REVIEW ARTICLE
Status epilepticus

M. G. Chapman,[1] M. Smith[2] and N. P. Hirsch[2]

1 Locum Consultant Neuroanaesthetist, and 2 Consultant Neuroanaesthetist, Department of Neuroanaesthesia and Intensive Care, The National Hospital for Neurology and Neurosurgery, University College London Hospitals, Queen Square, London WC1N 3BG, UK

Summary
Status epilepticus is a medical emergency that requires rapid and vigorous treatment to prevent neuronal damage and systemic complications. Failure to diagnose and treat status epilepticus accurately and effectively results in significant morbidity and mortality. Cerebral metabolic decompensation occurs after approximately 30 min of uncontrolled convulsive activity, and the window for treatment is therefore limited. Therapy should proceed simultaneously on four fronts: termination of seizures; prevention of seizure recurrence once status is controlled; management of precipitating causes of status epilepticus; management of the complications. This article reviews current opinions about the classification, aetiology and pathophysiology of adult generalised convulsive status epilepticus and details practical management strategies for treatment of this life-threatening condition.

Status epilepticus is a major medical emergency that is commonly seen in the community, the Accident and Emergency Department and the Intensive Therapy Unit. It affects approximately 14 000 people each year in the United Kingdom [1], and population studies in the United States show a frequency of 50 patients per 100 000 residents per annum, giving an estimate of approximately 150 000 cases per year [2]. Failure to diagnose and treat status epilepticus accurately and effectively results in significant morbidity and mortality. This article reviews current opinions about the aetiology and pathophysiology of adult status epilepticus and details practical management strategies for treatment of the condition.

Classification, aetiology and pathophysiology

Definition of status epilepticus
Although mechanistic and electroencephalographic (EEG) definitions of status epilepticus exist, operational definitions are of more practical use in the clinical setting

[3]. Thus status epilepticus is usually defined as continuous seizure activity lasting 30 min or more *or* intermittent seizure activity lasting 30 min or more during which consciousness is not regained [4]. This definition allows a distinction between status epilepticus and typical epileptic seizures (isolated or serial) that generally last several minutes before cessation. The definition duration is specified as it is recognised that seizure activity lasting longer is associated with progressive physiological and neurochemical changes that may permanently alter neuronal function. However, no data exist as to precisely when these changes occur and recent publications have suggested that specifying durations of 10–20 min would result in safer definitions [5, 6].

Classification and diagnosis
Many types of epileptic seizures have been described and it therefore follows that there are many types of status epilepticus; this has led to complex classifications of status epilepticus [7, 8]. However, using electroclinical features, status epilepticus may be classified simply by the presence

Table 1 Classification of status epilepticus

	Convulsive	Non-convulsive
Generalised	Tonic-clonic (grand mal) seizures Tonic seizures Myoclonic seizures	Absence attacks (petit mal)
Partial	Partial motor seizures	Complex partial seizures

of motor convulsions (convulsive status epilepticus) or their absence (non-convulsive status epilepticus). They may be further subdivided into status epilepticus that affects the whole body (generalised status epilepticus) or only part of the body (partial status epilepticus). Thus status epilepticus may be generalised convulsive (tonic clonic status epilepticus), generalised non-convulsive (e.g. absence attacks), partial convulsive (simple partial motor seizures) or partial non-convulsive (complex partial seizures). Accurate diagnosis of the type of status epilepticus is essential, as management may be different for each. This review concentrates on generalised convulsive status epilepticus, which is the form most commonly observed in general hospital practice. Henceforth in this article, the phrase 'status epilepticus' will be taken to mean generalised convulsive status epilepticus (Table 1).

Status epilepticus is usually easily diagnosed by observation. Seizures are characterised by loss of consciousness, tonic−clonic muscle activity, tongue biting and urinary incontinence. However, it is important to understand that as the duration of seizures increases, convulsive activity may become more subtle, e.g. eyelid twitching only, despite continuing electrical seizure activity [9]. The diagnosis of status epilepticus is usually obvious but the differential diagnosis of status epilepticus includes rigors due to sepsis, myoclonic jerking, generalised dystonia and pseudostatus epilepticus. The latter consists of seizures that are psychogenic in origin and differentiation from true status epilepticus may be

difficult. However, the seizures seen in psychogenic status epilepticus tend to be flamboyant and, unlike its true counterpart, consciousness is often retained during convulsions [10]. Clinical features may not be reliable in differentiating between psychogenic and true status epilepticus [11]. It is important to note that psychogenic status epilepticus has been reported after general anaesthesia [12].

Non-convulsive status epilepticus is more difficult to diagnose [13]. Clinical features include blunting of consciousness that may fluctuate, agitation, abnormal eye movements (including ocular deviation and nystagmus), aphasia and abnormal limb posturing. The lack of specificity of clinical signs is reflected in the fact that there is no generally accepted classification of non-convulsive status epilepticus [14]. Diagnosis therefore requires a high degree of suspicion and can only be confirmed definitively by EEG examination. In a recent study, 8% of patients in coma met the diagnostic criteria for non-convulsive status epilepticus [15].

