Current Management of Epilepsy

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Disclosures

- Research-NINDS
- Royalties-Wiley, Up-to-Date

Learning Objectives:

S.M.A.R.T. (specific, measurable, attainable, realistic, and timely)

1) To determine when a person with a seizure has epilepsy and define seizure type, etiology and best syndromic fit
2) To learn risk factors associated with seizure recurrence for a new onset seizure patient
3) To understand the application of epilepsy quality measures to ongoing epilepsy care
4) To recognize the difference between patients who are "medication-resistant" and those who have "uncontrolled seizures" and management strategies for each
5) To learn the role of minimally invasive surgical techniques for appropriate epilepsy patients

Key Message

- Patients with epilepsy have a greater chance of achieving seizure freedom using a systematic approach to understanding and managing their illness.
- While epilepsy remains a mysterious disease, we have the skills to help most patients become seizure free.
- However, this does not happen without incorporating compassion, vigilance and ongoing efforts toward insight into our treatment paradigms.

The Disease of Epilepsy:

Revised epilepsy definitions by ILAE Task Force

(Fisher RS et al 2014)

- At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years (derived from Hauser WA et al NEJM 1998 and other sources)
- Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Recommended revised classifications: Seizure type (Berg AT et al. 2010)

Generalized — Generalized seizures are conceptualized as those that originate at some point within, and rapidly engage bilaterally distributed networks, which can be subcortical or cortical structures (tonic-clonic, absence and myoclonic)

Focal — The term focal has replaced partial to describe seizures that originate in networks limited to one hemisphere

No more simple partial, complex partial, and secondarily generalized

- Without impairment of consciousness or awareness
- Involving subjective sensory or psychic phenomena
- With impairment of consciousness or awareness, or dyscognitive
- Evolving to a bilateral convulsive seizure

Unknown — The term unknown mode of onset is used for seizure types where it remains unclear whether onset is focal, generalized, or perhaps either such as epileptic spasms

Recommended revised classifications: Etiology and Syndromic Classification (Berg AT et al. 2010)

- Genetic — A genetic etiology is defined when, as best understood, the epilepsy is the direct result of a known or presumed genetic defect and seizures are the core symptom of the disorder
- Distinct structural or metabolic conditions may be associated with a substantially increased risk of developing epilepsy.
  - Structural etiologies may be congenital (eg, cortical dysplasia, tuberous sclerosis) or acquired (eg, stroke, trauma, infection, immune-based).
- Unknown — the nature of the underlying cause is not currently known. All types of epilepsies with normal imaging and no documented genetic, metabolic or immune etiology are included in this category.

- An electroclinical syndrome represents the most precise diagnostic category of epilepsy, defined as a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical disorder.
  - West syndrome
  - Childhood absence epilepsy
- Distinctive constellation — Constellations are less precise than electroclinical syndromes but are distinctive groups based on specific lesions or underlying causes.
  - mesial temporal lobe epilepsy due to hippocampal sclerosis,
  - Rasmussen encephalitis,
  - gelastic seizures with hypothalamic hamartoma
- Structural or metabolic epilepsies — previously symptomatic focal epilepsy of a particular localization
  - epilepsy with focal seizures due to cortical dysplasia of the left frontal lobe
- Unknown-replaces term “cryptogenic”

AAN recommendations for management of first seizure in adults (Krumholz A, et al 2015)

- Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21%-45%) (Level A).
- Clinicians should also advise such patients that clinical factors associated with an increased risk for seizure recurrence include a prior brain insult such as a stroke or trauma (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), or a nocturnal seizure (Level B).

