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CONSENSUS STATEMENT

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ACVIM Consensus Statement on the management of status epilepticus and cluster seizures in dogs and cats

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Abstract

Background: Seizure emergencies (ie, status epilepticus [SE] and cluster seizures [CS]), are common challenging disorders with complex pathophysiology, rapidly progressive drug-resistant and self-sustaining character, and high morbidity and mortality. Current treatment approaches are characterized by considerable variations, but official guidelines are lacking.

Objectives: To establish evidence-based guidelines and an agreement among board-certified specialists for the appropriate management of SE and CS in dogs and cats.

Animals: None.

Materials and Methods: A panel of 5 specialists was formed to assess and summarize evidence in the peer-reviewed literature with the aim to establish consensus clinical recommendations. Evidence from veterinary pharmacokinetic studies, basic research, and human medicine also was used to support the panel's recommendations, especially for the interventions where veterinary clinical evidence was lacking.

Results: The majority of the evidence was on the first-line management (ie, benzodiazepines and their various administration routes) in both species. Overall, there was less evidence available on the management of emergency seizure disorders in cats in contrast to dogs. Most recommendations made by the panel were supported by a

Abbreviations: AES, American Epilepsy Society; ASMs, antiseizure medications; BZDs, benzodiazepines; CNS, central nervous system; CS, cluster seizures; CSE, convulsive status epilepticus; CSF, cerebrospinal fluid; DZP, diazepam; EEG, electroencephalography; ILAE, International League Against Epilepsy; IM, intramuscular; IN, intranasal; IV, intravenous; IVETF, International Veterinary Epilepsy Task Force; LZP, lorazepam; MDZ, midazolam; NCSE, non-convulsive status epilepticus; R, rectal; SE, status epilepticus.

combination of a moderate level of veterinary clinical evidence and pharmacokinetic data as well as studies in humans and basic research studies.

Conclusions and Clinical Relevance: Successful management of seizure emergencies should include an early, rapid, and stage-based treatment approach consisting of interventions with moderate to preferably high ACVIM recommendations; management of complications and underlying causes related to seizure emergencies should accompany antiseizure medications.

KEYWORDS

cat, dog, emergency seizure disorders, treatment

1 | INTRODUCTION

Seizure disorders, including status epilepticus (SE) and cluster seizures (CS), are common neurological emergencies for veterinary clinicians in primary care, emergency, and specialty practice, and are associated with high morbidity and mortality. Status epilepticus, in particular, remains a therapeutic challenge in animals with a mortality rate of 25.3%-38.5%,[1-3] and it can lead to irreversible brain damage and systemic complications, especially if treatment is delayed.[4-8] Complications and molecular changes can occur early in the course of the disease.[4-6,9,10] Seizures can rapidly become self-sustaining and refractory to standard antiseizure medications (ASMs).[4-6,11]

In veterinary medicine, several treatment schemes and algorithms have been proposed for the management of emergency seizure disorders. However, these recommendations are based mainly on individual expert opinions, lack official validation, and are characterized by considerable variation. Although official recommendations and consensus statements for the treatment of epilepsy have been published,[12-16] similar guidelines are lacking for the management of the emergency seizure disorders. Therefore, the aim of this Consensus Statement is to unify current practices and establish evidence-based guidelines and agreement among board-certified specialists, that can serve as recommendations for the appropriate treatment of SE and CS in dogs and cats.

2 | DEFINITION AND CLASSIFICATION

2.1 | Duration and frequency

Seizures are considered an emergency when their duration is prolonged and they are not self-limiting, or when they occur as a closely grouped series. Traditionally, seizures can be defined as "brief" or "prolonged" when their duration is <5 or between 5 and 30 minutes, respectively.[17,18] According to the International League Against Epilepsy (ILAE) and the American Epilepsy Society (AES), SE has been referred to as continuous seizure activity, or >1 sequential seizure without full recovery of consciousness in between, with a duration of >30 minutes.[17,19] The time frame of 30 minutes was based on the duration of convulsive SE that is required to cause permanent complications and neuronal injury.[9,10,17,18,20] However, because the majority of seizures are brief, and once a seizure lasts >5 minutes, it is most likely to be prolonged and potentially non-self-limiting,[21] researchers and clinicians have broadly adopted and accepted the 5-minute time frame as the defining element of SE. The aim of this 5-minute cut-off time is to (i) minimize the risk of systemic and brain complications associated with continuous seizure activity reaching up to 30 minutes, (ii) prevent worsening of the prognosis and drug resistance associated with increasing duration of uncontrolled seizure activity, and (iii) limit any potentially unfavorable outcomes and adverse effects associated with the prolonged administration of multiple therapeutic (including anesthetic) interventions for seizures that are brief and self-limiting.[17,18,22]

Accordingly, ILAE has revised the definition of SE to include both of these vital time points and defines SE as any prolonged seizure lasting >5 minutes.[19] Specifically, "SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point $T_1 = 5$ minutes); it is a condition that can have long-term consequences (after time point $T_2 = 30$ minutes), including neuronal death and alteration of neuronal networks." A similar time frame of 5 minutes was used to define SE by the International Veterinary Epilepsy Task Force (IVETF); the task force also included ≥ 2 seizures without recovery of consciousness in between in their definition of SE.[23] This definition of SE provides guidance as to when emergency treatment should be initiated. Overall, T_1 is the time point by which treatment should have already been initiated; T_2 represents the time at which neuronal damage or self-perpetuating alteration of neuronal networks progresses, and hence, is the latest time by which SE should be under control.[24]

Status epilepticus may be divided into 4 stages that differ in terms of treatment options, sensitivity to the drugs used, and underlying pathophysiological processes.[4-6,25-27] Details are provided in Figure 1.

Cluster seizures are broadly defined in humans[28,29] and animals[23] as >2 self-limiting seizures over a period of 24 hours. Cluster seizures, especially in high frequency, (i) can pose a risk similar to SE for seizure-related neuronal damage and complications, (ii) can progress to SE, and (iii) are unlikely to cease or be appropriately controlled without rescue medication.[30-32]

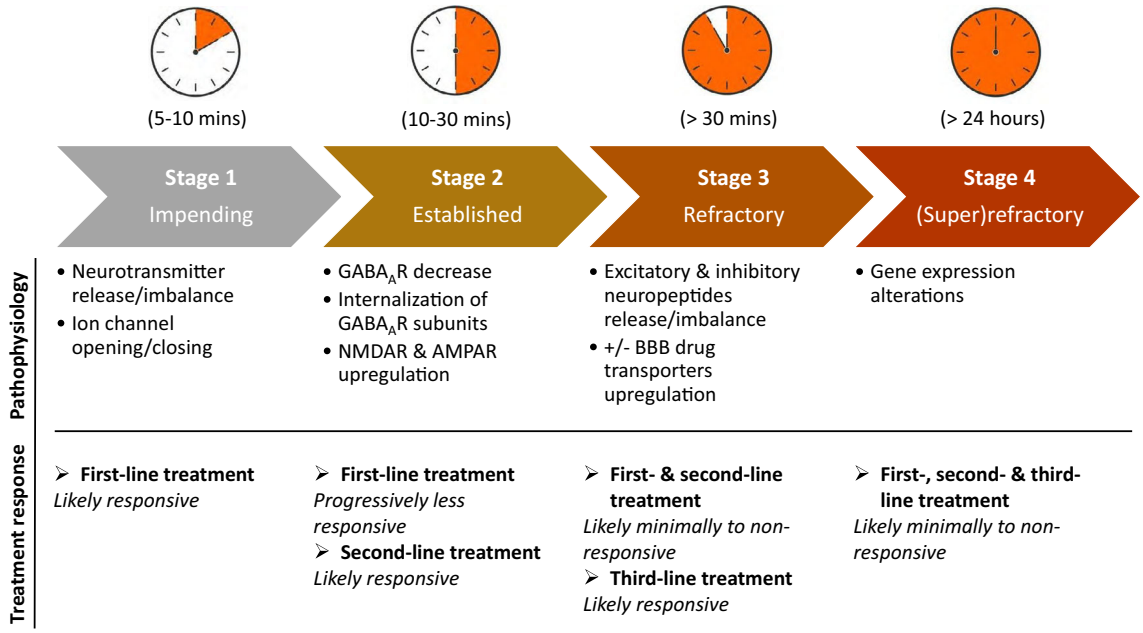

FIGURE 1 Illustration of the SE stages and their differences regarding underlying pathophysiological processes involved and sensitivity to the drugs used.

2.2 | Types and semiology

According to ILAE, the clinical forms of SE in humans are differentiated based on two taxonomic criteria: motor activity and impairment of consciousness. Therefore, SE can be characterized as (i) SE with prominent motor signs (ie, convulsive SE [CSE], myoclonic SE, focal motor SE, tonic SE, and hyperkinetic SE), or (ii) SE without prominent motor signs (ie, non-convulsive SE [NCSE]).[19,26,33,34] Each type can be divided again according to the degree of impairment of consciousness. Convulsive status epilepticus is characterized by impaired consciousness with generalized or generalized with focal onset motor signs. Non-convulsive status epilepticus can be comatose or non-comatose. Comatose NCSE usually is observed after CSE and is characterized by the absence of any motor activity, although subtle myoclonus or nystagmus may be observed. Non-comatose NCSE usually occurs in the form of generalized absence status (eg, human patients can be lethargic with altered behavior, have slow speech or abnormal movements including regional bilateral myoclonus of the eyelid, perioral or upper limb area), or in the form of focal SE with impairment of consciousness (eg, human patients can be conversant and interactive but confused and experiencing autonomic, sensory, visual, olfactory, gustatory, auditory or emotional symptoms).[19,34-36] Overall, although apparent convulsions are absent in NCSE, subtle motor signs such as twitching, blinking, extrapyramidal signs, or myoclonus may be observed.[19,34] In addition, despite the absence of convulsive activity, NCSE still can lead to neuronal injury and apoptotic cellular mechanisms, making early recognition and treatment as important as in CSE.[34] Ictal electroencephalography (EEG) is a valuable tool in the diagnosis of all types of SE but most importantly for NCSE, because the clinical signs are often subtle and nonspecific.[19,35] In CSE, the combination of clinical diagnosis by means of seizure-related motor activity and the fact that EEG can be overloaded with movement and muscle artifacts makes EEG of limited clinical value.

