PANDA Journal Club

Febrile Seizures *and other stories*

12th June 2024

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Declarations

- Advisory board for South African branches of Sanofi and Novartis

Definition and epidemiology - febrile seizures

A febrile seizure is generally accepted to be

- **a seizure accompanied by fever**
  - (temperature **more than 38°C** or 100.4°F by any method),
- **without central nervous system infection**,
- in infants and children aged **6 months up to 6 years**.

- Febrile seizures occur in **2% to 5%** of all children
  - the **most common convulsive event in children younger than 60 months**.

NICE, 2018

Definition- Simple febrile seizures

- Under 15 minutes (usually 1-2 minutes)
- Generalised tonic clonic convulsion
- Clear focus of infection
- 1 event isolated to illness

Practice parameter: the neurodiagnostic evaluation of the child with a first simple febrile seizure. American Academy of Pediatrics. Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. *Pediatrics.* 1996;97:769-775.

Complex febrile convulsion (CFS)

- Prolonged seizure
  - Focal, or generalized
  - Greater than 15 min duration
- Recurring more than once in 24 h,
- And/or associated with postictal neurologic abnormalities, (Todd's palsy)

American Academy of Pediatrics 1996;

Berg & Shinnar, 1996; Knudsen,2000

Capovilla et al Epilepsia 2009

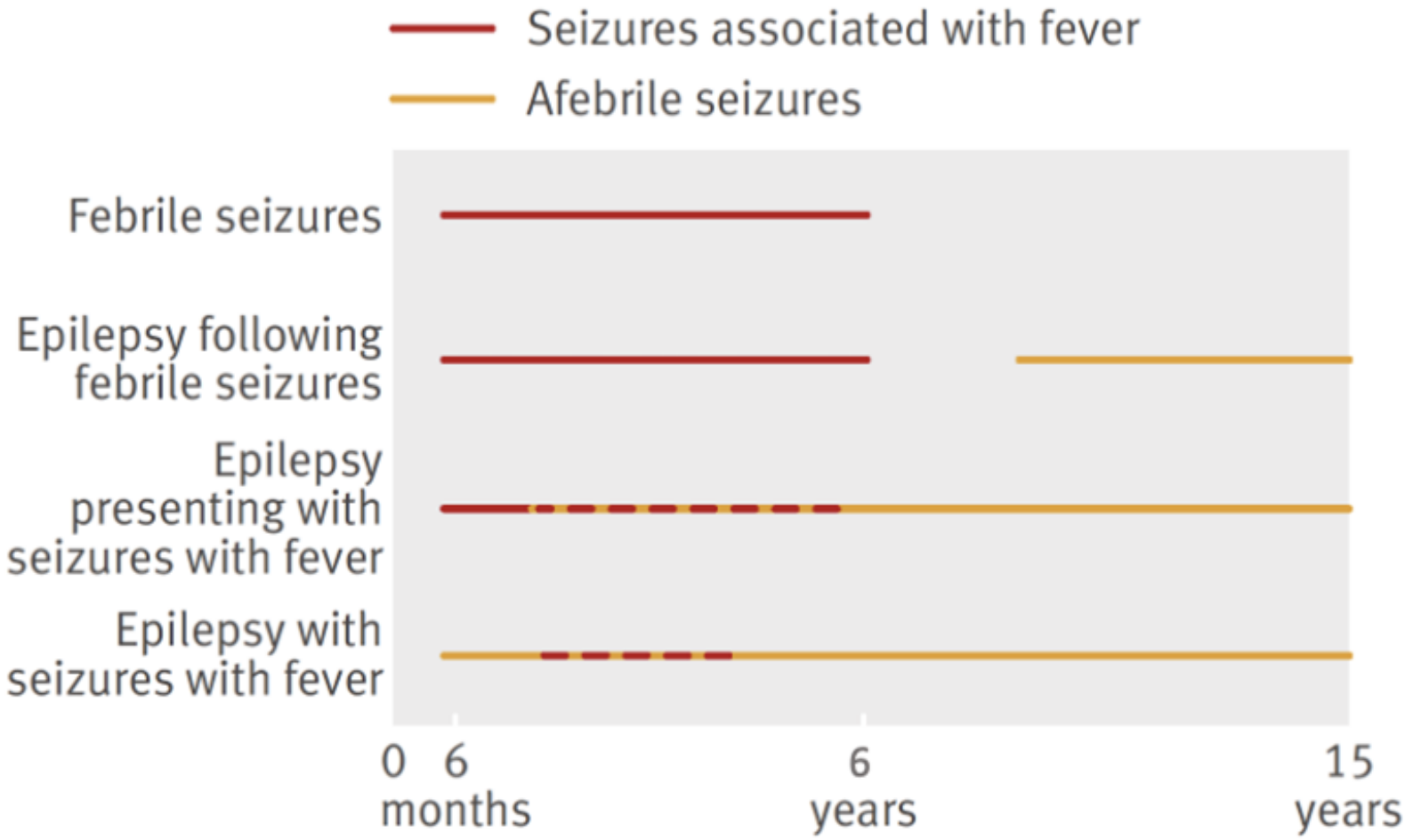
In comparison

Simple Febrile Seizures (70%)	Complex Febrile Seizures (30%)
GTCS AND	Focal features (16%) OR
<10 minutes in duration (USA <15 minutes) AND	**≥10 minutes in duration (8%)** **(USA ≥ 15 minutes)** OR
No recurrence within 24 hours or within same febrile illness	2 or more within 24 hours or within the same febrile illness (6%)

