The current state of epilepsy guidelines - what is applicable in sub-Saharan Africa.

Jo Wilmshurst
Paediatric Neurology
Red Cross War Memorial Children's Hospital
University of Cape Town

8th Regional Teaching Course in sub-Saharan Africa. Maputo 2016

Guidelines for Neonatal Seizures (2011)

http://www.who.int/mental_health/publications/guidelines_neonatal_seizures/en/

WHO / ILAE recommendations

Key findings

- Treat after 3 minutes duration of seizure
  - Or clusters
- Do **not** use Pb prophylaxis for HIE (wait for the seizure)
- All clinical seizures should be treated
  - **ideally use monitoring** to detect subclinical
- Exclude treatable causes – glucose / elec / infections
- First line Pb – to maximal tolerated
  - then midaz or lidocaine - No ideal agent
- Withdraw AEDs 72 hours seizure free & **normal EEG**.
  - Abnormal neurology less likely to be effective

FULL-LENGTH ORIGINAL RESEARCH

Treatment of infants with epilepsy: Common practices around the world

*Jo M. Wilmshurst, *Richard Burman, †William D. Gaillard, and ‡J. Helen Cross

Epilepsia, 56(7):1033–1046, 2015
doi: 10.1111/epi.13003

SPECIAL REPORT

Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics

Working Group: *Jo M. Wilmshurst, †William D. Gaillard, ‡Kollencheri Puthenveettil Vinayan, §Tammy N. Tsuchida, ¶Perrine Plouin, #Patrick Van Bogaert, **Jaime Carrizosa, ††Maurizio Elia, ‡‡§§Dana Craiu, ¶¶Nebojsa J. Jovic, ##Doug Nordli, ***Deborah Hirtz, †††‡‡‡Virginia Wong, §§§Tracy Glauser, ¶¶¶###Eli M. Mizrahi, and ****J. Helen Cross

Epilepsia, **(*):1–13, 2015
doi: 10.1111/epi.13057

Infantile seizure key findings

- Get the diagnosis correct
- EEG useful – video might be better
- No indication for EEG / imaging / AED for SFS
- Treat after 2nd sz (Ep En declare themselves)
- Aetiologies – **level A evidence for MRI**
- Consider treatable metabolic conditions eg **KD**
- Genetics – **EOEE including Dravet**
- **Interventions** only good evidence for Eplileptic spasms ……

Guidelines – relevance to RPC – the clinical setting

- In many RPC settings guidelines are **impossible to follow**
- Based on the assumption that the **diagnosis** of epilepsy accurately made…
- Challenging
  - *Lack of clinical skills (training)*
  - *Recommendations suggesting EEG in many cases*
- Recommended **AEDs** are not available / or lack of sustained supply
  - Health care workers not equipped to manage PWE – unskilled in AEDs
- Potentially then end up with a 2 tiered system of practice / recommendations
  1. For equipped settings
  2. Resource poor settings
- *Ethically wrong*

Guidelines - accessibility

- Totally pointless if not circulated, read, and widely available
- Many doctors unaware of published guidelines
  - (*JCN Children with epilepsy in Africa 2013*)
- RPC
  - where most people with epilepsy reside
  - have no access to guidelines
  - or do not believe they are of relevance to them

Soooo however good it is - The guideline is pointless unless the health care worker reads it and understands it.

For epilepsy – this is often at a primary health care level to ensure early intervention..

Epidemiology / Terminology

- Cannot direct capacity if do not understand frequency of epilepsy demographics
  - Guided by multicentre community based research
  - Results vary in different regions based on different aetiologies
  - Overall prevalence of Epilepsy in childhood ~0.5-0.8%

- ILAE new organisation of epilepsy terminology is aimed to improve categorisation and future concepts to improve the management of people with epilepsy
  - It has led to significant debate!
  - 6 groups
    - genetic / metabolic / structural / infectious / inflammatory / unknown

Sillanpaa Epilepsia 1992; Serdaoglu et al JCN 2004;Kariuki et al 2014
Berg et al Epilepsia 2010; Scheffer Epilepsia 2012; Fisher et al 2014

