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WHAT'S NEW IN INTENSIVE CARE

What's new in refractory status epilepticus?

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Refractory status epilepticus (RSE) is defined by persistent seizures, resistant to first-line (benzodiazepines) and second-line ("classic" anticonvulsant therapy, such as valproate, phenytoin/fosphenytoin or levetiracetam), usually requiring general anesthesia and continuous electroencephalogram (EEG) monitoring [1]. This is of particular importance since up to 43 % of patients with status epileptics will progress to RSE. Rossetti and Bleck recently proposed an update on the management of status epilepticus [2]. Here, we have reviewed recent literature on convulsive RSE in adults, aiming to summarize advantages/disadvantages and comparative studies of "standard" intravenous anesthetics (propofol, midazolam, barbiturates) and describe the emerging use of the alternative anesthetic agent, ketamine. Wehave also proposed an algorithm for the management of RSE in the ICU.

Standard anesthetics

General anesthesia with propofol, midazolam or barbiturates is the mainstay of therapy of RSE. Pro and cons of these agents should be considered when individualizing patient therapy.

Propofol

Propofol is generally administered using an initial 1- to 2-mg/kg bolus followed by serial boluses every 3–5 min until clinical and EEG seizures are suppressed. Increasing doses of propofol may be necessary to successfully treat RSE, but also commonly cause hypotension. In a prospective study ($n = 10$ patients), in which burst-suppression was achieved using continuous EEG monitoring, infusion rates of more than 4 mg/kg/h up to a median 8 mg/kg/h over the first 24 h were required to effectively treat RSE, and mechanical ventilation lasted a median of 4 days [3]. Seven patients received vasopressors. Although very rare, propofol-related infusion syndrome (PRIS) should be systematically monitored since it can be fatal [4]. The necessity of high doses and prolonged infusions may limit propofol use in RSE.

Midazolam

Midazolam is the other most frequently used agent for RSE. It has minimal intrinsic pharmacological side effects and can therefore be administered at high doses. In a retrospective study ($n = 100$ RSE patients), maintenance continuous infusion from 0.1 up to 3 mg/kg/h for 24 h were given to treat EEG seizures [5]. Withdrawal seizure occurred in 15 % of patients and up to 53 % of them had hypotension requiring vasopressors.

Barbiturates: thiopental and pentobarbital

Nowadays, barbiturates are generally reserved for patients in whom propofol and/or midazolam failed to control RSE. Either thiopental or pentobarbital can be used, with thiopental being more frequently used in Europe. In a prospective study of 10 RSE patients, thiopental (median initial bolus of 20 mg/kg and maintenance infusion rate of 5–8 mg/kg/h) allowed seizure termination and a burst-suppression EEG pattern in a median time of 29 (11–56) min after treatment initiation [6]. In all but one case, the therapeutic goal of burst-suppression was maintained for 12 h with no further boluses and no patients experienced relapsing seizures after thiopental withdrawal, thereby highlighting treatment efficacy of barbiturates in the context of RSE. The downside, however, was the prevalence of hypotension (100 % of patients) and other barbiturate-related complications, including prolongation of mechanical ventilation (7.5–13 days) and ventilator-acquired pneumonia (90 %

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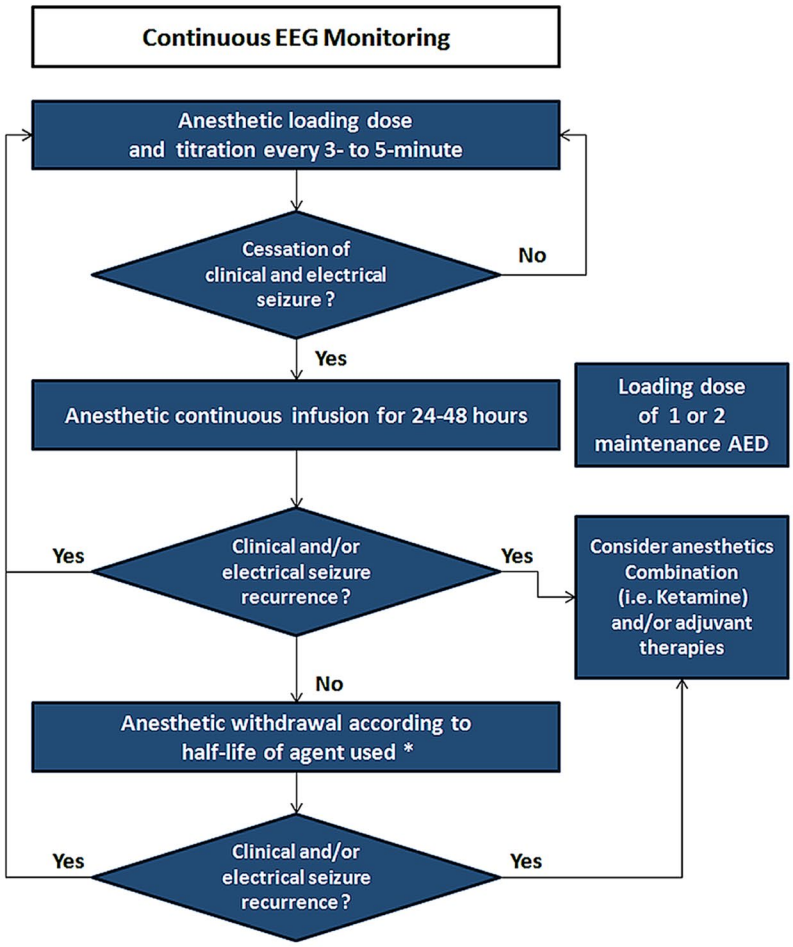
Panel A