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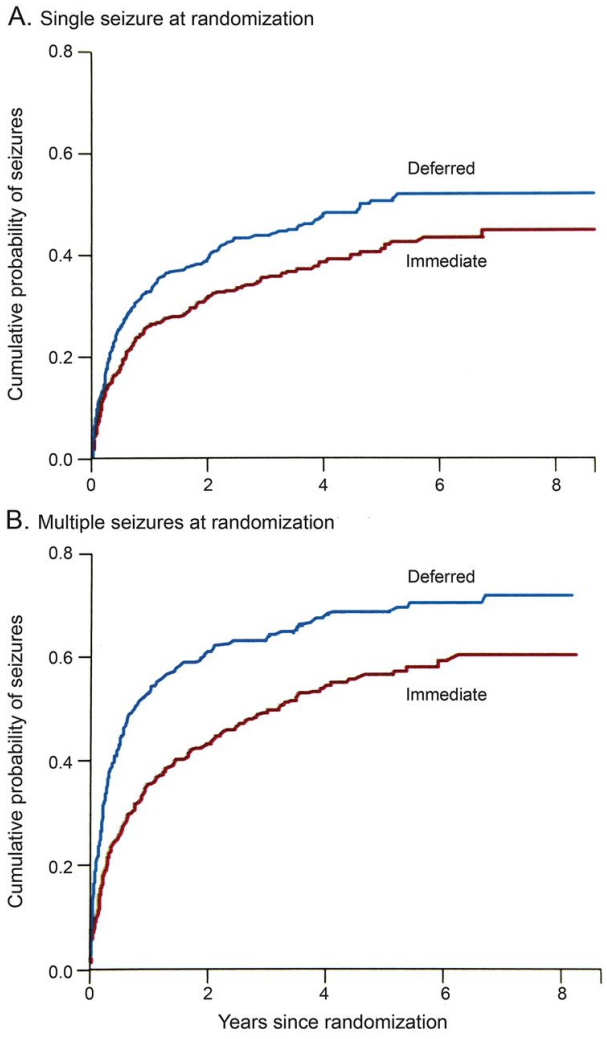
How much does treatment reduce risk of recurrence?

Seizure recurrence after immediate vs. deferred treatment (Marson et al. 2005)



Who should be treated after first seizure? Risks

- A prior brain insult as a seizure cause was associated with an increased relative rate for seizure recurrence at 1 to 5 years of 2.55 (95% confidence interval [CI] 1.44–4.51) as compared with that in patients with seizures of unknown cause (Hauser WA, et al 1990)
- An EEG with epileptiform abnormalities was associated with a relative rate increase for seizure recurrence at 1 to 5 years of 2.16 (95% CI 1.07–4.38) as compared with that in patients without such EEG abnormalities (Hauser WA, et al 1990)
- Abnormal brain imaging was associated with a hazard ratio increase for seizure recurrence at 1 to 4 years of 2.44 (95% CI 1.09–5.44) as compared with that in patients without imaging abnormalities (Hui AC, et al 2001)
- A nocturnal seizure was associated with an increased recurrence risk odds ratio at 1 to 4 years of 2.1 (95% CI 1.0–4.3) as compared with a seizure while the patient was awake (Bora I, et al 1995)

Considering these risk factors, how do we get to the 60% chance of recurrence to meet definition of epilepsy?

- In 1400 subjects with new onset seizures (allowing 1 or more prior to study entry) with normal EEG and a normal neurological status, if untreated, had a risk of a recurrence that was approximately 20%, 25%, and 30% at 1, 2, and 4 years after randomization (Kim et al., 2006).
- In 64 subjects with only one seizure previously including both treated and untreated with idiopathic seizures who had normal results on neurologic examination and normal EEG, negative family histories, recurrence rates were 10% and 14% at 1 and 2 years after entering study(Hauser WA et al 1990)

- Risk of prior brain insult multiplied by rate of "normal neurologic status" or "normal examination"
  - 20% x 2.55=51% at 1 year (Kim)
  - 25% x 2.55=64% at 2 years (Kim)
  - 10% x 2.55=26% at 1 year (Hauser)
  - 14% x 2.55= 35% at 2 years (Hauser)
- EEG abnormality
  - 20% x 2.16=43% at 1 year (Kim)
  - 25% x 2.16=54% at 2 years (Kim)
  - 10% x 2.16=22% at 1 year (Hauser)
  - 14% x 2.16=30% at 2 years (Hauser)
- Abnormal imaging-rates not stated
- Nocturnal seizures-rates not stated

