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Editorial

Optimizing status epilepticus care during the COVID-19 pandemic

The Coronavirus disease 2019 (COVID-19) pandemic has created a huge surge in demand for intensive care resources in a short time frame, overwhelming some national and subregional health systems, and resulting in the need for resource rationing. Coronavirus disease 2019 will likely have major implications on the management of status epilepticus (SE) in the intensive care unit (ICU) because of potential limits in ventilator and staff capacity.

Status epilepticus is one of the commonest serious neurological emergencies in the ICU, with arguably one of the most modifiable early trajectories, potentially reducing the need for ICU admission. Incident rates of patients with SE are as high as 74/100,000 population per year [1], with one population study suggesting 6/100,000 being refractory to first- and second-line therapy (*refractory* convulsive SE) thereby requiring ICU [2]. The other major form of SE treated in ICU is nonconvulsive SE (NCSE) in coma, either from de novo acute brain injuries or "subtle" SE after convulsive SE. The case fatality from population-based studies composed of different etiologies ranges from 5% to 39% [1].

In these difficult times, we urge the neurological community to take ownership by reconsidering SE care and how best to assist our ICU colleagues by consideration of the following four key points.

1. Reducing the volume of referrals or shorten the time spent in ICU

Proactive neurological decision-making on the appropriateness of referrals to ICU and actively considering interventions to minimize time in ICU will reduce ICU bed days during the surge phase. Some strategies are suggested.

1.1. Psychogenic nonepileptic status

It is said that convulsive SE is "easily diagnosed", but psychogenic nonepileptic status may be mistaken for SE by inexperienced clinicians (up to 10% of presenting cases with SE were psychogenic nonepileptic status [3]). There is a great educational need to assist non-neurologists in confidently identifying these disorders. However, a timely accurate diagnosis by a neurologist can avoid intubation and the potential iatrogenic physical and psychological harm. Shared hospital records, "seizure-code" teams, telemedicine links, and video recording of the ictal event could all improve diagnostic accuracy. Inadvertent intubation should be urgently de-escalated once a diagnosis is made. Emergent electroencephalography (EEG) is invaluable for nonconvulsive events. In the absence of neurology support, convulsive SE presentations associated with diagnostic doubt, should be treated as convulsive SE to minimize risk from systemic or cerebral complications which could occur if untreated.

1.2. Convulsive (tonic–clonic) SE

Given possible delays before hospitalization, patients or carers of those with benzodiazepine rescue plans should have the appropriate rescue medication supplied. Prehospital and hospital teams should use local or national protocols to appropriately treat convulsive SE with weight-based drug dosing administered promptly [3]. Intravenous options include fosphenytoin (20 mg phenytoin equivalent (PE)/kg, max: 1500 mg PE/dose), valproate (40 mg/kg, max: 3000 mg/dose), and levetiracetam (60 mg/kg, max: 4500 mg/dose). For inexperienced staff redeployed to emergency/ICU departments, clear protocols are essential.

Convulsive SE evolving to a patient becoming comatose, with no improvement in level of consciousness over hours, should be investigated once convulsions have subsided with an urgent EEG to distinguish ongoing subtle SE from postictal/drug-induced encephalopathy. The treating physician should consider using multiple antiseizure drug (ASD) trials for subtle SE as many may thus avoid anesthesia [4]. Rapid treatment reduces the risk of systemic and neurological complications and likelihood of requiring ICU care.

1.3. Ambulatory forms of nonconvulsive status epilepticus

The ambulatory forms of NCSE (absence status, focal status with or without impaired consciousness) almost never require ICU. These usually respond to benzodiazepines or second-line parenteral nonsedating therapies, including multiple trials of different oral or intravenous ASDs, including fos/phenytoin, valproate, levetiracetam, or lacosamide 200–400 mg. Caution is urged with intravenous phenobarbital because of sedation risk. There is rarely any benefit from an ICU admission in terms of mortality or functional outcome [1].