Management challenges

Recognise	Recognise underlying CNS infection requiring acute intervention •Meningitis (TBM, haemophilus), •encephalitis (herpes), •(ADEM) (post-infective)
Consider	Recognise epilepsy syndrome e.g. Dravet, GEFS+
Impact	Impact of recurrent or prolonged FS • Implications of possible development of hippocampal sclerosis

'Seizures with fever'
- illustrations of distinct scenarios over time



Sadleir L & Scheffer I. BMJ, 2007
Modified with authors' permission

Management options

Best care approaches

- Full history and examination
- Any concern of intracranial infection, or otherwise unwell **admit, investigate and treat appropriately**
- Only request laboratory investigations if indicated **for the fever** and other clinical features
- **Antipyretic** measures
  - (will not be protective against seizure recurrence)
- No EEG or neuroimaging is indicated for **simple febrile seizures**

American Academy of Pediatrics. Clinical Practice Guideline—Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure. PEDIATRICS Volume 127, Number 2, February 2011

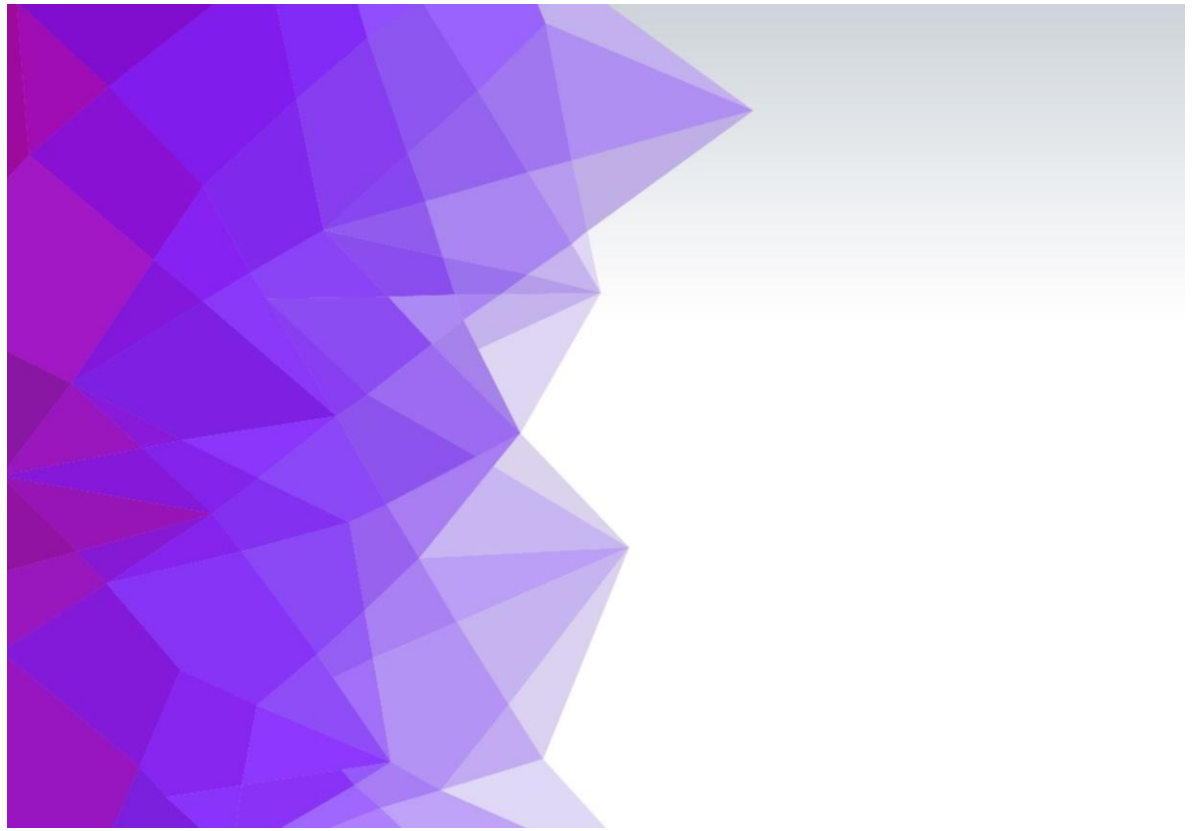
Consider Cerebrospinal fluid assessment.....

- where CNS infection cannot be excluded eg
  - Infant with unexplained fever
  - Meningeal symptoms
  - Preceding antibiotics

  NB check no contraindications

No LP if simple febrile seizure

(Febrile) Status Epilepticus



SPECIAL REPORT

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, 56(10):1515–1523, 2015
doi: 10.1111/epi.13121

- Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1).
- It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

Trinka et al 2015 Epilepsia

Time points t1 and t2.

- Length of the seizure and the time point (t1) beyond which the seizure should be regarded as “continuous seizure activity”
  - 5 minutes
- Second time point (t2) is the time of ongoing seizure activity after which there is risk of long-term consequences.
  - 30 minutes
- Time points are estimated based on incomplete animal experiments and clinical research.