Panel B

	Propofol	Midazolam	Sodium thiopental	Pentobarbital	Ketamine
Pharmacologic class	Anesthetic	Benzodiazepine	Barbiturate		Anesthetic
Loading dose	1-2 mg/kg slow IV	0.2 mg/kg slow IV	2-7 mg/kg slow IV	5-15 mg/kg slow IV	0.5–3 mg/kg slow IV
Bolus titration	0.5-2 mg/kg slow IV every 3-5 min	0.2 mg/kg slow IV every 3-5 min	1 - 2 mg/kg slow IV ≤ 50 mg/min	5 - 10 mg/kg slow IV ≤ 50 mg/min	0.5 g/kg slow IV every 3-5 min
Maintenance dose	2-4 mg/kg/h ± 1 mg/kg/h Maximum 5 mg/kg/h for 48 hours	0.1-2 mg/kg/h ± 0.1 mg/kg/h Every 3-4 hours Maximum 3 mg/kg/h	0.5-5 mg/kg/h ± 0.5 - 1 mg/kg/h Every 12 hours		0.3 to 4 mg/kg/h ± 1 mg/kg/h Maximum 10 mg/kg/h
Discontinuation modalities	20% reduction every 3 hours	50% decrease every 3 hours	Stop with no prior dosage reduction†	20% reduction every 3 hours†	20% reduction every 3 hours
Specific effects	Tachyphylaxis Risk of propofol infusion syndrome Hypotension Cardio-respiratory depression	Tachyphylaxis Hypotension Respiratory depression Accumulation if renal insufficiency	Immunosuppressant Paralytic ileus Hypotension Cardio-respiratory depression Adipose tissue accumulation		Hypertension Tachycardia

Fig. 1 Treatment strategy for refractory status epilepticus. **a** Therapeutic management strategy to treat refractory status epilepticus. **b** Practical modalities for using anesthetic drugs to treat refractory status epilepticus. *Asterisk* note that it takes 4–5 half-lifes to reach steady state levels. *Hash* indicates high-dose phenobarbital may be used to avoid withdrawal seizures

of patients). There are no recent studies evaluating pentobarbital use in adult RSE patients.

Comparative studies

When compared to midazolam, thiopental was not superior in treating RSE but had more side effects [7]. In a systematic review, pentobarbital appeared more effective than propofol or midazolam in achieving burst-suppression EEG pattern but was indeed again associated with higher need for vasopressors to correct hypotension and did not achieve better survival outcomes [8]. Finally, a recent Cochrane review found propofol and thiopental were equally effective in treating RSE, and both were associated with inherent side effects and complications [9].

Of note, the single randomized controlled trial that compared propofol versus thiopental in RSE patients was prematurely stopped due to slow enrollment after only 24 patients [10]; despite a small sample size, this trial found that barbiturates were associated with greater side effects (mainly hypotension) than propofol.

In the absence of strong evidence supporting RSE management, the choice of initial anesthetic agent, potential for combination therapy (e.g. midazolam with propofol) and overall strategy mainly depend on the advantages and disadvantages of each agent as well as local practice.

Ketamine

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is emerging as the most promising alternative amongst anesthetic agents for the treatment of RSE. The main and most attractive theoretical advantage of ketamine is that—while standard anesthetics act on the GABA receptor—ketamine targets a different pathway via the NMDA receptor and therefore offers new opportunities for the management of RSE [11]. Whether ketamine should be used only in "super-refractory" cases, after standard agents have failed, or earlier on—in combination with standard general anesthetics—is still controversial. Recent trends seem more in favor of this latter option, adding ketamine to propofol and/or midazolam at an early stage of therapy. Clinicians should be aware of the theoretical risk of raised intracranial pressure.

Adjuvant therapies for super refractory status epilepticus

Adjuvant therapies for so-called super-refractory status epilepticus is outside the scope of this update. The use of therapeutic hypothermia has been advocated based on experimental evidence. Large clinical trials are needed [12] and until then avoidance of hyperthermia with the use of targeted temperature management can be recommended as a general neuroprotective strategy. Volatile anesthetics such as isoflurane and desflurane have been tested; their theoretical advantages include ease of titration, rapid onset of action and treatment efficacy, but their practical use is logistically difficult and is not without side effects [13]. Increasing brain levels of ketone bodies is experimentally known to reduce seizures, therefore nutritional modifications with the use of ketogenic diet can be considered in patients with RSE, under careful monitoring of blood lipids, particularly if propofol is used [14]. Steroids and immunotherapy are suggested in immune-mediated RSE [15].

Practical approach to RSE

Practical modalities for the use of anesthetics in the treatment of RSE are summarized in Fig. 1.

The immediate treatment goal must be the cessation of clinical and EEG seizures [1]. Propofol and/or midazolam are preferred to thiopental/pentobarbital and ketamine may be considered as adjuvant therapy, particularly in more refractory cases. In some cases, anesthetic combinations may be required. Continuous EEG monitoring is mandatory to titrate therapy and for treatment withdrawal [1, 16]. Simultaneously, a loading dose and maintenance doses of one or two long-acting anticonvulsant agents should be given routinely in combination with the continuous infusion anesthetic agent and continued after its withdrawal.

Treatment intensity is still controversial: guidelines recommend suppression of seizures as Class I evidence [1]. The benefit of escalating therapy aiming to obtain EEG burst-suppression [EEG pattern with periods of high-voltage electrical activity ("bursts") alternating with periods of suppression] is not based on high levels of evidence and remains under debate.

Also, while treating RSE to achieve EEG burst-suppression for 12–24 h is associated with a lower rate of relapse when compared to EEG seizures suppression alone, it is not associated with reduced mortality [8].

There is also no consensus on the optimal duration of anesthetic infusion for RSE, though guidelines recommend seizure control for 24–48 h [1].

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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