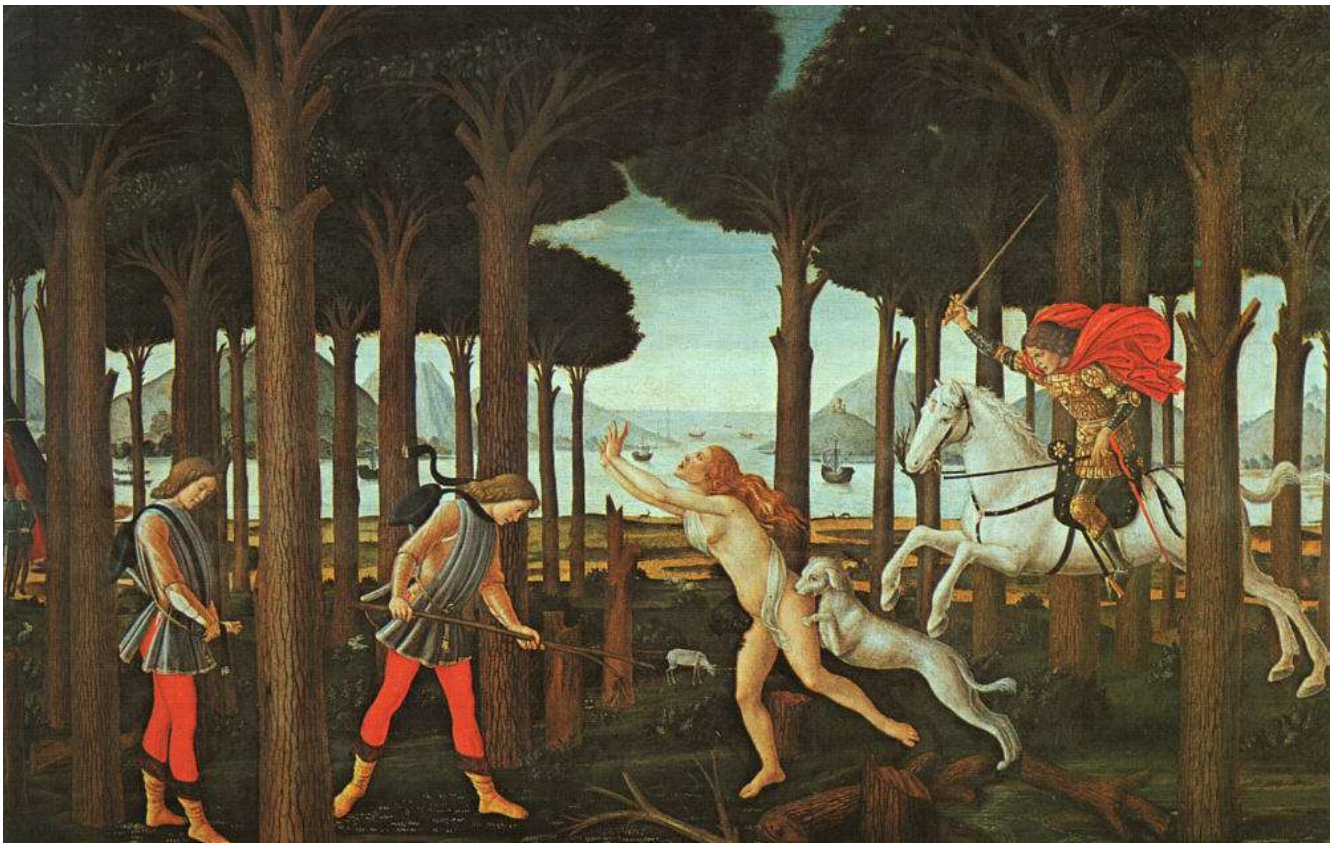
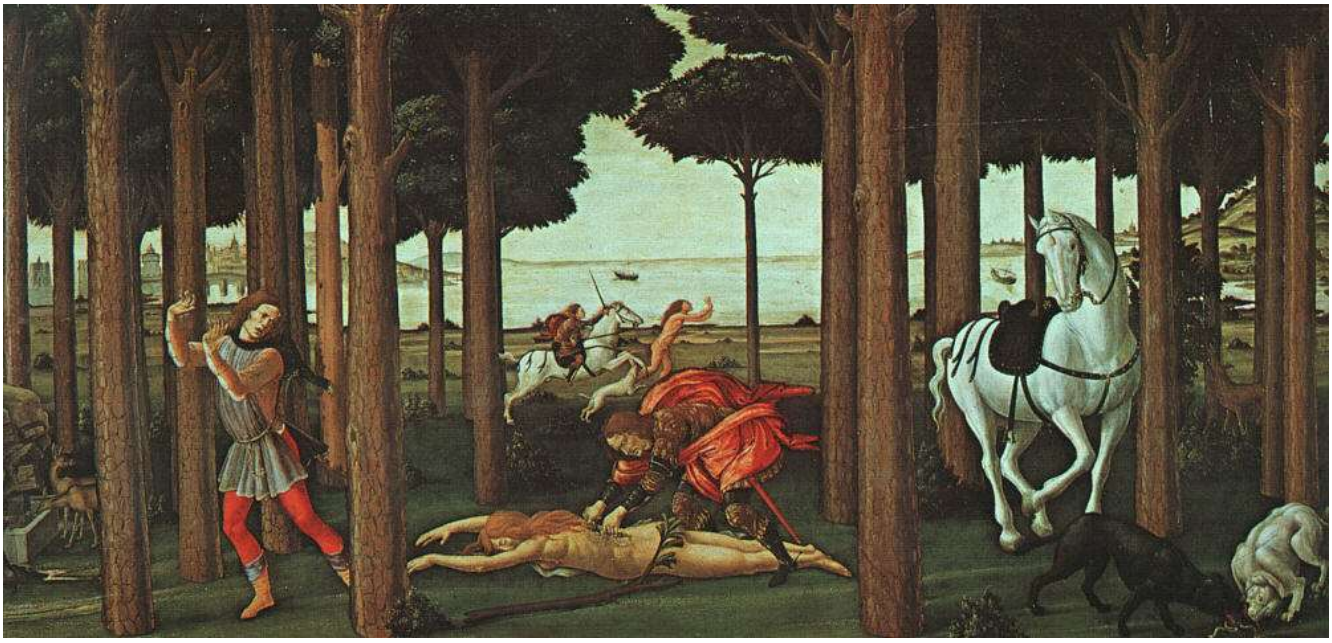
