What Can We do to Extinguish FIRES?
Febrile Infection-Related Epilepsy Syndrome

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Pharmacy Grand Rounds
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Objectives

• Describe etiology, presentation, and disease course of febrile infection-related epilepsy syndrome (FIRES)

• Identify treatment options available for FIRES

• Review the ketogenic diet and its utilization in refractory epilepsy
Q1-True/False: FIRES commonly affects children with an underlying neurological condition or a family history of seizures.

- A. True
- B. False
FIRES: Definition

- Rare, severe seizure disorder
- Develops in previously healthy children after a fever
- Very sudden onset of nearly continuous seizures
  - Leading to:
    - Refractory epilepsy
    - Irreversible neurological damage/impairment
- Overlapping signs and symptoms of other causes of encephalopathy and seizures
  - Status epilepticus (SE): most common neurologic emergency in children

FIRES A.K.A.

- Acute encephalitis with refractory, repetitive partial seizures (AERRPS)
- Severe refractory status epilepticus due to presumed encephalitis
- Idiopathic catastrophic epileptic encephalopathy
- New-onset refractory status epilepticus (NORSE)
- Devastating epileptic encephalopathy in school aged children (DESC)

Ismail FY, Kossoff EH. Epilepsia. 2011; 52(11):e185-e189
FIRES: Etiology

- Immunologic source
- Genetic predisposition/metabolic glitch
- Inflammation-mediated process

Ismail FY, Kossoff EH. Epilepsia. 2011; 52(11):e185-e189
Cherian PJ, Nickels, KC. Journal of Pediatric Epilepsy; 2014;3:67-74
FIRES: Epidemiology

- FIRES annual incidence: 1/1,000,000
- FIRES prevalence: 1/100,000
- Encountered in both adults and children
  - More frequent in children
  - 3-15 years old

FIRES: Disease Course

Initial  Acute  Chronic

Phase 1  Phase 2

## Initial Phase Presentation

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Year</th>
<th>Preceding illness</th>
<th># of Days*</th>
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<td>India (15)</td>
<td>2016</td>
<td>Nonspecific respiratory infection (12), acute diarrheal disease (2), fever with nonspecific lymphadenopathy (1)</td>
<td>1-12 (4)</td>
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<td>2013</td>
<td>Upper respiratory tract infection (9) and gastroenteritis (3)</td>
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<tr>
<td>Australia (7)</td>
<td>2012</td>
<td>All: Fever, headache, confusion, lethargy Variable: upper respiratory tract infection and myalgias</td>
<td>3-6</td>
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<tr>
<td>I/I/F/G/T/A USA (77)</td>
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<td>Upper respiratory tract infections, gastroenteritis</td>
<td>1-14 (4)</td>
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<tr>
<td>Germany (22)</td>
<td>2010</td>
<td>Respiratory or nonspecific infections</td>
<td>2-14 (5)</td>
</tr>
<tr>
<td>France (9)</td>
<td>2010</td>
<td>Pharyngitis, influenza, gastroenteritis, vaccination administration</td>
<td>1-6 (4)</td>
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</tbody>
</table>

*Study location: (__) = number of patients
Presentation (___) = number of patients
*# of days between febrile illness and onset of seizure

CASE: Initial Presentation, AH

- 2 year old female
- Generally healthy
  - Normal development
  - Normal birth, without complications
- Presented after having two seizures
- Mother reported:
  - 5 days ago she developed a fever to 102°F
  - 4 days ago she was seen in OSH ED and diagnosed with acute otitis media
Mayo Clinic Guidelines for the Management of Pediatric Status Epilepticus (1 month – 18 years)

Step 1: ABCs, vitals, labs, line, abx/cx, airway

2: Lorazepam or midazolam

3: Repeat

4: Levetiracetam or fosphenytoin

5: Levetiracetam/fosphenytoin OR Valproic acid/phenobarbital

6: Midazolam load + infusion

7: Midazolam bolus and increase infusion

8: Pentobarbital bolus + infusion OR isoflurane

**Alternative: lacosamide**

Authors: E. Payne, MD; T. Hellmich, MD; M. Mannenbach, MD; R. Kahoud, MD; K. Bjur, MD; G. Arteaga, MD; O. Olson, PharmD; K. Graner, RPh; E. Wirrell, MD.~Jan 2016.
## Initial Treatment