ILAE Classifications of Epilepsy and Seizures

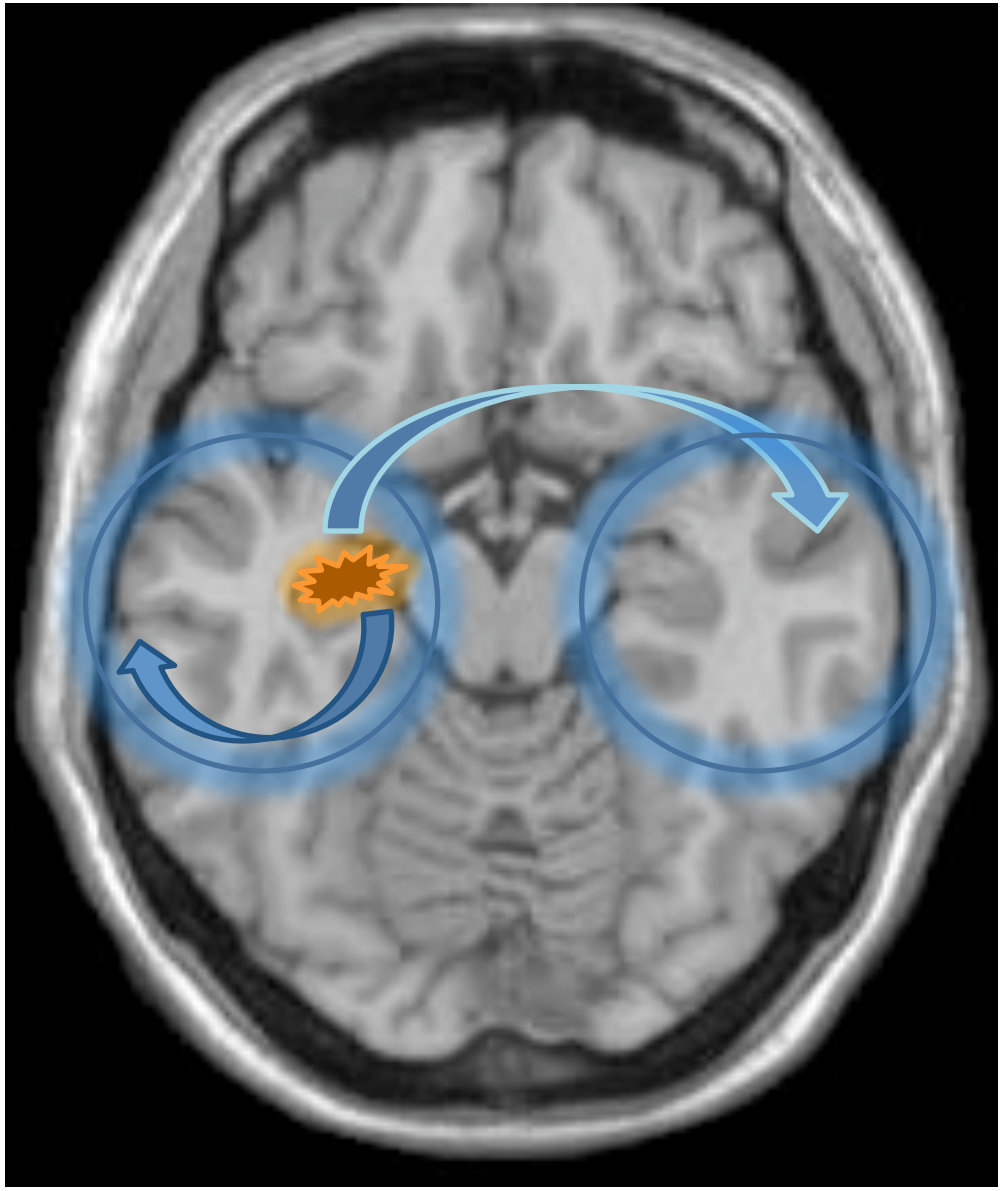
- 1969 – Gastaut – Proposals - seizures & epilepsies
- 1970 – Gastaut – Classification - seizures
- 1970 – Merlis – Classification - epilepsies
- 1981 – Commission – Classification – seizures
- 1985 – Commission – Classification - epilepsies
- 1989 – Commission – Classification - epilepsies
- 1993 – Commission – epidemiological standards
- 2001 – Blume – Glossary of ictal semiology
- 2001 – Engel – Proposed diagnostic scheme
- 2005 – Fisher – Definition of seizure and epilepsy
- 2006 – Task Force – report – seizures & epilepsies

Purpose of the International Classification of Seizures and Epilepsies

- To provide a common international terminology and classification
- Largely for clinical (treatment) purposes
- Purpose of classification: to organize items according to their fundamental relationships

Focal seizures

- Originate within networks limited to one hemisphere
- May be discretely localized or more widely distributed….



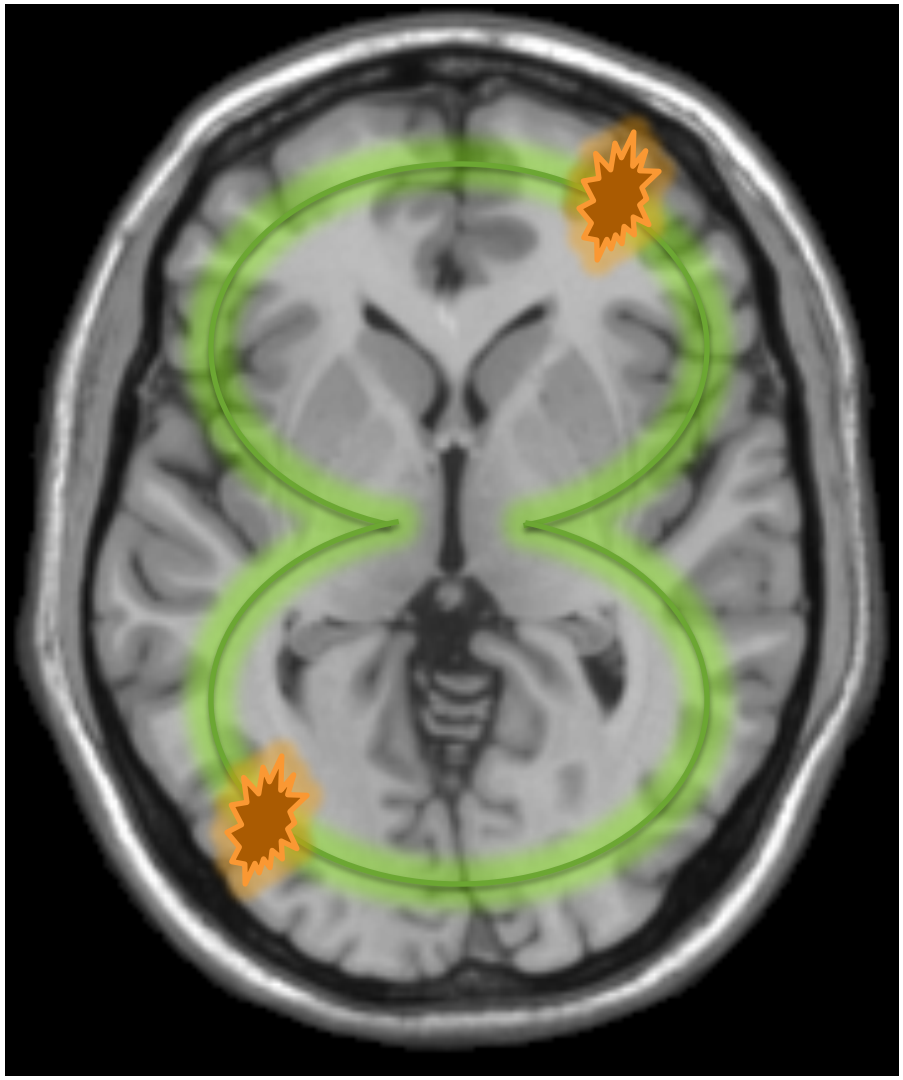
Focal seizures

Blume et al Epilepsia 2001

- Previous term: simple partial
  - No impairment of awareness or consciousness
  - Motor or autonomic components eg. focal clonic
  - Subjective sensory or psychic features -> Aura
- Previous term: complex partial
  - Impairment of awareness or consciousness
    → loss of awareness
- Previous term: secondarily generalised
  - Evolving to bilateral, convulsive seizure
  - With tonic, clonic or tonic and clonic components

Generalised seizures

- **Originate at some point within and rapidly engage bilaterally distributed networks**
- **Can include cortical and subcortical structures but not necessarily the entire cortex**



Epilepsies

- Generalized epilepsies
- Focal epilepsies

} Use where they work!

