

# THE MANAGEMENT OF STATUS EPILEPTICUS

Simon Shorvon

**S**tatus epilepticus is defined usually as a condition in which epileptic activity persists for 30 minutes or more. The seizures can take the form of prolonged seizures or repetitive attacks without recovery in between. There are various types of status epilepticus and a classification scheme is shown in table 1.

## TONIC-CLONIC STATUS EPILEPTICUS

The annual incidence of tonic-clonic status is estimated to be 18–28 cases per 100 000 persons. It occurs most commonly in children, the mentally handicapped, and in those with structural cerebral pathology especially in the frontal lobes. Most episodes of status develop without a prior history of epilepsy, and these are almost always caused by acute cerebral disturbances; common causes are cerebral infection, trauma, cerebrovascular disease, cerebral tumour, acute toxic or metabolic disturbances, or childhood febrile illness. In patients with pre-existing epilepsy, status can be precipitated by drug withdrawal, intercurrent illness or metabolic disturbance, or the progression of the underlying disease, and is more common in symptomatic than in idiopathic epilepsy. About 5% of all adult patients attending an epilepsy clinic will have at least one episode of status in the course of their epilepsy; in children the proportion is between 10–25%.

The physiological changes in status can be divided into two phases, the transition from phase 1 to 2 occurring after about 30–60 minutes of continuous seizures (table 2, fig 1). In phase 1, compensatory mechanisms prevent cerebral damage. In phase 2, however, these mechanisms break down, and there is an increasing risk of cerebral damage as the status progresses. The cerebral damage in status is caused by systemic and metabolic disturbance (for example, hypoxia, hypoglycaemia, raised intracranial pressure) and also by the direct excitotoxic effect of seizure discharges (which result in calcium influx into neurons and a cascade of events resulting in necrosis and apoptosis).

The main purpose of treatment is to prevent cerebral damage. As this is, at least in part, caused by the direct effect of seizure activity, it is imperative to control overt and electrographic seizure discharges. The risk of cerebral damage increases progressively after 1–2 hours of continuous status. If seizures are not controlled within this period, the patient should be considered to be in *refractory status* and general anaesthesia should be instituted.

**Table 1** Classification of status epilepticus. Reproduced from Shorvon SD. *A handbook of epilepsy treatment*, with permission of the publisher, Blackwell Science

- Status epilepticus confined to early childhood*
  - ▶ Neonatal status epilepticus
  - ▶ Status epilepticus in specific neonatal epilepsy syndromes
  - ▶ Infantile spasms
- Status epilepticus confined to later childhood*
  - ▶ Febrile status epilepticus
  - ▶ Status in childhood partial epilepsy syndromes
  - ▶ Status epilepticus in myoclonic-astatic epilepsy
  - ▶ Electrical status epilepticus during slow wave sleep
  - ▶ Landau-Kleffner syndrome
- Status epilepticus occurring in childhood and adult life*
  - ▶ Tonic-clonic status epilepticus
  - ▶ Absence status epilepticus
  - ▶ Epilepsia partialis continua
  - ▶ Status epilepticus in coma
  - ▶ Specific forms of status epilepticus in mental retardation
  - ▶ Syndromes of myoclonic status epilepticus
  - ▶ Simple partial status epilepticus
  - ▶ Complex partial status epilepticus
- Status epilepticus confined to adult life*
  - ▶ De novo absence status and late onset

Correspondence to: Professor Simon Shorvon, Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK  
s.shorvon@ion.ucl.ac.uk

**Table 2** Physiological changes in status epilepticus. Reproduced from Shorvon SD. *A handbook of epilepsy treatment*, with permission of the publisher, Blackwell Science**Phase 1: compensation**

During this phase, cerebral metabolism is greatly increased because of seizure activity, but physiological mechanisms are sufficient to meet the metabolic demands, and cerebral tissue is protected from hypoxia or metabolic damage. The major physiological changes are related to the greatly increased cerebral blood flow and metabolism, massive autonomic activity, and cardiovascular changes

