AED resistance, and multifocal seizures and personal or family history of autoimmunity. Paraclinical findings suggestive of an autoimmune etiology include the detection of a neural autoantibody, inflammatory CSF (leukocytosis or CSF-exclusive oligoclonal immunoglobulin bands), or MRI characteristics suggesting inflammation (T2 hyperintensities, contrast enhancement on gadolinium studies, and/or restricted diffusion) and /or inflammatory neuropathology on biopsy.

Recurrent seizures are a common symptom in autoimmune neurologic disorders, especially in limbic encephalitis or multifocal paraneoplastic disorders. Autoantibody specificities reported in the setting of paraneoplastic limbic encephalitis include antineuronal nuclear antibody type 1 (ANNA-1), collapsin response-mediator protein 5 (CRMP-5), and Ma2. Autoantibodies with a commonly nonparaneoplastic etiology include Voltage-gated potassium channel (VGKC) complex or associated proteins including leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and contactin 2 and glutamic acid decarboxylase 65 (GAD65) antibodies and have been reported in patients with limbic encephalitis and idiopathic epilepsy with AED-resistant seizures. More recently identified autoantibodies that strongly correlate with clinical seizures include *N* -methyl-D-aspartate receptor (NMDAR), 23 γ-aminobutyric acid B ($GABA_B$) receptor, metabotropic glutamate receptor type 5 (mGluR5) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

No randomized clinical control trials on the use of corticosteroids in autoimmune epilepsies have been conducted to date. In an observational, retrospective case series by Quek et al. (Class IV evidence), neural autoantibodies were identified in 29/32 patients (91%). VGKC complex IgG antibodies were detected in 18/29 (62%) of which 14 were bound to LGI1 (78%), 1 was bound to Caspr2 and 3 were of unknown specificity. In addition, GAD65 was found in 7/29 (24%), and CRMP-5 was found in 2/29 (Quek et al. 2012).

In this study, 27 people underwent immunosuppressive treatment that comprised intravenous methylprednisolone alone (IVMP) (n = 12); intravenous immune globulin alone (IVIg) (n = 3); and combinations of IVMP, IVIg, cyclophosphamide, or plasmapheresis (n = 12). In 22/27 patients (81%), this therapeutic trial was positive with 18 patients becoming seizure free for at least 3 months and 4 patients having improved seizure frequency. Early treatment was associated with a favorable outcome ($P < .05$).

Although strong evidence is lacking (Class IV), the authors recommended that if autoimmune epilepsy is suspected, a trial of 6 to 12 weeks of immunotherapy (IVMP or IVIg daily for 3 days and then weekly) is justifiable in the absence of other treatment options and may serve as additional evidence for an autoimmune etiology when a favorable seizure response is observed. They also recommended considering long-term immunosuppressive treatment, overlapping with gradual taper of IVMP or IVIg, for patients whose seizures respond favorably to the initial trial of immunotherapy. Despite this, relapses may still occur.

Dietary Therapy

Diet therapy for epilepsy is a nonpharmacologic treatment used worldwide for children with medically-refractory epilepsy (Kossoff et al. 2009). Dietary therapies, most often the classic ketogenic diet, have been shown to be particularly beneficial in treating certain specific epilepsy syndromes in children with frequent, medically-refractory seizures. Dietary therapy has been reported as effective in the treatment of seizures associated with glucose transporter 1 deficiency, pyruvate dehydrogenase deficiency, infantile spasms, absence epilepsy, myoclonic atonic epilepsy (Doose syndrome), Dravet syndrome, tuberous sclerosis complex, mitochondrial disorders, Lennox-Gastaut syndrome, Sturge-Weber syndrome, and Rett syndrome (Cervenka and Kossoff 2013).The common element of these different approaches is variable reduction in the amount of carbohydrate with appropriate increase in fat.

Diets that produce a state of ketosis are referred to as "ketogenic" (Cervenka and Kossoff 2013). When deprived of glucose through restriction of carbohydrate intake, the human body begins metabolizing fat. In doing so, ketone bodies (acetoacetate, acetone, and hydroxybutyrate) are produced. There is no direct correlation between seizure reduction and the degree of either acidosis or ketosis achieved. The mechanisms of action are much more complicated and may involve alteration in mitochondrial function, direct effects of ketone bodies on neuronal function and neurotransmitter release, antiepileptic effects of fatty acids, and/or glucose stabilization (Cervenka and Kossoff 2013). Results from the randomized control trial indicated that 38% of children had more than 50% reduction in seizure frequency, and 7% had more than 90% reduction in seizure frequency three months after starting classic ketogenic diet. Retrospective studies reported a higher rate of seizure control (Neal et al. 2008).

Classic ketogenic diet (KD) is restrictive where all the components of diet are weighed/measured with strict control of daily calorie intake. The ketogenic ratio is defined as the ratio of grams of fat to grams of carbohydrate plus protein. For example, 4:1 ratio classic KD contains 4 grams of fat for every 1 gram of protein and carbohydrate combined. There is no evidence to support the use of fasting before diet initiation. There is no scientific evidence to suggest that fluid restriction is needed or beneficial. Because of concerns of possible nephrolithiasis, most centers no longer restrict fluids. In humans, no study to date has shown a benefit of calorie restriction (Wirrell 2008). While excessive weight gain is perceived to correlate with poorer efficacy, no link was found between either ideal body mass index or change in body mass index over time and seizure control in children treated with the KD (Hamdy et al. 2007).

Less restrictive diet therapies include Modified Atkin's Diet (MAD), Low Glycemic Index therapy (LGIT), and Medium Chain Triglyceride (MCT) Ketogenic Diet (Miranda et al. 2012; Neal et al. 2009). In order to make the diet therapy less onerous and more palatable (less weighing and measuring, less restriction on food choices, and gradual introduction of diet) a regimen that uses principles of MAD, LGIT, MCT Ketogenic Diet, and outpatient initiation can be used. A dietitian should be consulted for considerations of targeted diet therapies for epilepsy patients. Each centre should have protocols, whether for child or adult, that includes appropriate investigations prior to initiating a diet therapy and for monitoring during the course of treatment (see Appendix 7).

Any child with medically-refractory epilepsy who is not a surgical candidate, or who is awaiting surgical evaluations, should be considered for diet therapy, regardless of age, comorbid conditions and cause of the epilepsy. In considering the epilepsy population as a whole, the International Consensus Statement for the Ketogenic Diet (2009) stated that "the KD should be considered in a child who has failed two to three anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies (Kossoff et al. 2009).

Absolute contraindications for the use of diet therapy include carnitine deficiency (primary), carnitine palmitoyltransferase (CPT) I OR II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency, and porphyria.