- Not every patient can be classified as either focal or generalized
  - Overlap not unusual
  - Especially many epileptic encephalopathies
    - e.g. Dravet syndrome

Approaches to epilepsy diagnosis

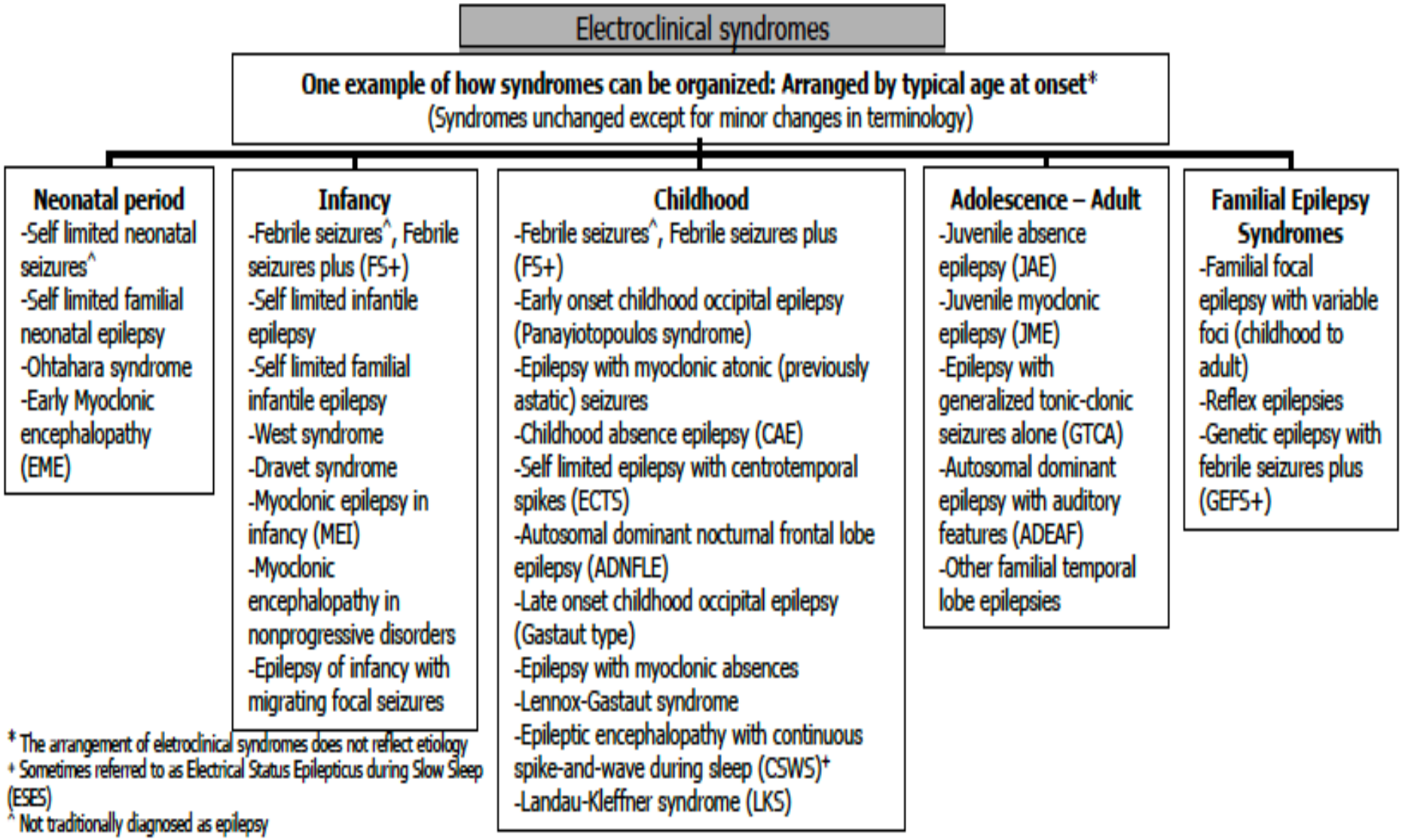
- **Electroclinical syndromes**
- **Clinicoradiological syndromes**
- **Aetiologic-based diagnoses**
- **Unknown**

Electroclinical epilepsy syndromes

- **Unchanged!**
- **A diagnosis can be made as previously**

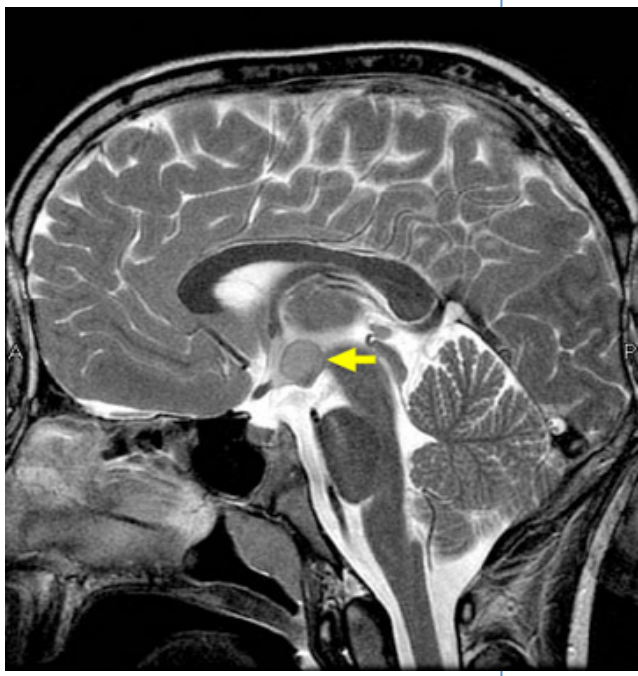
  e.g.
  - **Lennox-Gastaut syndrome**
  - **Childhood Absence Epilepsy**
- **A diagnosis is *not* the same as a classification**

