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VPAT Academy 2023-2024: What's new in the updated guidelines & consensus statement ครั้งที่ 14

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

ผศ.ดร.สพ.ญ.ดวงทิพย์ ฉัตรชัยศักดิ์

ผู้ช่วยศาสตราจารย์
ประจำภาควิชาเวชศาสตร์คลินิก และการสาธารณสุข
คณะสัตวแพทยศาสตร์ มหาวิทยาลัยมหิดล

ON AIR วันศุกร์ที่ 22 มีนาคม 2567
เวลา 20.00 น.

Facebook Group: VPAT Academy (ไม่ได้รับหน่วยกิต)

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CONSENSUS STATEMENT

Journal of Veterinary Internal Medicine
Open Access

ACVIM
American College of Veterinary Internal Medicine

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

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- The Aim of this Consensus Statement

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

Seizure epilepticus(SE) and cluster seizures (CS)

- Common neurological emergencies
- High morbidity and mortality
- Status Epilepticus
  - a mortality rate of 25.3%- 38.5%
  - Lead to irreversible brain damage and system complications, especially if treatments is delayed

Seizure

- Brief or prolonged
- Brief < 5 mins or prolonged between 5 and 30 mins
- Seizures are considered an emergency when their duration is prolonged and not self-limiting
- Prolonged between 5 and 30 mins……an emergency

Status epilepticus (SE)

- International League Against Epilepsy (ILAE), American Epilepsy Society (AES), the International Veterinary Epilepsy Task Force (IVETF)
- Continuous seizure activity, or >1 sequential seizure without full recovery of consciousness in between, with a duration of >30 minutes
- ≥2 seizures without recovery of consciousness
- 5-minute cut-off time frame
  - Based on the duration of convulsive SE that is required to cause permanent complications and neuronal injury

The 5-minute cut-off time

- 1. minimize the risk of systemic and brain complications associated with continuous seizure activity reaching up to 30 minutes
- 2. prevent worsening of the prognosis and drug resistance associated with increasing duration of uncontrolled seizure activity
- 3. limit any potentially unfavorable outcomes and adverse effects associated with the prolonged administration of multiple therapeutic interventions for seizures

Status epilepticus (SE)

- The vital time points and defines SE as any prolonged seizure lasting > 5 minutes
- 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 T1= 5mins); it is a condition that can have long-term consequences (after time point T2 = 30mins), including neuronal death and alteration of neuronal networks

Status epilepticus (SE)

- Definition of SE provides guidance as to when emergency treatment should be initiated
- T1 (5 mins) is the time point which treatment should have be initiated
- T2 (30 mins) is the latest time by which SE should be under control

Cluster seizure

- > 2 self-limiting seizures over a period of 24 hours
- 1. a risk similar to SE for seizure-related neuronal damage and complications
- 2. can progress to SE
- 3. are unlikely to cease or be appropriately controlled without rescue medication

Status epilepticus (SE)

4 stages

- Treatment options
- Sensitivity to the drugs used
- Underlying pathophysiological processes

Figure 1 illustration of the SE stages and their differences regarding underlying pathophysiological processes involved and sensitivity to the drugs used