<table>
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<td>Abx/AV</td>
<td>Benzo(s) Initial AED</td>
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<tr>
<td>India</td>
<td>Yes Yes Phenytoin→Phenobarbitone</td>
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<tr>
<td>Argentina</td>
<td>Yes Yes Phenytoin→phenobarbital, levetiracetam, valproic acid</td>
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<tr>
<td>Australia</td>
<td>Yes Yes N/A</td>
</tr>
<tr>
<td>I/I/F/G/T/A/USA</td>
<td>N/A Yes N/A</td>
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<tr>
<td>Germany</td>
<td>N/A Yes N/A</td>
</tr>
<tr>
<td>France</td>
<td>N/A Yes Phenytoin</td>
</tr>
</tbody>
</table>

CASE: Initial treatment, AH

- Ativan 0.1mg/kg x2 → + succinylcholine → intubation
- Fosphenytoin 20 PE units/kg
- Vancomycin, ampicillin, and ceftriaxone
- Propofol bolus + infusion
- Versed IV push 0.2mg/kg and improved
- Dispo: PICU
Treatment Options

- **Antiepileptic drugs**
- **Burst suppression coma**
- **Intravenous immunoglobulin**
- **Anakinra (Kineret ®)**
- **Ketogenic diet**
- Steroids
- Cannabinoids
- Ketamine
- Rituximab
- Vagal Nerve Stimulation
- Plasmapheresis
- ……many more

Cherian PJ, Nickels, KC. Journal of Pediatric Epilepsy; 2014;3:67-74
### AED Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Range</th>
<th>PHY</th>
<th>PHB</th>
<th>SV</th>
<th>LVT</th>
<th>TOP</th>
<th>BNZ</th>
<th>CZP</th>
<th>LTG</th>
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<td>14</td>
<td>12</td>
<td>12</td>
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<td>12</td>
<td>6</td>
<td>12</td>
<td>5</td>
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<td>Australia</td>
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<td>2</td>
<td>4</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
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<td>3-15 (5)</td>
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<td>15</td>
<td>7</td>
<td>5</td>
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<td>4</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>8</td>
<td>1</td>
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</table>

PHY=phenytoin  PHB=phenobarbitone  SV=sodium valproate  LVT=levetiracetam  TOP=topiramate  BNZ=benzo  CZP=carbamazepine  LTG=lamotrigine

Treatment Options

• Antiepileptic drugs
• Burst suppression coma
• Intravenous immunoglobulin
• Anakinra
• Ketogenic diet

# Burst Suppression Coma

<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>Drugs Used</th>
<th>Duration</th>
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<tbody>
<tr>
<td>India</td>
<td>8/15</td>
<td>Phenobarbitone Thiopentone</td>
<td>2-90 days Median: 3 days</td>
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<tr>
<td>Argentina</td>
<td>8/12</td>
<td>Phenobarbital</td>
<td>N/A</td>
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<tr>
<td>Australia</td>
<td>Only barbiturates stopped clinical seizures</td>
<td></td>
<td></td>
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<tr>
<td>I/I/F/G/T/A/USA</td>
<td>46/77</td>
<td>Phenobarbital Pentothal</td>
<td>1.5 – 49 days Mean: 14.3 Median: 7</td>
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<tr>
<td>Germany</td>
<td>14/22</td>
<td>Barbiturates</td>
<td>1-42 days</td>
</tr>
<tr>
<td>France</td>
<td>6/9</td>
<td>Pentothal</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Majority of patients resume seizure activity following its cessation
- Standard care in severe refractory status epilepticus
- Efficacy and safety questionable

Treatment Options

• Antiepileptic drugs
• Burst suppression coma
• Intravenous immunoglobulin
• Anakinra
• Ketogenic diet