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis



Clinicoradiological syndromes

- Replace “constellation” as does not translate
- Denote associated findings with treatment implications such as surgery
  - Mesial temporal lobe seizures and hippocampal sclerosis
  - Gelastic seizures and hypothalamic hamartoma



Aetiologic-based diagnoses

- **Use terms that mean what they say!**
- **Replace old fashioned terms:**
  idiopathic, symptomatic, cryptogenic

- **Genetic**
- **Structural**
- ***Metabolic***
- ***Immune***
- ***Infectious***
- **Unknown**

ILAE Revised Terminology for Organization of Seizures and Epilepsies 2011 - 2013

Major changes in terminology and concepts

New Term and Concept	Examples	Old Term and Concept
Etiology (an individual may fit into more than one group)		
Genetic: *genetic defect directly contributes to the epilepsy and seizures are the core symptom of the disorder*	*Channelopathies, GLUT1 deficiency, etc*	**Idiopathic:** *presumed genetic*
Structural: *caused by a structural disorder of the brain*	*Tuberous sclerosis, cortical malformations, mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS), gelastic seizures with hypothalmic hamartoma*	**Symptomatic:** *secondary to a known or presumed disorder of the brain*
Metabolic: *caused by a metabolic disorder of the brain*	*Pyroxidine deficiency, GLUT1 deficiency , etc*	**Symptomatic**
Immune: *epilepsy with evidence of autoimmune mediated CNS inflammation*	*NMDA receptor antibody encephalitis, voltage gated potassium channel antibody encephalitis*	**Symptomatic**
Infectious: *an infectious etiology refers to a patient with epilepsy, rather than seizures occurring in the setting of acute infection such as meningitis or encephalitis. These infections sometimes have a structural correlate.*	*Tuberculosis, HIV, cerebral malaria, neurocysticerosis, subacute sclerosing panencephalitis, cerebral toxoplasmosis*	
Unknown: *the cause of epilepsy is unknown*		**Cryptogenic:** *presumed symptomatic*

Terminology	Terms no longer recommended
Self-limited: *tendency to resolve spontaneously over time*	**Benign**
Pharmacoresponsive: *highly likely to be controlled with medication*	**Catastrophic**
Focal seizures: *seizure semiology described according to specific subjective (auras), motor, autonomic, and dyscognitive features*	**Complex Partial**
	Simple Partial
Evolving to a bilateral convulsive seizure	**Secondary generalized**

We would welcome your thoughts on this proposal. Please visit the "Request for Comments" page on the ILAE website to read the full document and register your comments.

http://www.ilae.org/Visitors/Centre/Organization.cfm

References: 1.Berg AT et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-685. 2.Blume WT et al. Glossary of descriptive terminology for ictal semiology: Report of the ILAE task force on classification and terminology. *Epilepsia* 2001:42;1212-1218. 3. Scheffer IE et al. The Organisation of the Epilepsies: Report of the ILAE Commission on Classification and Terminology (ILAE website as above)

Conclusions & ways forward

- **Increasing discovery from genetics led to enhanced understanding of the epilepsies**
- **Moving toward an aetiology directed approach, with more targeted treatment**
- **Need for more applicable organisation of the epilepsies, for both clinical and research practice – moves forward with progress**
  - **Diagnostic manual**

Moving forwards…The ILAE Classifications TF

Epilepsia Open

SPECIAL REPORT

Classification of the epilepsies: New concepts for discussion and debate—Special report of the ILAE Classification Task Force of the Commission for Classification and Terminology[1]

*†‡Ingrid E. Scheffer, §Jacqueline French, ¶#Edouard Hirsch, **Satish Jain, ††Gary W. Mathern, ‡‡Solomon L Moshé, §§Emilio Perucca, ¶¶Torbjorn Tomson, ##Samuel Wiebe, ***Yue-Hua Zhang, and †††‡‡‡Sameer M. Zuberi