<i>Cerebral changes</i>	<i>Systemic and metabolic changes</i>	<i>Autonomic and cardiovascular changes</i>
Increased blood flow Increased metabolism Energy requirements matched by supply of oxygen and glucose (increased glucose and oxygen utilisation) Increased lactate concentration Increased glucose concentration	Hyperglycaemia Lactic acidosis	Hypertension (initial) Increased cardiac output Increased central venous pressure Massive catecholamine release Tachycardia Cardiac dysrhythmia Salivation Hyperpyrexia Vomiting Incontinence

**Phase 2: decompensation**

During this phase, the greatly increased cerebral metabolic demands cannot be fully met, resulting in hypoxia and altered cerebral and systemic metabolic patterns. Autonomic changes persist and cardiorespiratory functions may progressively fail to maintain homeostasis

<i>Cerebral changes</i>	<i>Systemic and metabolic changes</i>	<i>Autonomic and cardiovascular changes</i>
Failure of cerebral autoregulation; thus cerebral blood flow becomes dependent on systemic blood pressure Hypoxia Hypoglycaemia Falling lactate concentrations Falling energy state Rise in intracranial pressure and cerebral oedema	Hypoglycaemia Hyponatraemia Hypokalaemia/ hyperkalaemia Metabolic and respiratory acidosis Hepatic and renal dysfunction Consumptive coagulopathy, DIC, multiorgan failure Rhabdomyolysis, myoglobinuria Leucocytosis	Systemic hypoxia Falling blood pressure Falling cardiac output Respiratory and cardiac impairment (pulmonary oedema, pulmonary embolism, respiratory collapse, cardiac failure, dysrhythmia) Hyperpyrexia

The physiological changes listed above do not necessarily occur in all cases. The type and extent of the changes depicted depend on aetiology, clinical circumstances, and the methods of treatment employed.  
DIC, disseminated intravascular coagulopathy.

## General measures in the treatment of tonic-clonic status epilepticus

### Cardiorespiratory function

In all patients presenting in status, the protection of cardiorespiratory function takes first priority. Hypoxia is usually much worse than appreciated, and oxygen should always be administered.

### Emergency investigations

Emergency investigations should include assessment of the following: blood gases, glucose, renal and hepatic function, calcium, magnesium, full blood count, clotting screen, and anticonvulsant concentrations. Serum should be saved for toxicology or virology or other future analyses. An electrocardiogram (ECG) should be performed.

### Initial emergency treatment

Initial treatment should include:

- ▶ emergency intravenous antiepileptic drug treatment (see below)
- ▶ maintenance antiepileptic drugs orally or via a nasogastric tube
- ▶ intravenous thiamine and glucose if there is the possibility of alcoholism
- ▶ glucose if hypoglycaemia is present
- ▶ the correction of metabolic abnormalities if present
- ▶ the control of hyperthermia
- ▶ pressor therapy for hypotension if present
- ▶ the correction of respiratory or cardiac failure.

If the status is caused by drug withdrawal, the withdrawn drug should be immediately replaced, by parenteral administration if possible. Treatment may also be needed for cardiac dysrhythmia, lactic acidosis (if severe), rhabdomyolysis, or cerebral oedema (in late status).

### Establish aetiology

The outcome of status to a great extent depends on the aetiology, and the urgent treatment of causal factors is vital. Computed tomographic scanning and cerebrospinal fluid examination are often necessary. The choice of investigations depends on the clinical circumstances.