Implications

- Most seizures will stop within 5 minutes
- The longer it takes to gain control the worse the outcome and the harder it will be to terminate Sz
- Outcome influenced by underlying aetiology – encephalitis worst result
- Mortality 2-4% (*even 22%)* cases

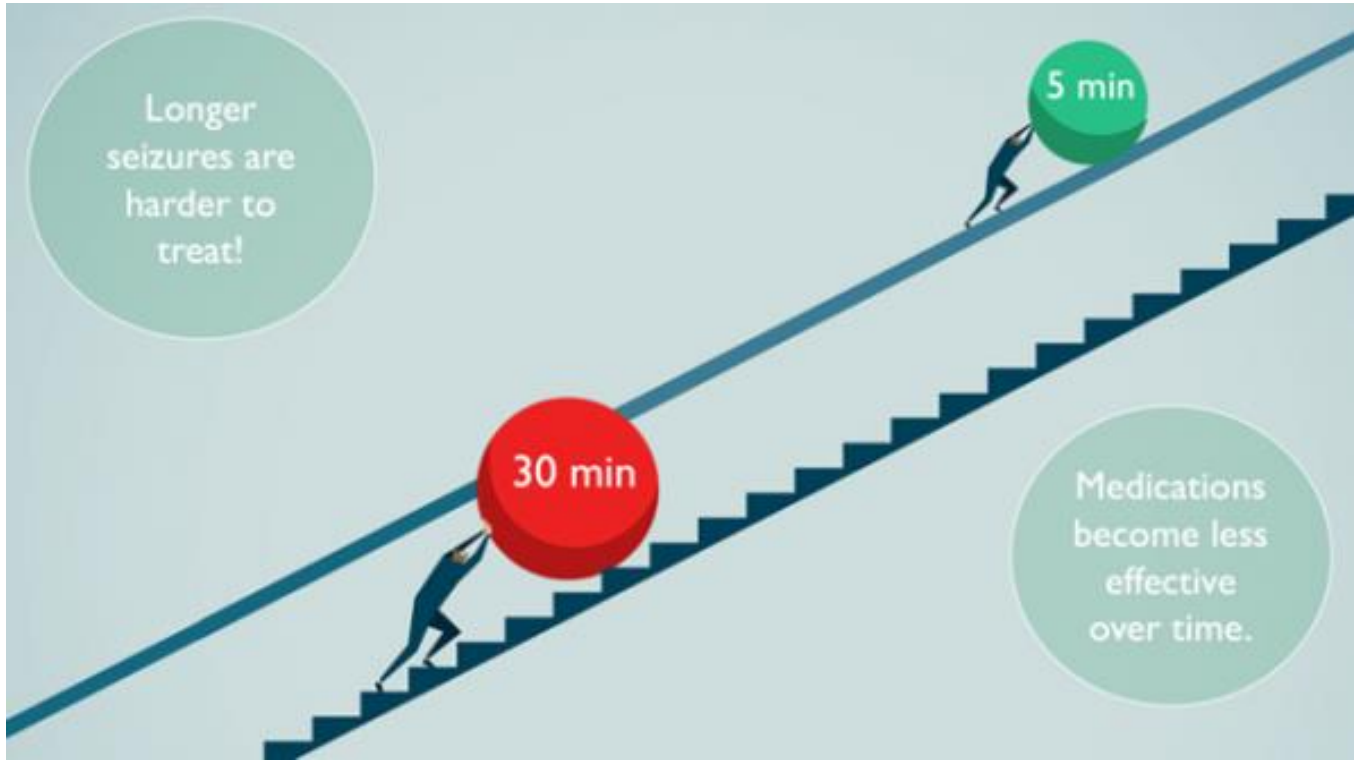
Scott et al, ARCH 1998

Holtkamp et al; JNNP 2005

Capovilla et al Epilepsia 2013;

Aguilar et al Semin Neurol 2020

Huang et al J Inflamm Res 2022.



Comparison LIC v HIC

	Low income countries	High income countries
Predominant aetiologies of CSE	Febrile seizures associated with • Resp Tract Inf, • Acute Gastro, • Infections • Eg Malaria	Epilepsy • breakthrough seizures, • low levels of ASMs

- Idro et al, The incidence,aetiology and outcome of acute seizures in children admitted to a rural Kenyan hospital
- Sanchez S,Status Epilepticus and Public Health needs. J Clin Med 2016

FEBSTAT STUDY TEAM

- Multi centre prospective study
- 5 recruiting sites
- Age 1month to 5 years
- Present with Febrile Status Epilepticus
- Relationship FSE and subsequent Hippocampal Sclerosis

Hesdorfer et al (and the Febstat team) Epilepsia 2012

- Abnormal CSF is never normal!
- FSE appears to be a combination of lower seizure threshold
  - younger age and lower temperatures
  - impaired regulation of seizure duration

Hesdorfer et al (and the Febstat team) J of Paediatrics 2013

WHAT EVIDENCE EXISTS FOR MANAGEMENT OF SE IN CHILDREN?

Level one

- Arrival – First Hospital intervention
- Benzodiazepine
  - IV lorazepam (Level 1B, Grade A)
    - Lower risk of respiratory depression
  - IV diazepam

  If No IV access
  - IM midazolam (Level 1B, Grade A)
  - Avoid > 2 total dose (including pre-hosp)

- Good specialist consistency, good study data
- Similar recommendations for adults *(Cruikshank et al J Neurol 2022)*

Scott et al;Lancet 1999; Jeannet et al;Europ J Paed Neurol 1999

DeNegri et al; Pediatr Drugs 2001;

Capovilla et al Epilepsia 2014; Welch et al Epilepsia 2015;

Lawton et al Curr Opin Pediatr 2018

Transmucosal pharmacological therapy is effective

- Intranasal midazolam as effective as intravenous diazepam
- Buccal midazolam as effective as rectal diazepam.
- Intravenous formulations of midazolam (given buccal or intranasal routes) are relatively inexpensive.
- Buccal midazolam compares favourably to intramuscular midazolam
- Caregivers prefer intranasal midazolam to rectal diazepam.