Relative contraindications include inability to maintain adequate nutrition, surgical focus identified by neuroimaging and video EEG monitoring, and parent or caregiver noncompliance (Kossoff et al. 2009). Children who require thickened fluids by mouth due to difficulties with swallowing cannot use the ketogenic diet, as thickening agents are not compatible with the diet. In those children, tube feeding is an alternative that may be considered.

Neurostimulation

As an alternative to epilepsy surgery, there is a long history of neurostimulation at a variety of sites for epilepsy. Early attempts included cerebellar stimulation attempted for a number of disorders including epilepsy, with results that were not eventually widely accepted. Other targets attempted have included the centromedian nucleus of the thalamus, the hippocampus, the subthalamic nucleus, caudate nucleus, with other efforts being directed towards cortical stimulation for epilepsy. However, a number of modalities of electrical stimulation for drug-resistant epilepsy have support from randomized controlled clinical trials and are accepted as options for use in select cases of drug-resistant epilepsy, namely Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS) at the anterior nucleus of the thalamus and responsive neurostimulation applied cortically to the site of seizure onset. Trigeminal Nerve Stimulation (TNS) has similarly been described and approved for use by Health Canada.

Evaluation

Since general neurostimulation devices are less effective than epilepsy surgery, patients with medically-intractable epilepsy should not be considered for such devices until more effective treatment options such as effective surgical resections have been considered.

An appropriate comprehensive assessment at a RESC would include video-EEG monitoring, and evaluation by radiology, neuropsychology, nursing, an epileptologist and neurosurgeon with a multidisciplinary discussion of all available therapeutic options. Such an evaluation would serve not only to assess candidacy for epilepsy surgery, but also to exclude alternative diagnoses masquerading as epilepsy such as psychogenic non-epileptic seizures.

Patients considered for neurostimulation should have epilepsy refractory to medical therapy and not be candidates for focal resection epilepsy surgery (e.g. seizure onset zone within eloquent cortex, or more than one seizure focus).

Patients considering neurostimulation should be carefully counseled about relative effectiveness of neurostimulation compared to other available medical and surgical treatment options as well as potential adverse events.

Neurostimulation should be undertaken only under the care of the multidisciplinary team and appropriately trained personnel. Patients should be followed up on a regular basis at either a regional epilepsy surgery center or a district epilepsy center comfortable with the care of such devices to adjust the device parameters, and monitor safety and efficacy.

IV. Non-pharmacologic Management of Epilepsy

Currently there are no randomized control trials of non-pharmacological interventions in treating people with epilepsy.

Cannabinoids

Over the past few years considerable attention has been on the use of cannabidiol the major non psychotropic compound of Cannabis sativa. Research on animals has shown some efficacy but there is currently no evidence for their use clinically. The lack of a pure pharmacologically active compound has prevented clinical research but there is a current study being done in the US on a pure cannabinoid in patients with Dravet syndrome. The trial is ongoing but results of this will give data on the dose, efficacy as well interaction with other anticonvulsants.

At the present time there is no evidence to support that marijuana or cannabinoids are effective in controlling epilepsy. Further trials are required.

Vitamins

Currently there is no evidence to support that folic acid, thiamide, Vitamin D or Vitamin E improve seizure control of prevent side effects in people with epilepsy. Further studies are needed.

Yoga

Currently there is no evidence to support the efficacy of yoga as a treatment in the management of medically-refractory epilepsy.

Currently there are RCTs of non-pharmacological interventions in treating people with epilepsy.

Melatonin

Currently there is no evidence to support the use of melatonin as add-on therapy for the treatment of epilepsy.

Exercise

Currently there is no evidence indicating that exercise is effective in treating epilepsy.

Herbal treatments

There is laboratory evidence for use of some herbal medication such as kava (Piper methysticum) and mistletoe (Viscum sp) but no clinical evidence to support their use.

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Appendix 1: Guideline on managing excess ketosis, metabolic acidosis, and hypoglycemia

Managing excess ketosis and acidosis

- Each institution may have its own protocol for managing excess ketosis
- Excess ketosis can manifest in the context of recent diet therapy initiation which requires further fine tuning, or during illness.
- Common symptoms of severe acidosis include: nausea, vomiting and lethargy. Acidosis can be enhanced when carbonic anhydrase inhibitor medications are also concurrently being administered with the diet therapy.
- Excess ketosis must be managed immediately with the administration of carbohydrates.
    - Immediately treat with 15 mL or orange juice or 10 mL or apple juice and recheck urine ketones
    - If symptoms of excess ketosis do not improve 15-20 minutes after juice was administered, repeat treatment with juice
    - If ketone levels are persistently elevated and the child is symptomatic, contact the dietitian as a diet change may be indicated
    - 2.5% or 5% dextrose/saline IV solution may be administered in children who are unable to tolerate oral fluids due to excessive vomiting. Hospitalization will be required for these children including further evaluation and investigation. Laboratory investigations should include urea, creatinine, electrolytes, glucose, capillary blood gases and infection screen as indicated upon further clinical evaluation
- Ensuring all fluid requirements (particularly the water) are being provided or consumed helps minimize acidosis.
    - Consider increasing the water intake by 100-200 ml also help manage acidosis.
    - The strength of the diet can also be reduced so to include more carbohydrates and less fat.
    - If acidosis occurs under acute circumstances bicarbonate can be given orally or IV to support correction (Kossoff et al. 2009)
    - Adjusting the carbonic anhydrase inhibitor medications may also need to be considered.

Managing Symptomatic Hypoglycemia

- Each institution may have a different method of identifying and managing hypoglycemia in children on the diet. Correction of hypoglycemia usually requires the use of a small volume of juice (20-30 ml) and closer monitoring.
- Contact the RD in the team for assistance in managing.