AAN Quality measures
(Fountain NB, et al 2015)

- #1A Did you ask your patient about seizure frequency and document this information in the medical record?
  - Seizure Frequency documented at all visits
- #1B If the seizure frequency was greater than zero, did you offer/discuss an intervention to reduce seizure frequency?
  - Intervention for continuing seizures documented at each visit

AAN Quality measures cont'd: Etiology or syndrome

- #2 Did you document etiology or syndrome or order testing to determine etiology, type, or syndrome?
  - Document at all visits
  - Incorporates the important information about EEG and imaging results

AAN Quality measures, cont'd

- #3 Did you ask your patient about anti-seizure side effects and discuss intervention?
  - Querying and Intervention for Side Effects of Anti-seizure Therapy at all visits
- #4 Was your patient educated on safety issues and provided safety resources?
  - Personalized Epilepsy Safety Issue and Education Provided Percent of all patients with a diagnosis of epilepsy, or their caregivers, who were provided with personalized safety issue and epilepsy education at least once annually.
    - What are examples? Driving, rescue meds, sleep habits, drinking ETOH, sports(?)

Quality Measures Cont'd

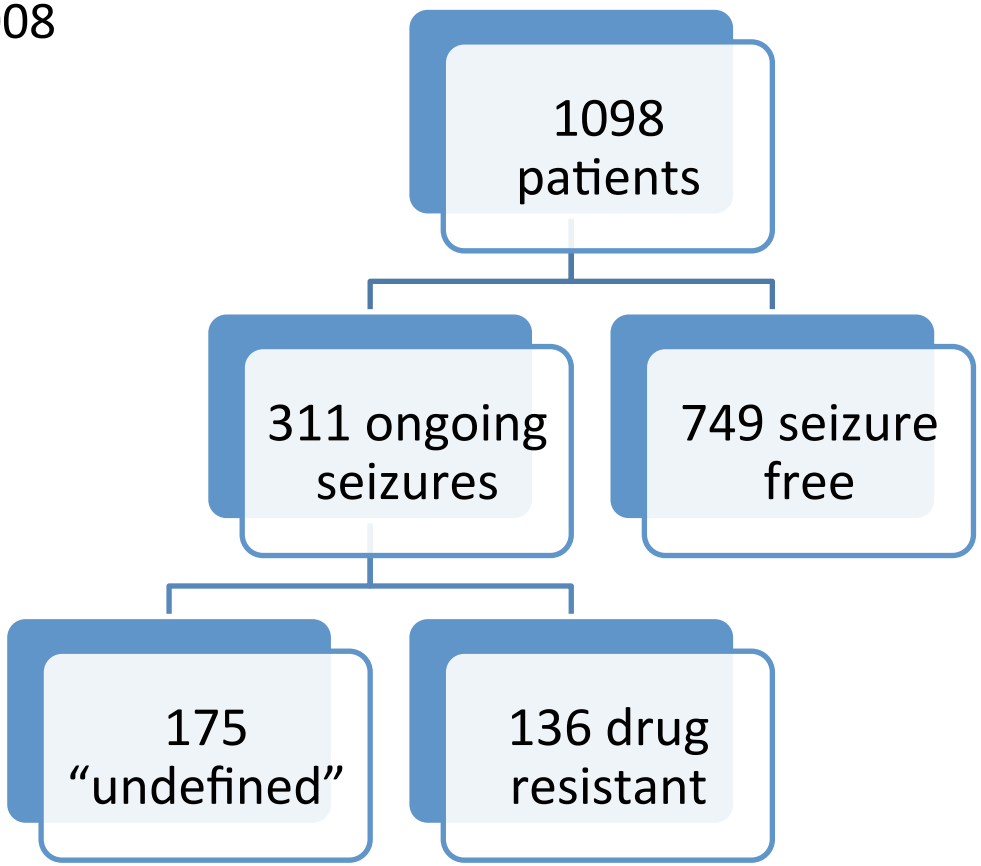
- #5 Was there any type of screening performed to identify psychiatric or behavioral health disorders?
  - Screening for Psychiatric or Behavioral Health Disorders Percent of all visits for patients with a diagnosis of epilepsy
- #6 Were female patients of childbearing age couseled regarding how epilepsy may affect contraceptive choices and pregnancy?
  - Counseling for Women of Childbearing Potential with Epilepsy All female patients of childbearing potential (12 to 44 years old) diagnosed with epilepsy who were counseled or referred for counseling for how epilepsy and its treatment may affect contraception OR pregnancy at least once a year.
- #7 Was the patient referred for a consultation at a comprehensive epilepsy center?
  - Referral to Comprehensive Epilepsy Center Percent of all patients with a diagnosis of treatment resistant (intractable) epilepsy who were referred for consultation to a comprehensive epilepsy center for additional management of epilepsy; specifically assessed every two years.