Appleton R et al Cochrane Database Syst Rev 2008 Jul 16;(3); Alansari et al Pediatr Neurol 2020; Yoshinga et al Epilepsy Research 2021

Level 2 intervention

Typical practice in many regions of the world (LIMCs)

- Phenytoin IV
  - over 20 mins, cardiac monitor, large vein, not mixed with glucose
- Phenobarbital IV/IM
  - Push, flush through, monitor for resp depression and hypotension
- Both agents fairly accepted
- BUT studies becoming more limited
  - small numbers
  - less children

Shanner et al;Neurol 1988

Prasad et al;Ann Neurol 2002

Burman et al Frontiers Neurol 2019

A comparison of parenteral phenobarbital versus parenteral phenytoin as second-line management for paediatric convulsive status epilepticus in a resource-limited setting

Richard J. Burman[1, 2], Sally Ackerman[1], Alexander Shapson-Coe[1], Alvin Ndondo[1], Heloise Buys[3, 1], Jo M. Wilmshurst[1*]

- Open label single centre randomised study
- 144 children 1mth–15yrs presenting with CSE
- 35% events required second line intervention - PB v PHT

- PB terminated the CSE faster and more effectively than PHT (RR0.03, p=0.0003)

Acute Medicine & Surgery 2022;9:e717 doi: 10.1002/ams2.717

Mini Review Article

Phenytoin versus other antiepileptic drugs as treatments for status epilepticus in adults: a systematic review and meta-analysis

Eisei Hoshiyama,[1,2] Junji Kumasawa,[3] Masatoshi Uchida,[1] Toru Hifumi,[4]

- 10 RCTs
- Intravenous PHT was found to be significantly inferior to other medications in terms of cessation of seizures
- No significant differences in mortality or neurological outcomes

But what about levetiracetam?

Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial

Lancet 2019; 393: 2125–34

Mark D Lyttle, Naomi E A Rainford, Carrol Gamble, Shrouk Messahel, Amy Humphreys, Helen Hickey, Kerry Woolfall, Louise Roper, Joanne Noblet, Elizabeth D Lee, Sarah Potter, Paul Tate, Anand Iyer, Vicki Evans, Richard E Appleton, with support of Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative*

Open label RCT 30 UK emergency deps

6mths - <18yrs CSE

LEV v PHT

Primary outcome time to cessation of sz

N=286 pts

Sz controlled 70% LEV group v 64% PHT (not significant)

Outcome similar efficacy but recommended LEV over PHT for safety profile and ease of admin

Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial

Stuart R Dalziel, Meredith L Borland, Jeremy Furyk, Megan Bonisch, Jocelyn Neutze, Susan Donath, Kate L Francis, Cynthia Sh
A Simon Harvey, Andrew Davidson, Simon Craig, Natalie Phillips, Shane George, Arjun Rao, Nicholas Cheng, Michael Zhang,
Christine Brabyn, Ed Oakley, Franz E Babl, on behalf of the PREDICT research network

Lancet 2019; 393: 2135–45

- Open-label, RCT, 13 centres, Australia and New Zealand
- Children 3mths-16yrs
- 233 children allocated PHT or LEV

- Concluded LEV was NOT superior to PHY for second line management of SE in children

Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial

Lancet 2020; 395: 1217–24

James M Chamberlain, Jaideep Kapur, Shlomo Shinnar, Jordan Elm, Maija Holsti, Lynn Babcock, Alex Rogers, William Barsan, James Cloyd, Daniel Lowenstein, Thomas P Bleck, Robin Conwit, Caitlyn Meinzer, Hannah Cock, Nathan B Fountain, Ellen Underwood, Jason T Connor, Robert Silbergleit, for the Neurological Emergencies Treatment Trials* and the Pediatric Emergency Care Applied Research Network investigators†

- USA adults and children, 58 emergency centres
- Double-blind, response-adaptive, RCT
- >2 yrs of age – allocated LEV v FOS v VPA
- 225 children recruited (< 18 yrs)
- Efficacy in about 50% of cases.

- Found similar efficacy for all 3 agents and across all ages.

Original Article
Journal of Epilepsy Research
pISSN 2233-6249 / eISSN 2233-6257

Comparative Efficacy of IV Phenytoin, IV Valproate, and IV Levetiracetam in Childhood Status Epilepticus

Mudasir Nazir, MD[1], Rayees Ahmad Tarray, DM[2], Ravouf Asimi, DM[2], Wajid Ali Syed, MD[2]

Departments of [1]Paediatrics and [2]Neurology, SKIMS, Srinagar, India

(2020;10:69-73)

- RCT n= 150 3 equal groups – PHY / VPA / LEV
- LEV and VPA – safe and effective
- No statistical difference in sz recurrence for the 3 agents

- Time to regain consciousness and sz recurrence at 3 mths
  - significantly less effective for in VPA group.