Appendix 2: Managing Intercurrent Illness

When Vomiting Occurs

- Treat vomiting with dimenhydrinate suppositories.
- Discontinue giving the specific prescribed diet (foods or formula)
- Use diluted electrolyte solution (paediatric rehydration solution) calculated based on patient's need.
- Measure urine ketones with every void and blood glucose if signs of hypoglycemia
- Once vomiting has stopped, gradually reintroduce either the appropriate diet foods or formula
- Contact the RD for guidance

Appendix 3: NPO Guidelines (following is just an example of management)

- In situations where a child on the diet therapy requires a procedure for which they must be NPO, request that the procedure be done as early as possible to minimize the time required for the child to be NPO.
- Use IV normal saline for maintenance fluids.
- No IV dextrose solutions unless absolutely indicated. If required, use ½ or ¼ strength
- Check blood glucose every 6 hours
- If blood glucose is < 2.5 mmol/L or if symptomatic for hypoglycemia, treat immediately with 50 mL DW5 and recheck blood glucose in 1 hour.
- If blood glucose is 2.5 – 3.0 mmol/L, treat with 25 mL D5W
- Check urine ketones with each void
- If urine ketones are > 16 mmol/L, treat with 25 mL D5W
- If urine ketones are between 8 mmol/L and 16 mmol/L, treat with 12.5 mL D5W

Appendix 4: Children on the Diet therapy for epilepsy who Require Surgery

- Communicate with the surgeon and anaesthesia to learn the length of time required for the child's surgical procedure
- Each institution may have its own specific surgical protocol for children on the diet therapy who will undergo surgery
- Provide written therapeutic diet management guidelines to the same day admission unit, anaesthetist, surgeon, recovery room and unit to which the child will return to ensure that the child remains in ketosis before, during and after surgery
- Ask the anaesthetist and/or surgeon to maintain normoglycemia during the surgical procedure.
- Prolonged surgical procedures increase the risk for developing metabolic acidosis. Check serum pH or bicarbonate levels to monitor for acidosis. Check these levels every 2-3 hours during surgical procedures that last longer than 3 hours.
- Monitor blood pH levels and/or bicarbonate levels in the postoperative period until the child is on the full therapeutic diet.

Helpful online resources

- http://www.gosh.nhs.uk/health-professionals/clinical-guidelines/the-ketogenic-diet-in-the-management-of-epilepsy/
- www.charliefoundation.org

Appendix 5: Information to Patients and Families

Patients and families should receive written information about the different types of diet therapies for epilepsy, side effects and complications of diet therapy. Educational materials should discuss contraindications, process of diet initiation and ongoing maintenance and monitoring, admission to hospital, members of the diet therapy team, supplies required including cost, financial considerations, sources of financial assistance, and additional resources available. This should be provided to patients and families either prior to the clinic consultation visit, or at the visit. Specific hospitals may have their own written materials regarding the diet therapy service.

Conducting information sessions is an effective way to allow patients and families to hear information about the types of diets, ask questions of the diet therapy team members, and to receive peer-to-peer support. These sessions can be instrumental in providing excellent information to help patients and caregivers make more informed decisions.

Other sources of information about the diet therapy include:

- http://www.aboutkidshealth.ca/En/ResourceCentres/Epilepsy/TreatmentofEpilepsy/DietaryTherapies/Pages/default.aspx
- www.charliefoundation.org
- www.matthewsfriends.org
- Kossoff et al. 2011

Appendix 6: Diet Therapy Team

Diet Therapy Team

The multidisciplinary team should include epileptologist(s), registered dietitian(s), nurse(s) and social worker(s) within a comprehensive epilepsy program. If resources are available, services of child life specialist, nurse practitioner and pharmacist are encouraged.

Role and Responsibilities:

1. Epileptologists
    - Provides leadership to the multidisciplinary team of health professionals in the diet therapy team and is responsible for the quality of care delivered.
    - Determine medical suitability of patients with epilepsy for diet therapy, and the type of diet in discussion with the dietitian
    - Oversees and participates in the clinical management of patients from initial consultation to the diet therapy service through to discharge and transition to adult care, and shall be the most responsible clinician (MRC) or physician (MRP) for the patient.
    - Oversee the management of complications of the diet.
    - Determine the macronutrient distribution goal for each patient in collaboration with the dietitian.

2. Registered Dietitian
    a) Pre-diet assessment:
        - Refer to section 7b

    b) Initiating the diet:
        - Determine the diet plan for patients
        - Educate the caregivers to safely manage the diet at home including managing the diet during times of illness (can be done by nurse practitioner too).
        - Review monitoring expectations that needs to be performed: e.g. ketones, blood glucose, weight, height/length (can be done by nurse practitioner too),
        - Monitor for complications (e.g. hypoglycemia, severe ketoacidosis, vomiting, diarrhea, poor intake).
        - Modify the diet if necessary based on pre-set goals of therapy.
        - Complete the nutrition assessment to determine the supplemented micronutrient requirements
        - Coordinate with physicians/nurse practitioners and family pharmacies to ensure sufficient diet formulas/products are ready at time of discharge, in cases of inpatient initiation.

    c) Fine-tuning and Follow-up:
        - Provides support to the families via phone or e-mail (can be done by NP too)
        - Completes frequent full nutritional assessments
        - Make adjustments to the micronutrient supplements
        - Implement adjustments to diet as needed.

3. Nurses
   a) Ambulatory Setting:
      - Medication reconciliation
      - Provision of preliminary information about the diet therapy in epilepsy, be it written information or in the form of teaching during an information session
      - Obtaining vital signs, height, weight, head circumference
      - Obtain Initial or interval history including seizures
      - Providing instructions on obtaining fasting blood work and urine testing for follow-up visits as needed
      - Provision of telephone triage and support when issues arise (e.g. child experiencing complications)
      - Participation in the diet therapy information sessions
      - Assists in connecting families for peer-to-peer support

   b) In-Patient Setting:
      - Orientation to the inpatient unit
      - Nursing assessment
      - Obtaining vital signs, height, weight, head circumference
      - Medication reconciliation
      - Review of blood work results (if done on morning of diet initiation)
      - Teach/review with parents how to use the commercial glucometer and review parameters for hypoglycemia
      - Teach/review how to measure urine ketones using prescribed strips
      - Teach parents how to measure urine specific gravity
      - Monitor for side effects of the diet during initiation
      - Monitor for complications of the diet including vomiting, diarrhea, hypoglycemia, hyperketosis, acidosis
      - Monitor parental progress with diet initiation
      - Monitor child's reaction to the diet and watch for signs of food refusal
      - Ensure all medications from pharmacy are in tablet form and not liquid form with certain exceptions that have been reviewed by the epileptologist, pharmacist, and dietitians and approved for use
      - Monitor and record all seizures
      - Communicate any complications and management issues to the physician/nurse practitioner and RD.
      - Reinforce how to manage hyperketosis, hypoglycemia, dehydration
      - Monitor for constipation (if on therapeutic diet) or diarrhea (if on MCT oil)
      - Ensure all medications are in tablet form with the exception of those liquid forms approved (e.g. specially formulated omeprazole), and that IVs do not contain dextrose (unless clinically indicated) including pre-mixed IV antibiotics
      - Monitor blood glucose and ketones

4. Social Worker
      - Work collaboratively with the members of the multidisciplinary team to understand the patient and family's social and emotional needs and how they impact the patient's medical condition and attitude toward treatment (e.g. food refusal, force-feeding)