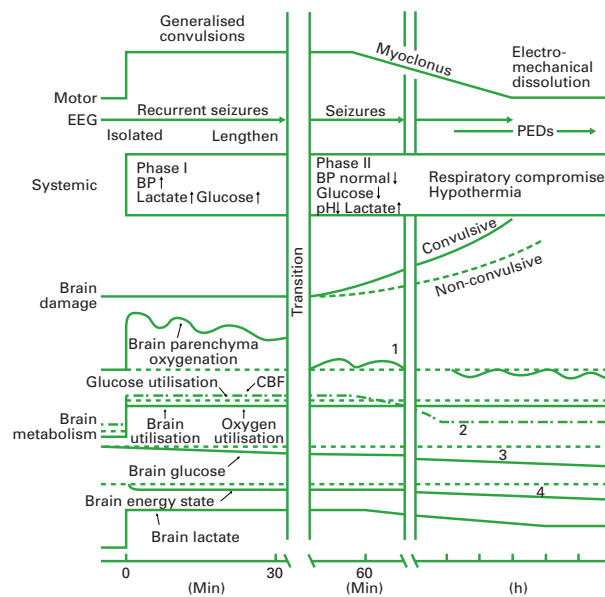
### Other complications

Table 3 lists some of the complications encountered in status and these often need emergency treatment in their own right. Failure to do so can perpetuate the status and worsen outcome.

### Intensive care and seizure/EEG monitoring

If seizures are continuing in spite of the measures taken above, the patient must be transferred to an intensive care setting, where intensive monitoring is desirable, including: intra-arterial blood pressure, capnography, oximetry, and central venous and arterial pressure monitoring.

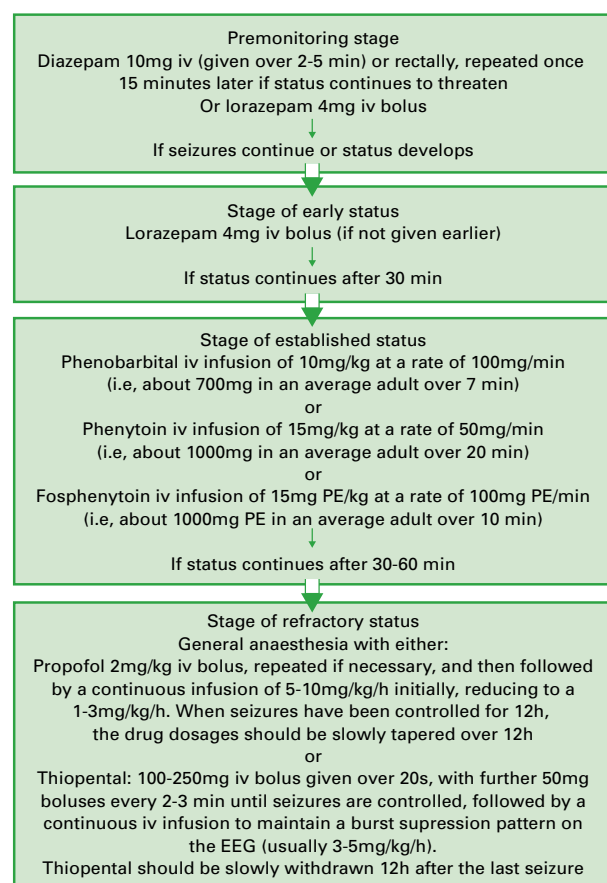
Motor activity in status diminishes over time, and may cease in spite of ongoing epileptic electrographic activity, especially in comatose or ventilated patients. Such electrographic activity is potentially damaging to the cortical neurones and anaesthetic treatment is targeted to suppress it by the attainment of the anaesthetic level of burst suppression. Both ongoing epileptic activity, and also burst suppression, require neurophysiological monitoring and this can be provided by either a full EEG or a cerebral function monitor (CFM). The CFM has to be calibrated for each individual patient, but then has the advantage over EEG of simplicity of use. Burst suppression provides an arbitrary physiological target for the titration of barbiturate or anaesthetic treatment, with drug dosing commonly set at a level which aims to produce burst suppression with inter-burst intervals of between 2–30 seconds.