Aetiology

Although individuals with a history of epilepsy constitute a group that is particularly at risk of developing status epilepticus, approximately 50% of cases occur in the absence of previous epilepsy [16]. Many cases arise in patients with acute neurological or medical illnesses. Epidemiological studies reveal that the aetiology of status epilepticus may be divided into acute and chronic processes [17]. These are summarised in Table 2. The search for a precipitating factor is of fundamental importance, as it will dictate appropriate therapy. In addition, the aetiology of status epilepticus has a direct bearing on mortality [18].

Pathophysiology

Five sequential stages of electroencephalographic progression in status epilepticus have been described in animal models [19]. Discrete seizures give way to seizures that merge and these are followed by continuous ictal activity that

Table 2 Aetiology of generalised convulsive status epilepticus

Acute processes	Chronic processes
Electrolyte imbalance, e.g. Na^+, Ca^{2+}	Pre-existing epilepsy
Cerebrovascular accident	Poor anticonvulsant drug compliance or change of anticonvulsant therapy
Cerebral trauma (including surgery)	Chronic alcoholism
Drug toxicity	Cerebral tumours or other space-occupying lesions
Cerebral anoxic/hypoxic damage	
Central nervous system infection, e.g. encephalitis, meningitis	
Sepsis syndrome	
Renal failure	

EEG activity

discrete seizure activity

merging seizure activity

continuous seizure activity

intermittent suppression of seizure activity

periodic epileptiform discharges

Clinical seizure activity

discrete muscular twitching

continuous muscular twitching

minimal muscular twitching
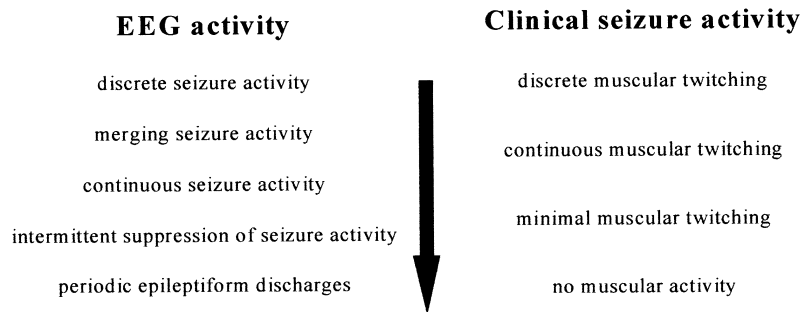
no muscular activity

Figure 1 Electrical and clinical seizure activity in evolving status epilepticus.

becomes punctuated by low-voltage flat periods. Finally, periodic epileptiform discharges appear on an almost flat (isoelectric) background. These stages of changing EEG activity largely correspond to changes in clinical seizure activity [20] and are shown schematically in Fig. 1.

Animal models have helped elucidate the neurophysiological changes that occur during the progression of status epilepticus. For the purposes of clarity, Lothman [21] divides the derangement into two phases (Fig. 2). During Phase 1, the increased cerebral metabolic demand caused by abnormally discharging cerebral cells is satisfied by an increase in cerebral blood flow and an increase in autonomic activity that results in increased arterial blood pressure, increased blood glucose levels, sweating, hyperpyrexia and salivation. After approximately 30 min of seizure activity, Phase 2 is characterised by failure of cerebral autoregulation, decreased cerebral blood flow, an increase in intracranial pressure and systemic hypotension.

These result in a decrease in cerebral perfusion pressure. At this stage, cerebral oxygen delivery cannot keep pace with demand and electromechanical dissociation may occur, in which, although electrical cerebral seizure activity continues, the clinical manifestations may be restricted to minor twitching [19].