- Work with patients and families to understand their beliefs about the illness
- Work as a resource to the interdisciplinary team in responding to challenges
- Work as a resource to the interdisciplinary team in helping them to respond to challenging patient and family situations
- Provide support to patients and families when required to help manage feelings of anxiety regarding dietary treatment to facilitate adherence to diet treatment
- Work with the members of the team in order to assist the patient in understanding the complexity of epilepsy and diet treatment
- Address patient and family needs as they relate to resources, funding and advocacy
- Provide individual, couple and family therapy as needed to support the wellbeing of the patient
- Assist with the transition from paediatric to adult epilepsy care
- Refer to community agencies and community-based support services as needed
- Participate in group teaching/information sessions
- Work with schools to help teachers and support workers understand the diet therapy and the importance of supporting successful adherence in the school setting and acceptance among peers

5. Child Life Specialist
    - Assess the physical, social and emotional responses of the child and family to the diet therapy for epilepsy
    - Enhance patient coping by utilizing therapeutic play interventions
    - Assist the child in preparing for the diet by utilizing creative meals and developing self-mastery.
    - Advocate for the psychosocial needs of patients and families.

6. Nurse Practitioner
    - Screening of referrals to the 'diet therapy for epilepsy' service.
    - Initial patient clinical consultation including completing a comprehensive medical history, seizure history, clinical course and treatment of seizures, medication history, review of current medications, physical examination
    - Assessment of potential complicating factors such as poor food or fluid intake, failure to thrive, constipation, gastroesophageal reflux, chronic metabolic acidosis, renal calculi
    - Ordering of laboratory tests and appropriate diagnostic studies to further assess potential complication factors such as a feeding study, consultation for gastrostomy tube
    - Review of medical record to ensure there are no contraindications to the diet such as metabolic disorders
    - Adjustment of liquid medications to tablet form in preparation for the diet
    - Assess developmental and psychosocial history and potential psychosocial barriers to the diet

7. Pharmacist
    - Provides guidance regarding carbohydrate content of medications and supplements
    - Advise on effect of diet on efficacy of medication (e.g. high fat diet, decreased absorption of medication)

Appendix 7: Different Types of Diets for Dietary Therapy

Classic Ketogenic Diet (KD)

- Food-based long-chain triglycerides (LCT) are the main source of fat in this diet
- Usually consists of approximately 70% to 90% of energy from fat
- Carbohydrate and protein intake are usually limited to 10-30% of energy combined
- It can be provided to patients through food or formula by enteral tube feeding or by mouth, or a combination of food and formula

Medium Chain Triglycerides (MCT) Ketogenic Diet

Medium-Chain Triglycerides (C6-C12), delivered as an oil, are the main sources of fat in this diet. They require little to no pancreatic lipase for digestion and are quickly hydrolyzed into medium-chain fatty acids. The absorption of MCT is faster than LCT, yielding a quick and efficient ketone source for energy. Since MCTs are more ketogenic than LCTs, addition of MCT oil allows for more carbohydrate and is thus more palatable than the classic 3:1 ratio KD (Huttenlocher et al. 1971). MCTs consist of approximately 70% to 90% of energy from fat with up to 60% of energy from MCT oil (Liu 2008). MCT oil in variable amounts can be used along with any type of diet therapy in the treatment of epilepsy. It is successfully used with limited side-effects when diet is administered carefully (Neal et al. 2009; Liu 2008).

Modified Atkin's Diet (MAD)

Modified Atkin's diet (MAD) provides a more palatable and less restrictive outpatient-initiated dietary treatment for older children and adults (Kang et al. 2007; Kossoff et al. 2006; Kossoff and Dorward 2008).

In children, the carbohydrates (excluding the fibre content) are limited to 10-20 g/day. In adults, the carbohydrates (excluding the fibre content) are limited to 15-30 g/day as tolerated based on seizure control. There is no calorie, protein, fat and fluid restriction. Fat intake from food is not defined but rather encouraged (Kossoff et al. 2013).

In contrast to the popular Atkin's diet, weight loss is not the goal of the modified Atkin's diet for seizures, unless nutritionally indicated (Kossoff and Dorward 2008).

Low Glycemic Index treatment (LGIT)

The glycemic index (GI) is a measure of how much a particular food will elevate the blood glucose compared to glucose (equivalent amount) (Jenkins et al. 1981). LGIT allows a more liberal amount of carbohydrate, restricted to carbohydrates with a glycemic index of less than 50 (Pfeifer and Thiele 2005).

LGIT reduces the blood glucose by altering the quality and the types of carbohydrates in the diet. It is hypothesized that low GI carbohydrates would produce a smaller increase in blood glucose and thereby less variability in the blood glucose throughout the day. These metabolic changes might have anticonvulsant effect by themselves (Valencia et aI. 2002).

Typically, the LGIT consists of 60–70% fat, 20–30% protein and 10% carbohydrates with low glycemic index (GI < 50). The usual carbohydrate intake per day is 40-60g (Pfeifer and Thiele 2005; Coppola et al. 2011).

Individualized Modifications to Diet

There is evidence to suggest all forms of diet therapy mentioned above help control seizures. Exact mechanism of action is unclear.

Rapid lowering of daily carbohydrate intake can be difficult to implement in some patients on MAD and LGIT diet. A more gradual reduction in the amount of carbohydrates consumed can be undertaken over days to weeks depending on tolerability, palatability and seizure control. This is similar to the practice of outpatient slower initiation of classic KD. For a given ratio of classic KD, further reduction in carbohydrate is possible by increasing the protein intake without changing the amount of fat. Variable amount of MCT oil can be added to any type of diet to increase the ketogenic potential.

Common Indications and Contra-Indications

Patients with GLUT-1 transport deficiency and for those with pyruvate dehydrogenase deficiency, the KD is considered a first-line therapy and should be implemented as soon as the patient is identified (Lee and Kossoff 2011).

Initiation methods

Each center should have a protocol for diet initiation and follow-up.

Inpatient Initiation

All the variations of diet therapy for epilepsy can be initiated through an inpatient admission. However, MAD and LGIT are typically initiated on an outpatient basis. The diet therapy will require a titration to reach the goal prescription. This titration can involve adjustments in daily calories, ketogenic ratios or macronutrient energy distributions. Careful daily monitoring for metabolic abnormalities (eg. acidosis, hypoglycemia, excessive ketosis) and associated symptoms such as vomiting will be required. The purpose of the inpatient admission is to reach the initial goal diet prescription more quickly. If the patient is tolerating this goal prescription they can be discharged home. Seizure control may not yet be optimized therefore further adjustments to the diet prescription can be made on as an outpatient.

