Audit of treatment in refractory status epilepticus

Monica Ferlisi, Sara Hocker, Madeline Grade, Eugen Trinka, Simon Shorvon

Unit of Neurology A, Verona, Italy
Outline

- Reasons for a registry
- Methods
- Preliminary results
- Conclusion
Reasons for a registry
### Staged approach to treatment balancing: risk of disease - risk of treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Stage</th>
<th>Treatment</th>
<th>Evidence base</th>
<th>Morbidity/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5’</td>
<td>1. Early SE</td>
<td>Benzodiazepines</td>
<td>14 RCTs</td>
<td></td>
</tr>
<tr>
<td>&gt;30’</td>
<td>2. Established SE</td>
<td>PHT, PB VPA, LEV, LCM</td>
<td>8 RCTs ESETT</td>
<td></td>
</tr>
<tr>
<td>&gt;60’ - 120’</td>
<td>3. Refractory SE</td>
<td>General anaesthesia</td>
<td>“evidence-free&quot; zone</td>
<td></td>
</tr>
<tr>
<td>&gt;24h</td>
<td>Super-refractory SE</td>
<td>General anaesthesia  + various</td>
<td>1 RCT...</td>
<td></td>
</tr>
</tbody>
</table>
Difficulties for RCTs in Refractory SE

- Rare condition: 4.1-5.3/100,000
  - Multicentre studies needed
  - Long period of recruitment
- Narrow time window for enrolment
- Outcomes vary by age and etiologies
  - Large populations is needed to control
- Multiple therapies used in parallel
  - Difficult interpretation of efficacy
- Double blinding? (different side effects and precautions)
- Ethic approval issues
Medical registries

**PROS**
- No limitations of a RCT
- More generalizable to real-world practice
- Useful information if:
  - Good range of participation
  - High quality of data

**CONS**
- Selection bias
- No monitoring for data entry
- No “generalizability”

“...care must be taken when they go beyond their original purpose and attempt to answer effectiveness questions”
Byar, 1980
Methods
Methods

- “Operative definition”: Status epilepticus not responding to first line therapy and requiring general anesthesia in an intensive care unit (ICU)
- Adult and pediatric cases
- All forms of status epilepticus
- All etiologies

- Audit: no ethics approval needed in most of the countries
- De-identified data
- No need for patients’ note
Global Audit of Treatment of Refractory Status Epilepticus

Dear Colleague,

There is no consensus about the best form of therapy for refractory and super-refractory status epilepticus. As RCTs are difficult to perform in this condition, we are appealing to doctors to take part in an online global audit. The participating doctors provide audit information about the treatment and outcome of cases prospectively encountered. Data collection is on very simple online forms which take only a few minutes to complete.

**Aim:** To discover what range of treatment are used, and their outcomes, in the treatment of cases of refractory status epilepticus around the world. The information will then form the basis of future research and guidelines.

**Case definition:** status epilepticus not responding to first-line therapy and requiring general anesthetics in an intensive care unit (ICU).
- Adult and paediatric cases
- All forms of status epilepticus
- All settings

This is an academically-driven exercise, with no external funding. Furthermore, as this is a simple audit of physician practice preferences, totally anonymised, ethics approval and patient consent are not usually required.

You can download further [information](#) and the audit [procedure](#), so your IRBs may review it if necessary.

The study aim is to collect 1000 cases.

You can see some preliminary and interim results [here](#).

The latest findings will be discussed at the next Status Epilepticus Colloquium in London in April 2015

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To register for the audit, please enter your e-mail address below.

Once registered, you will receive monthly reminder to report new cases of status epilepticus. You can unregister your e-mail address any time.

All data will be entirely confidential. The e-mail address will not be handed to any third party. All communications for the audit team will be made by e-mail.

If you need help you can refer to your local member of the international steering committee or contact us.