Prolonged status epilepticus is associated with widespread systemic derangement that compounds the problem of inadequate cerebral oxygen supply (Table 3). It is unsurprising that respiratory changes occur during seizures; Phase 1 is generally accompanied by an increase in minute ventilation but this gives way to apnoea and hypopnoea in Phase 2 [22]. Pulmonary vascular resistance is persistently elevated [23] and the development of pulmonary oedema during status epilepticus is well documented [24, 25]. A decrease in the sensitivity of laryngeal reflexes can result in pulmonary aspiration of stomach contents. These factors contribute to the
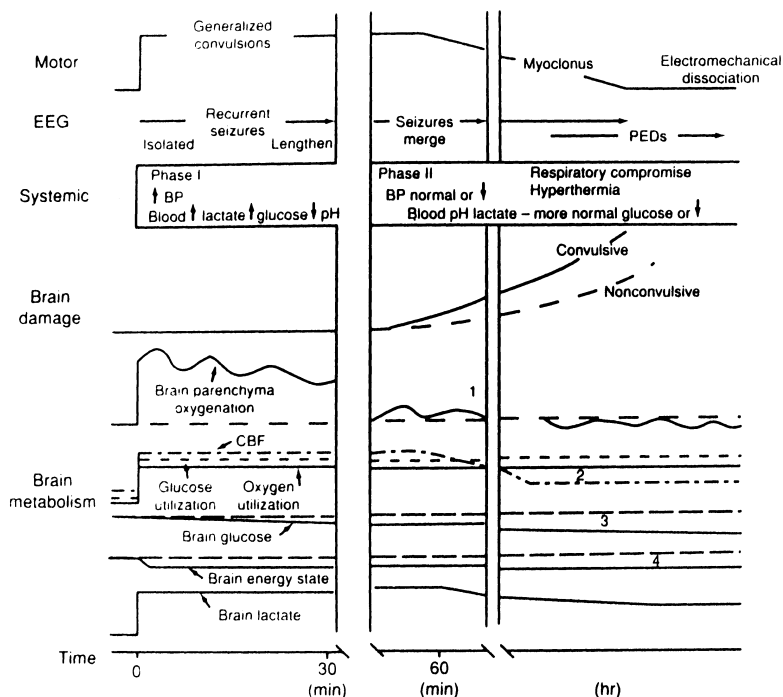

Figure 2 Neurophysiological changes in status epilepticus. Reproduced with permission from Advanstar Communications Inc. as reprinted from *Neurology* 1999; 40: 13–23. PEDs: periodic epileptiform discharges. CBF: cerebral blood flow.

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Table 3 Systemic complications of generalised convulsive status epilepticus.

Central nervous system
  Cerebral hypoxia/anoxia
  Cerebral oedema
  Cerebral haemorrhage
  Cerebral venous thrombosis
Cardiovascular system
  Myocardial infarction
  Hypo/hypertension
  Arrhythmias
  Cardiac arrest
  Cardiogenic shock
Respiratory system
  Apnoea/hypopnoea
  Respiratory failure
  Aspiration pneumonia
  Pulmonary hypertension and oedema
  Pulmonary embolus
Metabolic derangements
  Dehydration
  Electrolyte disturbance, e.g. hyponatraemia,
    hypoglycaemia, hyperkalaemia
  Metabolic acidosis
  Acute tubular necrosis
  Acute hepatic necrosis
  Acute pancreatitis
Other
  Multiple organ dysfunction syndrome
  Disseminated intravascular coagulopathy
  Rhabdomyolysis
  Fractures

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development of hypoxaemia that further reduces cerebral oxygen supply. Cardiovascular changes are invariably seen during status epilepticus. Although an increase in cardiac output is seen in Phase 1 [26], cerebral oxygen delivery may be compromised by hypotension during Phase 2 [27] because of cerebral, metabolic and endocrine changes as well as drug therapy. Arrhythmias are common and potentially life threatening in approximately 60% of patients with prolonged status epilepticus [28].

Metabolic derangement may also contribute to neuronal damage. An increase in body temperature occurs in up to 80% of cases and is caused by excessive muscle activity and massive catecholamine release [29]. Research on animals has demonstrated that hyperthermia plays an important role in the mechanism of neuronal, and especially cerebellar, damage [30]. Anaerobic muscle metabolism is widespread during status epilepticus and the resultant lactic acidosis may be severe. Aminoff and Simon found that pH was < 7.3 in 81% of cases of status epilepticus and < 7.0 in 35% [23].

Neuronal damage

Animal models of status epilepticus, in which systemic factors are kept within normal physiological limits, have shown that acute and chronic histopathological changes