Epilepsia Open, **(*):1–8, 2016
doi: 10.1002/epi4.5

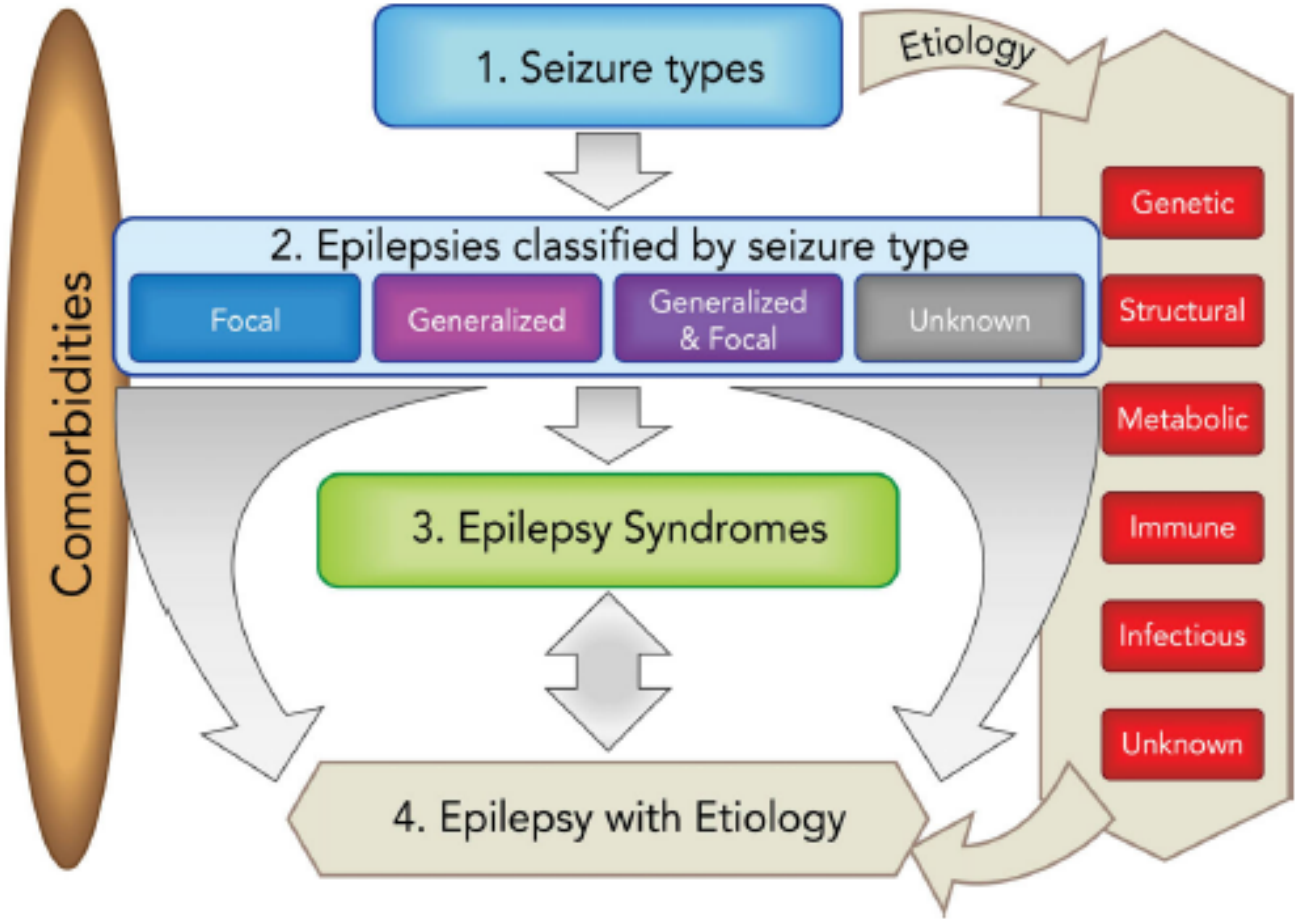
Developing a road map ➔

- Development of an updated, relevant classification of the epilepsies
- 4 diagnostic levels
  - Seizure type (level 1)
  - Epilepsy category (level 2)
  - Epilepsy syndrome (level 3)
  - Epilepsy with (specific) aetiology to denote specific levels of diagnosis) (level 4)
- Expand on the 6 aetiological categories with treatment implications
- See how the 2010 version has undergone further change

Figure 1.

Framework for epilepsy classification. The etiological framework can also be used for acute seizures. The term "genetic" refers to the etiology in an individual if there is an epilepsy syndrome that is known to be primarily genetic based on evidence from family and twin studies. Although the underlying gene may be identified for some individuals, in most cases, the underlying genetic mutation will not be known.