New Definition of Drug Resistant Epilepsy (Kwon et al, 2010)

- 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.*
- No seizure frequency requirement is necessary to meet the definition
- An individual with one seizure per year can be regarded as treatment resistant.

How many patients have drug resistant epilepsy? (Hao X et al, 2013)

- Patients in whom epilepsy was diagnosed and the first antiepileptic drug prescribed between July 1, 1982, and April 1, 2006, were followed up until March 31, 2008



The large "undefined" group is where people with epilepsy are "falling through the cracks" in care (Hao X et al, 2013)

- Uncontrolled epilepsy is not necessarily the same as drug-resistant epilepsy.
- The most common reasons were
  - trying just one AED usually at the patient's behest (n=68; 39%);
  - intermittent compliance (60; 34%);
  - adverse effects at low dosage (51; 29%);
  - Inadequate dosing (49; 28%);
  - social issues such as imprisonment, alcohol, and recreational drug use (34; 19%);
  - psychiatric problems affecting documentation, attendance, etc. (32; 18%);
  - patient choice accepting less than optimal control (14; 8%); and seizure freedom of less than 12 months (12.7%).

How can we control “uncontrolled epilepsy” and get them into the 68% seizure free category?

- Patient education including self-management strategies-The Modular Service Package Epilepsy (MOSES) participation reduced seizure frequency (May and Pfafflin 2002)
- Ready adjustment of meds when patients have problems-availablility
- Strong therapeutic alliance
- Treat depression-it affects compliance and on-line effective treatment protocols have been used
  - (Ettinger et al, 2014 and Schroder, et al 2014)

Risk factors for True Drug Resistance
(Brodie 2013)

- The response to the first AED trial is the most important – drug resistance may be declared early
- High seizure frequency
- Depression
- Unknown etiology for both generalized and localization-related epilepsy, have a better prognosis than symptomatic epilepsy in both pediatric and adult populations
- Epilepsy of structural cause underlies more than half of the cases of DRE in adults.
  - Mesial temporal sclerosis (MTS), cortical dysgenesis, or dual pathology.
  - Of persons with MTS 40 to 80 percent are intractable

Minimally invasive epilepsy surgery techniques: Seizure onset zone (SOZ) localization

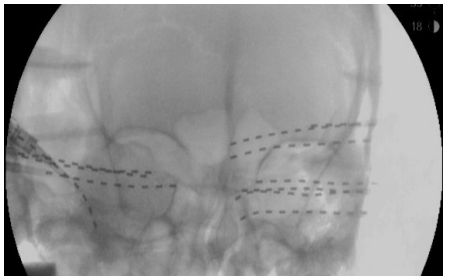
Intracranial Grids and strips

- The major complications : 7.8% of delayed subdural hematoma at the site of the subdural grid, 3.9% of infection 2.0% of epidural hematoma (Lee et al 2000. Surg Neurol)
- Allows cortical mapping of SOZ borders and eloquent areas
- Larger sampling zone with more volume conduction 3 mm
- More difficult for patient-needs craniotomy