Outpatient Initiation

MAD and LGIT-diets usually begin on an outpatient basis. Many centers use outpatient initiation method for classic KD as well (Vaisleib II et al. 2004). The variations of the diet therapies for epilepsy can also be implemented as an outpatient. There are two types of practices. Common practice is rapid titration of diet to a higher ratio within 3-5 days. However, it is possible that this approach results in some patients receiving a higher ratio than they require. Many patients achieve seizure control with lower ketogenic ratios, with improved tolerability of the diet. However, in a minority, higher ratios result in better efficacy (Wirrell 2008; Seo et al. 2007; Kossoff and McGrogan 2005). An alternative approach is to initiate classic KD on

an outpatient basis with initial titration to a very low ratio diet (0.6-1:1). Depending on the tolerability and desired seizure control, the ratio can be increased gradually (in increments of 0.15-0.67:1) every 2-3 weeks (current practice at McMaster Children's Hospital, Hamilton, and Children's Hospital, London Health Sciences Center, London, Ontario).

Pre-Diet Assessment

Referral & Screening

Diet therapy for epilepsy should be undertaken only after thorough clinical evaluation of the patient. In most situations, diet therapy is offered to patients with medically-refractory epilepsy. It is essential to establish correct epilepsy diagnosis, and ensure appropriate medical therapies have been tried before considering diet therapy. Patients who are potential surgical candidates should have appropriate work up to decide whether they are in fact surgical candidates, as surgical treatment may provide a more definitive epilepsy treatment than diet therapy. Therefore it is essential that all patients who are being considered for diet therapy be first evaluated by an epileptologist. Evaluation should include video EEG monitoring to capture the clinical events/seizures.

Pre-initiation Diet Assessment

The pre-initiation diet assessment should include the following:

- Anthropometrics (height, weight, IBW)
- Nutritional Intake
- Nutrition-focused Clinical Assessment
- Biochemical indexes
- Social Determinants of Health

The information gathered from the assessment will assist in determining the type of diet therapy required, need for possible commercial dietary products, estimate of financial burden, method of diet initiation and potential complications during diet therapy.

Baseline Laboratory and Diagnostic Testing

The International ketogenic diet study group recommended the following (Kossoff et al. 2009):

- Complete blood count with platelets
- Electrolytes to include serum bicarbonate, total protein, calcium, zinc, selenium, magnesium, and phosphate
- Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine)
- Fasting lipid profile
- Serum acylcarnitine profile
- Urinalysis
- Urine calcium and creatinine
- Anticonvulsant drug levels (if applicable)
- Urine organic acids

- Serum amino acids
- EKG (routine practice in Ontario centers to ensure QT interval is normal)
- Ancillary testing (optional)
    - Renal ultrasound and nephrology consultation (if a history of kidney stones)
    - EEG
    - Brain MRI
    - Cerebrospinal fluid (CSF) (if no clear etiology of seizures/epilepsy has been identified)
    - Team to decide on other tests depending on co-morbid conditions, and use of drugs including antiepileptic drugs

Feeding Assessment

If during the initial assessment there is concern of aspiration, a feeding assessment and a video fluoroscopy should be ordered to rule out risk of aspiration. Children who are found to aspirate on further investigation should be offered the option of receiving the diet via enteral feeding tube.

When assessing a child to determine candidacy for the diet therapy, they should be assessed for the following symptoms when eating and drinking:

- Vomiting
- Eating and gagging on textures
- Eating a limited variety of food/selective
- Slow weight gain
- Refusal to eat
- Limited volume/not eating enough
- Difficulty swallowing
- Refusal to swallow/holding of food in mouth
- Difficulty progressing to table food

Financial Assessment

It is important to provide information about the cost of the prescribed diet to patients and families. The exact costs will be determined at the time of diet initiation depending on how the patient tolerates the diet, and on their individual micronutrient needs. Families should be encouraged to review the costs and determine whether their insurance will cover some of the costs or whether they require financial assistance. The social worker can help families navigate through the various funding sources.

Other associated costs include food storage supplies, artificial sweeteners, artificial flavorings, carbohydrate free creams, lotions, toothpaste, and cost of parking for follow-up visits to the hospital.

Child Life Assessment

The Child Life Specialist may meet with the child and family prior to commencing a diet. By utilizing age appropriate methods, the Child Life Specialist assists with the transition to the new diet and encourages children to actively participate in activities to support diet initiation.

Diet Initiation Planning

All medications are to be assessed for carbohydrate content. Liquid suspensions should be converted to tablet form, if possible. For some children who are unable to swallow tablets, compounded preparations may be created using certain sweeteners. The compounding pharmacist should consult with the dietitian to determine the carbohydrate content of the medication and proposed liquid vehicle in which the medication is to be formulated to see if it can be incorporated into the diet. Prescriptions for diet testing supplies should also be provided to patients and their families. Parents are instructed to order a decimal gram scale and bring it with them on admission so that the scale can be calibrated and it can be used during the diet initiation admission so parents become familiar with using the scale.

A letter that summarizes the diet therapy should also be provided to patients and caregivers. The letter should summarize the purpose of the diet therapy and that it is being monitored by the diet team. Suggestions on management (eg. avoid liquid medications, dextrose containing IVs fluids including IV antibiotics premixed in dextrose, and IVIG with high dextrose content) along with suggested monitoring can also be included. Parents are instructed to present this letter to health care providers that may become involved with their child's care (e.g. EMS, emergency room staff, pharmacist, dentist, home care staff).

Setting the Goals

The multidisciplinary team and the patients (and or caregivers) should discuss the goals of diet therapy. Practical goals with respect to seizure control, change/reduction in antiepileptic drugs, and in case of epileptic encephalopathy the desired neurocognitive outcome or sleep EEG parameters (in encephalopathy associated with electrical status epilepticus of sleep) should be set. Appropriate response to seizure recurrence might include change in AEDs, fine tuning the diet or both. This goal should be set, if possible, at the time of diet initiation.

Follow Up Guidelines

Follow Up Visits

Frequency of follow-up with the epileptologist, dietitian, and other members of the multidisciplinary team (if applicable) should be should be decided by the multidisciplinary team. If clinically indicated, children less than 1 year of age should be evaluated more frequently as should those with growth, feeding issues, or nutritional deficiencies. Ongoing contact with children and families between the dietitian and nurses should be maintained for fine-tuning/maintenance of the diet between visits and for any troubleshooting. Any change in the pre-set goals should be approved by the most responsible provider.