A similar classification can be applied to animals. However, the broad clinical semiology of CSE and NCSE reported in humans has not been observed or officially described in animals. The most commonly reported form of SE in animals is generalized (tonic-clonic) CSE.[4,37-41] However, the diagnosis of CSE and, in particular, NCSE can be overlooked in veterinary patients mainly because of the broad lack of utilization of and expertise in ictal EEG.[42] There are only a few reports of the use of EEG for the diagnosis of NCSE.[43,44] In the absence of EEG, NCSE should be suspected in any animal with a prolonged period of altered consciousness (comatose or non-comatose types) after successful management of convulsive seizures, especially after the withdrawal of any general anesthetic or sedative drugs. Ideally, EEG should be performed in any neurological veterinary patient with impaired or absent consciousness to assess the possibility of NCSE and before applying any specific treatment plan, but the panel acknowledges that doing so might not be practical in most veterinary settings.

3 | METHODOLOGY

This Consensus Statement is intended to produce guidelines for the management of emergency seizure disorders in dogs and cats. A Consensus Panel, consisting of 5 members, including 1 chairperson (MC) and 4 panelists (KM, NP, SP, HV), was formed with the aim to (i) perform a thorough assessment and systematic review of the literature, (ii) identify any gaps and share knowledge and clinical expertise,

and (iii) introduce recommendations regarding the management of SE and CS in dogs and cats. The recommendations of the panel were based on current relevant evidence and clinical experience. Experimental laboratory animal and basic research studies, as well as guidelines used in human medicine, also were reviewed to support the panel's statements, especially when veterinary clinical studies and experience were lacking.

After the establishment of the Consensus Panel, the chairperson drafted the methodology which was approved by the panelists. After approval, all members (chairperson and panelists) proceeded separately through the steps of searching, screening, and assessing the evidence before drafting their recommendations. A modified Delphi process was used. Each panel member individually performed assessments of the evidence and drafted recommendations. The results from each panel member's assessments and recommendations were gathered and anonymized by an independent ACVIM staff member and then were subjected to multiple rounds of review, through meetings that the panel convened. Remaining differences were resolved before a consensus was reached.

Overall, the procedure included (i) a literature search, (ii) a screening of each study, (iii) an assessment of the quality of evidence and treatment outcomes in each study, and (iv) drafting of recommendations.

3.1 | Literature search

Three scientific databases (MEDLINE/PubMed, Google Scholar and CAB Abstracts) were used. Final electronic searches were carried out during November 2022 by each member separately, with no date or language restrictions. The search terms used are provided in Supplementary file 1. Searching for articles from the reference lists of publications and the proceedings of major veterinary neurology conference meetings (ie, the annual forum of the American College of Veterinary Internal Medicine [ACVIM] and the symposium of the European Society and College of Veterinary Neurology [ESVN/ECVN]) was also performed. All items returned by the search were gathered and entered into the screening process.

The inclusion criteria during the search were:

1. Peer-reviewed studies of dogs and cats with no limitations on year or language of publication.
2. Any type of clinical or pharmacokinetic study.
3. Studies evaluating or describing the efficacy (clinical studies), safety (clinical and pharmacokinetic studies), or pharmacokinetic properties (pharmacokinetic studies) of antiseizure medications (ASMs) and other treatment modalities.
4. Studies conducted with the aim of evaluating the use of ASMs for emergency seizures only. Studies that evaluated the use of ASMs in chronic epileptic disorders (eg, idiopathic or structural epilepsy) but that did not refer to SE or CS were excluded. Regarding CS, only studies focusing on the short-term (emergency) treatment phase, rather than long-term (preventive) treatment, were included.

3.2 | Screening

A 2-stage selection process was used. At stage 1, studies retrieved from the search were included based on the title and abstracts. Only studies describing therapeutic outcomes regarding the management of emergency seizures in companion animals were included. At stage 2, the papers included from stage 1 were selected for full data extraction according to the inclusion criteria and were assessed on the grounds of the quality of evidence and treatment outcomes.

3.3 | Quality of evidence assessment

The quality assessment method included modified criteria from previous systematic reviews and meta-analysis.[13-15] The elements of assessment included study design, study group sizes, and methods of evaluating treatment outcomes. A numeric scale was allocated to each element, with higher scores indicating studies with a lower risk of bias.

3.3.1 | Study design

- Blinded, randomized comparison group clinical trials (score 6).
- Open-labeled, randomized comparison group clinical trials (score 5).
- Open-labeled non-randomized clinical trials (score 4).
- Retrospective case series (score 3).
- Case reports (score 2).
- Expert opinions or personal views (score 1).

3.3.2 | Study group sizes

- >30 subjects in total (score 3).
- 10-30 subjects in total (score 2).
- <10 subjects in total (score 1).

3.3.3 | Assessment of methods for evaluating study treatment outcomes

This element referred to the study's evaluation methods for determining an intervention's efficacy (seizure termination). Seizure termination was defined as the cessation of seizure-related convulsive activity (clinical confirmation) or epileptiform discharges based on ictal electroencephalography (EEG confirmation).

- EEG confirmation (score 3).
- Clinical confirmation only (ie, studies reporting details of seizure termination such as cessation of convulsive activity including precise cessation times; score 2).
- No objective confirmation mentioned (ie, studies reporting successful termination without further details or explanation on the assessment criteria for seizure termination; score 1).

3.3.4 | Overall assessment scores

For each study, the scores from all of the elements were summed up to provide an overall score. Based on this score, the overall quality of evidence for each study was characterized as high, moderate or low.

- High overall study quality (scores 9-12).
- Moderate overall study quality (scores 5-8).
- Low overall study quality (scores <4).

3.4 | Treatment outcomes assessment

Each study's treatment outcome regarding a specific intervention was analyzed. A modified methodology from previous systematic reviews and meta-analysis was followed.[13-15] Specifically, a clinical study was considered in favor of an intervention if >50% of the members of study population in each treatment group were responders (ie, seizure termination). The 95% confidence interval (CI) was calculated using standard statistical methods with the aim to identify the true population of responders. The interpretation of the 95% CI results for each study was as follows:

- 95% CI of the study's proportion of responders falling within a range of >50%: the intervention was considered as likely effective.
- 95% CI of the study's proportion of responders overlapping within a range between <50% and >50%: the intervention was considered as possibly effective.
- 95% CI of the study's proportion of responders falling within a range of <50%: the intervention was considered as likely ineffective.

For pharmacokinetic studies, parameters, such as plasma or serum maximum concentrations, time to maximum concentration, and bioavailability, were evaluated to determine whether the study reported a favorable pharmacokinetic profile in companion animals that could be extrapolated to emergency seizure management. For instance, a drug was considered to have a favorable pharmacokinetic profile if, when administered by a specific route, it reached the specific minimum plasma or serum concentrations required for an anti-seizure effect within a short period of time as defined by the reference values used in each study and needed in emergency settings. Lastly, the safety profile of each intervention also was considered as part of a study's treatment outcomes assessment. The number of animals affected by specific adverse effects for each intervention was recorded.

3.5 | Drafting the recommendations

The ACVIM recommendations for each individual therapeutic option were based on the combination of 2 elements, (i) current evidence from published studies and (ii) each panel member's expert opinion taking into consideration the overall knowledge in the field. Regarding element (i), for each specific intervention, the panel members independently gathered and summarized the results from the evaluation of the quality of evidence available and the treatment outcomes from all of the studies. The members indicated the number of studies that were in favor of or against the use of each intervention and provided a "level of evidence" scale for each intervention. Specifically, the "level of evidence" scale was based on the overall quality of evidence scores of the studies and included:

- I—"High level of evidence for or against the intervention": when at least 2 clinical studies with an overall high-quality score evaluated the use of the intervention for the management of SE or CS in dogs or cats.
- II—"Moderate level of evidence for or against the intervention": when at least 2 clinical studies with an overall moderate quality score or 1 clinical study with an overall high-quality score evaluated the use of the intervention for the management of SE or CS in dogs or cats.
- III—"Low level of evidence for or against the intervention": when ≥1 clinical study with an overall low-quality score or 1 clinical study with an overall moderate quality score or when only pharmacokinetic studies exist, without any existing study with an overall high-quality score, evaluated the use of the intervention for the management of SE or CS in dogs or cats.
- IV—"Conflicting level of evidence": when a minimum of 2 clinical studies (particularly with overall high-quality scores) evaluated the use of a specific intervention for the management of SE or CS in dogs or cats as a primary treatment outcome; however, conflicting results regarding the intervention's efficacy or safety or both were shown.
- V—"Absence of evidence": when there were neither clinical nor pharmacokinetic studies evaluating the use of the intervention for the management of SE or CS in dogs or cats.

Regarding the assessment of element (ii), this was based not only on the assessment of evidence derived from element (i) but also on the panel's own critical assessment (personal experience and knowledge, information from the use of intervention in primary and specialty clinical practice, and literature reviews or textbooks). As previously described, when there was limited or no evidence from veterinary clinical or pharmacokinetic studies regarding the use of a specific intervention in emergency seizure disorders, experimental and fundamental research or studies of humans were recruited to support the panel's recommendations.

The ACVIM recommendation scale used by the authors for this consensus statement included:

- A— High recommendation: intervention is most likely an effective and safe treatment.
- B—Moderate recommendation: intervention is possibly an effective and safe treatment.

- C—Low recommendation: intervention is possibly an inadequately effective and safe treatment.
- D—Intervention is not supported for use: ineffective or unsafe treatment or both.
- E—Recommendation withheld: intervention might be a potentially effective and safe treatment, but there is currently limited to absent evidence, clinical experience or both regarding its applicability, feasibility, and efficacy.

Finally, in addition to creating the recommendations regarding the use of each intervention in SE and CS of dogs and cats, the Consensus Panel also introduced specific clinical concepts in the treatment of emergency seizure disorders supported by current scientific evidence, knowledge, and clinical experience.