occur, with cell loss consistently occurring in limbic structures such as the hippocampus [31]. This suggests that neuronal damage during status epilepticus is due to seizure activity *per se* and is compounded, but not initiated, by systemic physiological derangements. The neuronal damage that occurs is reflected by increased levels of neurone-specific enolase, a sensitive marker of seizure-induced cell damage [32].
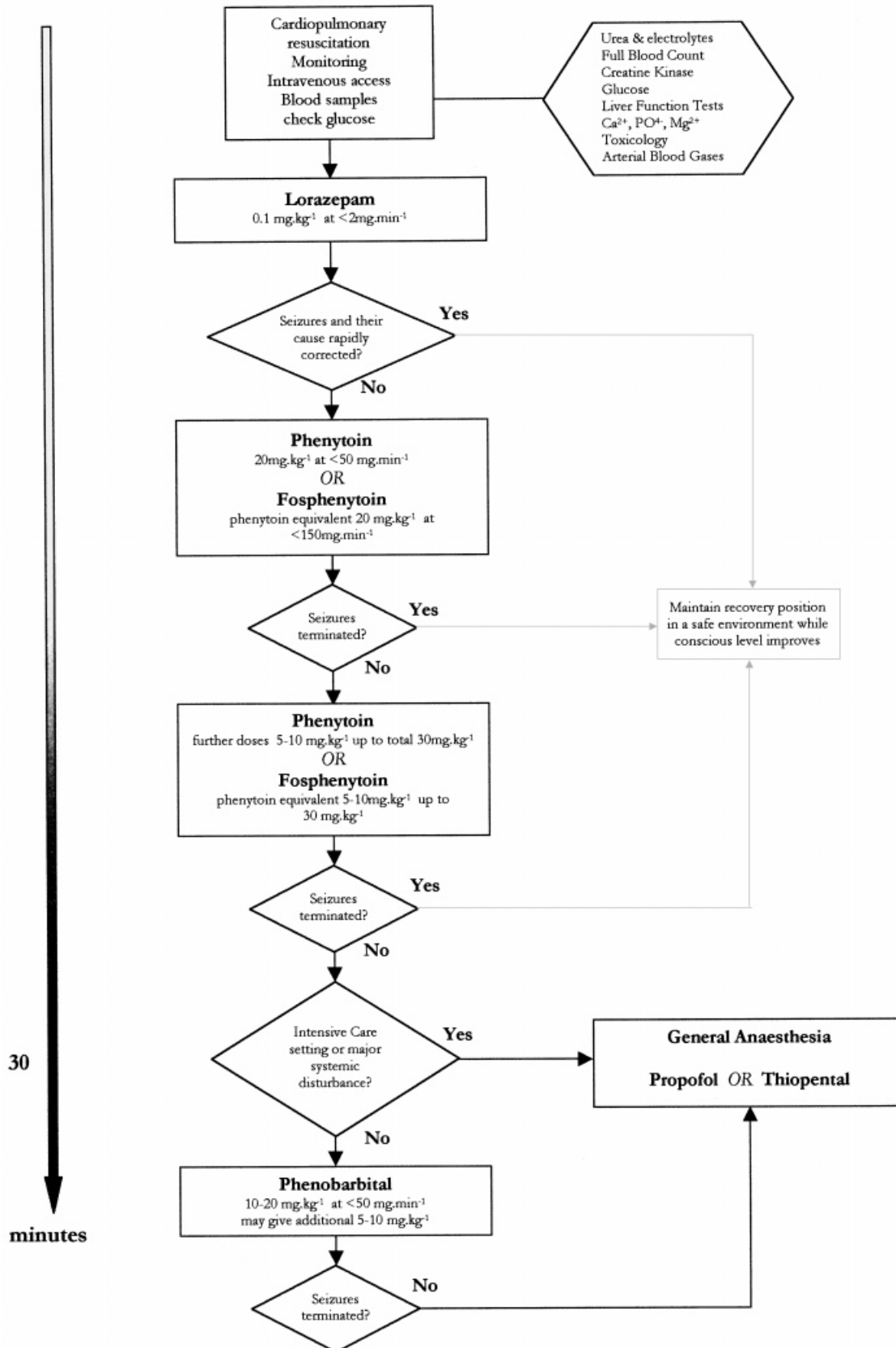
Many mechanisms have been proposed for the cell damage that occurs in status epilepticus but glutamate, an excitatory amino acid with the ability to destroy neurones by causing an influx of calcium, is the likely perpetrator [28]. However, reduction of $GABA_A$ receptor inhibition is also likely to be involved in this process [33].

Treatment

Status epilepticus is a medical emergency that requires rapid and vigorous treatment to prevent neuronal damage and systemic complications. As previously discussed, cerebral metabolic decompensation occurs after approximately 30 min of uncontrolled convulsive activity, and the window for treatment is therefore limited. In addition, there is evidence that the longer an episode of status epilepticus continues, the more refractory to treatment it becomes and the greater is the likelihood of chronic epilepsy [34]. Therapy should proceed simultaneously on four fronts: termination of status epilepticus; prevention of seizure recurrence once status epilepticus is terminated; management of precipitating causes of status epilepticus; management of complications [35]. In addition, EEG confirmation of the diagnosis should be sought as early as possible so that pseudostatus epilepticus may be excluded. In this review, treatment strategies will be divided into emergency management, pharmacotherapy and the management of complications.

Emergency medical management

The essential principles of emergency management are those of basic life support, namely maintenance of the airway and breathing and ensuring an adequate circulation. In status epilepticus, the airway must be maintained from the earliest stages and tracheal intubation will usually be required while seizures are being controlled. This should ensure adequate ventilation and oxygenation and will prevent the pulmonary aspiration of gastric contents. The use of neuromuscular blockade is clearly essential to aid tracheal intubation, but should not be extended beyond this period because it will obscure clinical seizure activity. There are few other indications for the use of neuromuscular blocking drugs in status epilepticus, although if longer-term neuromuscular blockade is indicated, continuous EEG monitoring must be initiated

Cardiopulmonary
resuscitation
Monitoring
Intravenous access
Blood samples
check glucose

Urea & electrolytes
Full Blood Count
Creatine Kinase
Glucose
Liver Function Tests
Ca^{2+}, PO^{4-}, Mg^{2+}
Toxicology
Arterial Blood Gases