**Figure 1** Temporal changes which occur as tonic-clonic status epilepticus progresses. Motor activity lessens, the electroencephalogram (EEG) evolves and profound physiological changes occur, both systematically and cerebrally. In the first 30 minutes or so, physiological changes are largely compensatory, but as the seizures continue these compensatory mechanisms break down. The biphasic evolution is emphasised periodic epileptic discharge (PED). 1, loss of reactivity of brain oxygen tension; 2, mismatch between the sustained increase in oxygen and glucose utilisation and a fall in cerebral blood flow; 3, a depletion of cerebral glucose and glycogen concentrations; 4, a decline in cerebral energy state. Reproduced from Shorvon SD. *A handbook of epilepsy treatment*, with permission of the publisher, Blackwell Science.

**Table 3** Medical complications in status epilepticus. Reproduced from Shorvon SD. *A handbook of epilepsy treatment*, with permission of the publisher, Blackwell Science

<b>Cerebral</b>	
►	Hypoxic/metabolic cerebral damage
►	Seizure induced cerebral damage
►	Cerebral oedema and raised intracranial pressure
►	Cerebral venous thrombosis
►	Cerebral haemorrhage and infarction
<b>Cardiorespiratory and autonomic</b>	
►	Hypotension
►	Hypertension
►	Cardiac failure, tachy- and bradycardia, cardiac arrest, cardiogenic shock
►	Respiratory failure
►	Disturbances of respiratory rate and rhythm, apnoea
►	Pulmonary oedema, hypertension, embolism, pneumonia, aspiration
►	Hyperpyrexia
►	Sweating, hypersecretion, tracheobronchial obstruction
►	Peripheral ischaemia
<b>Metabolic and systemic</b>	
►	Dehydration
►	Electrolyte disturbance (especially hyponatraemia, hyperkalaemia, hypoglycaemia)
►	Acute renal failure (especially acute tubular necrosis)
►	Acute hepatic failure
►	Acute pancreatitis
<b>Other</b>	
►	Disseminated intravascular coagulopathy/multi-organ failure
►	Rhabdomyolysis
►	Fractures
►	Infections (especially pulmonary, skin, urinary)
►	Thrombophlebitis, dermal injury



**Figure 2** Emergency drug treatment of tonic-clonic status in adults (PE = phenytoin equivalents). Reproduced from Shorvon SD. *A handbook of epilepsy treatment*, with permission of the publisher, Blackwell Science.

### Drug treatment of tonic-clonic status epilepticus

It is convenient to divide the treatment of status into stages. This is in recognition of the fact that the risk of cerebral damage caused by seizure activity is slight in the first hour or two of status, and increases with duration of ongoing electrographic activity after this. Initially relatively simple treatment is given, but within two hours, if the epileptic activity is not under control, general anaesthesia is recommended.

Many drugs can be given, and the author's recommended regimen is shown in fig 2 and table 4. There is little evidence that this regimen is greatly superior to other rational schemes. What is essential, however, is to have a *protocol* for the treatment of status, and this simple measure has itself been shown to reduce the morbidity and mortality of status.

#### Premonitory stage of status epilepticus

In patients with established epilepsy, there is often a prodromal period before status develops in which there is a gradual (over hours) increase in the frequency of epileptic seizures. Parenteral drug treatment during this stage will usually terminate the seizures and prevent true status developing. The conventional treatment is with either intravenous or rectal diazepam. Intravenous diazepam is given at a rate not exceeding 2–5 mg/min, using the Diazemuls formulation. Rectal administration is either as the intravenous preparation infused from a syringe via a plastic catheter, or as the ready made proprietary rectal tube preparation Stesolid which is convenient and easy. Diazepam

**Table 4** Drug dosages for convulsive status epilepticus. Reproduced from Shorvon SD. *A handbook of epilepsy treatment*, with permission of the publisher, Blackwell Science