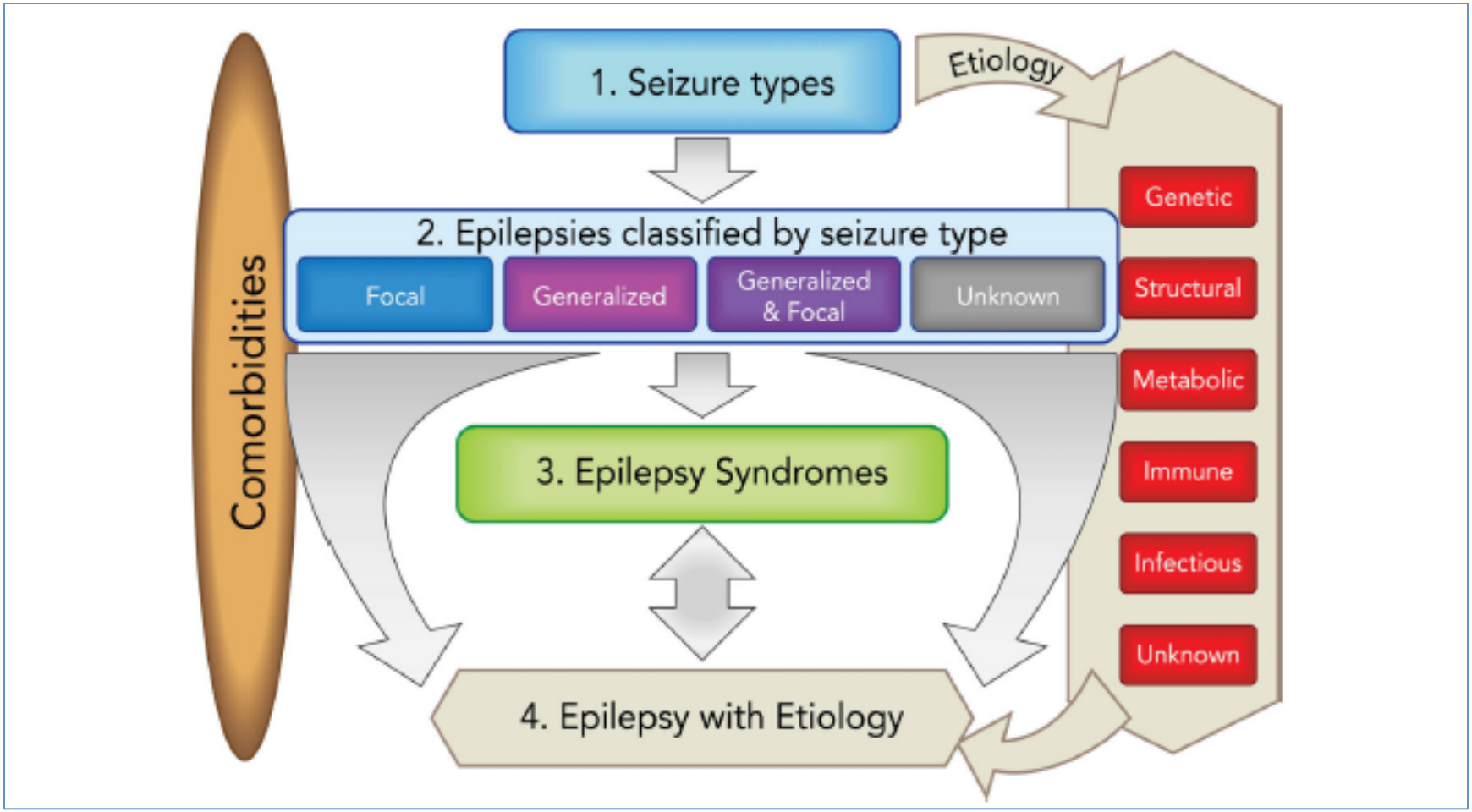
Epilepsia Open © ILAE



Limitations

- Local capacity affects level of diagnosis reached
  - If have all facilities / investigations can make level diagnosis of epilepsy type with confidence.
- But may have:-
  - limited resources – may not be able to fully investigate
  - Limited information
  - Possible to make only a level 2 diagnosis (epilepsy category)

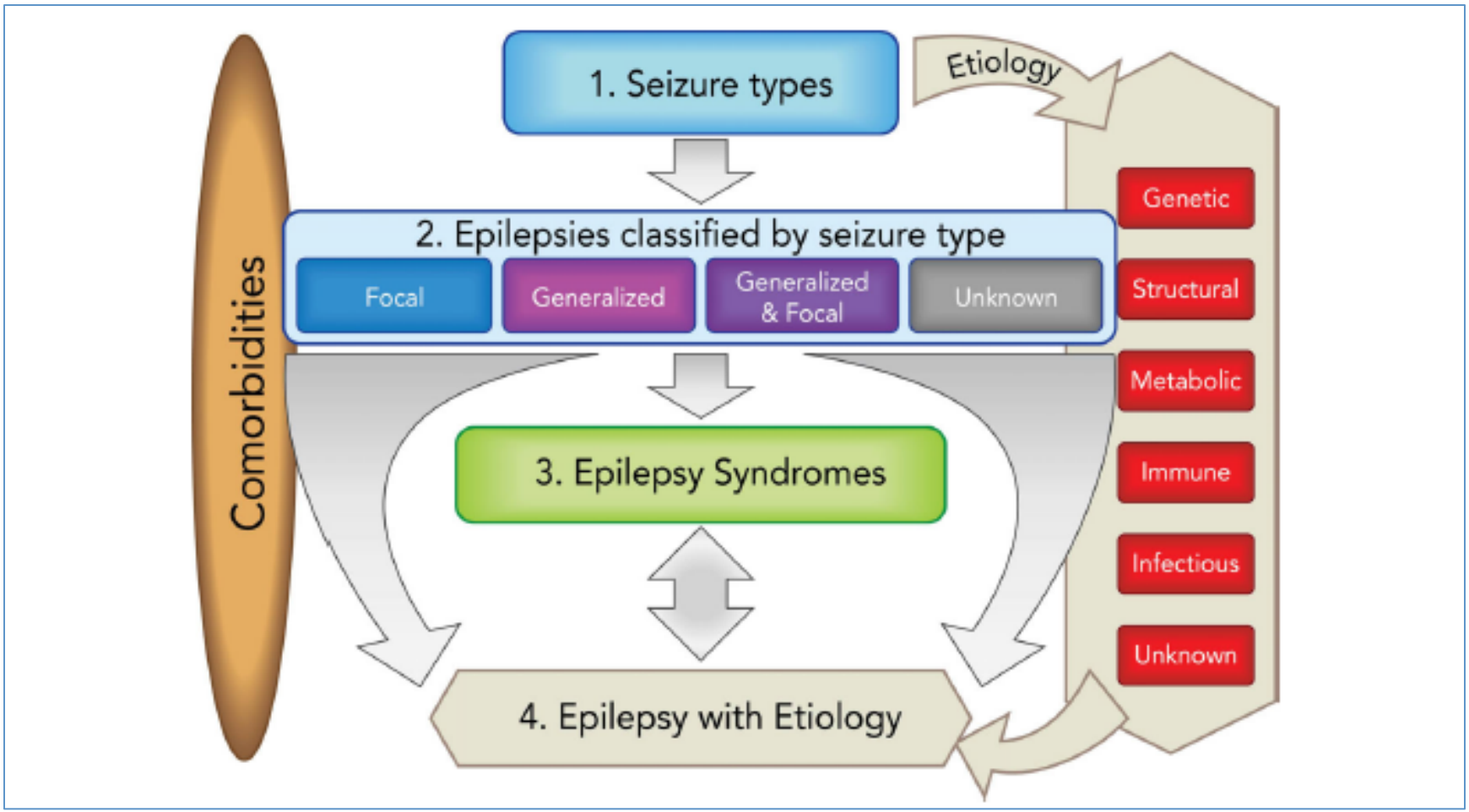
Level 3


1. Seizure types
Etiology
Comorbidities
2. Epilepsies classified by seizure type
Focal
Generalized
Generalized & Focal
Unknown
Genetic
Structural
Metabolic
Immune
Infectious
Unknown
3. Epilepsy Syndromes
4. Epilepsy with Etiology

Level 3 – Epilepsy syndromes

- Aim to make an epilepsy syndrome diagnosis
- Encourage use of the ILAE educational resource
  - Epilepsydiagnosis.org
- Great resource with teaching videos and good clinical and EEG examples