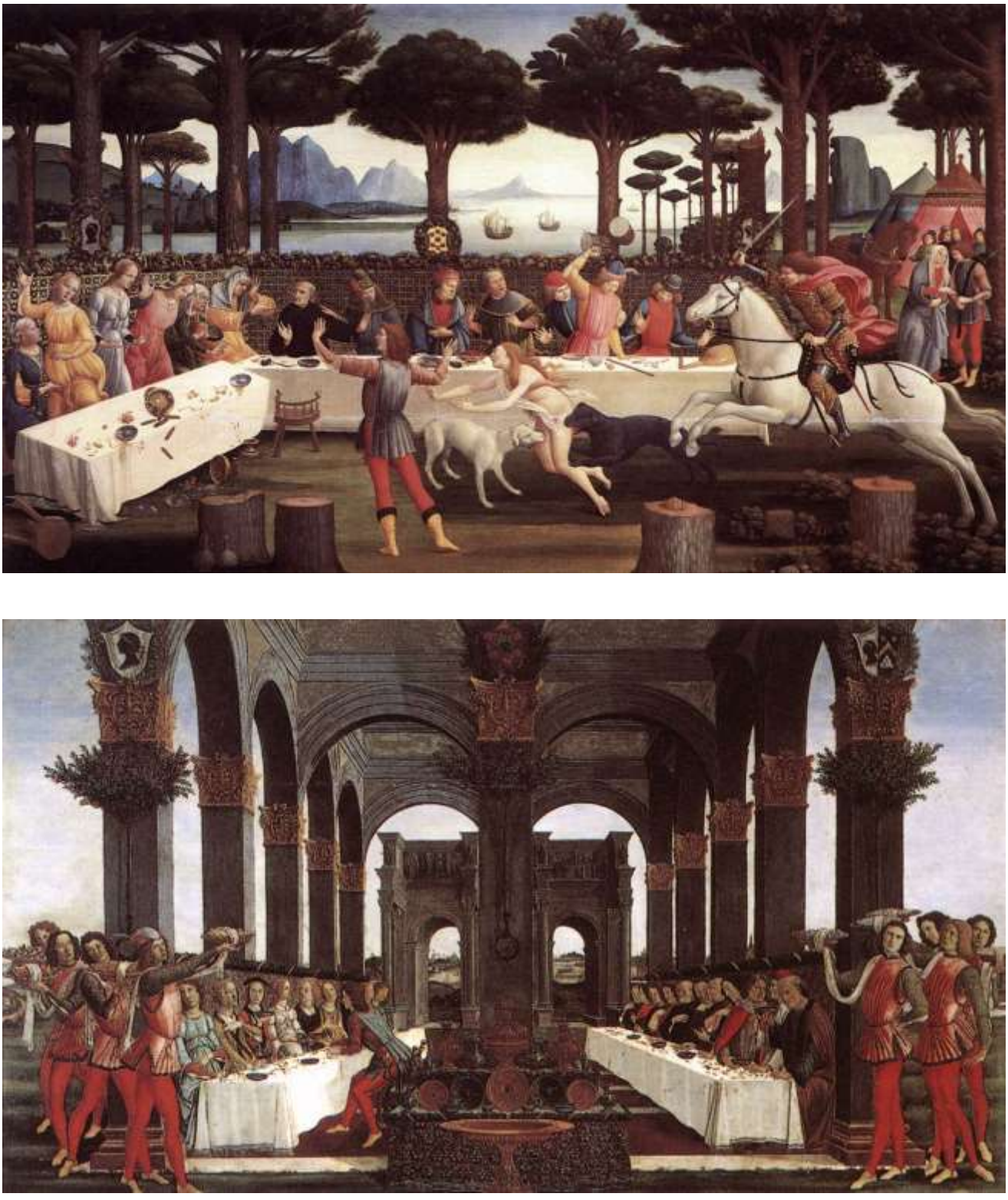
THE NORTHERN HOSPITAL