<table>
<thead>
<tr>
<th>E-mail:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Please choose</td>
</tr>
<tr>
<td>Title:</td>
</tr>
<tr>
<td>First name:</td>
</tr>
<tr>
<td>Family name:</td>
</tr>
</tbody>
</table>

Yours sincerely,

Dr. Monica Fritschi
Dr. Sara Hooker
Prof. Simon Shervin
Prof. Eugen Trinka

(Audit Coordinators)

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“active surveillance”
- Monthly mail asking to report new cases
Demographics

Global Audit of Treatment of Refractory and Super-Refractory Status Epilepticus
## Details of Status Epilepticus

### Prior history of epilepsy
- **Yes**
- **No**
- **Not known**

### Cause(s) of status epilepticus
- Unknown (cryptogenic)
- Vascular (incl. stroke)
- Anoxic (incl. cardiac arrest)
- Trauma
- Acute encephalitis
- Acute meningitis
- Other infection, please specify: [blank]
- Alcohol
- Other toxins, please specify: [blank]
- Metabolic, please specify: [blank]
- Cerebral tumour
- Antiepileptic drug reduction/withdrawal
- Genetic/chromosomal, please specify: [blank]
- Immunological – NMDA receptor Antibodies +
- Immunological – VGK A Antibodies +
- Immunological – Lupus (seropositive)
- Immunological – other, please specify: [blank]
- Mitochondrial disease, please specify: [blank]
- Other, please specify: [blank]
### Details of Status Epilepticus-2

**Type of status epilepticus**
- Convulsive (including tonic-clonic SE)
- Nonconvulsive, please specify: [ ]
- Convulsive evolving to nonconvulsive
- Other, please specify: [ ]
- Not known

**Duration of status epilepticus before any treatment:**
- 1 hour or less
- 1-6 hours
- 6-12 hours
- 12-24 hour
- 1-7 days
- >7 days
- Other: [ ] days
- Not known

**Duration of status epilepticus before first anaesthetic administered:**
- Less than 1 hour
- Less than 1 day
- Longer than 1 day
- Not known
## Anaesthetics

**Sequence of anaesthetics used to treat status epilepticus**

If no anaesthetics, or no more, were administered, please select "none". If you do not exactly know the duration, please give your best estimate.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Duration of use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First anaesthetic therapy used</td>
<td>Midazolam</td>
<td>24 hours or (\uparrow)</td>
</tr>
<tr>
<td>Second anaesthetic therapy used</td>
<td>Propofol</td>
<td>Still being tr (\uparrow)</td>
</tr>
<tr>
<td>Third anaesthetic therapy used</td>
<td>None</td>
<td>[Please choose] (\uparrow)</td>
</tr>
<tr>
<td>Fourth anaesthetic therapy used</td>
<td>None</td>
<td>[Please choose] (\uparrow)</td>
</tr>
</tbody>
</table>

Global Audit of Treatment of Refractory and Super-Refractory Status Epilepticus
Antiepileptics

Please list here the antiepileptics used on the ITU. Please mention all drugs, whether used IV or via the nasogastric tube/PEG.

If you do not exactly know the duration, please give your best estimate.

<table>
<thead>
<tr>
<th>No antiepileptics administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>First antiepileptic used</td>
</tr>
<tr>
<td>Second antiepileptic used</td>
</tr>
<tr>
<td>Third antiepileptic used</td>
</tr>
<tr>
<td>Fourth antiepileptic used</td>
</tr>
<tr>
<td>Fifth antiepileptic used</td>
</tr>
</tbody>
</table>

Is there anything else we should know about the antiepileptic therapies regarding this patient? Please also leave a note if more than five antiepileptics were used.

Global Audit of Treatment of Refractory and Super-Refractory Status Epilepticus
Other therapies

<table>
<thead>
<tr>
<th>Other therapies used to treat status epilepticus</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you do not exactly known the duration, please give your best estimate.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Duration of use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>1-7 days</td>
<td></td>
</tr>
<tr>
<td>IVlg</td>
<td>1-7 days</td>
<td></td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>Still being tr</td>
<td></td>
</tr>
<tr>
<td>[Please choose]</td>
<td>[Please cho</td>
<td></td>
</tr>
</tbody>
</table>
Summary