Level 4 – Epilepsy with aetiology



Level 4- Epilepsy with aetiology

- Opens up the option for "precision medicine" leading to targeted therapy.
- Dramatically influenced by the genetic and neuroimaging scientific progress.
- Direct implications to management
  - Dravet syndrome – *SCN1A*
  - *CHD2* encephalopathy
  - *KCNQ2* encephalopathy
  - *STXBP1* encephalopathy

Heterogeneity in expression

- An epilepsy syndrome may not have one-to-one correlation with a specific mutation
- *SCN1A*
  - – also seen in patients with GEFS+ (genetic epilepsy with febrile seizures plus)
  - Milder disorder and may not even need AEDs
- GLUT1 def
  - Rx Ketogenic diet
  - range of types of expression
    - Myoclonic atonic epilepsy
    - Juvenile absence epilepsy
    - GLUT1 encephalopathy

Precision medicine

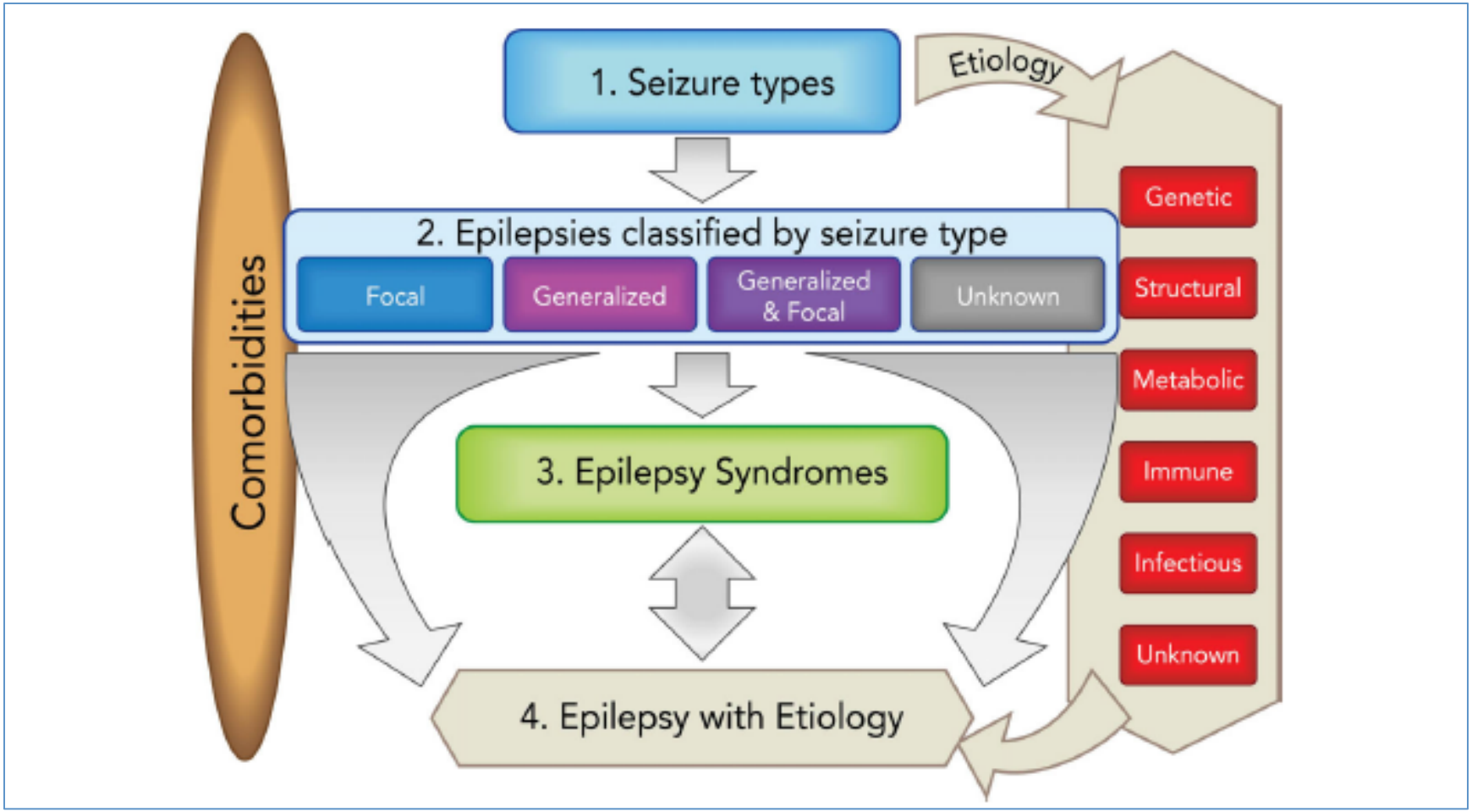
- *KCNT1* mutations
  - 50% patients with epilepsy of infancy with migrating focal seizures
  - Treatment option with quinidine
  - Targets the KCNT1 potassium channel
  - Currently limited to case reports / studies

Aetiological cross-over

Possible to fall under >1 aetiological category

- Tuberous sclerosis complex
  - Mx differs depending on category
  - Structural → tuberectomy
  - Genetic → mTOR inhibitors

Comorbidities



Co-morbidities

- Relevant across all levels 1-4
- Recent increased awareness
  - Screen for learning, psychological and behavioural difficulties
  - Aim for earlier intervention
- Identification specific phenotype can also aid diagnosis / management
  - E.g. girls with *PCDH19* mutations
    - –severe behavioural and autism

Genetics - 1

- Previously under “idiopathic”
- Most genetic cases *de novo* mutations
- Often no family history
- Not hereditary but reflect “genetic make-up”
  - ie “genetic” does not equate to “inherited”

Genetics - 2

Other situations

- Partial penetrance
  - range of epilepsies in one extended family
- Complex inheritance
  - several genes contribute to expression
- Strong FH but no identifiable mutation

Genetics - 3

Implications

- Stigma
- Cultural implications

- Emphasises the importance of access to genetic counselors
  - even beyond the actual screens

Development and epileptic encephalopathies

"Epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g. cortical malformation)."