STATUS EPILEPTICUS (CONVULSIVE)







"The Story of Nastagio degli Onesti", (top to bottom, First, Second, Third and Fourth episodes) Sandro Botticelli, Tempera on panel 1483, Museo del Prado Madrid.

The fifth hour of the day was already spent, and he had advanced at least half a mile into the woods, oblivious of food and everything else, when suddenly he seemed to hear a woman giving vent to dreadful wailing and ear-splitting screams. His pleasant reverie being thus interrupted, he raised his head to investigate the cause, and discovered to his surprise that he was in the pinewoods. Furthermore, on looking straight ahead he caught sight of a naked woman, young and very beautiful, who was running through a dense thicket of shrubs and briars towards the very spot where he was standing. The woman's hair was disheveled, her flesh was all torn by the briars and brambles, and she was sobbing and screaming for mercy. Nor was this all, for a pair of big fierce mastiffs were running at the girl's heels, one on either side, and every so often they caught up with her and savaged her. Finally bringing up the rear he saw a swarthy looking knight, his face contorted with anger, who was riding a jet black steed and brandishing a rapier, and who, in terms no less abusive than terrifying, was threatening to kill her.

The spectacle struck both terror and amazement into Nastagio's breast…he hastily took up a branch of a tree to serve as a cudgel, and prepared to ward off the dogs and do battle with the knight. When the latter saw what he was doing, he shouted to him from a distance: "Keep out of this Nastagio! Leave me and the dogs to give this wicked sinner her deserts!" He had no sooner spoken than the dogs seized the girl firmly by the haunches and brought her to a halt. When the knight reached the spot he dismounted from his horse, and Nastagio went up to him saying: "I do not know who you are, or how you come to know my name, but I can tell you that it is a gross outrage for an armed knight to try and kill a naked woman, and to set dogs upon her as though she were a savage beast. I shall do all in my power to defend her, of that you may be sure."