Cherian PJ, Nickels, KC. Journal of Pediatric Epilepsy; 2014;3:67-74
### IVIG

<table>
<thead>
<tr>
<th>Study</th>
<th># of patients</th>
<th>Successful?</th>
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<td>India</td>
<td>6/15?</td>
<td>Limited success</td>
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<tr>
<td>Argentina</td>
<td>10/12</td>
<td>1 patient: seizure ↓ 50%</td>
</tr>
<tr>
<td>Australia</td>
<td>2/7</td>
<td>No improvement</td>
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<tr>
<td>I/I/F/G/T/A/USA</td>
<td>30/77</td>
<td>2 patients: seizure ↓ 75%</td>
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<tr>
<td>Germany</td>
<td>6/22</td>
<td>?</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td>Not discussed</td>
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</table>

Treatment Options

- Antiepileptic drugs
- Burst suppression coma
- Intravenous immunoglobulin
- Anakinra
- Ketogenic diet

Cherian PJ, Nickels, KC. Journal of Pediatric Epilepsy; 2014;3:67-74
Anakinra

- Recombinant version of the human interleukin-1 (IL-1) receptor antagonist
- As a selective antagonist of IL-1 receptor type 1 (IL-1R1), it inhibits the biological actions of IL-1β and IL-1α
Anakinra

• **Use**
  - Neonates & Children: Approved for treating auto-inflammatory disorders
  - Animal models: powerful anticonvulsant properties
• **Dose range**: 1-10mg/kg/day (100mg/day max)
• **Side effects**: skin rash, N/V/D, fever, infection, injection site reaction, eosinophilia; RARE: metastases, opportunistic infection
• **Monitoring**: CBC, TB & HBV screening, s/sx infection or malignancy, LFTs, periodic skin examination
• **Route of Administration**: IV or SQ
• **Cost**: 100mg/0.67mL = $158.41

Treatment Options

- Antiepileptic drugs
- Burst suppression coma
- Intravenous immunoglobulin
- Anakinra
- **Ketogenic diet**

Cherian PJ, Nickels, KC. Journal of Pediatric Epilepsy; 2014;3:67-74
Ketogenic Diet History

1st modern use of starvation

1911
Dr. Wilder at Mayo Clinic coins Ketogenic Diet term

1921

1938
Merritt and Putnam discovered diphenylhydantoin

1990

Present

The Charlie Foundation = KD Re-surge

Wheless, JW. Epilepsia. 2008; 49(Suppl. 8):3-5
Ketogenic Diet (KD): what is it?

- ↑↑↑↑ fat, adequate protein, ↓↓↓↓ carbohydrate
- Changes the way energy is used in the body
- Elevated level of ketone bodies in the blood
  - Reduction in the occurrence of seizures
- Goal → 4:1 ratio
  - 4 times more fat than protein + carbohydrate
- Monitor: ketone bodies in the urine

Cherian PJ, Nickels, KC. Journal of Pediatric Epilepsy; 2014;3:67-74
### Ketogenic Diet Trial

<table>
<thead>
<tr>
<th>Study</th>
<th># of pts</th>
<th>Successful?</th>
</tr>
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<tbody>
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<td>India</td>
<td>2/15</td>
<td>“minimal response”</td>
</tr>
<tr>
<td>Argentina</td>
<td>2/12</td>
<td>1-good and sustained response with 50-75% decrease in seizures, 1-&lt;50%</td>
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<td>4/77</td>
<td>1-showed immediate and sustained effect</td>
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<td>France</td>
<td>9/9</td>
<td>7-efficient within 4-6 days</td>
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</table>

- Side effects: nephrolithiasis, hypoglycemia, N/V, constipation, GERD, poor growth, hyperlipidemia
- Contraindications: metabolic disorders, defects in fatty acid oxidation, hyperlipidemia, and renal stones

Ketogenic Diet Considerations

• Challenge:
  • Occult carbohydrates in concurrently administered medications
  • Stay at <1 gram for ALL medications/day
• Use an IV med as PO
• Switch to a carb-free medication
• Toothpaste, chap stick, lotion must be carbohydrate free

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name, if branded product</th>
<th>Strength</th>
<th>Manufacturer</th>
<th>Quantity</th>
<th>Total CHO content (mg)</th>
<th>Last update</th>
<th>Contact info</th>
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<td>Tegretol</td>
<td>100 mg</td>
<td>Novartis</td>
<td>1 chew</td>
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<td>Novartis</td>
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<td>1/mL</td>
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<td>&lt;30</td>
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<td>Carbamazepine</td>
<td>Onfi</td>
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<td>Novartis</td>
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<td>1998</td>
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<td>1/2006</td>
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</tbody>
</table>
Examples of Ketogenic Recipes