4 | RESULTS AND RECOMMENDATIONS

The search identified 1892 unique citations for SE and 1284 for CS; 112 (SE) and 53 (CS) studies fulfilled stage 1 screening criteria. After the exclusion of duplicates, 87 (SE) and 28 (CS) studies remained and entered stage 2 screening. Of these, 38 clinical studies[2,3,37-40,43-74] (SE; dogs, n = 36; cats, n = 5) and 12 clinical studies[37,40,48,49,57,64,75-80] (CS; dogs, n = 12; cats, n = 0) as well as 37 pharmacokinetic studies[49,57,65,81-114] (dogs, n = 33; cats, n = 4) fulfilled stage 2 criteria and were selected for review. Some clinical studies included a mixed populations of dogs and cats.

In dogs, the overall quality of evidence included 17% (SE, n = 6) and 25% (CS, n = 3) high quality studies, 50% (SE, n = 18) and 58% (CS, n = 7) moderate quality studies, and 33% (SE, n = 12) and 17% (CS, n = 2) low quality studies. In cats, the overall quality of evidence included 20% (SE, n = 1) high quality studies, 60% (SE, n = 3) moderate quality studies, and 20% (SE, n = 1) low quality studies; no studies for CS based on the inclusion criteria were identified.

The results from the assessment of the quality of evidence and treatment outcomes from each study are provided in Supplementary files 2–4. The level of evidence and recommendations regarding each intervention used for the management of SE and CS are summarized in Supplementary file 5 in addition to the pyramids of hierarchy (Figures 2–5).

5 | SPECIFIC GUIDELINES AND RECOMMENDATIONS FOR THE TREATMENT OF STATUS EPILEPTICUS

Although, most studies and clinicians focus on the pharmacotherapy of SE, the approach to neurological emergencies also includes supportive treatment and a thorough search for a cause, which are equally important for achieving seizure cessation and providing further neuroprotection.[4-6,115-118] Therefore, addressing complications (eg, hyperthermia, metabolic disturbances, hypoxemia) and the underlying cause of seizures (eg, hypoglycemia, electrolyte imbalances) are vital for a successful outcome. Such measures should be initiated early in the course of the disease, in parallel with ASM treatment.

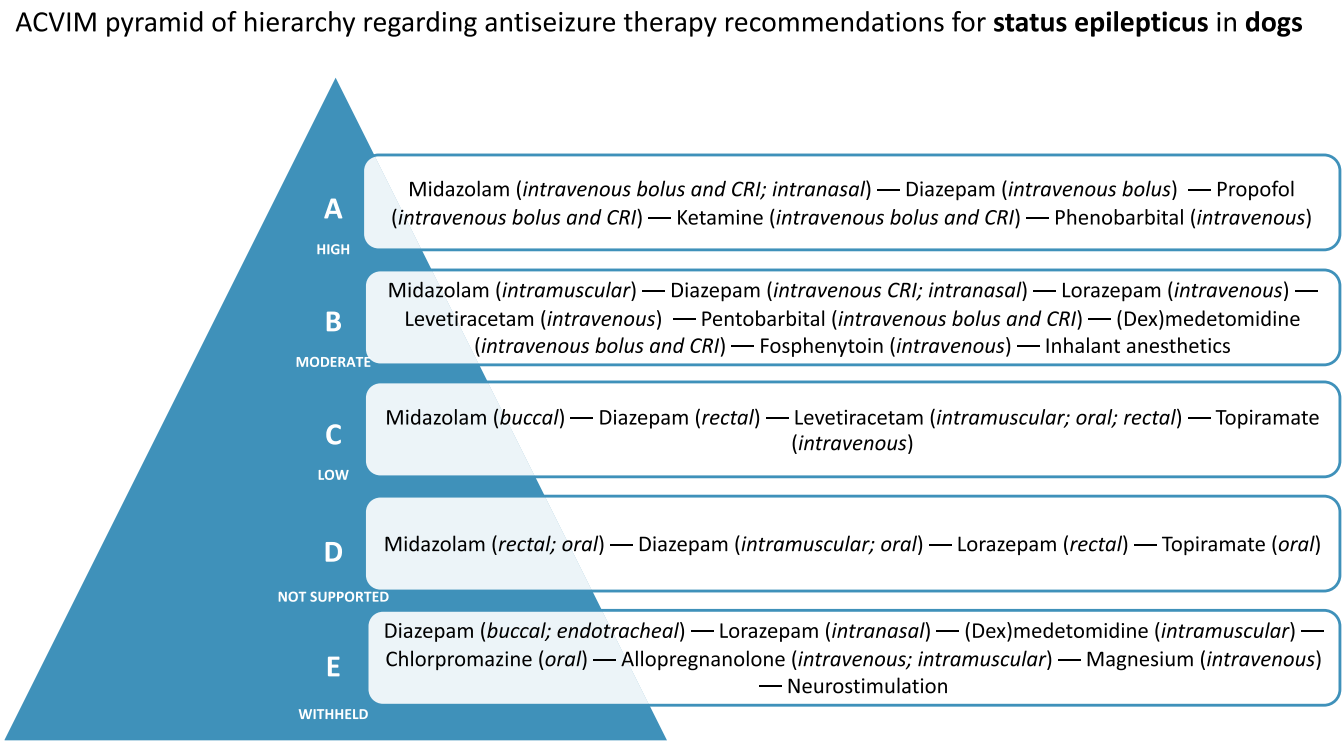

FIGURE 2 Pyramid of hierarchy regarding antiseizure therapy recommendations for SE in dogs.

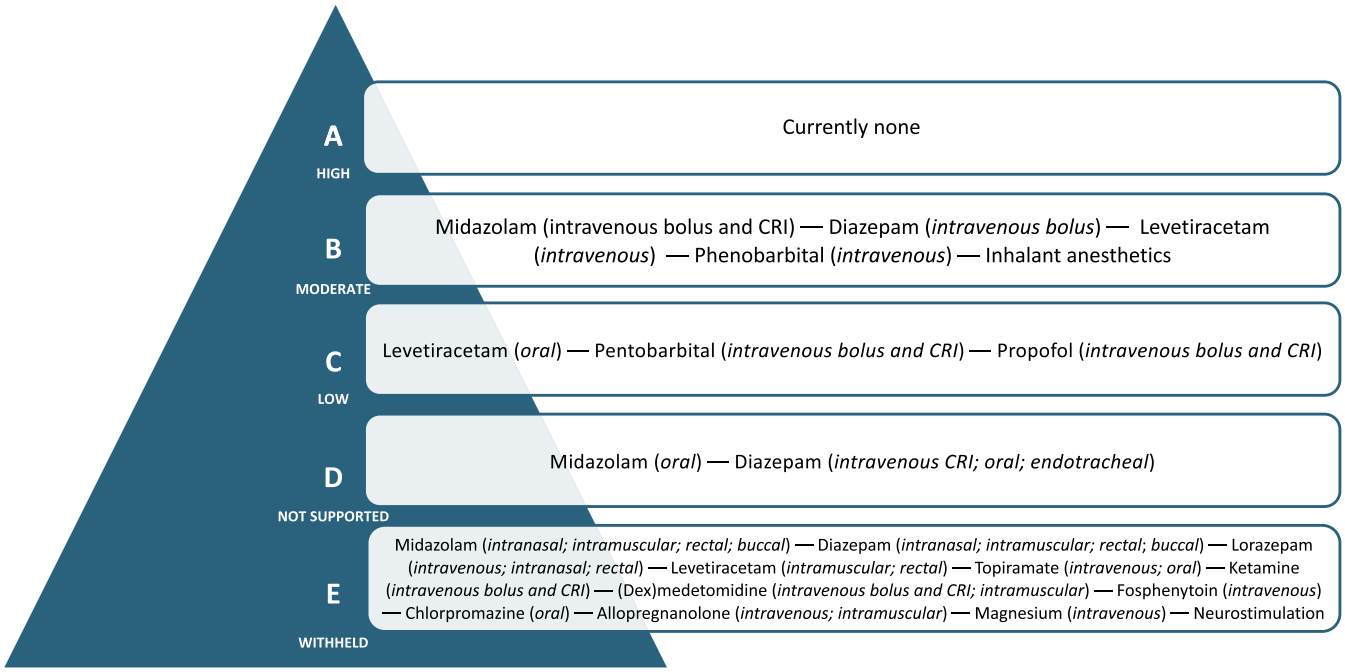

FIGURE 3 Pyramid of hierarchy regarding antiseizure therapy recommendations for SE in cats.

6 | FIRST-LINE TREATMENT

6.1 | What are the first-line medications for the treatment of SE in the out-of-hospital and in-hospital settings?

- *Intravenous (IV; in-hospital settings) and intranasal (IN; out-of-hospital and in-hospital settings) routes currently are considered the most effective and safest methods of benzodiazepine (BZD) administration.*

***Out-of-hospital settings*:**

- *IN-midazolam (MDZ) in dogs (ACVIM **recommendation A**) or cats (ACVIM **recommendation E**).*
- *Rectal (R)-diazepam (DZP) in dogs (ACVIM **recommendation C**) or cats (ACVIM **recommendation E**).*
- *Intramuscular (IM)-MDZ in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation E**); this option can be used in out-of-hospital settings if the caregivers are medically-trained.*

***In-hospital settings*:**

- *IV-MDZ in dogs (ACVIM **recommendation A**) or cats (ACVIM **recommendation B**).*
- *IV-DZP in dogs (ACVIM **recommendation A**) or cats (ACVIM **recommendation B**).*
- *IN-MDZ in dogs (ACVIM **recommendation A**) or in cats (ACVIM **recommendation E**); IN-MDZ could be advantageous for providing a rapid antiseizure effect when IV access is not possible or until an IV catheter is placed.*
- *IM-MDZ in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation E**).*

6.2 | Rationale

A recent comprehensive review published by panel members provides further information and evidence regarding the advantages and limitations of the various administration routes.[6] In summary, evidence in dogs has shown that the efficacy and safety of the IN administration route, may be equivalent or, in some clinical settings, even superior to the IV route.[5,6,39] This is more relevant when the time to place an IV catheter in a seizuring dog is considered.[39] In such cases, the overall period from the establishment of IV access until the administration of the IV-BZD might be longer compared to preparation and administration of IN-BZD.[39] In addition, R-DZP, which had been the most commonly recommended choice for treating SE at home, is unlikely to be as potent or fast acting as IN-MDZ for terminating seizure