Lorazepam
0.1 mg.kg^{-1} at <2mg.min^{-1}

Seizures and their cause rapidly corrected? — **Yes**

No

Phenytoin
20mg.kg^{-1} at <50 mg.min^{-1}
OR
Fosphenytoin
phenytoin equivalent 20 mg.kg^{-1} at <150mg.min^{-1}

Seizures terminated? — **Yes**

No

Maintain recovery position in a safe environment while conscious level improves

Phenytoin
further doses 5-10 mg.kg^{-1} up to total 30mg.kg^{-1}
OR
Fosphenytoin
phenytoin equivalent 5-10mg.kg^{-1} up to 30 mg.kg^{-1}

Seizures terminated? — **Yes**

No

Intensive Care setting or major systemic disturbance? — **Yes**

No

General Anaesthesia

Propofol *OR* **Thiopental**

Phenobarbital
10-20 mg.kg^{-1} at <50 mg.min^{-1}
may give additional 5-10 mg.kg^{-1}

Seizures terminated? — **No**

30

minutes

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to allow confirmation of the continued absence of seizures.

Two large gauge intravenous catheters should be inserted to allow fluid resuscitation and pharmacotherapy. Inotrope therapy may become necessary later, particularly if general anaesthesia is required to control the seizures. As already discussed, cerebral autoregulation becomes disrupted after approximately 30 min of status epilepticus and systemic blood pressure must be maintained at normal or supranormal levels to ensure an adequate cerebral perfusion pressure. This is vital to maintain adequate brain perfusion at a time of high cerebral metabolic demand.

Monitoring should be initiated during the early phase of management of status epilepticus and should include ECG, non-invasive blood pressure and pulse oximetry in all patients. Direct arterial blood pressure, central venous pressure and oesophageal Doppler cardiac output monitoring, as well as pulmonary artery catheterisation, should be considered in unstable patients, especially if there are increasing inotrope requirements. Urinary catheterisation and temperature monitoring should also be instituted.

Blood samples should be taken for urgent analysis of full blood count, electrolytes, blood glucose, arterial blood gases and anti-epileptic drug levels (if the patient is on long-term therapy). Liver function tests, a toxicology screen and measurement of creatine kinase levels should also be performed.

A bedside measurement of blood glucose should be made. If significant hypoglycaemia is present, glucose 50% 50 ml should be administered without waiting for the formal laboratory result to become available. However, it is important that hypoglycaemia is confirmed before glucose is administered because hyperglycaemia may exacerbate neuronal damage caused by status epilepticus [36, 37]. If there is a history or suspicion of alcoholism, intravenous thiamine 100 mg should be given at the same time as the glucose to avoid precipitating Wernicke's encephalopathy. Bicarbonate should only be given if the pH is low enough to be of immediate concern. It is unlikely that status epilepticus-induced acidosis results in permanent injury and it is possible that acidosis may be neuroprotective. Furthermore, administration of large volumes of bicarbonate may result in a residual alkalosis when the seizures have been controlled, as well as comprising a large fluid load.

When the situation has been stabilised and the seizures brought under control, the cause of the patient's seizures should be sought. A careful history from relatives or friends might highlight precipitating factors such as a recent change in anticonvulsant medication, alcohol withdrawal, drug overdose, and stroke or central nervous system infection. A description of the initiating seizure might also reveal clues as to the cause and the need for other urgent investigation such as computerised tomography or magnetic resonance imaging. These might reveal a focal process or the presence of subarachnoid haemorrhage that requires further investigation and treatment. Cerebrospinal fluid examination might also be indicated in the absence of raised intracranial pressure. It is crucial that pharmacotherapy is not delayed whilst relatives or friends are being interviewed or laboratory and radiological investigations obtained.

Pharmacological therapy

The drug treatment of status epilepticus has recently been reviewed in detail [38]. The fundamental goal of therapy is the rapid and safe termination of the electroencephalographic seizure and prevention of its recurrence. This should be attained if possible without adverse effects on the cardiovascular or respiratory systems and without altering the level of consciousness. Unfortunately, there is no ideal drug and a compromise between effective therapy and its inevitable side-effects often has to be accepted. There have been many attempts to determine the optimum treatment regimen, and a recent 5-year, randomised, multicentre study compared four options for initial intravenous therapy [39]. In this study, lorazepam 0.1 mg.kg^{-1} was effective as initial therapy in 65% of patients, phenobarbital 15 mg.kg^{-1} in 58%, diazepam 0.15 mg.kg^{-1} followed by phenytoin 18 mg.kg^{-1} in 56% and phenytoin 18 mg.kg^{-1} in 44%. Only the difference in efficacy between lorazepam and phenytoin was statistically significant. This trial did not include a lorazepam plus phenytoin treatment arm, which is a favoured regimen [17]. An algorithm for the drug treatment of status epilepticus is shown in Fig. 3.