Case summary

<table>
<thead>
<tr>
<th>Date reported</th>
<th>04/08/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting doctor</td>
<td>Dr. Monica Ferlisi</td>
</tr>
<tr>
<td>Hospital</td>
<td>Borgo Trento Hospital</td>
</tr>
<tr>
<td>Country of the Hospital</td>
<td>Italy</td>
</tr>
<tr>
<td>Patient age</td>
<td>52 years</td>
</tr>
<tr>
<td>Patient gender</td>
<td>Male</td>
</tr>
<tr>
<td>Duration of status epileptic before first treatment</td>
<td>1 hour or less</td>
</tr>
<tr>
<td>Duration of status epileptic before first anaesthetic administered</td>
<td>Less than 1 day</td>
</tr>
<tr>
<td>Prior History of epilepsy</td>
<td>No</td>
</tr>
<tr>
<td>Cause(s) of status epilepticus</td>
<td>Unknown (cryptogenic)</td>
</tr>
<tr>
<td>Type of status epilepticus</td>
<td>Convulsive (including tonic-clonic SE)</td>
</tr>
</tbody>
</table>

Therapy reported by 04/08/2015

**Anaesthetics**

1. Midazolam - duration of therapy 24 hours or less - low dose
2. Propofol - duration of therapy Still being treated with this drug

**Antiepileptics**

1. Lorazepam - duration of therapy 24 hours or less - bolus repeated
2. Levetiracetam - duration of therapy Still being treated with this drug
3. Phenytoin - duration of therapy Still being treated with this drug

**Other Therapies**

1. Steroids - duration of therapy 1-7 days
2. IV/g - duration of therapy 1-7 days
3. Ketogenic diet - duration of therapy Still being treated with this therapy
Current status

What is the current status of therapy, as far as you are aware?

- Continuing intensive therapy
  (including cases in whom anaesthesia is being tapered)
- Recovered from status epilepticus
  (seizures improved or stopped and anaesthetics discontinued)
- Therapy withdrawn
- Patient died
- I am no longer aware of his/her therapy
Follow up questionnaires are automatically sent fortnightly (taking 1-3 minute to complete) until the patient is no longer in ICU

Outcome questionnaire
- Modified Rankin scale
- Number of days in ICU

Long-term outcome questionnaire at 3 and 6 months
Coordinators

• Simon Shorvon (UK)
• Monica Ferlisi (Italy)
• Eugen Trinka (Austria)
• Sara Hocker (US & Canada)
Steering Committee Members

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- Eva Kumlien (Sweden)
- Marko Ercegovac (Serbia)
- Yasiri Zeid (Iraq)
- Alla Guecht (Russia)
- Tony Wu (Taiwan)
- Rima Nabbout (France)
44 countries
145 physician
Preliminary results
553 cases
10 duplicated
55 not in inclusion criteria
488
<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>36.8 y mean</td>
<td>0-92 y range</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>M 54%</td>
<td>F 46%</td>
</tr>
<tr>
<td><strong>Prior history of epilepsy</strong></td>
<td>Yes 38%</td>
<td>No 62%</td>
</tr>
<tr>
<td><strong>Etiologies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Acute encephalitis</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Anoxic</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Other infection</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>AEDs withdrawal</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Immunological</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Cerebral tumor</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>
Type of status epilepticus

- Convulsive (including tonic-clonic SE): 56%
- Non Convulsive: 19%
- Convulsive evolving to non convulsive: 21%
- Other**: Absence status EPC: 3%
Timing of treatment

Before any treatment

%  

CSE  

NCSE  

p<0.001
First line treatment

Benzodiazepines

- Diazepam
- Lorazepam
- Midazolam
- Clonazepam
- Clobazam
Timing of treatment

Time before first anaesthetic

- <1 h
- <1 d
- >1 d
Number of different anaesthetics used in sequence

- Just one: 44%
- Two: 33%
- Three: 17%
- Four: 6%
- Five: <1%
Choice of anaesthetics

![Bar chart showing choice of anaesthetics as 1st, 2nd, 3rd, and 4th. MDZ, PRO, BBTs, Ketamine, and Other (Lidocaine, Sufentanil, Remifentanil).]
Duration of a single anaesthetic agent

- 24 hours or less
- 1-7 days
- 8-14 days
- >14 days
Other therapies

In 173/488 cases
Outcome of status epilepticus

- Seizures stopped: 74%
- Died in SE: 22%
- Therapy withdrawn: 4%
Neurological outcome at the end of anaesthesia

% out of 394 cases

- 0 - No Symptoms
- 1 - No significant disability
- 2 - Slight disability
- 3 - Moderate disability
- 4 - Moderately severe disability
- 5 - Severe disability
- 6 - Dead