Whereupon the knight said: "I was a fellow citizen of yours, Nastagio, my name was Guido degli Anastagi, and you were still a little child when I fell in love with this woman. I loved her far more deeply than you love that Traversari girl of yours, but her pride and cruelty led me to such a pass, that one day, I killed myself in sheer despair with this rapier that you see in my hand, and thus I am condemned to eternal punishment. My death pleased her beyond measure, but shortly thereafter she too died, and because she had sinned by her cruelty and by gloating over my sufferings, and was quite unrepentant, being convinced she was more of a saint than a sinner, she too was condemned to the pains of Hell. No sooner was she cast into Hell than we were both condemned to a special punishment, which consisted in her case of fleeing before me, and in my own of pursuing her as though she were my mortal enemy rather than the woman with whom I was once so deeply in love. Every time I catch up with her, I kill her with this same rapier by which I took my own life; then I slit her back open, and (as you will now observe for yourself) I tear from her body that hard, cold heart to which neither love nor pity could ever gain access, and together with the rest of her entrails I cast it to these dogs to feed upon".

"Within a short space of time, as ordained by the power and justice of God, she springs to her feet as though she had not been dead at all, and her agonizing flight begins all over again, with the dogs and myself in pursuit. Every Friday at this hour I overtake her in this part of the woods, and slaughter her in the manner you are about to observe, but you must not imagine that we are idle for the rest of the week; because on the remaining days I hunt her down in other places where she was cruel to me in thought and deed. As you can see for yourself I am no longer her lover but her enemy, and in this guise I am obliged to pursue

her for the same number of years as the months of her cruelty towards me. Stand aside, therefore, and let me carry out the judgment of God. Do not try to oppose what you cannot prevent".

On hearing these words, Nastagio was shaken to the core, there was scarcely a single hair on his head that was not standing on end, and he stepped back to fix his gaze on the unfortunate girl, waiting in fear and trembling to see what the knight would do to her. This latter, having finished speaking, pounced like a mad dog, rapier in hand, upon the girl, who was kneeling before him, held by the two mastiffs, and screaming for mercy at the top of her voice. Applying all his strength, the knight plunged his rapier into the middle of her breast and out again at the other side, whereupon the girl fell on her face, still sobbing and screaming, whilst the knight, having laid hold of a dagger, slashed open her back, extracted her heart and everything else around it, and hurled it to the two mastiffs, who devoured it greedily on the instant. But before very long the girl rose suddenly to her feet as though none of these things had happened, and she sped of in the direction of the sea, being pursued by the dogs, who kept tearing away at her flesh as she ran. Remounting his horse, and seizing his rapier, the knight too began to give chase, and within a short space of time they were so far away that Nastagio could no longer see them.

Day 5 Story 8, Giovanni Boccaccio, The Decameron, (1350-53).

In medieval times medical knowledge was virtually non-existent compared to what we now know. Patients with conditions such as epilepsy simply defied any rational explanation. To some the condition could only be explained as a possession by the devil or some other evil demon, but it could also equally reflect a punishment sent from God for some evil doing either real or imagined on the part of the sufferer. Any unfortunate trapped in status epilepticus would have been considered by some to have been especially deserving of their fate - as if trapped within a Boccaccian vision of hell - condemned to relive a terrible punishment over and over again from which there would be no awakening between these punishments. In one of the most famous stories of Boccaccio's Decameron, Nastagio witnesses the horrific spectacle of two souls condemned to the torments of hell for their Earthly sins. He later arranges, on the pretext of a large banquet, a gathering for all his acquaintances at the very spot in the dark pinewoods where this recurring apparition manifests itself, in order to demonstrate to all the wrath of God towards those who commit sin. His main motivation however is not for the salvation of the souls of his acquaintances, rather he schemes to send a message to the woman he is in love with but who has most cruelly rejected his overtures! All at the banquet are horrified when the ghostly knight and the girl play out their sickening punishment, but none more so than the woman who has jilted him. So terrified is she by what she has witnessed she decides to be kind to Nastagio - in fact so kind as to happily accept his proposal of marriage! Boccaccio's "moral" was that women should be more accommodating to the advances of men - otherwise they were "cruel" and deserving of unimaginable punishment in the next world - an interesting conclusion that appears to say a lot about the position of women in society in the Fourteenth century! Nastagio's tree branch was no defense against the ghostly knight. Fortunately in the Twenty First century we can rescue those unfortunate souls trapped in a Boccaccian Hell of the recurring torment of status epilepticus with a powerful range of magical potions.