EPILEPSY CURRENTS

Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

American Epilepsy Society Guideline

Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society

- In children IV lorazepam / IV diazepam effect at stopping sz at 5 or more minutes (Level A)
  - Rectal diazepam, IM midazolam, IN midazolam probably effective (Level B)
- Second therapy appears less effective and no data about third therapy efficacy (Level C)

Level 3 intervention

- Basically heading into refractory status
- Disastrous situation
- Resistant seizures –
  - prob exacerbated by underlying cause (eg encephalitis),
  - secondary complications from drugs
    - hypotension,
    - respiratory depression
  - all affecting brain perfusion

Sahin et al;Neurol 2003

Scott et al, ARCH 1998

Holtkamp et al; JNNP 2005

Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee

Epilepsy Currents
2020, Vol. 20(5) 245-264

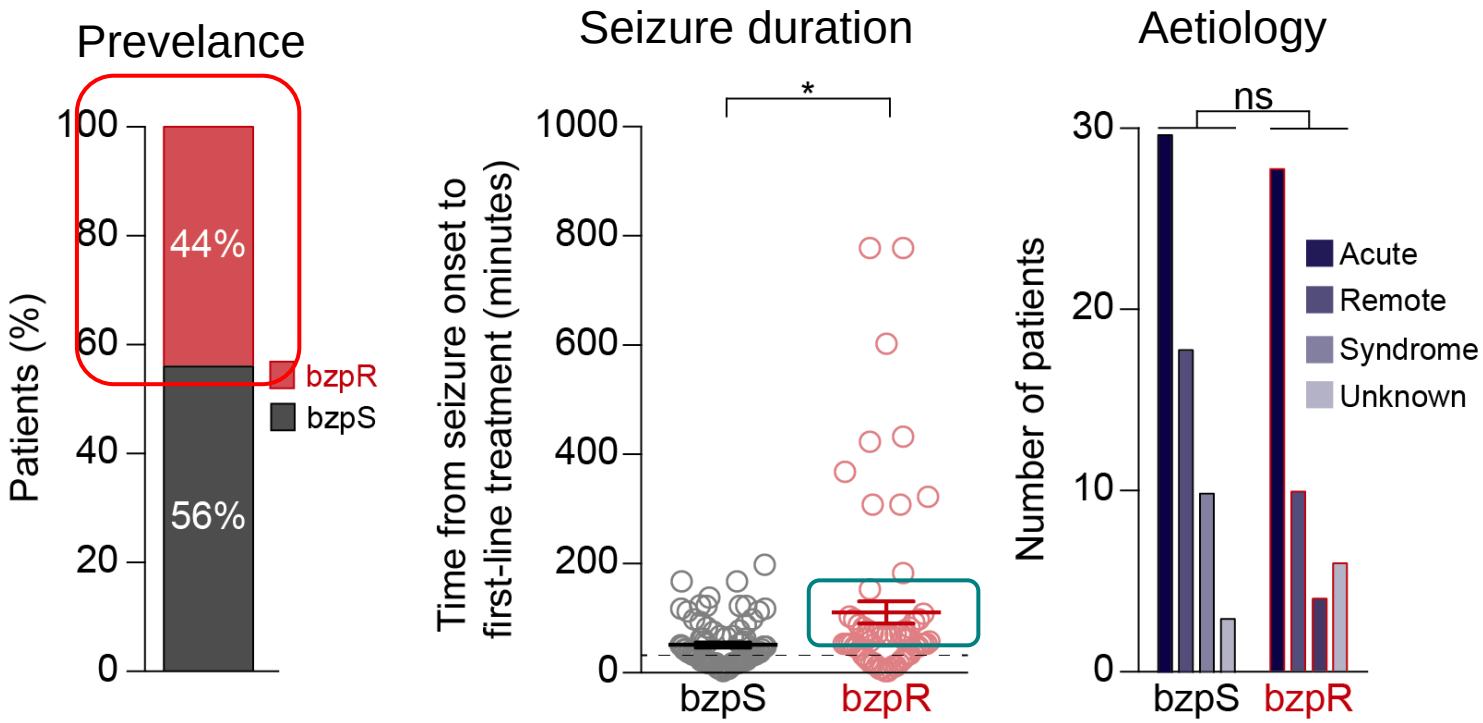
DOI: 10.1177/1535759720928269
journals.sagepub.com/home/epi
SAGE

Conclusions

- Mostly insufficient evidence on the efficacy of stopping RCRSE using brivacetam, lacosamide, LEV, VPA, ketamine, MDZ, PTB, and PTO either as the last ASM or compared to others of these drugs.
  - ACTH, IVIG, corticosteroids and pyridoxine used in special situations but not studied for CRSE.
- For established convulsive SE (ie not RSE) LEV, VPA and fosphenytoin may be equally effective, but not known if also true for RCSE.
- *Triple-masked, RCTs are needed to compare the efficacy of parenteral anasethetizing and nonanaethestizing ASMs in the treatment of CRSE.*

Benzodiazepine resistance

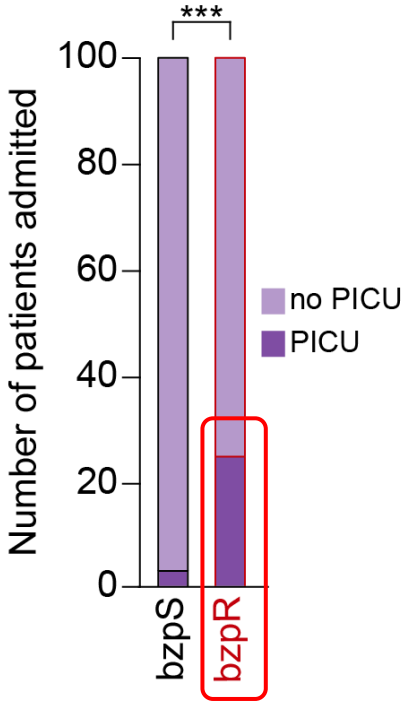
Resistance to **1st line benzodiazepines** is **prevalent** problem