Intracranial Stereo-EEG

- Intracranial bleeding 2.4% (Cardinale et al 2013)
- Less than complete comfort level with cortical mapping of brain function, esp language
- Small sampling area 1.2 mm electrodes-need good hypothesis
- Less distortion on MRI
- Easier on patient

-2 mm twist drill holes for electrode placement



Minimally invasive surgical techniques: Laser ablating the seizure-onset zone

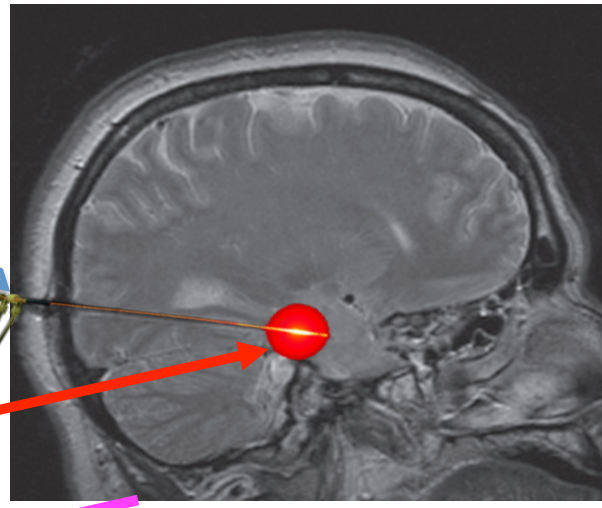
(Quigg and Harden 2014)

- 5mm incision
- Implantation of probe under stereotactic guidance
- Treatment in MRI suite
  - Relies on MRI-based measurement of temperature
  - Real time (<10 second) feedback to control amount of treatment delivery.
- 1 day hospital stage
- Postoperative swelling < 1 week managed with steroids.

Visualase System

Visualase Workstation

Disposable Laser Probe

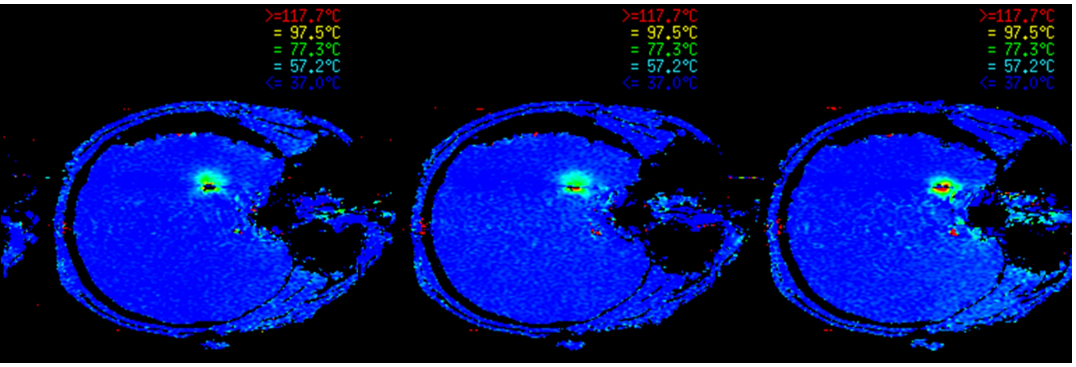


Laser treatment controlled by temperature measured by MRI

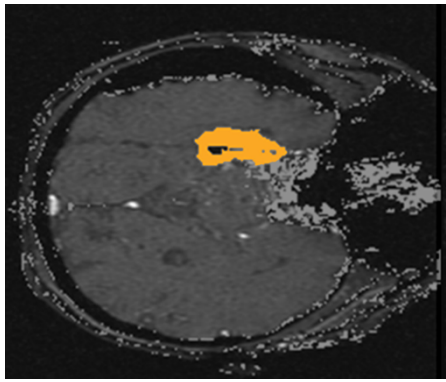
Imaging Data Flows From MRI to CPU

Probe may be advanced or withdrawn to generate adjacent lesions

Real time thermal imaging



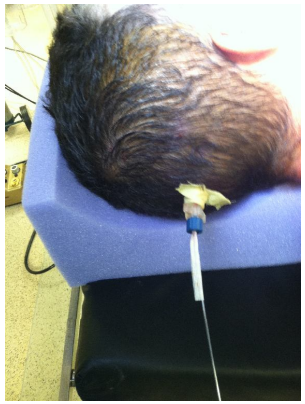
Heat sink in ventricle and ambient cistern prevents thermal injury to neocortex and brain stem