1.4. Nonconvulsive status in coma

If initiation of anesthesia is delayed, consider sequential administration of further nonsedating second-line ASD. Simultaneous polytherapy while beneficial in animal models has not been established as beneficial in human studies. In situations where patients may not be ventilated because of resource allocations, options such as ketamine which target glutamatergic pathways may yet prove helpful at low doses. Low-dose continuous midazolam infusions and low-dose phenobarbital infusions are also worth considering.

In the ICU, some measures may be considered to shorten the admission duration. Guidelines suggest 24–48-h treatment before initiating the first anesthetic drug wean. Shorter time frames can be considered once 1–2 maintenance ASDs are established. Some evidence suggests

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that anesthetic coma may increase admission duration, nosocomial infection risk, inhospital mortality, and result in worse functional outcome [5]. During weaning from anesthetic coma, reinstating sedating medications should only be considered for clear electrographic seizures or high-risk ictal–interictal patterns.

2. How can we ensure cases with SE get fair consideration for ICU care?

In recent days, clinical recommendations on ethical approaches to decision-making regarding resource allocation were published [6]. Avoiding the "exclusion of large groups of patients" to uphold the principle of justice is called for. Cases with COVID-19 and SE will require potentially similar ICU care durations and should be offered equal opportunity. Patients with new-onset refractory SE (NORSE) are challenging as they are labor intensive, have potentially prolonged admissions, and may require immunosuppression even during the pandemic phase. However, each case should be considered on its own merits. In other cases where a terminal prognosis is likely, palliative care should be consulted early. Multiprinciple allocation frameworks are proposed to allow fair comparison between disorders [6]. While laudable, it is important to recall the limitations of any individual prognostic scoring tool in SE. Multidisciplinary team-based decisions are recommended rather than an individual treating clinician making resource allocation decisions.

3. Are prognostication tools sufficient to determine who will benefit from ICU?

Underlying SE etiology is the most powerful predictor of prognosis, with acute symptomatic causes having the worst outcome. Age >65 years and a greater impairment of consciousness at presentation represent markers of poor prognosis. One exception is that ambulatory NCSE may have markedly reduced consciousness but potentially excellent prognosis. The current prognostic scoring tools for SE are limited by only having a moderately good positive predictive value of a poor outcome, meaning patients who can return to baseline may have a predicted poor outcome.

Epidemiology-based mortality score in SE (ESME) considers etiology, age, comorbidity, EEG, and impairment of consciousness. It predicted 90% of the deaths in one cohort and performed better in comparison with the Status Epilepticus Severity Score (STESS) [7].

4. Special considerations in COVID-19 and co-occurring status epilepticus

No detailed reports of co-occurring COVID-19 and SE are reported. A key challenge will be the drug–drug interactions between ASD and proposed trial drug agents, such as certain antiviral agents. Lorazepam, levetiracetam, valproate, lacosamide, topiramate, and thiopental have no reported interactions with the proposed trial agents, but other benzodiazepines, phenytoin, phenobarbitone, propofol, and ketamine have interactions [8]. Certain agents may result in increased risk of cardiac arrhythmia, and it may be of use to monitor cardiac parameters through electrocardiogram (EKG). Extracorporeal membrane oxygenation (ECMO) used in COVID-19 may result in unpredictable drug levels, and monitoring is advisable. Certain drugs can become sequestered in the tubing of the ECMO machine, resulting in this problem. Low protein-bound and nonlipophilic drugs have the lowest risk of being sequestered. Contingency plans in wards and ICUs for nursing patients with COVID-19 in a separate area from routine patients without COVID-19 where possible make sense from an infection control perspective.

5. Conclusion

In treating SE, physicians will be challenged by the need for ICU resources and ventilators in the era of the COVID-19 pandemic. The optimal approach will be to follow management pathways that avoid sedation if possible and taking into consideration ASD-antiviral medication interactions. Coordinated multidisciplinary efforts are required that will use creative solutions, nonsedating ASDs, and risk–benefit calculations when embarking on emergency SE management in this resource-constrained time.

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PK: Unsponsored grand rounds and published books on EEG, status epilepticus, and epilepsy, for which he received honoraria, and is on the Qatar Research Foundation grant on continuous EEG monitoring in status epilepticus.

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