Good outcome 36%
Poor outcome 39%
Dead 25%
ICU stay duration

<table>
<thead>
<tr>
<th>Total ICU stay</th>
<th>N</th>
<th>% out of 353</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 days</td>
<td>108</td>
<td>31</td>
</tr>
<tr>
<td>7-14 days</td>
<td>99</td>
<td>28</td>
</tr>
<tr>
<td>15-29 days</td>
<td>79</td>
<td>22</td>
</tr>
<tr>
<td>30-59 days</td>
<td>51</td>
<td>14</td>
</tr>
<tr>
<td>60-210 days</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>353</td>
<td>100</td>
</tr>
</tbody>
</table>

Media = 18.07
Dev. stand. = 22.717
N = 352
## Factors affecting outcome

<table>
<thead>
<tr>
<th></th>
<th>Recovered</th>
<th>Died/therapy withdrawn</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior History of epilepsy</strong></td>
<td>Yes 86% No 67%</td>
<td>Yes 14% No 33%</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Mean 34.5 years</td>
<td>Mean 45.7 years</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Type of SE</strong></td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Time to any treatment</strong></td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Time to first anaesthetic</strong></td>
<td>&lt;1 day: 182 (70%)</td>
<td>&lt;1 day: 76 (30%)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>&gt;1 day: 111 (81%)</td>
<td>&gt;1 day: 26 (19%)</td>
<td></td>
</tr>
</tbody>
</table>
Adjusted for
- SE duration
- STESS
- critical conditions (liver or renal insufficiency; heart or pulmonary disease; tumors)

But...

IVAD administration was not strictly standardized. Clinicians possibly selected patients for IVADs who had seemingly more refractory or severe SE, a bias that cannot be excluded completely.
## Influence of etiologies

<table>
<thead>
<tr>
<th>Cause</th>
<th>Recovered</th>
<th>Died/therapy withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEDs withdrawal</td>
<td>28 (90%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Genetic/chromosomal</td>
<td>6 (86%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Cerebral tumour</td>
<td>18 (82%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Unknown (cryptogenic)</td>
<td>63 (80%)</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>12 (80%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>42 (74%)</td>
<td>15 (26%)</td>
</tr>
<tr>
<td>Acute meningitis</td>
<td>8 (73%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Other infection</td>
<td>23 (72%)</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>12 (67%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Other toxins</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Immunological, all</td>
<td>17 (65%)</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Acute encephalitis</td>
<td>32 (65%)</td>
<td>17 (35%)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>13 (62%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Anoxia</td>
<td>22 (49%)</td>
<td>23 (51%)</td>
</tr>
</tbody>
</table>
Factors affecting outcome

- **No of anaesthetics tried**
  - Recovered: 1.5
  - Not recovered: 2.5
  - p<0.001

- No influence on which anaesthetics is given as first agent
Last anaesthetic used and outcome

**Last anaesthetic used**

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Recovered</th>
<th>Not recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDZ</td>
<td>147</td>
<td>27</td>
</tr>
<tr>
<td>PRO</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td>BBTs</td>
<td>67</td>
<td>29</td>
</tr>
<tr>
<td>Ketamine</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

**Number of anaesthetics tried and last anaesthetic**

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Just one</th>
<th>More than one</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDZ</td>
<td>103</td>
<td>44</td>
</tr>
<tr>
<td>PRO</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>BBTs</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

**Neurological outcome and last anaesthetic tried**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Good (mRS 0-3)</th>
<th>Poor (mRS 4-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDZ</td>
<td>67</td>
<td>98</td>
</tr>
<tr>
<td>PRO</td>
<td>36</td>
<td>53</td>
</tr>
<tr>
<td>BBTs</td>
<td>35</td>
<td>57</td>
</tr>
<tr>
<td>Ketamine</td>
<td>4</td>
<td>34</td>
</tr>
</tbody>
</table>

**p < 0.01**
What’s new?

- High number cryptogenic “de novo” SE
  - 1/3 of patients received “other therapies”

- Very severe cases / good rate of seizure control
  - 56% used >1 anaesthetic agent
  - 70% > 1 week of ICU

- 1st line treatment often delayed and different from BDZ

- Common practise to delay anaesthesia in less severe cases
Steering Committee Members

- Simon Shorvon (UK)
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Thanks!

www.status-epilepticus.net
monica.ferlisi@ospedaleuniverona.it