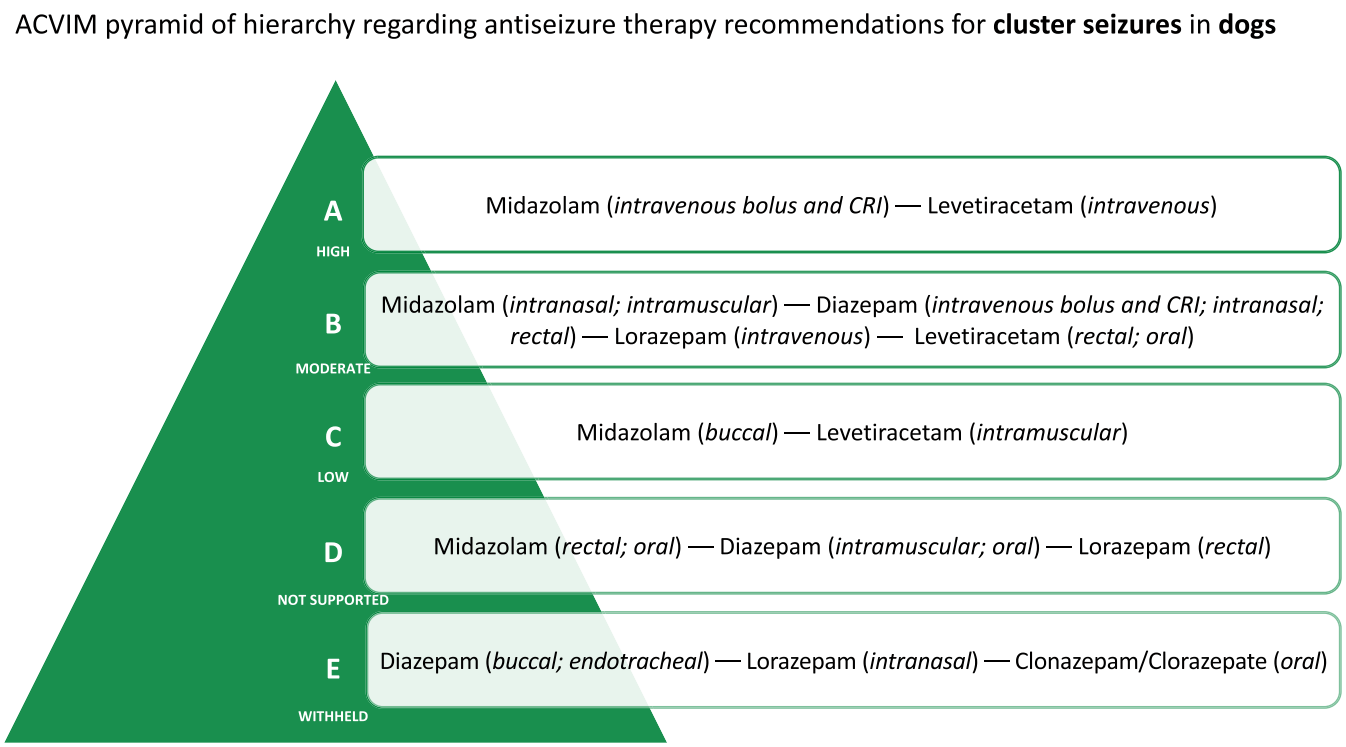

FIGURE 4 Pyramid of hierarchy regarding antiseizure therapy recommendations for CS in dogs.

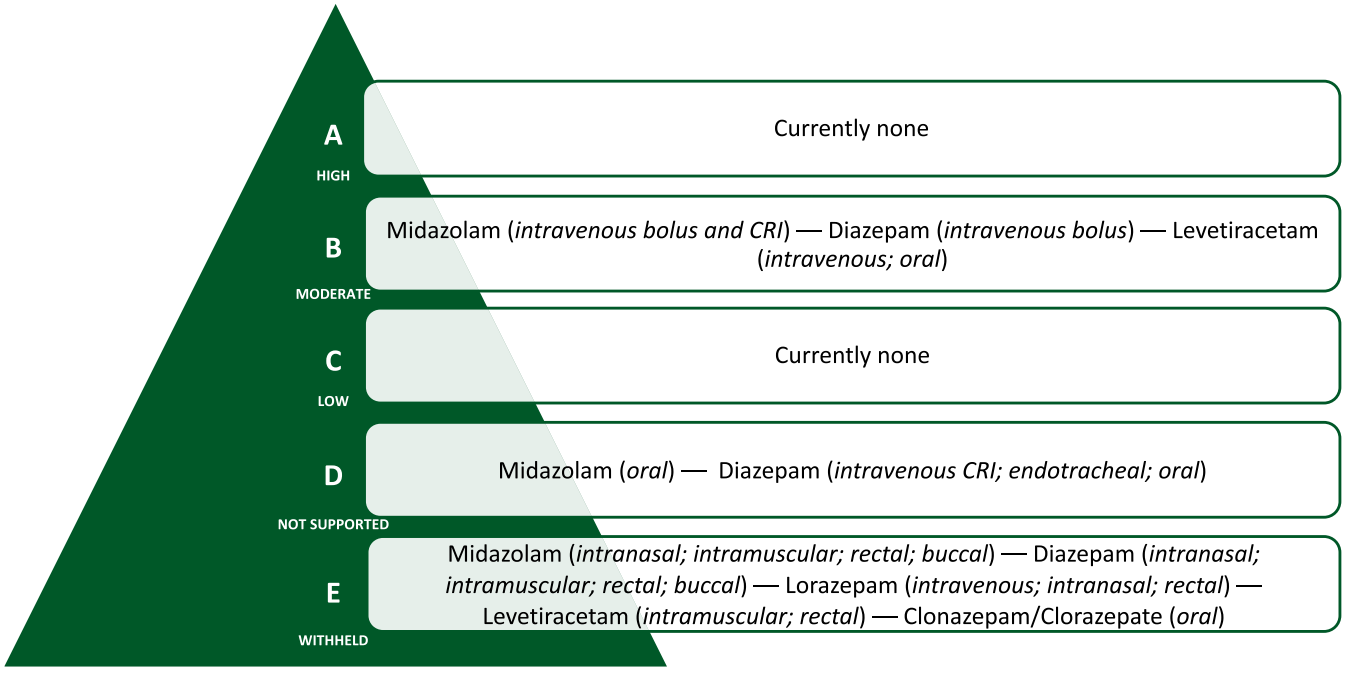

FIGURE 5 Pyramid of hierarchy regarding antiseizure therapy recommendations for CS in cats.

activity.[6,38,105] However, when IN-MDZ is not available, owners can opt for R-DZP (the parenteral formulation) because it still may result in favorable outcomes in some cases.[38,97,99] The IN pathway of drug delivery for SE provides several advantages as an administration method, which have been thoroughly analyzed in previous publications.[5,6,38,39,42] Intramuscular-MDZ can be an alternative

effective and safe option for managing SE, when IV or IN routes are not available. The level of evidence as well as the therapeutic clinical outcomes and pharmacokinetic profiles of the BZDs and their various administration routes are provided in Supplementary files 2–5.

6.3 | Midazolam or diazepam?

- *Although both BZDs are potent and safe for the management of SE in dogs and cats, MDZ may be considered a more potent or safer BZD than DZP.*

6.4 | Rationale

Although there are more veterinary reports regarding the use of DZP in SE, particularly in dogs, evidence from both humans and animals shows that MDZ might be considered to be a more potent BZD compared to DZP. In one study of dogs, MDZ showed a higher suppressive effect on lidocaine-induced seizures compared to DZP.[60] In 2 clinical studies of dogs, MDZ was shown to be safe, and resulted in seizure termination in approximately 70% of the dogs with SE regardless of the route of administration.[38,39] In a pharmacodynamic and encephalographic study of humans, MDZ was found to be approximately 5 times more potent than DZP.[119] In a systematic review and meta-analysis in humans with SE, MDZ was superior to DZP, by any route, for terminating seizure activity.[120] In another systematic review in humans with emergency seizures, the time to seizure control and incidence of seizure recurrence were decreased in patients treated with MDZ compared to DZP.[121] In addition, in a SE mouse model study, treatment with MDZ resulted in fewer seizure relapse episodes and milder hippocampal atrophy, neuronal loss, and gliosis when compared to DZP or pentobarbital.[122] In the same study, MDZ was shown to possess a strong antiseizure effect and benefits against epileptogenesis, hence, it was recommended as a primary treatment choice for SE.[122] However, the panel considered the fact that MDZ can have a shorter half-life and duration of action than DZP in dogs that might eventually require a MDZ constant rate infusion (CRI) to achieve sustained seizure control. Lastly, MDZ has gained more popularity in the management of SE because of its safer drug profile (ie, MDZ-induced central nervous system and respiratory depression are less severe compared to DZP and lorazepam [LZP]).[123,124] However, in a meta-analysis in humans with SE, the risk of respiratory complications requiring intervention was low and similar for both BZDs.[120]

6.5 | After what time frame should a BZD bolus be considered effective? When should BZD IV CRI be initiated?