STATUS EPILEPTICUS

Introduction

Status epilepticus is a true Neurological emergency.

It is commonly defined as:

- **Continuous seizure activity lasting more than 30 minutes**

Or

- **Two or more seizures without full recovery of consciousness between the seizures.**

The following refers to "generalized convulsive" status epilepticus". *Generalized* refers to abnormal excessive and widespread cortical electrical activity, while *convulsive* refers to the motor activity of a seizure.

This is in distinction to "non-convulsive" status epilepticus which includes such conditions as absence status epilepticus, complex partial status epilepticus, and other epileptic "twilight states".

Current recommendations for the treatment of status epilepticus, emphasizes earlier escalation to anesthetic agents, in order to avoid **neuronal injury** and **pharmaco-resistance** that is associated with prolonged seizures.

Three "lines" of pharmacological agents are used to terminate seizures.

First line:

First line agents to terminate seizures are benzodiazepines

Second line:

Traditionally the preferred **second line** agent has been IV **phenytoin**.

More recently and increasing evidence suggests a role for newer agents such as **levetiracetam** or **valproate** and as "first choice" second line agents.

Although its efficacy is equal to phenytoin, [4,5] in status epilepticus, levetiracetam is being increasingly used as a first choice, second line agent (after benzodiazepines) in cases of both convulsive and non-conclusive status epilepticus, with phenytoin being relegated to third line treatment.

Although the two agents seem to be of equal efficacy as second line agents, levetiracetam is being favoured by many due to:

- **Its superior safety profile (predominantly CVS safety profile)**
- **Its ease of drawing up**
- **It's much quicker rate of delivery (over just 5 minutes)**

Third line:

Anesthetic agents such as **propofol** and **phenobarbitone** constitute **third line** agents, usually in combination with **intubation, muscle paralysis and mechanical ventilation.**

It is important to understand that seizure activity can be both "**clinical**" and "**electrical**".

The latter is where neuronal seizure activity is occurring without apparent motor activity, (end stage status or when the patient is paralyzed and ventilated). In the latter **EEG monitoring** will be required to diagnose this.

The role of acute and real time EECG monitoring continues to evolve.

See also separate documents on

- **Non-convulsive Status Epilepticus (in Neurology folder).**
- **Levetiracetam (in Drugs folder).**

Pathophysiology

Causes:

The causes of generalized seizures and status epileptic include:

1. Primary epilepsy.
2. Head trauma.
3. Cerebral tumors (primary or secondary)
4. Infection:
    - Febrile seizures in children
    - CNS, meningitis, encephalitis, cerebral abscess
    - Severe generalized sepsis.
5. Stroke:
    - This may be of any type including subarachnoid hemorrhage.

6. Raised intracranial pressure of any cause, including:

   - Cerebral edema (of any cause).
   - Blocked V-P/A shunts.
   - Space occupying lesions.

7. Metabolic causes:

   - **Hypoglycemia**
   - Hypoxia / hypercarbia / severe hypocarbia
   - Electrolyte disorders, especially **hyponatremia.**

     Less commonly:

     ♥ Hypernatremia/ hypocalcaemia/ hypomagnesemia.

   - Hyperthyroid storm
   - End stage organ failure, including hepatic encephalopathy and uremia.

8. Drug related:

   Overdose:

   - In particular TCAs, theophylline, cocaine, sympathomimetic agents, and isoniazid.

   Withdrawal syndromes:

   - Alcohol / benzodiazepines / barbiturates

   Drugs that lower seizure threshold:

   Particularly in those who are predisposed. Many drugs have been anecdotally implicated. Some of the more common ones include:

   - Tramadol
   - Clozapine

   Hyperthermic drug reactions:

   - Serotonin syndromes

- Neuroleptic malignant syndrome
- Malignant hyperpyrexia
- Toxidrome - Anticholinergic Syndrome
- Toxidrome - Sympathomimetic Syndrome

9. Toxins / poisons
    - Alcohol related
        - ♥ Seizures may be related to **acute intoxication** as well as to withdrawal states.
    - **Many** other drugs and toxins can produce seizures.
10. Hyperthermia of any cause.
11. Pregnancy related:
    - Eclampsia.
12. Previous brain injury:
    - This is due to presumed scarring from previous neurological insults such as stroke, trauma or congenital cerebral palsies.
13. Degenerative brain disorders of any cause.