Benzodiazepines

These drugs act as agonists at GABA$_A$ receptors and potentiate inhibition of neuronal firing. They are potent and rapidly acting and therefore have a place in the control of early status epilepticus (premonitory phase and first 30 min). Intravenous lorazepam 0.1 mg.kg^{-1} is widely considered to be the drug of choice for the acute management of status epilepticus. It is less lipophilic than diazepam, but the slight delay in brain uptake compared to diazepam is not clinically significant and the mean time to seizure cessation is 3 min [40]. It has a long effective duration of action (> 12 h), with recurrence rates probably similar to phenobarbital and phenytoin when used as initial therapy [39]. Lorazepam has been

Figure 3 Algorithm for the treatment of status epilepticus.

found to be superior to phenytoin alone in the most comprehensive controlled clinical trial directly comparing the efficacy of standard regimens in the control of status epilepticus, when it was effective in controlling status epilepticus in 65% of patients. It was also found to be the easiest and quickest drug to administer [39]. In an earlier study, lorazepam was successful in 85% of cases [40] but clinical cessation of seizures was used as the criterion for success in this study and it is likely that 20% of patients in whom status epilepticus appears to have been terminated actually remain in electrophysiological status [39]. Some physicians continue to start treatment with intravenous diazepam 0.15 mg.kg^{-1}, but this drug has a very short effective duration of action because of rapid redistribution to body fat stores [41]. It must therefore be followed within 20 min of administration by a long-acting drug such as phenytoin. Diazepam can be given by the rectal route, although the bioavailability is not as good. However, it can be administered by family members and thus decrease the time to treatment of patients with recurrent status epilepticus. Intravenous midazolam 0.2 mg.kg^{-1} has also been used as initial therapy but this drug is short acting. Continuous infusion has been used in the treatment of refractory status [42]. All benzodiazepines cause sedation and respiratory depression, and repeated doses have a cumulative effect. Respiratory depression with standard clinical doses has been reported in 10% of patients receiving lorazepam and 9.8% receiving diazepam [40]. The sedative effects may delay recovery of consciousness after cessation of status epilepticus. Concurrent administration of barbiturates increases the risk of respiratory depression and sedation.

Hydantoins

If lorazepam fails to stop seizure activity within 10 min, or if intermittent seizures persist for more than 20 min, another drug should be added. Phenytoin (or fosphenytoin) remains the drug of choice for second-line therapy in status epilepticus that does not respond to lorazepam [43]. Phenytoin is highly lipid soluble and reaches peak brain levels within 15 min after intravenous administration. However, levels vary between different areas of the brain, with lower levels being found in active epileptogenic and acutely damaged areas. The loading dose of phenytoin (20 mg.kg^{-1}) should be given on a strict weight basis [4] and requires a large vein for administration because of the high pH of the solution. It should be mixed with normal saline and concurrent administration of other drugs should be avoided, as there is a risk of precipitation. The pharmacokinetics of phenytoin make it a difficult agent to control because of saturable metabolism at therapeutic levels and individual variations in metabolism. Serum levels should be monitored, but there are several considerations that need be taken into account. The therapeutic window and clinical efficacy are poorly related and patients often require levels above the therapeutic range to achieve control of status epilepticus without apparent side-effects [44]. Phenytoin is 96% protein bound and, given the variability of serum proteins in acute illness, only the free concentration is of value in monitoring dosage. Infusion of phenytoin carries a significant risk of hypotension and arrhythmias, particularly QT prolongation, and ECG and arterial blood pressure monitoring are mandatory. A 5.9% incidence of purple-glove syndrome has also been reported after intravenous infusion of phenytoin distal to the antecubital fossa [45]. This soft tissue reaction is sometimes devastating and is characterised by profound swelling of the hand and is occasionally severe enough to cause arterial occlusion and tissue necrosis, necessitating amputation. The use of intravenous phenytoin is associated with a high incidence of side-effects, and the recent introduction of fosphenytoin (a phenytoin prodrug), as a safer way of rapidly achieving an effective serum concentration, is likely to change clinical practice significantly [46]. Fosphenytoin is a water-soluble prodrug that is enzymatically converted to phenytoin by serum phosphatases. Seventy-five milligrams of fosphenytoin results in 50 mg of phenytoin in the serum after enzymatic conversion; 75 mg of fosphenytoin is therefore labelled as '50 mg phenytoin equivalent'. The

Table 4 Bolus doses and infusion rates of intravenous agents used in the treatment of status epilepticus.