Includes: butter, cheese, whipping cream, mayonnaise, meat, poultry, fish, and non-starchy vegetables

• **McCafe® Shamrock Shake**
  - Vanilla reduced-fat ice cream
  - Shamrock Shake syrup
  - Whipped topping
  - Maraschino cherry
  - Green sugar crystals

• **Shamrock Smoothie**
  - 1 Hass avocado
  - 1/2 cup coconut milk, full fat, unsweetened
  - 10 mint leaves
  - 1 heaping teaspoon cacao nibs
  - Sweetener of choice
  - 1 cup crushed ice
  - Optional: a few drops of mint extract if desired

https://www.charliefoundation.org/explore-ketogenic-diet/explore-1/introducing-the-diet
Question 2: The goal of a ketogenic diet is to promote ketogenesis in order to stimulate mitochondrial biogenesis and ultimately to stabilize synaptic function. This is best achieved by:

- A. Increase carbohydrate, decrease fat (4:1 ratio)
- B. Increase fat, decrease carbohydrate (4:1 ratio)
- C. Increase carbohydrate, decrease fat and protein intake (4:1 ratio)
- D. Increase fat, decrease carbohydrate and maintain adequate protein intake (4:1 ratio)
Question #3: Which of the following formulations would be best for a patient on the ketogenic diet?

• A. Acetaminophen chewable
• B. Acetaminophen gel caps
• C. Acetaminophen suspension
• D. Acetaminophen suppository
Answers with carb count

- A. Acetaminophen chewable = 220-370 mg
- B. Acetaminophen gel caps = <50 mg
- C. Acetaminophen suspension = 2350-4800 mg
- D. Acetaminophen suppository = 0 mg
Q4: Anakinra’s mechanism of action is?

- A. IL-1 receptor agonist
- B. IL-6 receptor agonist
- C. IL-1 receptor antagonist
- D. Anti-viral
FIRES: Outcomes

- Poor
  - Rare: full recovery
  - Intellectual disability ~66-100% of survivors
  - Death
    - Up to 30%
- Risk Factors
  - Younger age at onset
  - Higher doses and duration of BSC

Anakinra: Case Report

Day 1-6
- Midazolam, phenobarbital, lacosamide, methylprednisolone
- Average seizures day: 5.8
- Maximum hourly seizure burden: 10 min/hr

Day 6-23
- Anakinra started at 5mg/kg twice daily (200mg/day) SQ
- Ketogenic diet start
- Average seizures day: 1.3
- Maximum hourly seizure burden: 0.75 min/hr

Day 23
- Severe drug reaction with eosinophilia and systemic symptoms
- Many medications were discontinued (including anakinra and phenobarbital)

*not successful: levetiracetam, fosphenytoin, ketamine

**Anakinra: Case Report**

| Day 23-53 | • Ketogenic diet and midazolam continue  
• Average seizures day: 8  
• Maximum hourly seizure burden: 8.5 min/hr  
• Day 42: topiramate and propofol administered → ketamine and felbamate added |
| Day 54-65 | • Anakinra re-started  
• Current treatments: midazolam, ketogenic diet, felbamate, topiramate  
• Average seizures day: 0.17  
• Maximum hourly seizure burden: 0.08 min/hr |
| Day 54-191 | • Day 88 weaned off midazolam  
• Day 98 weaned off KD  
• Remaining treatments: anakinra, felbamate, and topiramate |
| Day 191-current | • Anakinra weaned to discontinuation 5 months ago  
• Currently controlled on: felbamate 400mg in the AM and 600mg HS (54mg/kg/day), and levetiracetam 700mg BID (75mg/kg/day) |

Summary

• **FIRES**: catastrophic syndrome that represents an explosive epileptic disease following a febrile episode
• Currently available treatments remain unreliable
• Other options should potentially be trialed sooner, to prevent negative sequelae from induced comas
• Anakinra trial might be beneficial
• KD should be considered earlier on in the disease course and optimized before being considered a failed treatment
Questions & Discussion
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