Investigations

The International study group on ketogenic diet recommends the following laboratory diagnostic tests during follow-up (Kossoff et al. 2009):

- Complete blood count with platelets
- Electrolytes to include serum bicarbonate, total protein, calcium, magnesium, and phosphate
- Serum liver and kidney profile (including albumin, AST, ALT, blood urea nitrogen, creatinine)
- Fasting lipid profile
- Serum acylcarnitine profile
- Urinalysis
- Urine calcium and creatinine
- Anticonvulsant drug levels (if applicable)
- Optional investigations include
    - Serum β-hydroxybutyrate (BOH) level
    - Zinc and selenium levels
    - Renal ultrasound
    - Bone mineral density (DEXA scan)
    - EEG
    - Team to decide on other tests depending on co-morbid conditions, type diet used, and use of drugs including antiepileptic drugs

As part of their diet therapy training, parents should be taught to be prepared in the event of an emergency. In the event of an emergency, parents should bring in a letter from the diet therapy team indicating that they are on a diet and that their child may not have oral liquid medications, IV dextrose solution (only if clinically indicated).

Parents should be instructed to bring in their child's most recent diet recipe should an admission to hospital be required. This will allow for the Diet Office to be able to prepare the appropriate diet. After business hours, if parents anticipate that they may need to take their child to the Emergency Department, they should, if time permits, prepare some diet shakes to bring with them or meals in the event that the Diet Office is closed or there is delay in getting the specific diet from diet office. Parents should be encouraged to bring their glucometer, strips for checking ketones, lancets to hospital in the event that an admission is required during emergency situations.

Diet therapy order sets should be created if computerized orders are generated for patient care delivery. This will allow consistency in patient orders and for other treating teams (e.g. paediatrics) to ensure appropriate orders are entered and that the diet is adhered to should a child be admitted off service.

Weaning the Diet

The timing and actual method of discontinuation of diet therapy for epilepsy is often individualized based on the patient's response to the diet (Kossoff et al. 2009).

The International Study Group on ketogenic diet suggested consideration should be given to discontinue the diet therapy for epilepsy after 3 months if unsuccessful, and 2 years if completely successful, but longer diet durations are necessary for GLUT-1 and PDHD and may be appropriate based on individual responses for intractable epilepsy (Kossoff et al. 2009). Diet therapy for epilepsy works rapidly when effective, with 75% of children responding within 14 days (Kossoff et al. 2008). Therefore shorter diet therapy durations may be adequate to assess efficacy. Should seizures worsen for more than a few days after starting the diet therapy, similar to AEDs, it could be discontinued immediately.

During discontinuation, a gradual wean over 2–3 months is recommended, and during this time period, nutritional supplementation needs to be continued. If seizures worsen, the KD can be increased to the previously effective formulation (Kossoff et al. 2009) immediately.

Transition to Adult Care

Data on transition to adult service from paediatric service in diet therapy for epilepsy is limited. For the majority of adults with epilepsy, anticonvulsant management is not vastly different between paediatric and adult providers. However, continuation of diet therapy as an adult requires the services of a trained adult neurologist familiar with either the KD or MAD, and an adult dietitian as well. Although paediatric KD teams can continue to provide care, intermittent hospitalizations to adult units and issues such as pregnancy, living independently, and different nutritional requirements make this potentially problematic for adults (Kossoff et al. 2013). Based on a small series of patients, some authors have suggested that individual hospitals and paediatric neurology clinics can make their own personal decisions on how best to handle transitioning these patients, however, authors believed that having an adult epilepsy diet center is ideal (Kossoff et al. 2013).

Diet Therapy in Adults

The diet therapy for epilepsy can be used safely in the adult and adolescent population, with a response rate similar to those seen in children. Patients with symptomatic generalized epilepsy may be particularly good candidates for this type of dietary treatment (Nei M et al. 2014). Diets used to treat adults include the classic KD, MAD, and a LGIT (Cervenka et al. 2013). The classic KD is used for adults receiving the majority of their nutrition through enteral feedings. Liquid or powdered ketogenic formulas can meet an adult's nutritional requirements, although they may require additional supplements depending on their medical needs. Adults who are considering dietary therapy for the first time, who are independent, employed, and care for dependent children/other family members, MAD can provide a less restrictive and less time-consuming alternative to the classic KD (Cervenka et al. 2013).

Appropriate nutritional supplements are provided based on nutritional assessment, co-morbid conditions, type of diet used, use of antiepileptic drugs and biochemical evaluation.

We acknowledge the contributions of Dr. Elizabeth Donner (Medical Director, Comprehensive Epilepsy Program, The Hospital for Sick Children, Toronto), YM Liu & Helen Lowe (Registered Dietitians, The Hospital for Sick Children, Toronto), and Jennifer Fabe (Registered Dietitian, McMaster Children's Hospital, Hamilton) to the diet therapy section of this document.

Appendix 8: Different Neurostimulation Techniques

Vagus Nerve Stimulator

Stimulation is done through leads which are surgically implanted usually on the left vagus nerve, since stimulation of the right vagus nerve which innervates the sino-atrial node could cause bradycardia. After the carotid sheath is opened, two electrodes are wrapped around the vagus nerve and connected to a programmable pulse generator sitting sub dermally on the chest wall. The pulse generator then can be programmed wirelessly through a wand placed over the chest wall, and optionally can also be activated on demand by the patient or caregivers to treat epileptic auras or seizure warnings.

Sometime after the device implantation, it is turned on, with the stimulator programmed to deliver intermittent pulses of electrical stimulation lasting several seconds (usually between 7 and 30 seconds) at intervals of several minutes. Over the course of several weeks, the output current of the device is increased gradually, limited by the patient's ability to tolerate the sensation. A typical output current would be 1.5mA, but can range between 0.25 to 3.0 mA. Other parameters include the frequency of the stimulation (between 20-50Hz, usually 30Hz), and the pulse width, usually 500μs. In addition to this continuous intermittent electrical stimulation, individual pulses of electrical stimulation can also be delivered on demand, signaled to the generator by passing a magnet over it. This is usually done by patients in response to their anticipation of a seizure by feeling an aura or seizure premonition.

The efficacy of the VNS is supported by a number of randomized clinical trials. After initial pilot studies in an open label design, the first E03 blinded randomized group for VNS was performed at 17 sites in the US, Canada and Europe. Patients between 13 and 60 years old were enrolled and randomized to high (presumably therapeutic) pulse generator settings and to low (less or nontherapeutic) settings, with the hypothesis that the low stimulation might be ineffective, but would still could be felt by patients, thus providing some degree of blinding. Initial published reports on the first 67 patients described a 31% mean seizure reduction in the high stimulation group compared to 11% in the low stimulation group ($p=0.029$), and 39% vs 19% of patients experiencing a 50% seizure reduction ($p=0.0704$) (The Vagus Nerve Stimulation Study Group, 1995). A follow-up study converting the initial 67 patients to the high stimulation paradigm for open label treatment up to 18 months showed 44% of patients with >50% seizure reduction. A later report on all 114 patients randomized into the trial showed 31% of patients had a >50% seizure reduction compared to 13% in the low group ($p=0.02$). A later E05 study randomized 198 patients to high and low stimulation as well, and showed a 27.9% vs 15.2% decreased in seizure frequency relative to baseline ($p=0.02$), and a significant difference in patients with 75% reduction in seizures, though statistical significance was not shown for difference in patients with 50% reduction in seizures. Some studies have suggested that the efficacy of the VNS device may improve over longer periods of device implantation.