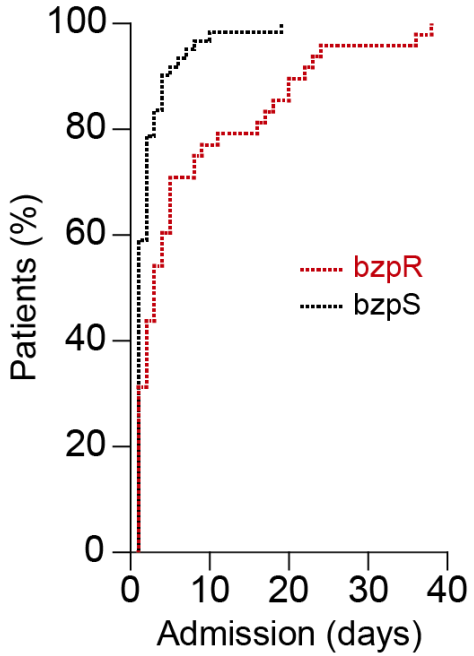
Burman et al Brain 2019

Resistance to **1st line benzodiazepines** is **prevalent** problem

PICU admission



Admission duration



Burman et al Brain 2019

DOI: 10.1111/epi.16825

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Epilepsia, 2021;62:2795–806.

Patterns of benzodiazepine underdosing in the Established Status Epilepticus Treatment Trial

Abhishek G. Sathe[1] | Ellen Underwood[2] | Lisa D. Coles[1] | Jordan J. Elm[2] | Robert Silbergleit[3] | James M. Chamberlain[4] | Jaideep Kapur[5] | Hannah R. Cock[6] | Nathan B. Fountain[7] | Shlomo Shinnar[8] | Daniel H. Lowenstein[9] | Eric S. Rosenthal[10] | Robin A. Conwit[11] | Thomas P. Bleck[12] | James C. Cloyd[1]

- Established Status Epilepticus Treatment Trial (ESETT)
- US based multicentre study
- N=460 pts given 1170 doses of benzos
- First dose of benzo lower than guideline recommendation in 76% midazolam and 81% lorazepam administrations
- Similar issues with subsequent dose

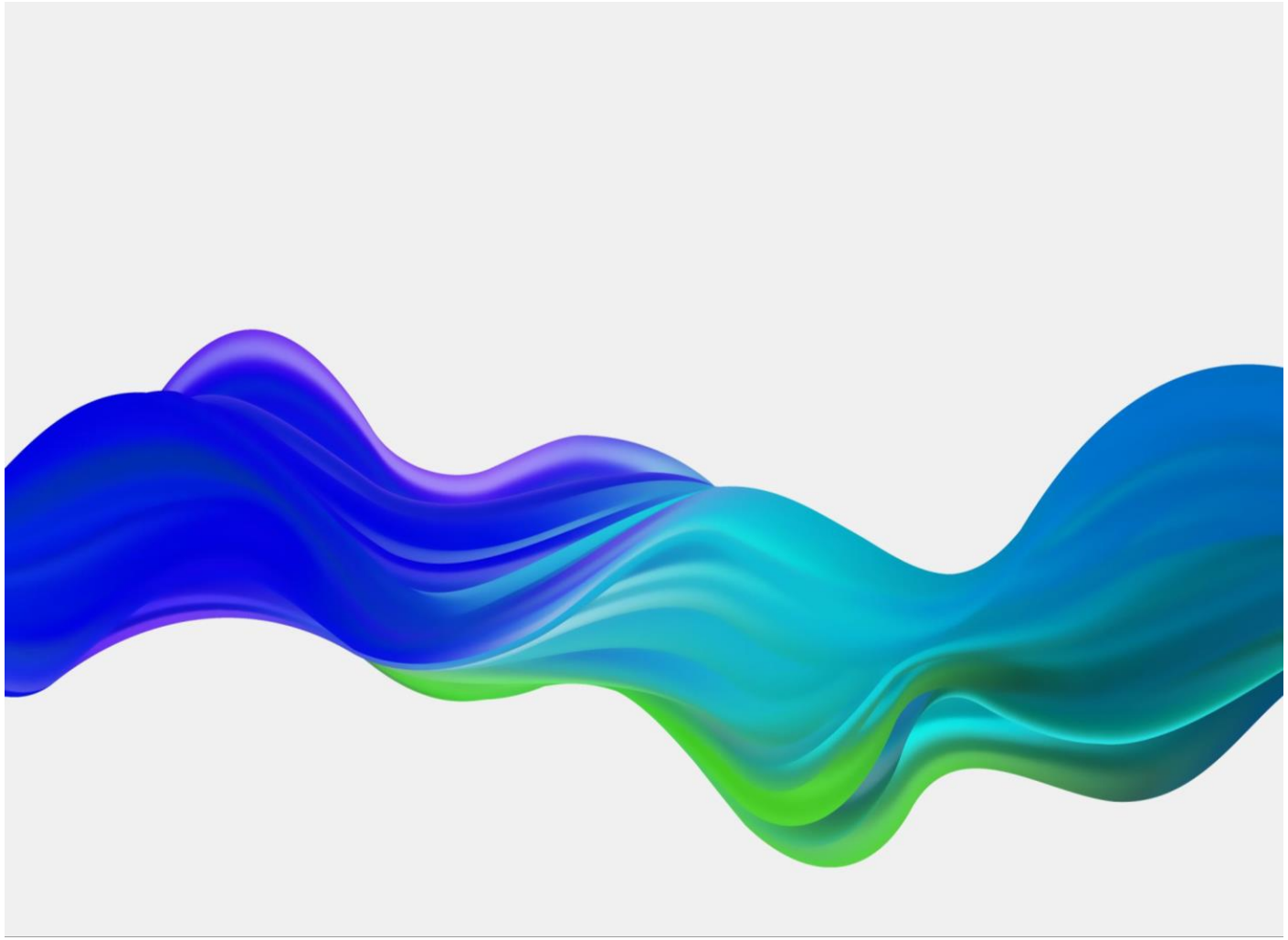
Post event management approaches for Febrile Seizures