Complications:

1. Airway:
    - Hypoxia
    - Aspiration
2. Injury:

    Including:
    - Fractures due to falls
    - Secondary to severe muscle contractions:
        - ♥ Fractures

- ♥ Avulsions of bone or tendon.
- ♥ Tongue laceration is very common due to jaw clenching.

- Joint dislocations:
  - ♥ Posterior shoulder dislocations are typical

3. Metabolic:
   - Hypoglycemia
   - Hyperthermia:
     - ♥ This is more commonly due to seizure activity itself than to infection.
   - Lactic acidosis
   - Rhabdomyolysis
4. Todd's paresis:
   - This is a transient non-progressive focal paralysis occurring in the post ictal period generally lasting 1-2 hours.
5. Neuronal damage:
   - If seizures are prolonged beyond **30-60 minutes** irreversible neuronal damage may occur independently of any secondary complications.
6. **Pharmaco-resistance**:
   - This is associated with *prolonged* seizures.

     The more prolonged seizures are the more resistant they become to pharmacological intervention.
7. End stage complications:
   - Ultimately muscle contractions cease even though seizure activity continues and this will present diagnostic difficulty if the patient is brought to the ED at this stage.

     It is important to understand that seizure activity can be both "**clinical**" and "**electrical**". The latter is where neuronal seizure activity is occurring without apparent motor activity, (end stage status or when the patient is

paralyzed and ventilated). In the latter EEG monitoring will be required to diagnose this.

At end stage the patient is **comatose** and may be **hyperthermic**.

Death can occur from:

- ♥ Neuronal injury/ cerebral edema
- ♥ Hyperthermia
- ♥ Metabolic derangement:
  - ♥♥ Hypoglycemia
  - ♥♥ Lactic acidosis
- ♥ Multi-organ failure.

Prognosis:

Prognosis is dependent on two critical factors:

1. **The underlying pathology**
2. **The duration of seizure activity:**

   Other factors being equal this can be defined as:

   - Seizure duration under 1 hour: mortality approximately 3 %.
   - Seizure duration over 1 hour: mortality approximately 30 %.

Clinical features

Typical features of convulsive status epilepticus include:

1. Persistent abnormal generalized muscular contractions which may be:
   - Tonic (uncommon)
   - Clonic
   - Tonic-clonic (most common)
2. Impaired consciousness.
3. A period of cyanosis is common due to impaired respiration.

4. The airway will often be compromised to a variable extent.

5. The pupils often dilate.

End stage convulsive status epilepticus:

It is important to note that following prolonged generalized seizures, motor acitivity may **diminish**, even to the point of **ceasing.**

Electrical cerebral seizure acitivity may still continue even in the *absence* of motor acitivity.

The patient remains unconscious, may become **hyperthermic**, and has increasing **metabolic abnormalities**, ultimately leading to **cerebral edema, multi-organ failure** and **death.**

Failure to regain consciousness:

Failure to regain consciousness following control of clinical seizures can be due to:

1. Ongoing electrical status epilepticus in end-stage seizure activity.
    - This can include a state of non-convulsive status epilepticus.
2. Ongoing causative pathology
3. Iatrogenic:
    - i.e. the effects of sedative, anticonvulsant, and anesthetic drugs.
4. Secondary complications:
    - Hypoglycemia
    - Neuronal injury/ cerebral edema
    - Hypoxic brain injury
    - Hypotension
    - Hyperthermia

Psychogenic seizures:

Occasionally pseudoseizures may be difficult to differentiate from genuine seizure activity, however the former will have none of the severe metabolic consequences of generalized convulsive status epilepticus.

See also separate document on Pseudoseizures.