Side effects of the device include hoarseness, vocal cord paralysis, wire fracture necessitating electrode repair, throat pain, paresthesias, shortness of breath, superficial wound infections, without persistent serious side effects. The rate of Sudden Unexpected Death in Epilepsy was calculated in a group of 791 patients with VNS for approximately 2 years each, for an incidence of SUDEP of 4.5 per 1000 person-years, a rate comparable to studies of young adults with intractable epilepsy not treated with VNS.

The American Academy of Neurology Therapeutics and Technology Assessment Subcommittee reported in 1999 their opinion that there was sufficient evidence to consider VNS for epilepsy as effective and safe, and "indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections such as lesionectomies or mesial temporal lobectomies". In 2013 the American Academy of Neurology published a guideline update on VNS recommending based on a number of subsequent Class III studies that VNS may be considered for seizures in children, for Lennox-Gastaut Syndrome associated seizures, and for improving mood in adults with epilepsy.

Following installation of the device patients, are often followed closely during the initial phase where the device parameters are adjusted to titrate to effect and tolerability. Most typically, the output current is adjusted while the patient is otherwise kept on a standard paradigm of a stimulator on time of 30 seconds and off time of 5 minutes, with 30Hz stimulation and pulse width of 500 μs. Other stimulation paradigms have been tried such as rapid cycling, which usually entails 7 seconds on and 30 seconds off stimulation. Such paradigms have not been conclusively shown to be better than the standard stimulation paradigm, although some authors have found that a later switch to rapid stimulation in non-responders can be associated with improvement in some patients. At the moment, optimal VNS settings are unknown, "and the evidence is insufficient to support a recommendation for the use of standard stimulation vs rapid stimulation to reduce seizure occurrence".

Deep Brain Stimulation

There is one multicenter randomized controlled clinical trial known as the SANTE trial, showing evidence for safety and efficacy in epilepsy of DBS at the anterior nucleus of the thalamus. The anterior nucleus of the thalamus is part of the circuit of Papez, which involves connections from the hippocampus, fornix, mammillary body, anterior nucleus of the thalamus and the cingulate gyrus, feeding back into the hippocampal formation. Electrical stimulation at the anterior nucleus of the thalamus theoretically inhibits this nucleus, but the mechanism by which DBS at this site exerts its effect is likely more complicated than simply impeding propagation of seizures through this network by inhibiting one part of the circuit, and is poorly understood.

Bilateral stereotactic placement of multicontact electrodes in the anterior nucleus of the thalamus is performed usually under general anaesthesia using a frame or frameless system, using three-dimensional MRI for targeting. After the leads are placed, the right and left side connectors are tunneled subcutaneously to the dual-channel pulse generator located subcutaneously on the chest wall. Intra-operative fluoroscopy or post-operative MRI is used to confirm correct placement of the leads. When the device is turned on, it is usually programmed to deliver stimulation at a voltage of 5 volts, with 90us pulses at 145Hz, on for 1 minute and off for 5 minutes. Parameters can be changed, including increases in output voltage up to 7.5V or stimulation frequency to 185Hz.

The SANTE study was conducted in 110 patients who were treated with a 3 month blinded phase in which half received active treatment and half received no stimulation before all were converted to unblinded stimulation. During the blinded phase, the stimulated group showed greater improvements in seizure frequency compared to the control group over each of the 3 months of follow-up such that by the end of the blinded phase, the stimulated group had a 40.4% decline in seizure frequency compared to 14.5% in the control group. In the

unblinded phase of the trial, the 50% responder rate was 43% at 13 months, 54% at 25 months and 67% at 37 months. The study investigators did note that subjects with temporal lobe origin seizures had greater benefit from stimulation in the blinded phase compared to those with extra-temporal or multifocal epilepsy.

Adverse events reported in the study included depression in 14.8% of active treatment arm compared to 1.8% of controls, memory impairment in 13% of active treatment arm compared to 1.8% of controls, paresthesias in 18.2% of participants, and implant site infections in 9% of patients, with 16.4% of patients withdrawing from the study due to adverse events. Asymptomatic hemorrhage was observed in 4.5% of patients. Death was observed in 5 patients (4.5%), one in the baseline phase before surgery attributed to SUDEP, none during the double-blind phase, one due to drowning in a bathtub, one due to suicide, and two more due to SUDEP in long-term follow-up. None of these deaths was judged to be device-related.

DBS at the centromedian nucleus of the thalamus has been studied in a number of case series and a single controlled trial. An initial pilot study in 1987 involving five patients with primary generalized or multifocal epilepsy described a 60-100% improvement in complex partial seizures and a 80-100% improvement in generalized tonic-clonic seizures. This report was followed in 1993 by a larger series of 23 patients from the same group who observed a good response to stimulation in 12 patients whom they divided into either patients with generalized tonic-clonic seizures (9), or epilepsia partialis continua (3), but a poor response in the remaining 11 patients who had either complex partial seizures (5) or tonic seizures (6). This group reported in 2001 that they had followed 49 patients over the course of between 6 months and 15 years for centromedian nucleus of the thalamus stimulation, and reported efficacy for generalized tonic-clonic seizures, tonic seizures, and atypical absence seizures, but not complex partial seizures.

Notably, the single controlled pilot trial of centromedian stimulation for epilepsy published in 1992, using a double-blind cross over protocol with 3 months blocks and a 3 month wash-out period did not show any efficacy for centromedian nucleus stimulation. However, it was too small to evaluate efficacy of CM stimulation, having only 8 patients, and using lower stimulation voltages than Velasco et al.

Responsive Neurostimulation

The ability to abort seizures through application of a current directly to the cortex has been known for years, both in animal models, as well as in humans undergoing electrocorticography. While DBS and VNS systems deliver their programmed impulses at regular intervals with the intent to prevent seizures, responsive neurostimulation continuously monitors EEG with chronically implanted depth and subdural strip electrodes, and only delivers an electrical stimulus when a seizure has been detected.