Berg *et al* 2010

Epileptic encephalopathy examples

- Abundant epileptiform activity interferes with development with cognitive slowing and often regression,
- plus sometimes psychiatric and behavioural consequences.
  - West Syndrome
  - Lennox Gastaut syndrome
  - CDKL5 encephalopathy
  - CHD2 encephalopathy

Implications

- Does improved epileptic activity = better level of function?
- But syndromes where interictal activity not marked at presentation, and still have regression / behaviour e.g. Dravet syndrome

- Implies process more complex than epilepsy alone.
  - Opted to expand the term to "developmental epileptic encephalopathy"

Delayed development + very active epileptiform abnormalities

- "**developmental epileptic encephalopathy**"
  - emphasizes that both features play a role in their disease.
- If genetic mutation of major effect identified, = etiology of a "gene name" encephalopathy
  - E.g. "STXBP1 encephalopathy".
- Genes are associated with both severe and self-limited, pharmacoresponsive epilepsies,
  - E.g. *KCNQ2* or *SCN2A*, addition of the term "encephalopathy" = the severe form.

Overall

- Evolving picture
- Classification standardisation globally in terms / language
- Aimed towards better care…

J Clin Epidemiol. 2011 July ; 64(7): 708–710. doi:10.1016/j.jclinepi.2010.07.016.

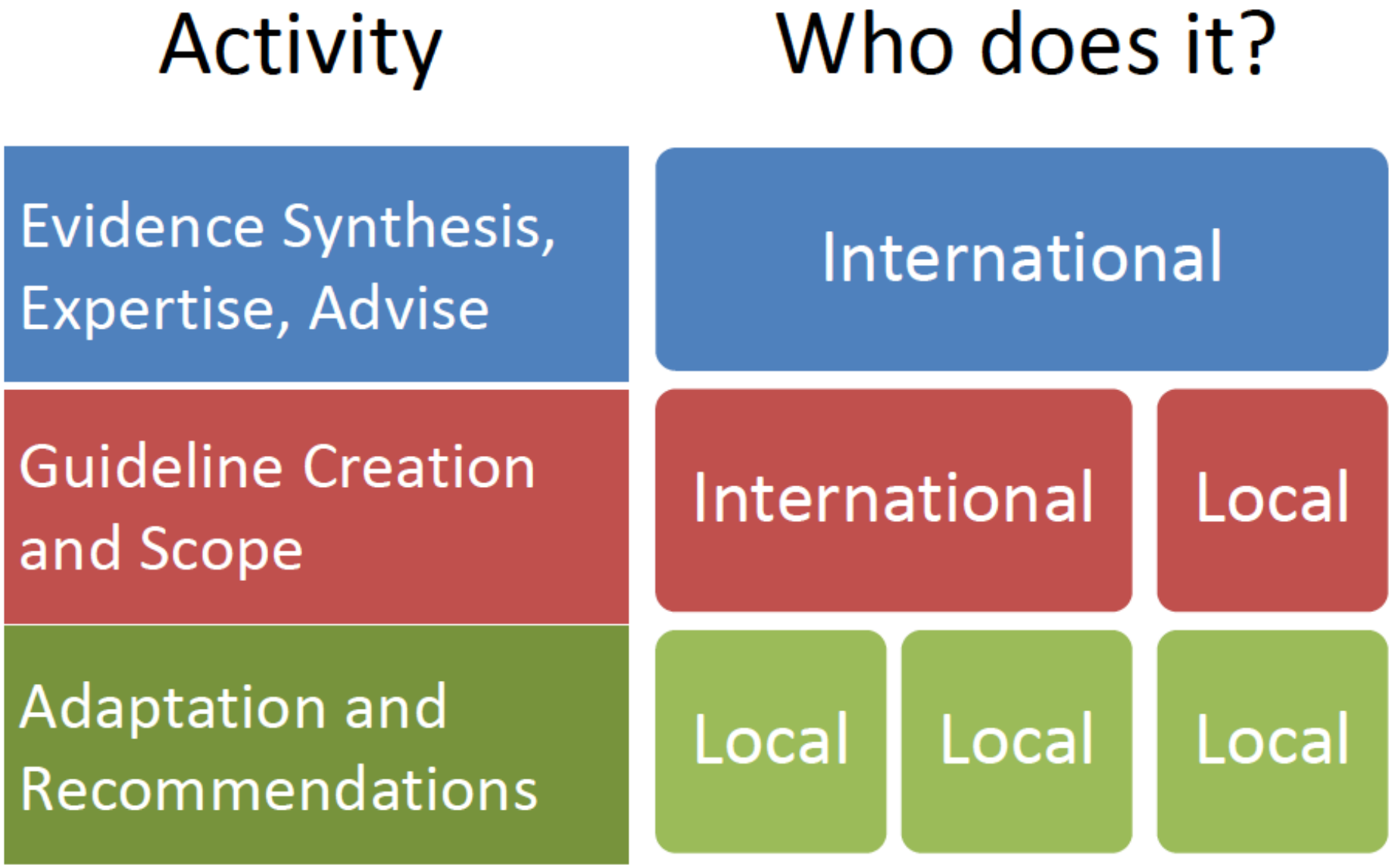
Getting to grips with GRADE—perspective from a low-income setting

Mike English[a,b,*] and **Newton Opiyo**[a]

[a]KEMRI/Wellcome Trust Research Programme, Nairobi 00100, Kenya

[b]Department of Paediatrics, John Radcliffe Hospital, University of Oxford, Oxford, UK

- Adapt guidelines as much as possible
- Share the evidence – create registers
- Incorporate lower quality evidence
- Build capacity locally
- Consider applicability at each country level


Activity
Who does it?
Evidence Synthesis, Expertise, Advise
International
Guideline Creation and Scope
International
Local
Adaptation and Recommendations
Local
Local
Local

Overall

- Most guidelines are not evidence based
- Few are relevant to RPC / clinical setting
- Most have never been read by the individuals they were devised for!!!!

Thank you

Acknowledgements

- Prof Helen Cross
- Pediatric Commission ILAE