Drug	Route	Adult dose	Paediatric dose
Clomethiazole	iv infusion of 0.8% solution	40–100 ml (320–800 mg) at 5–15 ml/min, then 0.5–20 ml/min	0.1 ml/kg/min increasing every 2–4 h as required
Clonazepam	iv bolus iv infusion	1 mg at < 2 mg/min* Maintenance dose 10 mg/24 h	250–500 µg at < 2 mg/min
Diazepam	iv bolus rectal administration iv infusion	10–20 mg at < 5 mg/min* 10–30 mg* 3 mg/kg/day	0.25–0.5 mg/kg at < 2–5 mg/min 0.5–0.75 mg/kg 200–300 µg/kg/day
Fosphenytoin	iv bolus	15 mg PE/kg at a rate of < 100–150 mg PE/min Maintenance dose: 4–5 mg/kg/day iv or im	
Isoflurane	inhalation	End tidal concentrations of 0.8–2% to maintain burst suppression	
Lidocaine	iv bolus iv infusion	1.5–2.0 mg/kg at < 50 mg/min* Maintenance dose: 3–4 mg/kg/h	
Lorazepam	iv bolus	4 mg*	0.1 mg/kg
Midazolam	im or rectally iv bolus iv infusion buccal	5–10 mg* 0.1–0.3 mg/kg at < 4 mg/min* 0.05–0.4 mg/kg/h 10 mg	0.15–0.3 mg/kg*  10 mg
Paraldehyde	rectally or im	5–10 ml (approximately 1 g/ml) in equal volume of water*	0.07–0.35 ml/kg*
Pentobarbital	iv infusion	5–20 mg/kg at a rate of < 25 mg/min, then 0.5–1.0 mg/kg/h increasing to 1–3 mg/kg/h	
Phenobarbital	iv bolus	10 mg/kg at a rate of < 100 mg/min Maintenance: 1–4 mg/kg/day	15–20 mg/kg at a rate of < 100 mg/min 3–4 mg/kg/day
Phenytoin	iv bolus/infusion	15–18 mg/kg at a rate of < 50 mg/kg	20 mg/kg at a rate of < 25 mg/min
Propofol	iv infusion	2 mg/kg, then 5–10 mg/kg/h initially, reducing to 1–3 mg/kg/h to maintain burst suppression	
Thiopental	iv infusion	100–250 mg bolus given over 20 s, then further 50 mg boluses every 2–3 mins until seizures are controlled. Then infusion to maintain burst suppression (3–5 mg/kg/h)	

\*May be repeated.

PE, phenytoin equivalents; iv, intravenous; im, intramuscular.

suppositories should not be used, as absorption is too slow. The adult bolus intravenous or rectal dose is 10–20 mg, and in children the equivalent bolus dose is 0.2–0.3 mg/kg.

More recent work has shown that midazolam or lorazepam can serve as alternatives and have some advantages over diazepam, although the long experience enjoyed by diazepam is not shared by these other drugs. Lorazepam can be given by an intravenous bolus of 4 mg in adults or 0.1 mg/kg in children; it is longer lasting than diazepam and the rate of injection is not critical. Midazolam has the advantage that it can be given by intramuscular injection or buccal instillation. A published randomised trial has shown that buccal midazolam has equal efficacy and as rapid an action as rectal diazepam—and is more convenient, potentially faster to administer, and less stigmatising. The dose used is 10 mg drawn up into a syringe and instilled into the mouth between the cheeks and gums.

### Early status epilepticus

This is defined as the first 30 minutes of status. It is usual to initiate treatment with a fast acting benzodiazepine, and intravenous lorazepam is the drug of choice. Alternatives include other intravenous benzodiazepines or intravenous lignocaine, the latter possibly being preferable in patients with respiratory disease. In most episodes of status, initial treatment will be highly effective. Even if seizures cease, 24

hour inpatient observation should follow. In persons without a previous history of epilepsy, chronic antiepileptic drug treatment should be introduced, and in those already on maintenance antiepileptic treatment this should be reviewed.