Indications for longer period of observation or admission

- Age <18 months
- Complex febrile seizure
- No identified focus of infection
- Currently or recently taking antibiotics
- High parental or carer anxiety

NICE 2013/2018

Counsel families / carers



Febrile seizure recurrence risk

The general risk of FS recurrence
30–40%

- Main risk factor is **age of febrile seizure**

<12 months	50% will have another febrile seizure
>3 years	20% will have another febrile seizure

- Complex features is **not** a risk factor

Knudsen FU. Febrile seizure: treatment and prognosis. Epilepsia 2000; 41:2–9

Febrile seizures: risk of recurrence

Other risk factors include:

- Family history of febrile seizures (first degree relative)
- Previous history of febrile seizures
- Temperature (<40°C/104°F) at time of seizure
- Short duration between onset of fever and seizures (<1hr)

More risk factors = more risk of recurrence

- No risk factors recurrence risk is 4%
- All risk factors recurrence risk is 76%

Berg et al, Arch Pediatr Adolesc Med, 1997
Blyth et al. BMC Peds, 2016
review in Sawires, Buttery and Fahey Frontiers in Pediatrics, 2022

What about when there are recurrent febrile seizures?

Recurrent febrile seizures

The events result in caregiver distress and frequent demand for intervention

When events are recurrent the management becomes more contentious

The role for ASMs is debated.

There is a lack of consistency in the recommendations of existing guidelines

Japanese guidelines – updated 2017

- Prophylactic DZP is not routinely needed in children with a history of FS (Grade C).

But prophylactic DZP can be used with the following criteria (Grade B):

- history of a prolonged febrile seizure lasting 15 minutes or longer,
- repeated FS,

and two of the following risk factors;

  - focal or repeated seizures within 24 hours,
  - preexisting neurological abnormality or developmental delay,
  - family history of FS or epilepsy,
  - aged younger than 12 months,
  - seizure within 1 hour after onset of fever,
  - or seizure occurring with body temperature less than 38 C.

- *When these criteria are present in most cases the child would not be considered to meet the definition of simple FS.*

Japanese guidelines – updated 2017

Regular use of ASMs is not recommended in children with a history of FS. (Grade C)

But in children with prolonged or repeated FS despite the use of prophylactic diazepam, regular use of ASMs can be considered. (Grade B).

Cochrane review (2017)

- 40 articles / 30 randomised trials / 4256 randomised participants
  - 13 on interventions of continuous or intermittent prophylaxis
- **Limitations in the methodologies for most studies resulted in moderate to poor quality data.**
- Found **no significant benefit** with interventions of
  - **intermittent** phenobarbital, phenytoin, valproate, pyridoxine, ibuprofen or zinc sulfate versus placebo or no treatment;

  Or
  - when initiated at the start of subsequent febrile illnesses in children with a history of febrile seizure

Cochrane review 2017

- No significant benefit for
  - continuous phenobarbital vs diazepam,

- **A significant reduction of recurrent febrile seizures with intermittent diazepam versus placebo or no treatment,**
  - **up to 60 months of age**

- Phenobarbital versus placebo or no treatment, reduced seizures at 6, 12 and 24 months but not at 18 or 72 month follow-up

Cochrane review 2017 – **Adverse events**

- The documentation of adverse effects was variable.
- Lower comprehension scores in phenobarbital-treated children were found in two studies
- Adverse effects were recorded
  - in up to **30%** of children in the **phenobarbital**-treated group
  - in up to **36%** in **benzodiazepine**-treated groups
- Most of the reviewed ASM trials were found to be of a methodological quality graded as low or very low

Cochrane follow up study 2021

- Reduced recurrence rates for intermittent diazepam and continuous phenobarbital,
  - with adverse effects in up to 30% of children.
- The apparent benefit for clobazam treatment in one trial needs to be replicated.
- Levetiracetam also shows benefit with a good safety profile; however, further study is required.
- Parents and families should be supported with
  - adequate contact details of medical services
  - information on recurrence,
  - first aid management,
  - most importantly, the benign nature of the phenomenon.

Is there a place for prophylaxis with antiseizure medications (ASMs)?

Regular or intermittent ASM are not recommended

- Simple febrile seizures themselves are not harmful
- There is a high risk of adverse effects from ASMs
- There is risk of masking of potential informative clinical features

AOCN 2017, WHO & Cochrane epilepsy group, 2021

Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. Strengell T, *et al.* 2009 Arch Pediatr Adolesc Med

- **231 children with first FS 1997-2003, Oulu, Finland**
- All febrile episodes were treated first with either rectal diclofenac or placebo. After 8 hours, treatment was continued with oral ibuprofen, acetaminophen, or placebo.
- FS recurrence
  - 23.4% (46 of 197) antipyretic group
  - 23.5% (8 of 34) placebo
  - (difference, 0.2; 95% confidence interval, −12.8 to 17.6; *P*=.99)
- Antipyretic agents are ineffective for the prevention of recurrences of Febrile Seizures and for the lowering of body temperature in patients with recurrent FS.