Agent	Bolus dose for 1st- or 2nd-line therapy (maximum rate of administration)	Infusion rate for refractory status
Lorazepam	0.05–0.1 mg.kg^{-1} (2 mg.min^{-1})	
Diazepam	0.15–0.25 mg.kg^{-1} (5 mg.min^{-1})	
Midazolam	0.2 mg.kg^{-1}	0.05–0.5 mg.kg^{-1}.h^{-1}
Phenytoin	20 mg.kg^{-1} (50 mg.min^{-1})	
Fosphenytoin	20 mg.kg^{-1} phenytoin equivalent (150 mg.min^{-1})	
Phenobarbital	10–20 mg.kg^{-1} (100 mg.min^{-1})	
Thiopental	3–5 mg.kg^{-1}	3–5 mg.kg^{-1}.h^{-1}
Propofol	1–2 mg.kg^{-1}	2–10 mg.kg^{-1}.h^{-1}

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pharmacology and pharmacokinetics of fosphenytoin have recently been reviewed [47]. It is administered by intravenous infusion at a faster rate than phenytoin (150 mg phenytoin equivalent per minute) to allow for conversion time. Therapeutic concentrations can be achieved in less than 10 min [48]. Conversion time is decreased in the presence of low serum protein, e.g. in patients with liver or renal failure, and slower infusion rates may therefore be indicated. Whether the greater speed of administration results in a higher rate of status epilepticus control remains to be demonstrated. The use of fosphenytoin is safer than that of phenytoin and there are no adverse effects of extravasation with the newer drug. The incidences of hypotension and arrhythmias are also reduced [46], but cardiovascular problems have still been reported after intravenous administration [49]. The usual care should be taken (including adequate monitoring) during its administration and the infusion rate reduced if necessary. Fosphenytoin is more expensive than phenytoin and this has discouraged its widespread introduction into clinical practice. However, cutaneous complications such as purple-glove syndrome can be avoided by using fosphenytoin and pharmaco-economic simulations suggest that its use might be cost effective [50].

Phenobarbital
Intravenous phenobarbital 10–20 mg.kg^{-1} is still used by some clinicians for the initial treatment of status epilepticus, but high doses are necessary to control seizures and prolonged sedation is inevitable, especially if benzodiazepines have also been given. Therefore, the use of phenobarbital tends to be limited to the management of refractory status, in which it is effective. Its mechanism of action is to prolong the inhibitory postsynaptic potential via an action on GABA$_A$ chloride channels [51]. Phenobarbital does not enter the brain as rapidly as more lipophilic drugs, but a therapeutic brain level is reached in 3 min and is maintained for many hours [52]. Interestingly, there is some evidence that brain uptake is enhanced by seizure activity [53]. The usefulness of phenobarbital is limited by its side-effect profile, namely excess sedation, respiratory depression, hypotension and drug interactions. It also has a half-life of > 48 h and neurological assessment may therefore have to be postponed for extended periods (Table 4).

General anaesthesia
This is the definitive treatment for refractory status epilepticus and should be undertaken in a specialist unit where continuous EEG monitoring is available to direct effective and rational therapy [54, 55]. It has been suggested that continuous EEG monitoring can influence medical decision-making in 81% of monitored patients [56]. However, the electrophysiological goal for treatment

of refractory status epilepticus remains a matter for debate. There is little evidence that burst suppression or iso-electric patterns are required for the termination of status epilepticus, although these are the electrophysiological end-points most commonly used. Seizure control can be achieved in many patients with a background of continuous slow activity on the EEG and there is no need to run the greater risks associated with the increased doses of anaesthetic agent required to maintain burst suppression. On the other hand, there are patients who continue to exhibit seizure activity despite a burst suppression pattern, and doses of anaesthetic agent that are sufficient to render the EEG isoelectric are required to control status epilepticus in such cases. One small study showed a trend for an improved outcome after achieving a completely flat EEG [57]. Continuous EEG monitoring is therefore essential to ensure that the patient does not receive either too little or too much treatment.

Long acting anti-epileptic drug therapy, such as phenytoin and phenobarbital, should be maintained during this phase of treatment and drug levels monitored and maintained at the upper limit of the normal range. There are no data to indicate how long patients should remain seizure-free before the level of anaesthesia can be decreased. Most recommend at least 24 h, but periods up to 96 h have been suggested [38]. If seizures return when the level of anaesthesia is reduced, the patient should be re-anaesthetised and further doses of long-acting anti-convulsants given or additional agents added. It is crucial that EEG evidence of epileptiform activity is not allowed to persist during treatment of refractory status epilepticus, and anaesthesia should be re-introduced until the seizures have been brought under control. This may take some time and it is important not to give up.