### Established status epilepticus

There are three alternative first line treatment options, but each has drawbacks and status at this stage carries an appreciable morbidity. These are subanaesthetic doses of phenobarbitone, phenytoin or fosphenytoin. All three are given by intravenous loading, and followed by repeated oral (phenytoin or phenobarbitone) or intravenous supplementation.

Subanaesthetic infusions of benzodiazepine drugs were once fashionable in the stage of established status. The infusions carry the risk of respiratory depression and hypotension. There is also a risk of sudden collapse caused by accumulation of the drug. For all these reasons, infusions at this stage should not be given. Chormethiazole infusion has been frequently used in the treatment of status, but carries similar risks. Intravenous valproate has been proposed as a suitable treatment, but again experience is limited. Lorazepam and lignocaine are essentially short term treatment, and so should not be employed at this stage.



### Refractory status epilepticus

In most patients, if seizures continue for 60–90 minutes in spite of the treatment outlined above, full anaesthesia is required. In some emergency situations (for example, postoperative status, severe or complicated convulsive status, patients already in the intensive therapy unit (ITU)), anaesthesia can and should be introduced earlier. The prognosis in status requiring anaesthesia is much poorer, and there is a high risk of mortality and morbidity. The principles of treatment are similar for all anaesthetics, and a wide range of barbiturate and non-barbiturate anaesthetic agents could be used.

Barbiturate anaesthetics are good antiepileptic drugs but have poor pharmacokinetics. Thiopental, for example, has saturable kinetics, has a strong tendency to accumulate (thus recovery times are very long), can cause profound hypotension, and is subject to acute tolerance. The non-barbiturates, such as propofol, have much more suitable pharmacokinetic properties, but have little if any intrinsic antiepileptic properties—their action is simply to reduce the EEG to a burst suppression pattern. Which of these two approaches is most successful in status has not been established. Benzodiazepine infusions can be given at anaesthetic doses, in an ITU setting. Drug induced hypotension is a common side effect and the risks of drug accumulation complicate their use. Midazolam is probably the benzodiazepine of choice because of its short half life and large volume of distribution, and encouraging early reports of its use in status have been published.

All the anaesthetic drugs are given in doses sufficient to induce deep unconsciousness; therefore assisted respiration, intensive cardiovascular monitoring, and the full panoply of intensive care are essential. The depth of anaesthesia should be that which abolishes all clinical and EEG epileptic activity (often requiring sedation to the point of burst suppression on the EEG), and cerebral electrical activity must by necessity be visualised, either with a formal EEG or a cerebral function monitor.

### Failure to respond to emergency treatment

In the great majority of cases, the above measures will control the seizures and the status will resolve. If drug treatment fails, there are often complicating factors. Common reasons for treatment failure are:

- (1) Inadequate drug treatment
  - ▶ Insufficient emergency antiepileptic drug treatment. A particular problem is the administration of intravenous drugs at too low a dosage (for example, with phenobarbitone or phenytoin).
  - ▶ Failure to initiate or continue maintenance antiepileptic drug therapy in parallel with the acute emergency treatment. This will result in recrudescence of seizures once the effects of the emergency drug treatment has worn off.
- (2) Additional medical factors
  - ▶ Medical complications can exacerbate seizures (table 3).
  - ▶ Failure to treat (or identify) the underlying cause can result in intractable status. This is particularly the case in acute progressive cerebral disorders and cerebral infections.
- (3) Misdiagnosis
  - ▶ A common problem is to fail to diagnose pseudostatus which, in specialist practice, is more common than true epileptic status.