Investigations

Once seizures have been controlled the following investigations need to be considered:

Blood tests:

1. FBE:
    - WCC can be elevated, but is non-specific, it may be due to sepsis or it may be due to the seizure activity itself.
2. **Glucose, (urgent bedside)**
3. U&Es:
    - Including urgent **sodium** level
4. CRP

    May indicate underlying sepsis.
5. VBGs / lactate:
    - A lactic acidosis may be seen
6. Magnesium / calcium / phosphate levels.
6. LFTs
7. CK
8. Serum myoglobin levels
9. Drug levels:
    - Blood alcohol levels.
    - Where available, such as **phenytoin, valproate, carbamazepine**.
    - Drug screens where indicated.
10. Blood cultures.

CXR

For infection or aspiration.

ECG

As for any unwell patient.

Urine

For FWT, micro and culture, drug screen, myoglobin, as clinically indicated.

CT Scan

This should be done in all cases, once the patient has been stabilized.

MRI

This may be considered, once a patient is stabilized and the diagnosis still remains unclear following a CT scan.

Status epilepticus can induce reversible changes on MRI.

Lumbar Puncture

Patients should always be stabilized before this procedure is contemplated.

It should never delay critical empirical treatments such as antibiotics or antiviral agents.

It should not be done in cases of raised intracranial pressure, (including space occupying lesions).

EEG

EEG may be required to make a definitive diagnosis, especially in unconscious intubated patients.

EEG recordings are important in end stage cases and in patients who are paralyzed or under anesthesia.

Access is problematic in most centers unless they have a specialist neurological unit. Specialist interpretation will also be required.

Management

Immediate treatment:

1. ABC measures:

- Attention to ABC, generally this means keeping patient in coma position, clearing secretions, providing oxygen and keeping the patient from physical injury.

- Airway adjuncts:

  ♥ Attempts at oral airways when the mouth is clenched should be *avoided* during the actual seizure.

  If required a **soft nasopharyngeal** airway will usually suffice.

- Supplemental oxygen:

  ♥ This can be provided if required by a Hudson mask or if this proves problematic then by nasal prongs

- Wall suction:

  ♥ To clear excess secretions if required.

- Patients usually require no other specific treatment for the first 5 minutes, other than the above measures.

2. Glucose:

   - For seizures lasting 5-10 minutes glucose should be checked and IV inserted.

3. Protect the patient from injury.

First line treatment:

1. Glucose

   Glucose should be given to any hypoglycemic patient.

   Adults:

   - In adults give **50 mls** of **50% dextrose (i.e. 25 grams) IV**

     Dose can be repeated as necessary.

     Infusions:

     ♥ **Glucose 10%, at 250 mls per hour, (i.e. 25 grams per hours) and then titrate as required.**

   Children:

- **Glucose 10% 2 ml/kg bolus IV** is preferred for children and neonates.

2. Benzodiazepines:

The first line treatment for seizures remains the **benzodiazepines.**

For seizures lasting longer than **5-10 minutes** benzodiazepines should be given.

Options include:

IV clonazepam

- Adults 0.5 - 2.0 mg bolus up to 10 mg.
- Children 0.25 - 0.5 mg bolus up to 5.0 mg

IV diazepam

- Adults 5.0 mg boluses up to 30.0 mg
- Children 0.1 - 0.25 mg/kg IV

Midazolam

- IV 0.1 mg/kg, (range 5-10 mg)
- IM 0.2 mg/kg

Note that if **IV access is impossible**, options include:

- Interosseous access
- PR diazepam (0.5 mg/kg).
- IM (or buccal), midazolam:
    - ♥ Midazolam solution for injection (hydrochloride salt) can be used.

      0.2 - 0.5 mg/kg/dose up to a maximum of 10 mg may be given.

3. Thiamine

Thiamine should be given for alcohol associated seizures or other known thiamine deficiency states

- **Give thiamin if the patient is alcoholic and especially if glucose has been given.**

Thiamine deficient patients should receive IV thiamine (100 - 500 mg) before or concurrent with glucose to avoid depleting available thiamine stores and causing an acute Wernicke's encephalopathy.

4. Specific antidotes where they exist in toxicology cases:

- The primary example being **pyridoxine** for isoniazid poisoning.