- *A BZD bolus should be considered effective if seizure cessation occurs <5 minutes after administration and seizures do not relapse in <10 minutes after cessation.*
- *Seizure activity that is controlled with BZDs but relapses within 10-60 minutes may be considered as recurrent SE.*
- *In the case of recurrent SE or SE that does not cease after the first bolus, a second bolus of BZD should be administered after a minimum 2-minute interval.*
- *If seizures persist after 2 BZD boluses, then (i) in case of recurrent SE, administration of another BZD bolus followed immediately by a BZD IV CRI should be instituted, and (ii) if SE does not cease, a final BZD bolus should be administered followed by second-line interventions.*
- *In dogs, options include MDZ IV CRI (ACVIM **recommendation A**) or DZP IV CRI (ACVIM **recommendation B**).*
- *In cats, MDZ IV CRI (ACVIM **recommendation B**) is the BZD CRI of choice; DZP IV CRI (ACVIM **recommendation D**) should be avoided because of safety concerns.*

6.6 | Rationale

The clinical time frame for an ASM to be considered effective was not well defined in the majority of veterinary studies included in this Consensus Statement. The majority of the current recommendations derive from various anecdotal reports or personal opinions and do not indicate a clear time frame. However, in 2 clinical studies of dogs, BZDs were considered effective if the seizure activity terminated within 5 minutes and no relapse occurred for at least 10 minutes after cessation.[38,39] Similar time frames for other rescue ASMs, such as ketamine and fosphenytoin, were utilized in other clinical studies of dogs.[40,65] Based on clinical guidelines and studies in humans, BZDs should terminate seizure activity within 5-10 minutes after administration to be considered effective.[115,124-131] According to current clinical data and the fact that delays in the treatment of emergency seizure disorders should be avoided, the panel considered a maximum clinical 5-frame of five minutes as a successful outcome for BZD administration. This time frame also could be applied to other rescue ASMs used in the treatment of emergency seizure disorders. Regarding the time interval between the initial BZD boluses, although a maximum of 5 minutes could be suggested as a waiting period after the first bolus before another bolus is administered, delays in treatment should be avoided. Therefore, the panel advises a shorter, 2-minute

interval between boluses. A 2-minute interval might be a reasonable waiting period between boluses based on data from clinical studies. Specifically, in 2 multicenter clinical trials,[38,39] median seizure cessation times after IV-MDZ, IV-DZP and IN-MDZ for the BZD-responder group of dogs were 1 minute (range, 0.2-5), 1.25 minutes (range, 0.6-4), and 0.8 minute (range, 0.1-5), respectively. In addition, based on data from pharmacokinetic studies,[84,92,93,98,103,105,107,112,113] the T-max after IV-BZD administration was <5 minutes for the majority of subject populations in the studies.

In case of recurrent SE after 2 BZD boluses, a third bolus immediately followed by a BZD IV CRI is recommended.[5,6] Multiple BZD boluses are not advised, especially in the case of DZP because accumulation could occur and high concentrations of the drug in the central nervous system (CNS), cerebrospinal fluid (CSF) and bloodstream could cause potentially severe CNS and cardiorespiratory depression.[132] As was previously mentioned, MDZ might be considered a more potent and safer BZD compared to DZP. Diazepam might pose some risks regarding its CRI administration, because DZP can adsorb to plastic leading to a loss of drug efficacy.[133-136] In 2 studies, DZP concentration decreased by 55% after 2 hours[137] and 70% after 24 hours[138] of storage in plastic bags and infusion lines. In another study, it was reported that >24% of DZP's potency was lost after storing in plastic material.[139] Therefore, DZP should not be stored in plastic syringes or infusion lines for any length of time; precoating the infusion lines with DZP before CRI administration is required. Diazepam is also light sensitive,[132] and therefore the infusion line should be wrapped in a dense material (such as aluminum foil) when DZP is administered as a CRI. In addition, DZP is diluted in a propylene glycol vehicle because of the drug's lipophilicity, which can cause phlebitis and hypotension with rapid administration (mainly a concern when rapid undiluted boluses are administered). Propylene glycol toxicity is especially of concern in cats. Such limitations are not documented with MDZ.[135] Overall, the panel recommends MDZ over DZP as an IV CRI option in dogs and particularly in cats. The level of evidence as well as therapeutic clinical outcomes and pharmacokinetic profiles of BZD IV CRI administration are provided in Supplementary files 2–5.

7 | SECOND-LINE TREATMENT

- *Second-line treatment options include levetiracetam, phenobarbital and fosphenytoin.*
- *Levetiracetam and phenobarbital typically are initiated as second-line medications when the first-line treatment has failed to terminate the seizures, however these medications also can be administered earlier, regardless of the response to first-line treatment, with the aim to maintain adequate seizure control in the short- and long-term (particularly in cases diagnosed with epilepsy).*
- *Treatment with IV levetiracetam should be initiated in dogs and cats (ACVIM **recommendation B**); if the IV route is not an option, then IM or R administration in dogs (ACVIM **recommendation C**) and cats (ACVIM **recommendation E**) can be considered.*
- *Treatment with IV phenobarbital also should be initiated in dogs (ACVIM **recommendation A**) and cats (ACVIM **recommendation B**); loading dosage schemes can be used, if necessary, in phenobarbital-naïve animals with normal hepatic function; for animals on long-term phenobarbital treatment, dosage increases ideally should be performed after evaluation of serum phenobarbital concentrations.*
- *An IV bolus of fosphenytoin can be administered as an adjunctive ASM in dogs (ACVIM **recommendation B**) when there is no or inadequate response to levetiracetam or phenobarbital.*

7.1 | Rationale

Phenobarbital and levetiracetam are 2 potent and safe ASMs with abundant evidence supporting their use for the management of both epilepsy and emergency seizure disorders in dogs and cats.[4,5,12-16,42] Although these ASMs are considered a second-line treatment, clinicians also should consider initiating them earlier (eg, concurrent with or after repeated BZD boluses and CRI) in animals presenting with seizure emergencies at the hospital as part of an early simultaneous polytherapy approach (see also Supplementary file 6).[5] Such a decision may provide a 2-fold benefit: (i) increased probability of terminating seizure emergencies earlier and thus preventing refractory stages of SE, and (ii) earlier establishment of a more effective long-term seizure management plan in particular for animals diagnosed with epilepsy. In addition, phenobarbital, levetiracetam and fosphenytoin can provide additional benefits for overcoming the therapeutic (pathophysiological) obstacles encountered in SE (ie, by acting on other gamma aminobutyric acid A [$GABA_A$] subunits [non-BZD site] and extra-synaptic $GABA_A$ receptors as well as manifesting multiple mechanisms of actions such as affecting N-methyl-D-aspartate [NMDA] or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptors, pre-synaptic glutamate release, and voltage-gated sodium and calcium channels [see Supplementary file 6]).[4-6,140,141] The level of evidence as well as therapeutic clinical outcomes and pharmacokinetic profiles of phenobarbital, levetiracetam and fosphenytoin, and their various administration routes are provided in Supplementary files 2–5.

8 | THIRD-LINE TREATMENT

- *Third-line treatment refers to anesthetic medications used for controlling seizure activity. When this stage has been reached, a four-step approach can be followed.*
- ***First step*:**
  - *Ketamine IV bolus, possibly followed by CRI, should be initiated in dogs (ACVIM **recommendation A**) and cats (ACVIM **recommendation E**).*
  - *Dexmedetomidine IV bolus and CRI should be initiated in dogs (ACVIM **recommendation B**) and cats (ACVIM **recommendation E**), if SE persists after ketamine administration (or vice versa).*
- ***Second step*:**
  - *Propofol IV bolus, possibly followed by CRI, should be initiated in dogs (ACVIM **recommendation A**) if SE persists after ketamine and* dexmedetomidine *IV CRIs.*
- *In cats, caution should be taken with repeated boluses of propofol and particularly with CRI (ACVIM **recommendation C**) because of safety concerns; propofol should be administered under close monitoring of clinical and hematological variables and preferably only after other anesthetics fail to terminate SE; efforts should be made to limit the duration of propofol IV CRI in cats to the minimum needed to achieve sustained seizure control.*
- ***Third step*:**
  - *Anesthetic* barbiturates *(pentobarbital or sodium thiopental) IV bolus and CRI can be initiated in dogs (ACVIM **recommendation B**) and cats (ACVIM **recommendation C**) if SE persists after propofol IV CRI.*
- ***Fourth step*:**
  - *Inhalational anesthesia* should *be initiated in dogs and cats (ACVIM **recommendation B**) if SE persists after the previous interventions.*

8.1 | Rationale

Anesthetics are agents of choice for humans and animals with refractory SE that has failed to terminate after previous combination treatment.[5,11,17,115,128,142-149] Recommended agents are ketamine, dexmedetomidine, propofol, barbiturates (thiopental or pentobarbital) and inhalant anesthetics. In humans and animals, there is no comparative evidence for (i) superiority of 1 particular anesthetic over another, (ii) combination strategies, (iii) the exact duration of CRI administration and reduction procedures, and (iv) the order in which recommended agents should be introduced. Because general anesthetics, in particular barbiturates followed by propofol and inhalant anesthetics, can be linked to safety issues and a higher rate of in-hospital complications, it is rational to attempt to control refractory SE first by administering agents with a better safety profile, that is, dexmedetomidine and ketamine. If dexmedetomidine is unavailable, medetomidine can be used as an alternative, although there is less clinical evidence for its use in SE management. Therefore, the panel recommends the administration of IV bolus and CRI dexmedetomidine and, if unsuccessful, IV bolus and CRI ketamine can be initiated, or vice versa. Administration of ketamine at earlier time points (ie, after BZD resistance has progressed or become established or during stage II) just before or combined with the second-line treatment, also could be considered part of early simultaneous polytherapy. The advantages and considerations, as well as supporting evidence regarding this approach, are presented in Supplementary file 6. When ketamine and dexmedetomidine CRI fail to control refractory SE, anesthetics such as propofol IV bolus and CRI, followed by barbiturate IV and CRI, and lastly inhalant anesthetics can be included in the therapeutic approach.

Dexmedetomidine is an α2-adrenoreceptor agonist that acts by decreasing excitatory neurotransmitters via suppression of sympathetic nervous system stimulation and norepinephrine release, mainly in the regions of the amygdala, hippocampus and cerebral cortex.[4,150,151] In addition, dexmedetomidine has neuroprotective properties by decreasing cerebral metabolic and oxygen demands, decreasing brain edema via vasoconstriction and contributing to maintaining normal mean arterial pressure.[4,152] In a study of cats, microinfusion of an α2-adrenoreceptor agonist into the amygdala led to protection against seizure induction.[153] In rats, dexmedetomidine administration led to the cessation of refractory SE.[151,154] Dexmedetomidine also can be beneficial in decreasing agitation during recovery.[4] Adverse effects include decreased respiration, bradycardia, cardiac arrhythmias and hypothermia, the latter however might be beneficial to the brain during prolonged SE. According to a case report of 3 dogs with IE that were presented with super-refractory SE, the combination of ketamine-dexmedetomidine IV CRI and mild hypothermia (36.7-37.7°C) resulted in termination of super-refractory SE.[53]

Ketamine increases blood pressure, which may counteract the adverse hemodynamic effects of other anesthetic agents in humans and animals. This effect was further supported in clinical studies in humans when ketamine was administered concurrently with propofol (a combination known as ketofol). Ketofol can lead to improved hemodynamics and respiratory function compared to propofol alone.[155-157] In a clinical study in humans with refractory SE, ketofol was successful in terminating seizure activity. In the same study, it was reported that the short-term or prolonged infusion of ketamine, with or without propofol infusion, was also effective in controlling super-refractory SE.[155] The reader is referred to Supplementary file 6 for details about the use of ketamine in SE.