40 year old male with right mesial temporal sclerosis

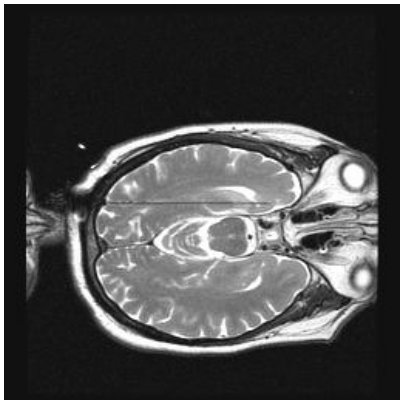
- Concordant noninvasive workup
- 1 hour operative procedure to place probe
- 2 hours MRI time to deliver treatment
- Postcontrast T1 study demonstrates treatment at the conclusion of the procedure
- Discharged home on POD1

Pre Ablation



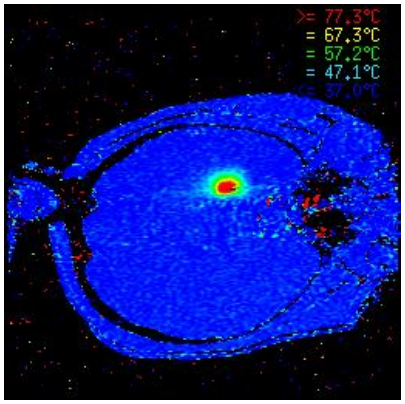
Laser Placed in the Operating Room

Placement Confirmation



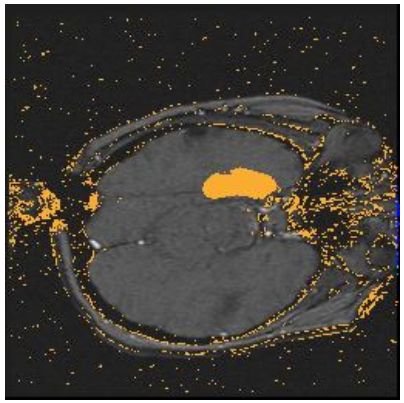
Confirms Laser in Target

Visualase Real-Time Temperature

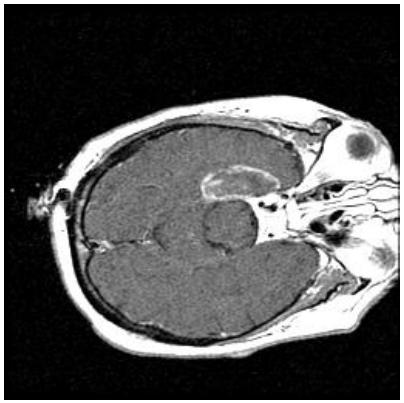


Live temperature Image

Visualase Real-Time Damage

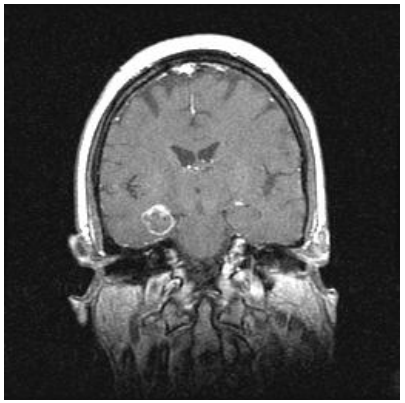


Live Damage Model - Final Image



Contrast Image- Axial

Post Ablation



Contrast Image- Coronal

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