There are no randomised comparative studies of treatments of refractory status epilepticus. Thiopental is a rapidly acting intravenous barbiturate that has been used in refractory status [58]. Peak brain levels are reached after 30 s but the drug rapidly redistributes to lipid-dense tissues and infusions are therefore difficult to manage. Elimination is also delayed and it may take many hours or days to eliminate the drug after relatively short infusion periods. Pentobarbital, itself an anticonvulsant, is one of the major metabolites of thiopental. Thiopental causes hypotension, often necessitating lowering of the infusion rate and/or vasopressor drug administration. Barbiturates are also potently immunosuppressive and prolonged use increases the risk of nosocomial infection [59]. Pharmacological considerations and the side-effect profile of high-dose barbiturate infusions severely limit their use as a useful treatment for status epilepticus and propofol has gained popularity as an alternative [60]. There are few comparative data between propofol and high-dose

barbiturate therapy in the management of refractory status epilepticus, although one small study found a significantly shorter time to attainment of seizure control with propofol than with barbiturates [61]. Propofol has barbiturate-like and benzodiazepine-like effects at the $GABA_A$ receptor and has a potent anticonvulsant action at clinical doses [61]. The role of propofol in refractory status epilepticus has recently been reviewed [60]. An initial bolus of 1 mg.kg^{-1} is given over 5 min and is repeated if seizure activity is not suppressed. A maintenance infusion should be adjusted to 2–10 mg.kg^{-1}.h^{-1} until the lowest rate of infusion needed to suppress epileptiform activity on the EEG is achieved [61]. Rapid discontinuation of propofol should be avoided because of the risk of precipitation of withdrawal seizures [62]. Propofol infusion may cause hypotension but this can be minimised by adequate intravascular filling and the use of modest doses of vasopressor drugs. Metabolic acidosis and lipidaemia may occur with prolonged use, although the incidence of the latter is reduced by use of the 2% formulation of propofol. Isoflurane has been used successfully in the treatment of refractory status epilepticus [63], but the difficulties of its administration on the ITU and the need for gas scavenging have limited its use.

New therapies
An intravenous preparation of sodium valproate has recently been introduced and animal data suggest that high serum concentrations might be effective in controlling refractory status epilepticus [64]. Although not licensed for use in status epilepticus, several trials have found the intravenous formulation of sodium valproate to be effective, with a good side-effect profile. European studies have reported control of status epilepticus in 80–83% of cases with a dose of 12–15 mg.kg^{-1} [65], but a case of severe hypotension in a child has recently been described [66]. However, controlled clinical studies have to be carried out before the role of sodium valproate in the treatment of status epilepticus becomes clear. There is also evidence that polypharmacy may be effective in the management of status epilepticus and that the order of drug administration might influence the efficacy of the treatment [67]. This has yet to be tested in humans.

Management of complications
Complications can arise as a consequence of status epilepticus itself or as a result of the drugs used to treat it. Pulmonary aspiration is not uncommon and neurogenic pulmonary oedema has been reported [24, 68]. The major systemic complications of status epilepticus include hyperthermia and rhabdomyolysis. Hyperthermia occurs in the majority of cases and is related to increased muscle activity during seizure activity. It usually resolves when

seizures are brought under control but active cooling should be applied if core temperature exceeds 40 °C. Patients should be screened for myoglobinuria and the serum creatine kinase measured. Forced diuresis and urinary alkalinisation should be considered in the presence of myoglobinuria or significantly elevated serum creatine kinase levels, in an attempt to prevent acute tubular necrosis and renal failure. Arrhythmias are not infrequently encountered [28] and ECG monitoring is mandatory to allow early recognition and treatment. Many of the pharmacological therapies effective in terminating status epilepticus cause sedation, respiratory depression and hypotension. Artificial ventilation will be required if seizures are not brought under rapid control and is mandatory if anaesthetic agents are used to treat status epilepticus. It is also important to maintain systemic blood pressure at normal or supranormal levels to ensure adequate cerebral perfusion. Fluid resuscitation and vasopressor or inotropic support should be directed using appropriate invasive cardiovascular monitoring.

Outcome
The overall mortality of status epilepticus in adults is approximately 25%. Patients over the age of 60 years have a higher mortality (38%), which may be related to the higher incidence of life-threatening aetiological factors, such as stroke, in this age group [2]. Approximately 89% of patients who die during or after status epilepticus do so as a result of the aetiology of the status, whereas only 2% of deaths are directly attributable to the status epilepticus itself [69]. The severity of the underlying brain injury that leads to status epilepticus has a major impact on mortality. About 90% of patients with status epilepticus secondary to anti-epileptic drug withdrawal, alcohol or trauma have good outcomes, compared to only 33% of patients with status secondary to stroke or anoxia [34, 70]. Other studies have also shown that status epilepticus associated with alcohol or anticonvulsant withdrawal has the best prognosis [70]. Patients with ECG changes, particularly arrhythmias, bradycardia, ischaemic changes and changes of axis, also have a higher mortality than those without ECG changes [28]. First-line therapy is effective in controlling seizures in 55% of cases of status epilepticus [39], so early treatment is vitally important. Duration of seizure activity also affects outcome [34]. In one study, patients with uncontrolled status epilepticus lasting more than 1 h had a mortality rate of 34.8% compared to 3.7% if the seizures were terminated within 30 min [70]. Status epilepticus may also lead to significant morbidity, with neurophyschological, cognitive and memory loss being reported [71, 72]. There is recent evidence that the post-status EEG might have some prognostic significance, with

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the presence of post-status ictal discharges being associated with a higher mortality [73].

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