### Summary

- ▶ Most episodes of status develop de novo, without a prior history of epilepsy. In such cases the status is almost always due to acute cerebral pathology
- ▶ In patients with pre-existing epilepsy, status can be precipitated by drug withdrawal, intercurrent illness or metabolic disturbance, or the progression of the underlying disease
- ▶ A main purpose of treatment is to prevent the cerebral damage which can result from status. As this is, at least in part, caused by the direct effect of seizure activity, it is imperative to control overt and electrographic discharges
- ▶ The risk of cerebral damage increases progressively after 1–2 hours of continuous status. If seizures are not controlled within this period, the patient should be considered to be in refractory status and general anaesthesia should be instituted
- ▶ General measures in the treatment of status include: attention to cardiorespiratory function, emergency investigation, initiation of maintenance antiepileptic drug treatment, use of intravenous glucose and thiamine, correction of metabolic abnormalities, attention to hypotension, cardiac dysrhythmia, hyperthermia, lactic acidosis, rhabdomyolysis, metabolic disturbance, cerebral oedema, EEG monitoring
- ▶ It is essential to have a protocol for the treatment of status. This simple measure has itself been shown to reduce the morbidity and mortality of status
- ▶ A typical protocol for emergency drug use is:  
Early status—lorazepam  
Established status—phenytoin, phenobarbitone or fosphenytoin  
Refractory status—anaesthesia with either thiopentone or propofol
- ▶ EEG monitoring is essential in the anaesthetised patient to assess both response to treatment and also the depth of anaesthesia

### Treatment of non-convulsive status epilepticus

Treatment of non-convulsive status epilepticus can take various forms (table 1).

Typical absence status (petit mal status) can usually be stopped by intravenous benzodiazepine: diazepam 0.2–0.3 mg/kg, clonazepam 1 mg (0.25–0.5 mg in children) or lorazepam 0.07 mg/kg (0.1 mg/kg in children), repeated if required. If this is ineffective, intravenous chlormethiazole, phenytoin or valproate may be needed. In childhood absence epilepsy, maintenance treatment with valproate or ethosuximide is required once the status is controlled.

De novo absence status of late onset is a condition which presents in later life, usually without a history of recent epilepsy. It is commonly caused by drug withdrawal (especially psychotropic drugs or benzodiazepines), and can be safely treated by intravenous diazepam, lorazepam or chlormethiazole. Long term maintenance treatment is not usually required.

Complex partial status is usually best treated by benzodiazepine therapy. There is controversy about the need for intravenous treatment in complex partial therapy, and in most recurrent or prolonged cases, oral therapy is probably optimum.

Atypical absence status is best treated with oral benzodiazepine or other conventional antiepileptics. Both atypical absence and complex partial status may be resistant to treatment, but most episodes are self terminating, albeit sometimes after hours of continuous seizure activity.

## Key references

- 1 **Brown JK, Hussain I.** Status epilepticus: 1. Pathogenesis. *Dev Med Child Neurol* 1991;**33**:97–109.  
 ► **A review of the pathogenesis of status, with an emphasis on childhood status.**
- 2 **Meldrum BS.** Excitotoxicity and epileptic brain damage. *Epilepsy Res* 1991;**10**:55–61.  
 ► **A review of the mechanisms of brain damage in status.**
- 3 **Shorvon SD.** *Status epilepticus: its clinical features and treatment in children and adults.* Cambridge: Cambridge University Press. 1994.  
 ► **A comprehensive review of all aspects of status epilepticus.**
- 4 **Shorvon SD.** Emergency treatment of acute seizures, serial seizures, seizure cluster and status epilepticus. In: Shorvon SD. *Handbook of epilepsy treatment.* Oxford: Blackwell Science, 2000:173–94.  
 ► **The current article is largely derived from this chapter in this book which is a review of all aspects of epilepsy treatment.**
- 5 **Treiman DM, Meyers PD, Walton NY, et al.** A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs status epilepticus cooperative study group. *N Engl J Med* 1998;**339**:792–8.  
 ► **This is a report of one of the few randomised controlled studies in the field of status epilepticus. However, the definition of status for inclusion into the study is wide, and not necessarily commensurate with routine neurological practice outside the USA.**

ii27



# Want to know more?

## Data supplements

Limited space in printed journals means that interesting data and other material are often edited out of articles; however, limitless cyberspace means that we can include this information online.  
 Look out for additional tables, references, illustrations.

**www.jnnp.com**