Propofol acts on $GABA_A$ receptors (non-BZD site; agonist) and also may interact with glycine (agonist) and NMDA (antagonist) receptors as well as calcium channels.[4,5] Adverse effects include cardiovascular and respiratory depression, pain at the injection site, and loss of gag reflex.[4] Endotracheal intubation should be performed when

propofol is administered. Propofol is usually formulated with 2% benzyl alcohol, but this formulation is not labeled for CRI use because it may cause adverse neurological or cardiovascular effects.[4] However, in a study of cats, no significant differences were detected between animals receiving several propofol boluses at a dose of up to 24 mg/kg with or without 2% benzyl alcohol.[158] Propofol IV CRI or multiple boluses in cats can cause adverse effects such as Heinz body anemia.[159-162] Most of these studies have reported that the anemia is not clinically relevant. However, in 2 studies, signs were clinically relevant.[159,160] In 1 study, malaise, anorexia, diarrhea, facial edema, and increased recovery time also were reported.[159] Based on these studies in cats, the total accumulated dose as well as the duration of propofol administration may be important factors for propofol-related adverse effects. However, none of these studies had long-term follow-up and the exact duration of propofol treatment responsible for the occurrence of clinically relevant signs was not well defined. In 1 study, a 30-minute propofol IV CRI administered for 5 to 7 consecutive days induced Heinz body formation, clinical illness, and increased recovery times in healthy cats, and clinical signs resolved within 1 to 2 days after discontinuation of propofol.[159] In another study, a total propofol dose exceeding 40 mg/kg over the duration of treatment might have been a factor contributing to Heinz body formation.[160] In the same study, cessation of propofol administration led to resolution of the Heinz body anemia within 4 to 7 days.[160] In addition, a propofol infusion syndrome (cardiac dysfunction, hyperkalemia, rhabdomyolysis, and acidosis) with high morbidity and mortality has been reported after prolonged anesthesia in humans.[163] However, a similar situation has not been widely reported in veterinary medicine except for a case report that described a propofol infusion-like syndrome in a dog presented with rhabdomyolysis, myoglobinuria, cardiac arrhythmias, increased liver enzyme activities, and methemoglobinemia after anesthesia with propofol.[164] Lastly, seizure-like phenomena have been reported with propofol administration in humans and animals, likely related to glycine antagonism at the level of the spinal cord.[4,70,165,166] This situation usually occurs after anesthetic induction because of changes in serum propofol concentrations.[166] Overall, the panel recommends the use of propofol IV bolus and CRI in animals with SE. In cats, however, it should be used cautiously with close monitoring and preferably only after other anesthetics have failed to terminate refractory SE.

Pentobarbitone and sodium thiopentone are barbiturates used to terminate refractory SE in animals.[5,142,144,145] Anesthetic barbiturates act on $GABA_A$ receptors (non-BZD site; agonists) and also have a neuroprotective effect by decreasing intracellular Na^+ and Ca^{2+}, glutamate release and cerebral oxygen consumption, while also scavenging oxygen free radicals.[4,5] Pentobarbitone is most commonly used, but it should be closely monitored because an overdose can be fatal.[4] Barbiturates can cause substantial cardiovascular and respiratory depression, hypotension, and hypothermia, and sodium thiopentone administration in animals carries a higher risk of cardiac toxicity compared to pentobarbital.[4,144,145] Endotracheal intubation should be performed when barbiturates are administered. During recovery from both pentobarbitone and sodium thiopentone administration, animals may display seizure-like movements and vocalization, phenomena that might be misinterpreted clinically as seizures.[4,144,145] In a systematic review and meta-analysis in humans with refractory SE, propofol decreased the time needed to control refractory SE and increased the disease control rate compared to anesthetic barbiturates.[167] In another systematic review in humans, both propofol and sodium thiopentone were comparable with regard to seizure control, rate of complications, mortality and long-term outcome in patients with refractory SE, but patients on sodium thiopentone required more days of mechanical ventilation compared to patients on propofol.[168] In a study in dogs comparing sodium thiopentone IV CRI to propofol IV CRI for the management of refractory SE, hospitalization time was longer for sodium thiopental compared to propofol.[51] Overall, the panel recommends the use of barbiturates IV CRI (thiopental or pentobarbital) in animals with SE only if previous treatment with dexmedetomine, ketamine, or propofol IV CRI fails to terminate SE.

Inhalant anesthetics usually are reserved as a last pharmacological option in refractory SE in veterinary medicine.[4,5,144,145,169] They act on $GABA_A$ receptors (non-BZD site; agonists), decrease thalamic neuronal membrane excitability and neurotransmitter release, and increase cerebral blood flow while minimizing oxygen cerebral consumption.[4,5,170,171] Isoflurane and desflurane cause a dose-dependent suppression of epileptiform discharges in humans.[172,173] Inhalation anesthetics require endotracheal intubation and ventilation and can cause hypotension because they decrease systemic vascular resistance.[4,144,145] Veterinary clinical studies specifically assessing the effect of inhalant anesthetics in refractory SE are lacking. Only a single study assessed their effects in cats with SE.[63] The level of evidence as well as therapeutic clinical outcomes and pharmacokinetic profiles of the anesthetic medications are provided in Supplementary files 2–5.

9 | WHAT IF THE COMBINED MEASURES WITH FIRST-, SECOND- AND THIRD-LINE TREATMENT AS WELL AS SUPPORTIVE CARE STILL FAIL TO TERMINATE SEIZURE ACTIVITY?

- *Other pharmacological interventions (ACVIM **recommendation E**), including but not limited to IV magnesium and allopregnanolone can be considered in dogs and cats.*
- *If these pharmacological interventions fail, non-pharmacological interventions (ie, neurostimulation in dogs and cats; ACVIM **recommendation E**) can be considered.*

9.1 | Rationale

Animals that are refractory to all lines of treatment, in which seizures persist either with anesthesia or recur immediately after withdrawing

general anesthesia, have progressed to the super-refractory stage. Continuation of intensive care, monitoring and all previous medications is important, but further adjunctive pharmacological and non-pharmacological interventions are required. Even in human medicine, limited data support such interventions. In veterinary medicine, evidence and clinical experience are limited to absent.[68,111,174] Pharmacological interventions such as IV magnesium[68] and allopregnanolone,[85,111] as well as mild hypothermia[53] might provide further antiseizure effects in dogs and cats with super-refractory SE.

Magnesium may inhibit NMDA receptors and calcium channels, and increase cerebral blood flow via vasodilatation.[175] Based on a case report in a dog, IV magnesium might be beneficial after third-line therapy.[68] Allopregnanolone may act on synaptic and mainly extrasynaptic $GABA_A$ receptors.[176] Two pharmacokinetic studies in dogs showed a favorable pharmacokinetic and safety profile for allopregnanolone in SE.[85,111] Hypothermia decreases excitatory neurotransmitters, calcium- and glutamate-induced excitotoxicity, and cerebral metabolic rate, and normalizes intracranial pressure.[177,178] According to a clinical report in dogs,[53] mild hypothermia (36.7-37.7°C) when combined with ketamine-dexmedetomidine IV CRI was effective in terminating super-refractory SE.

Emerging evidence suggests that systemic inflammation (eg, activation of signaling pathways including the toll-like receptor-interleukin [IL] 1 receptor signaling network and increased concentrations of inflammatory markers such as IL-1B, IL-6, and tumor necrosis factor alpha [TNF-a]) may play roles in triggering and maintaining seizure activity.[27,179] In humans, clinical studies and guidelines suggest that all stages and in particular the super-refractory stages of SE can benefit from immunomodulatory treatments such as corticosteroids.[128,143,148,149,174,180,181] In addition to their immunosuppressive effects, corticosteroids also may reverse the blood-brain barrier (BBB) leakage and the upregulation of transporters such as P-glycoprotein (P-gp), which may contribute to persistent and drug-refractory SE,[27] and may have positive effects on cerebral edema and intracranial pressure.[182] In veterinary medicine, no clinical studies are available on the use of immunomodulatory agents in cases with super-refractory SE and clinical experience with such cases is limited. Therefore, the panel did not further evaluate and provide specific recommendations, although the possibility that immunomodulatory drugs provide benefits in such cases cannot be completely disregarded currently.

Lastly, if all the pharmacological interventions fail, neurostimulation such as vagus nerve stimulation, repetitive transcranial magnetic stimulation and deep brain stimulation might serve as a last resort for terminating SE. Although the use of neurostimulation in human super-refractory SE is still emerging, current data from clinical studies have indicated that neurostimulation may terminate seizures in ≥80% of patients.[183] In veterinary medicine, neurostimulation such as transcranial magnetic stimulation[184] and particularly vagus nerve stimulation[185-188] only have been studied clinically in the management of drug-resistant epilepsy in dogs.[189] Deep brain stimulation was assessed in a dog with drug-resistant idiopathic epilepsy and showed that it could prevent SE over a follow-up period of 7 months, but its effect during SE was not assessed.[73] The level of evidence as well as therapeutic clinical outcomes and pharmacokinetic profiles (if applicable) of these interventions are provided in Supplementary files 2–5.

10 | WHEN TO STOP ADMINISTERING MORE ANTISEIZURE MEDICATIONS?