The first device with such capabilities underwent randomized clinical trials which were reported in 2011 (Morrell 2011). Two hundred and forty subjects experiencing three or more disabling partial seizures per month were enrolled, of which 191 were implanted. After a 3 month pre-treatment baseline, patients were implanted with the device; then after a 4-week perioperative phase, patients underwent a 12 week blinded period in which 97 subjects received active treatment, and 94 subjects received sham treatment. Both groups experienced an initial reduction in seizures after electrode implantation, but a reduction in mean seizure frequency could still be demonstrated in the treatment compared to sham group during the blinded

phase (-37.9% n=97 vs -17.3% n=94, p=0.012). In long term follow-up, a reduction in seizures of 53% was seen at 2 years of treatment (Heck et al. 2014).

Serious adverse events occurred in 2.5% of the 191 subjects enrolled in the trial. SAEs in the first month included site infection (5 patients) requiring explant of the device in one patient, intracranial hemorrhage in 4 patients, 3 of whom required surgical intervention, as well as transient apraxia and dysphemia in one patient, and a procedure to revise the location of the leads in one patient. In longer term follow-up, SAEs included increased frequency of seizures in one patient and need for surgical revision of implanted leads to improve lead location, or repair damaged leads. Six subjects died during the study, four due to possible or definite SUDEP (one being in the sham group without stimulation enabled), one due to lymphoma, and one due to suicide.

Hippocampal stimulation

Electrical stimulation of the hippocampus as a possible treatment for DRE has been studied by several groups. In a Canadian study, 4 patients with mesial temporal lobe epilepsy (MTLE) underwent implantation of a chronic stimulating depth electrode along the axis of the left hippocampus. This study used continuous, subthreshold electrical stimulation (90 microsec, 190 Hz) and a double blind, multiple cross-over, randomized controlled design, consisting of three treatment pairs, each containing two 1-month treatment periods. During each treatment pair the stimulator was randomly turned ON 1 month and OFF 1 month. Hippocampal stimulation produced a median reduction in seizures of 15% and 3 patient's seizures improved; however, the results did not reach significance. Effects seemed to carry over into the OFF period. This study demonstrated possible benefits and absence of adverse effects of hippocampal electrical stimulation. However, the effect sizes observed were smaller than those reported in non-randomized, unblinded studies.

The effect of continuous electrical stimulation of the hippocampus bilaterally on seizures and memory was assessed in 2 subjects with seizures from both mesial temporal lobes in another Canadian study. A double blind, randomized, controlled, cross-over trial design was utilized. Two electrodes with four contacts each were implanted along the axis of the hippocampus bilaterally. Simultaneous stimulation of all electrodes contacts was either on or off during each 3-month interval. Seizure frequency decreased by 33% in both patients during stimulation and remained lower by 25% for the 3 months after stimulation was turned off before returning to baseline ($p < 0.01$). No consistent change in objective or subjective measures of memory occurred. Hippocampal stimulation should be regarded as an experimental therapy for epilepsy.

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation technique which has been shown to suppress cerebral cortical hyperexcitability. A number of open-label and controlled studies in patients with various forms of focally originating drug-resistant epilepsy (DRE) have shown its potential benefits but different methods of stimulation have been used. Repetitive TMS (rTMS) was no better than placebo for seizure reduction among 43 persons with drug-resistant epilepsy in a randomized, double-blind, sham-controlled, crossover multicentre Italian study (Cantello et al., 2007). Paired-pulse TMS (ppTMS) has been of limited effectiveness so far, as well. Until large scale studies validate TMS role in epilepsy, it cannot be recommended as a routine clinical tool.

External Trigeminal Nerve Stimulation (eTNS)

Safety and efficacy of External Trigeminal Nerve Stimulation (eTNS) in patients with DRE was studied in one class II double-blind randomized controlled trial design in 50 persons with epilepsy over 18 weeks. This phase II study provided Class II evidence that trigeminal nerve stimulation might be safe and effective in reducing seizures in people with DRE, but additional studies with larger number of subjects and longer follow-up are required to replicate the findings before it can be recommended as a treatment option.

Transcutaneous Auricular Vagus Nerve Stimulation (ta-VNS)

Safety and efficacy of bilateral Transcutaneous Auricular Vagus Nerve Stimulation (ta-VNS) for the treatment of paediatric epilepsy was studied in 14 patients with DRE over 24 weeks with stimulation of the auricular concha using an ear vagus nerve stimulator. The responder rate was 53.85% from week 17 to the end of week 24 in 13/14 subjects. This is a single study and its findings need to be replicated in larger studies with longer follow-up. Therefore, ta-VNS cannot be recommended for the treatment of DRE at the present.

Appendix 9: Epilepsy Implementation Task Force Membership

Name	Title/Role	Organization
Dr. Carter Snead (Co-Chair)	Paediatric Neurologist	The Hospital for Sick Children
Brenda Flaherty (Co-Chair)	Executive Vice President & Chief Operating Officer	Hamilton Health Sciences
Dr. Sharon Whiting	Paediatric Neurologist	Children's Hospital of Eastern Ontario
Megan Wright	Chief Nurse Executive	Children's Hospital of Eastern Ontario
Mary Secco	Director of Strategic Initiatives	Epilepsy Support Centre
Rosalee (Rosie) Smith	Director of Adult Services	Epilepsy Toronto
Dr. Laurene Sellers	Family Practice Physician	Grand River Hospital Corporation
Dr. Michelle Shapiro	Adult Epileptologist	Hamilton Health Sciences
Kathryn LeBlanc	Director, Neurosciences	Hamilton Health Sciences
Louise MacRae	Director, Regional Stroke Program	Hamilton Health Sciences
David McNeil	Vice President Clinical Programs/CNO	Health Sciences North
Dr. Salil Gupta	Epileptologist	Health Sciences North
Dr. Athen MacDonald	Paediatric Neurologist	Kingston General Hospital
Dr. De Ribaupierre	Paediatric Neurosurgeon	London Health Sciences Centre
Dr. Jorge Burneo	Adult Neurologist	London Health Sciences Centre
Laurie Gould	EVP Patient-Centered Care	London Health Sciences Centre
Dr. Rajesh RamachandranNair	Paediatric Neurologist	McMaster Children's Hospital/HHS
Kirk Nylen	Manager, Knowledge Translation/Ops	Ontario Brain Institute
Liz Ferguson	Director, Centre for Brain and Behavior	The Hospital for Sick Children
Mike Tierney	VP Clinical Programs	The Ottawa Hospital
Dr. Hassan	Neurologist	Thunder Bay Regional Health Sciences Centre
Dr. Taufik Valiante	Adult Neurosurgeon	University Health Network
Janet Newton	Clinical Director	University Health Network