Second line treatment:

Traditionally the preferred **second line** agent has been IV **phenytoin**.

More recently and increasing evidence suggests a role for newer agents such as **levetiracetam** or **valproate** and as "first choice" second line agents.

Although its efficacy is equal to phenytoin, [4,5] in status epilepticus, levetiracetam is being increasingly used as a first choice, second line agent (after benzodiazepines) in cases of both convulsive and non-conclusive status epilepticus, with phenytoin being relegated to third line treatment.

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Options include:

1. Levetiracetam

Dosing for status epilepticus in two important recent trials (ConSEPT) and (EcLiPSE) as well as the current recommendation from the Monash Children's Hospital Paediatric Emergency Medicine Medication Book, (2nd ed) is as follows:

- **Levetiracetam 40 / kg IV given over 5 minutes**

  Using the 500 mg vials (in 5 mls) - dilute each vial used to 10 mls (Monash Children's Medication Book)

  The maximum dose is **3 grams.**

For patients who are known to be already taking Levetiracetam, some expert opinion suggests using a dose of

- Levetiracetam 20 / kg IV given over 5 minutes

2. Phenytoin:

In general terms, for recurrent seizures or seizures lasting longer than 20-30 minutes, IV phenytoin infusion should be commenced:

- Load with **15 mg/kg IV** (but up to **20 mg/ kg** can be used).

  The rate not exceed **50 mg/min** (in an average adult this will come to about 1 gram over 20 minutes).

  In children the rate should not exceed 1 mg/kg per minute, up to **25 mg per minute.**

- Traditionally there was concern that giving **phenytoin** to a patient already taking this drug would lead to toxicity.

  In practice however most patients (supposedly) on anticonvulsants who present in status epilepticus have negligible drug levels and the side effects of a full loading dose on top of a therapeutic level are minimal, especially when compared to the consequences of prolonged status epilepticus.

  The *full loading dose* should then be given even when the patient is known to be on this therapy. [3]

- Note that phenytoin is **not** effective in the control of **acute alcohol related seizures** or as a *preventative* for them. Other agents will be required to control these seizures.

Sodium Valproate:

The Neurology Therapeutic Guidelines recommends the following dosing regimen: [1]

- **Sodium valproate 40 mg/kg - up to 3000 mg intravenously over 3 - 5 minutes**.

Third line treatment:

Third line treatment is essentially anesthetic agents, given as bolus dose and frequently continued as an ongoing infusion together with possible intubation with paralysis mechanical ventilation.

Drug options include:

1. Midazolam (as ongoing infusion)

2. Propofol infusion

3. Phenobarbitone:

- **Phenobarbitone 20 mg/kg intravenously**, no faster than 1 mg/kg/minute (maximum 60 mg/minute)

4. Thiopentone

Intubation:

For generalized convulsive seizures lasting 30-60 minutes and not controlled by above measures, anesthesia (i.e **intubation** and **paralysis**) will need to be considered.

- **Note that where certain specific pathologies are suspected, such as trauma or drug overdose, intubation should occur much earlier than the generally quoted 30-60 minutes.**

- Anesthesia will ensure protection from many of the secondary complications of seizure activity by protecting the airway, providing oxygen and allowing paralysis.

  Paralysis will protect against the deleterious effects of prolonged muscular activity, (hyperthermia and rhabdomyolysis).

It is important to recognize that even in the intubated and paralysed patient, seizure activity may still be occurring. In this setting only an EEG will determine if seizures have been controlled.

Following intubation ongoing sedation with an infused anticonvulsant agent should continue.

Treatment of any underlying cause:

It is important to recognize that treatment may be ineffective unless an underlying reversible cause is treated.

Important underlying causes will include:

- Hypoglycemia
- Trauma
- Infection
- Hyponatremia
- Drugs / toxins / poisons:
  - ♥ Some drugs may have specific antidotes, such as pyridoxine in cases of isoniazid poisoning.

Empiric antimicrobials such as cefotaxime and aciclovir should be considered in cases where the diagnosis remains unclear.

Disposition:

All patients who have had status epilepticus should be admitted to hospital.

HDU/ICU consultation

Neurology Consultation

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