- *If no further seizure activity occurs for 24-48 hours after the addition or dosage adjustment of the last intervention, then no further anesthetic medication is needed.*
- *All current anesthetic treatments should be continued, at dosages that achieved seizure cessation, for 24-48 hours after resolution of seizures, but shorter durations (ie, 12 hours) also can be considered to decrease the risk of complications related to prolonged hospitalization and CRIs of anesthetic medications.*
- *Electroencephalography combined with clinical confirmation of seizure cessation is preferred compared to only clinical confirmation, especially in the case of NCSE.*

10.1 | Rationale

Continuous EEG monitoring can aid in guiding treatment, tapering of medications, detecting relapse, and avoiding under- or over-treatment. In humans, treatment usually is dictated by EEG findings and supported by clinical evaluation. In comatose patients or those suffering from NCSE, EEG is vital for assessment of seizure cessation.[115] The goal is cessation of EEG seizures or burst suppression, and no clinical manifestations of seizures.[115,128,143,149,190] Anesthetic treatment should be titrated to burst suppression, targeting an inter-burst interval of approximately 10 seconds for at least 24 hours.[149,191] However, no association between a specific inter-burst interval and outcome has been identified.[192,193] Patients do not necessarily require titration of IV anesthetics to achieve 10-second inter-burst intervals on EEG, which may allow lower dosages of IV anesthetics and result in fewer adverse effects.[149,193] Outcome might be independent of the specific anesthetic agent used and the extent of EEG burst suppression.[147] Apart from the inter-burst interval, other EEG characteristics that are related to successful treatment in SE are bursts without monomorphic sharp waves or high amplitude and recordings with epileptiform activity in <50% of bursts.[193] Seizure recurrence might be more likely after "highly epileptiform bursts" (with sharp waves or rhythmic,

potentially ictal activity in >50% of bursts) than after polymorphic bursts.[194] These EEG characteristics can help physicians tailor treatment to a less aggressive anesthetic polytherapy in human patients even if inter-burst intervals are <10 seconds. Overall, guidelines for humans traditionally recommend continuing anesthetic infusion for 24-48 hours, followed by gradual tapering of the infusion.[115,128,143,149] Although therapeutic coma induced using anesthetics is commonly needed in cases of refractory SE to achieve seizure termination, there is no strong evidence that therapeutic coma definitively decreases mortality.[195] Patients with SE in therapeutic anesthetic coma may have higher risks of infection and mortality compared to patients not receiving anesthetics.[196] Intravenous anesthetics have been linked to poor outcomes, mechanical ventilation, and cardiovascular complications.[197] Higher doses of IV anesthetics have been associated with higher rates of hypotension and vasopressor use compared to lower doses.[198] In a systematic review of the human medical literature, although IV pentobarbital was linked to a lower frequency of short-term treatment failure and recurrent SE, a higher frequency of hypotension was observed when compared to IV MDZ or propofol.[199] Overall, although the ideal recommendation would be a minimum 24-hour duration of IV CRI anesthetics based on guidelines used in humans, the panel considered a minimum duration of 12 hours, determined on an individual basis, according to the animal's clinical status and with the aim to decrease risks related to long-term hospitalization and adverse effects of medications. In a recent study in dogs, however, no superiority of shorter (12 hours) over longer (24 hours) duration of propofol or DZP IV CRI was found regarding the outcome or duration of hospitalization.[200] The panel suggests that, if seizures relapse within a 12-hour IV CRI duration of anesthetic administration, then a longer duration should be considered in clinically stable patients.

Overall, it is important to use adequate seizure cessation assessment tools to avoid over-treatment with IV anesthetics. In veterinary medicine, although EEG is the ideal tool for guiding treatment, it is not widely available and broad clinical expertise is lacking. Electroencephalography as a guidance tool for the management of SE in dogs and cats has been reported in only a small number of clinical studies.[43,67] In most clinical studies assessed for this consensus statement, the criteria used for treatment titration in SE were mainly clinical (ie, termination of seizure-related semiology). However, clinical criteria might not be sensitive or specific enough to determine seizure termination, which is even more important in the case of NCSE. Untreated NCSE increases the risk of excitotoxic neuronal damage and complications and can become more refractory to medications.[34,145] In the absence of EEG, clinicians not only risk under-treating but also over-treating by administering excessive dosages of multiple IV anesthetics for long periods of time. Persistent therapeutic coma can lead to severe respiratory and cardiovascular depression that can progress over time.[145] Therefore, although veterinary clinicians still can rely on clinical termination of seizure activity, the panel recommends the use of EEG, when available, for determining successful outcomes and appropriate individually-tailored treatment plans.

11 | IF SE HAS BEEN SUCCESSFULLY TERMINATED, HOW SHOULD I TAPER POLYTHERAPY?

- *Before starting anesthetic tapering, it is advised that animals be seizure-free for a 24 to 48-hour (minimum 12-hour) period.*
- *After termination of SE, progressive sequential discontinuation of anesthetic drugs should be performed ideally over a 24 to 48-hour period; shorter periods such as 12 hours also may be considered.*
- *Simultaneous tapering of >1 anesthetic is not recommended.*
- *Inhalation anesthetics can be discontinued first, followed by propofol or pentobarbital CRI, then ketamine CRI, and lastly, dexmedetomidine and BZD CRI (ie, in general, opposite to the order in which they were introduce) but variations in the order of discontinuation may apply based on the clinician's judgment.*
- *Inhalant anesthetics can be decreased and discontinued more rapidly compared to IV anesthetics.*
- *A CRI can be decreased by 25%-50% every 4-6 hours before discontinuation; if there is no relapse of SE, then the next CRI drug can be tapered in the same manner.*
- *If seizure activity relapses after discontinuation of a specific anesthetic agent, then its CRI dosage should be increased back to the previous dosage that was sufficient to control seizures (where seizures re-occurred during dosage reduction) or CRI should be re-introduced after a bolus (where seizures re-occurred after complete drug suspension).*
- *Non-anesthetic ASMs (eg, levetiracetam or phenobarbital) should be administered minimum until the animal is discharged from the hospital (in cases with reactive seizures) or over the long-term (in cases with an epilepsy diagnosis) using constant doses and, when applicable, at targeted serum concentrations of the drugs.*

11.1 | Rationale

Evidence is accumulating in human and veterinary medicine to support the adoption of an expeditious treatment approach for enhancing outcome in SE. However, conclusive evidence for a standardized regimen regarding the process of discontinuation of therapeutic agents previously introduced to terminate SE is lacking. Once SE has been successfully controlled, highly sedating anesthetic medications should be discontinued to avoid severe adverse effects and complications

related to anesthetic drugs and long hospitalization periods.[5,6,11,17,143,149] However, the discontinuation strategy should be diligent enough to prevent relapse of SE.[5,6,11,17,143,148] Therefore, a rational approach would be a careful, gradual, sequential discontinuation of anesthetic agents.

In humans, as previously mentioned, the treatment regimen usually is dictated by EEG findings and supported by clinical evaluation.[115,128,149,190] Once EEG-based clinical termination of SE has been achieved, discontinuation can be initiated. Specifically, guidelines in humans traditionally recommend continuing the infusion of an anesthetic medication for 24-48 hours after seizure cessation has been achieved, followed by a gradual 24-hour tapering until discontinuation[17,115,143,148] Simultaneous decrease of 2 anesthetics is not recommended because doing so might lead to increased risk of seizure relapse and does not allow the clinician to assess which agent is effective or needs to be continued.

Patients may have recurrent SE upon decrease or discontinuation of a therapeutic agent which will require a return to previous or higher doses of this medication for an additional cycle of anesthesia (usually 24-48 hours) before reattempting reduction, with or without the addition of another agent.[115,128,149] Recurrent isolated seizures also might occur upon drug withdrawal and, as a general rule, should be treated. However, it may be better to tolerate occasional EEG or even clinical seizures, especially if they are brief and infrequent, than to keep patients in the intensive care unit (ICU) for several more days for additional aggressive treatment. Balancing the risk of clinical relapse of seizures against the risks of longer ICU hospitalization and related complications is an important consideration in the management of SE.[11] Overall, there is no limit on the time or the number of cycles of general anesthesia. Although termination of SE should always remain the target, the limit comes down to defining at what point the therapeutic goal should change from total seizure control to accepting a particular frequency of isolated seizures in a patient.[148]

In veterinary medicine, although there are no standardized guidelines or studies specifically assessing the discontinuation strategy of anesthetic agents used for SE, it would be rational to follow an approach similar to the guidelines used for human patients. Based on clinical experience and tapering protocols in humans, a CRI decrease of 25%-50% is recommended every 4-6 hours before discontinuation of a specific drug.[4,6,144,169] The panel supports this scheme and recommends the gradual sequential decrease of anesthetic agents. The decrease of each individual agent can be performed preferably over a period of 12-48 hours in reverse order of initiation. Rapid decreases or simultaneous discontinuation of multiple anesthetic agents is not recommended.

12 | SPECIFIC GUIDELINES AND RECOMMENDATIONS FOR THE TREATMENT OF CLUSTER SEIZURES

The appropriate management of CS consists of a long-term and short-term plan (Figure 6). Long-term treatment focuses mainly on prevention of CS and is achieved with the appropriate implementation of antiseizure treatment of epilepsy (ie, optimization, monitoring and adjusting the dosages and therapeutic schemes of the long-term maintenance ASMs such as phenobarbital, potassium bromide, zonisamide, levetiracetam). Long-term management has been described in other consensus statements and systematic reviews.[12-16,42,43] Because this consensus statement focuses on emergency seizure disorders, and not the long-term management of epilepsy in dogs and cats, only the short-term emergency treatment of CS is addressed. Short-term treatment includes the institution of short-acting interventions (MDZ and DZP) and longer-acting interventions (levetiracetam). If the short- and longer-acting medications fail to control CS, then further interventions may be added to the short-term plan including longer-acting BZDs (ie, clonazepam and clorazepate) or additional doses of long-term ASMs such as phenobarbital (for cases diagnosed with epilepsy). Similar to SE, supportive treatment and addressing any systemic complications or underlying etiology are vital for successful outcomes and should be combined with ASMs.