Preventative interventions

There is no evidence to support that acute interventions prevent subsequent development of epilepsy

Baumann & Duffner, 2000; Knudsen, 2000.

Baumann RJ, Duffner PK. Treatment of children with simple febrile seizures: the AAP practice parameter. Pediatr Neurol 2000; 23:11–17.

What is the risk of developing epilepsy?

- The vast majority of febrile seizures are not associated with the development of epilepsy

- 3% develop epilepsy by 7 years of age
- 7% develop epilepsy by 23 years follow up
- Risk factors:
  - Prior abnormal neurological status
  - History of afebrile seizures in a first degree relative
  - Complex febrile seizure
- Risk factors are cumulative:
  - 0 risk factor 1%
  - 1 risk factor 2%
  - 2 or more risk factors 10%

Nelson & Ellenberg, Paediatrics, 1978

Vestergaard, Pedersen, Sidenius, Olsen, and Christensen 2007

Useful discharge advice

What advice would you give parents prior to discharge?

- Seizure first aid advice
- Antipyretic advice (although will not influence likelihood of further seizures in another illness)
  - Avoid fans and cold baths
- Offer rescue medication if febrile seizure was prolonged (rescue medication if ≥ 5minutes)
- Immunisation in line with the local schedule

Craiu D, et al. Vaccination and childhood epilepsies. EPNJ, 2022

Who needs Paediatric follow-up?

- >3 febrile seizures in separate illnesses
- Children <6 months or >6 years
- Febrile status epilepticus
- Febrile seizures with focal features
- Febrile seizures that are not tonic-clonic
- *New Zealand Epilepsy: guidelines & pathways for children and Young People, 2023*

Overall: 4 management priorities

1) terminating the seizure
2) excluding critical differential diagnoses
3) investigating fever aetiology
4) providing adequate counselling to families.

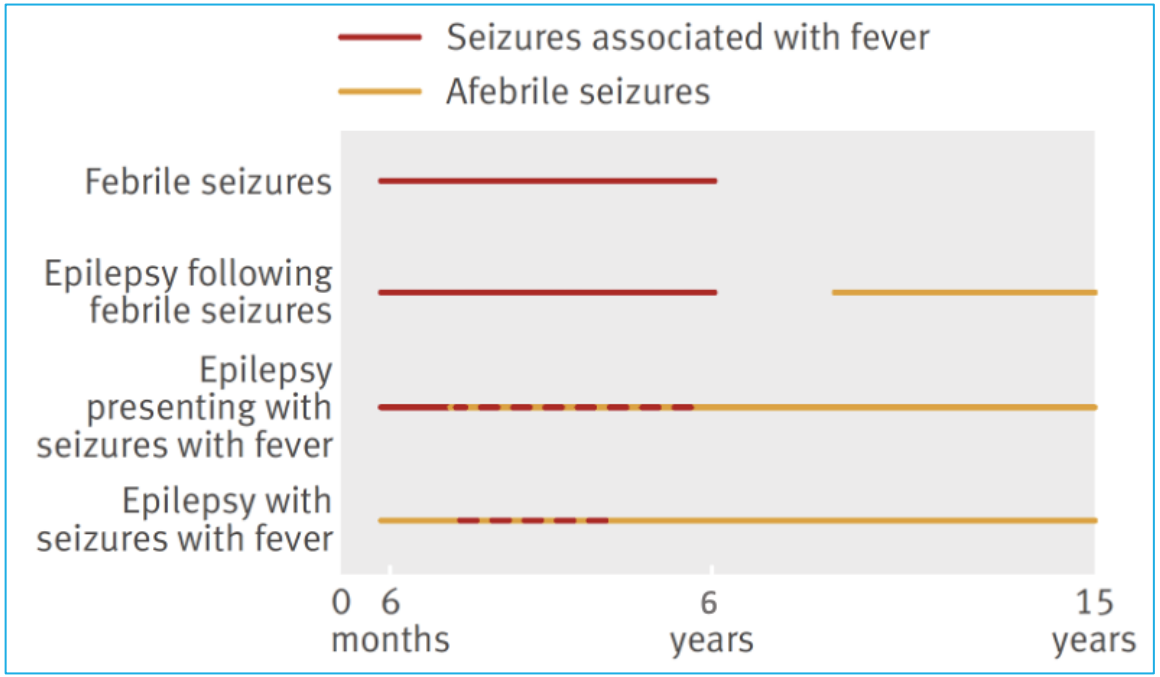
The clinical approach and prognosis of febrile seizure according to subtype.

i.e. complex or febrile status epilepticus require closer care than the vast majority of children with simple febrile seizures, who have excellent outcomes.

Leung J. Febrile Seizures: An Updated Narrative Review for Pediatric Ambulatory Care Providers. Curr Pediatr Rev. 2024;20(1):43-58.

Conclusions

- Febrile seizures are the most common convulsive event in children younger than 60 months.
- SFS have no long-term impact on the child
- Most children will not have recurrent febrile seizures (ie >3)
- Most children do not develop epilepsy
  - (although the risk of epilepsy is **slightly** increased)
- ASM prophylaxis is **not** required unless a diagnosis of epilepsy is established
- Rescue medication should be provided for children with prolonged febrile seizures



Thank you

Any questions??