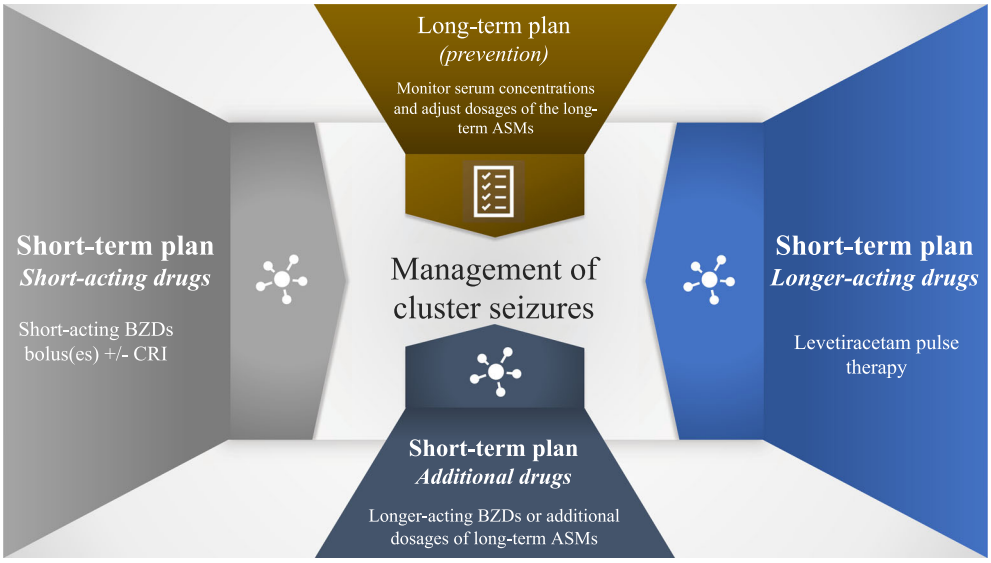

FIGURE 6 The long- and short-term plan for the management of CS in dogs and cats.

Overall, a 3-step short-term plan can be followed:

***First step*:**

***Out-of-hospital settings*:**

- *Short-acting medications*:
  - *IN-MDZ in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation E**).*
  - *R-DZP in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation E**).*
- *Longer-acting medication*:
  - *Levetiracetam pulse treatment administered PO in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation B**); if PO is not possible (eg, because of severe decrease in consciousness or inability to swallow), levetiracetam can be administered R in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation E**); IM levetiracetam also can be administered in dogs (ACVIM **recommendation C**) or cats (ACVIM **recommendation E**), but this option can be used in out-of-hospital settings if the caregivers are medically-trained.*

In-hospital settings:

- *Short-acting medications*:
  - *IV-MDZ in dogs (ACVIM **recommendation A**) or cats (ACVIM **recommendation B**).*
  - *IV-DZP in dogs (ACVIM **recommendation B**).*
  - *IN-MDZ in dogs (ACVIM **recommendation B**) or in cats (ACVIM **recommendation E**); IN-MDZ could be advantageous for providing a rapid antiseizure effect, when IV access is not possible or until an IV catheter is placed.*
  - *IM-MDZ in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation E**).*
  - *If there is relapse of seizures after the last BZD boluses, then another bolus should be administered followed immediately by MDZ IV CRI in dogs (ACVIM **recommendation A**) or cats (ACVIM **recommendation B**); alternatively, DZP IV bolus and CRI can be administered in dogs only (ACVIM **recommendation B**), if MDZ is not available.*
- *Longer-acting medication*:
  - *Levetiracetam pulse treatment administered IV in dogs (ACVIM **recommendation A**) or cats (ACVIM **recommendation B**); if IV is not possible, levetiracetam can be administered R in dogs (ACVIM **recommendation B**) or cats (ACVIM **recommendation E**) or IM in dogs (ACVIM **recommendation C**) or cats (ACVIM **recommendation E**).*

***Second step*:**

If the CS persist despite levetiracetam and short-acting BZD combination treatment, there are 2 further management options:

- *Longer-acting BZDs (ie, clonazepam or clorazepate) can be administered PO as a pulse treatment every 8-12 hours (especially for out-of-hospital settings) in dogs and cats (ACVIM **recommendation E**); however, in cats, attention should be given because of potential safety concerns (ie, hepatotoxicity).*

or

- *Additional dosages of antiseizure medications used for the long-term management of epilepsy, such as phenobarbital, can be administered (dogs and cats).*

***Third step*:**

If CS still persist after the aforementioned polytherapy, then further interventions, as indicated for (stage III) SE cases, should be initiated.

12.1 | Rationale

When CS occur, a short-term treatment plan can be initiated during or immediately after the first seizure (if the animal is known to exhibit CS when seizures occur) or, more commonly, during or after the second seizure; the aim is to terminate seizures and prevent further events in the short-term. If the frequency of the isolated seizures is increasing or CS are unresponsive to the short-term treatment plan, additional ASM should be administered in the same manner as in SE. Therefore, the concepts described for the management of SE also can apply for CS.

In addition to BZDs, longer-acting medications (eg, levetiracetam) are recommended by the panel as an effective and safe approach. Pulse treatment has been recommended instead of long-term continuous treatment, because it might prevent the development of tolerance associated with the drug's chronic use.[77] In the out-of-hospital setting, PO levetiracetam can be used as a first-choice; R administration also can be used in dogs, especially when PO administration is not possible.[49,76,77,101] In dogs that are receiving chronic phenobarbital treatment, a higher dose of levetiracetam may be needed.[77] In cats, although there is a lack of clinical studies assessing the use of levetiracetam pulse treatment in CS, the panel recommends its use based on levetiracetam's proven efficacy and safety in epilepsy[12,13,15,16] and the specialist's clinical experience.

For the in-hospital setting, IV-MDZ, in particular, should be used in both dogs and cats as the first option. Intravenous DZP also may be used in dogs only if MDZ is not an option; in cats it is not recommended because of safety concerns as discussed for SE. An IV BZD CRI, in particular MDZ, can be initiated if a relapse of seizures occurs, with the aim of achieving a steady and constant antiseizure effect. Levetiracetam can be initiated IV in dogs and cats and, if IV is not available, then R or IM administration can be performed. The level of evidence as well as the therapeutic clinical outcomes and

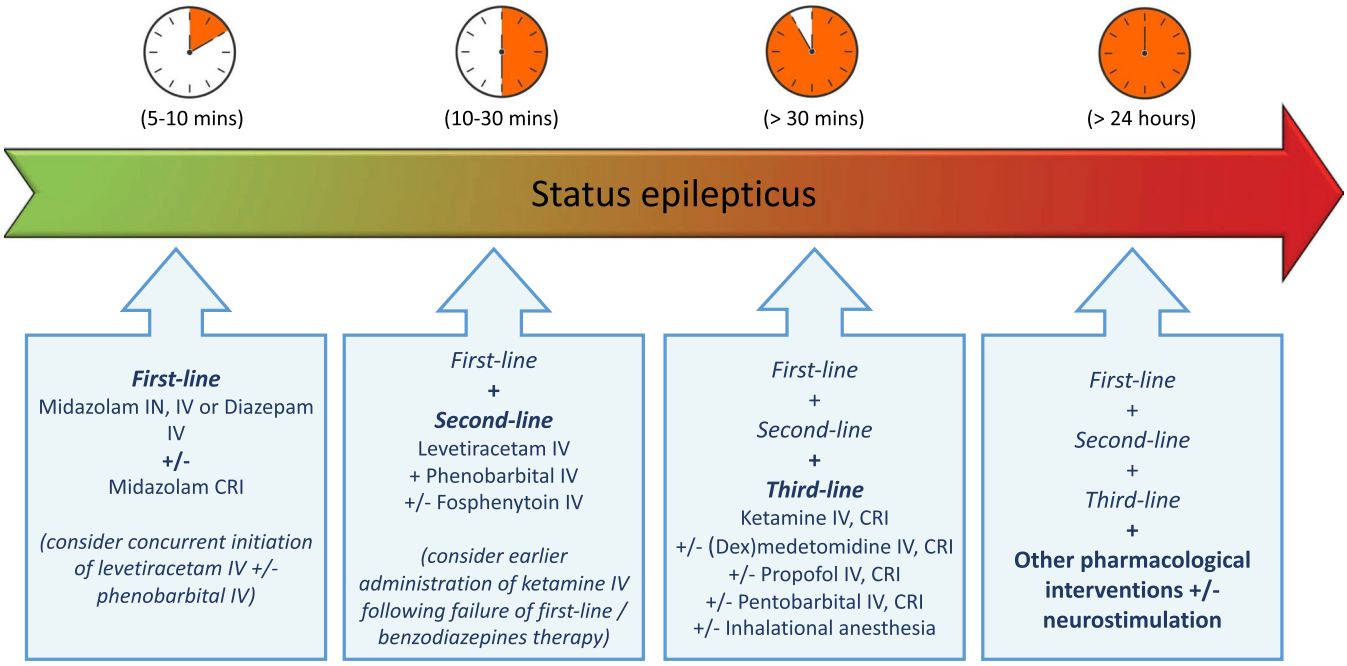

FIGURE 7 ACVIM therapeutic approach proposal in SE according to the stage.

pharmacokinetic profiles of BZDs and their various administration routes are provided in Supplementary files 2–5.

If CS do not adequately respond to the aforementioned combination, further measures include PO administration of longer-acting BZDs (clonazepam or clorazepate; dogs only) or additional dosages of long-term ASMs (dogs and cats). Regarding the latter, ASMs such as phenobarbital can be administered PO, IV or IM after every isolated seizure, in cases diagnosed with epilepsy, at a minimum of 1-hour intervals and up to a maximum of 3 times in a 24-hour period. For animals diagnosed with epilepsy that are not on any long-term ASM, loading dosage schemes of phenobarbital (dogs and cats), potassium bromide (dogs) or other medications can be considered. Although no studies specifically have evaluated or reported these approaches, the panel considers them as adjunctive treatments in dogs or cats with CS based on clinical experience. Blood sampling for assessing serum concentrations of the long-term ASMs (if applicable) should be performed and dosage adjustments made accordingly.

13 | CONCLUSIONS

Seizure emergencies are challenging, with complex pathophysiology and a rapidly-progressive drug-resistant and self-sustaining character. Successful management includes (i) a stage-based treatment approach comprised of interventions with moderate to preferably high ACVIM recommendations, (ii) addressing the pathophysiologically-based treatment obstacles and prevention of the refractory stages by following an early and rapid therapeutic approach, and (iii) management of the complications and underlying causes related to the seizure emergencies. A therapeutic approach in response to the SE stage (Figure 7) as well as treatment algorithms for SE (Supplementary file 7) and CS (Supplementary file 8) are provided as guidance for the management of seizure emergencies.

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CONFLICT OF INTEREST DECLARATION

Karen Muñana consults for MesaGreen Pharmaceuticals and Teliatry Inc, and Holger Volk for Purina and DomesPharma. No other authors declare a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare the use of some drugs mentioned in this Consensus Statement is considered off-label.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC, or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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