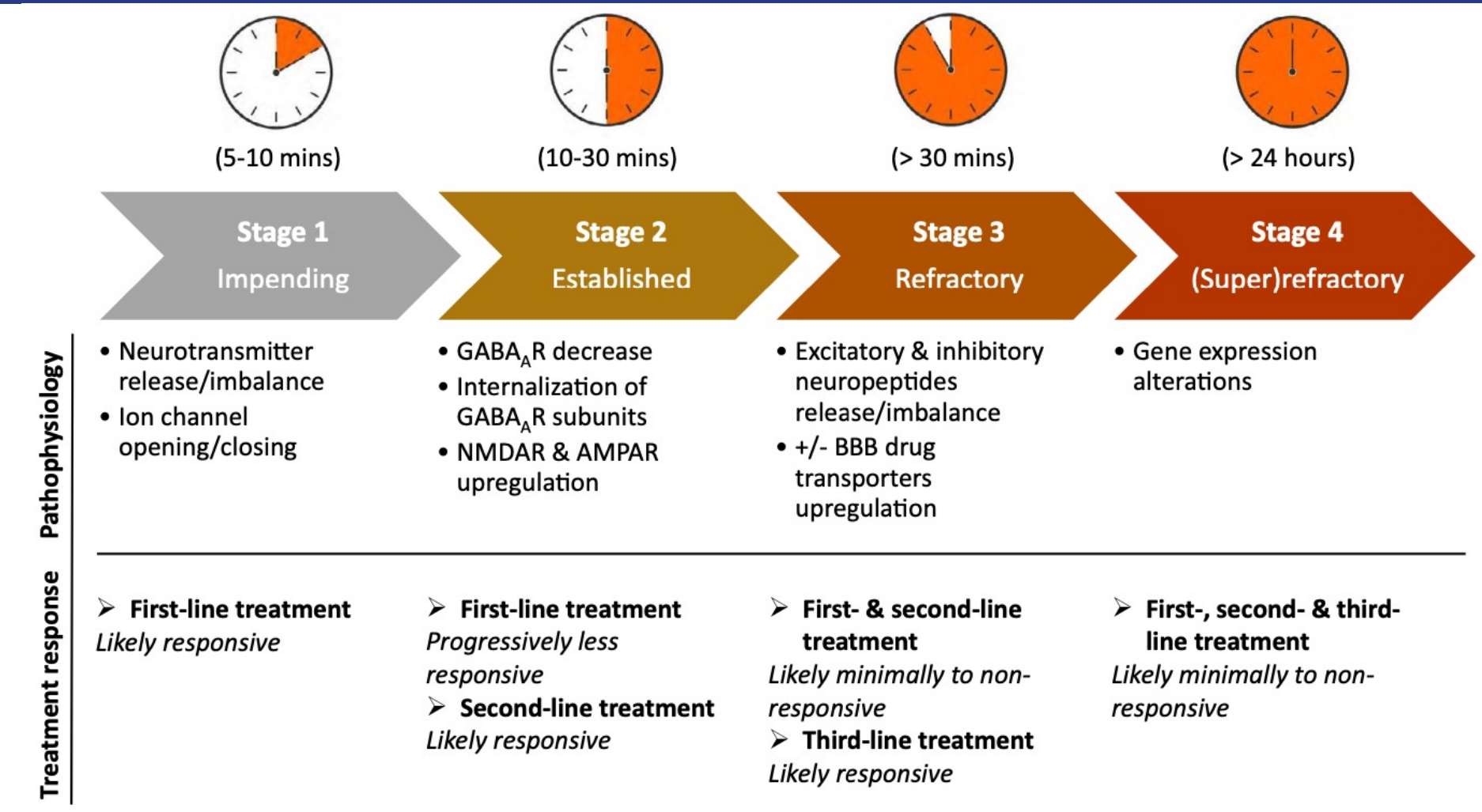
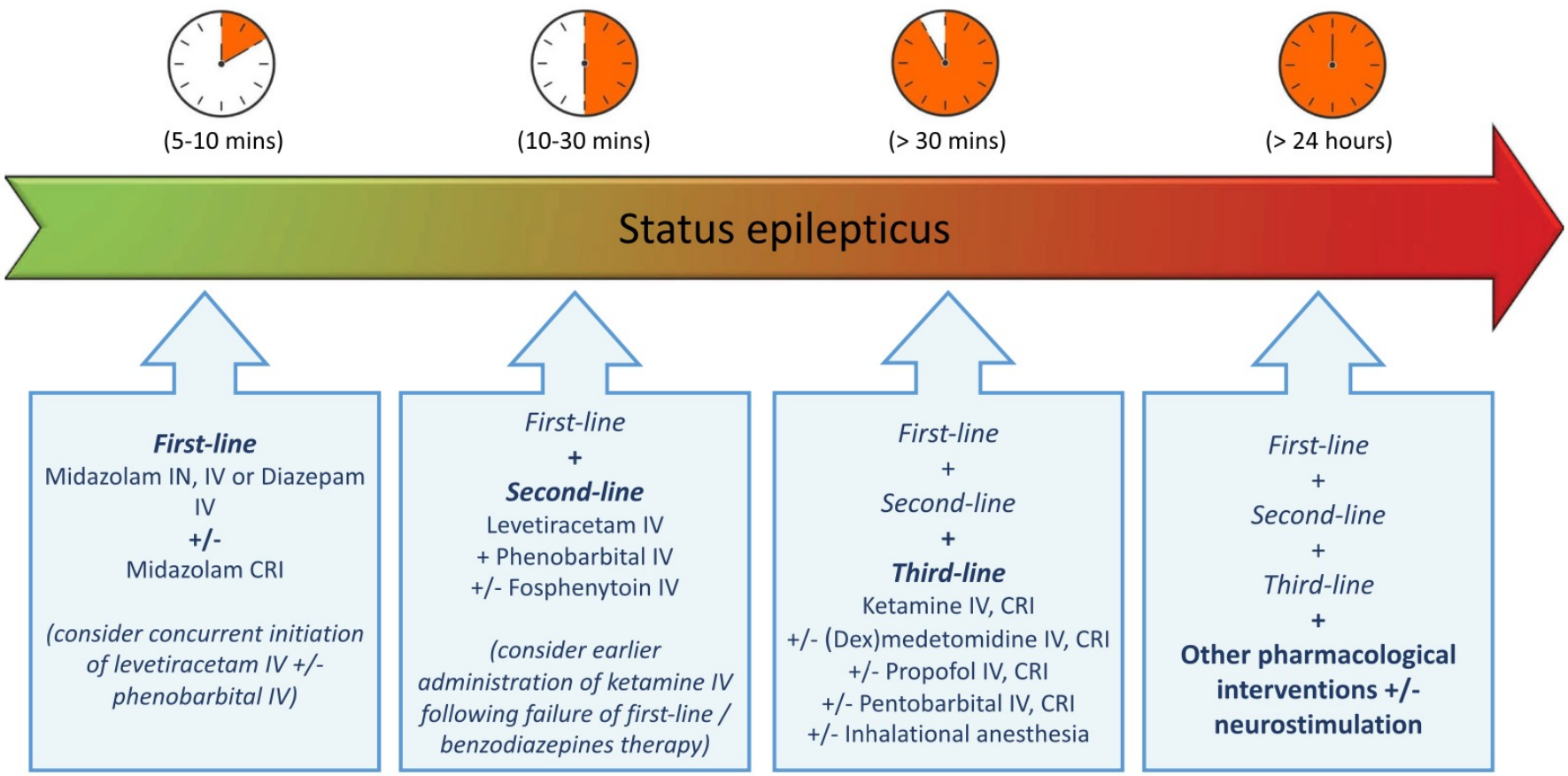
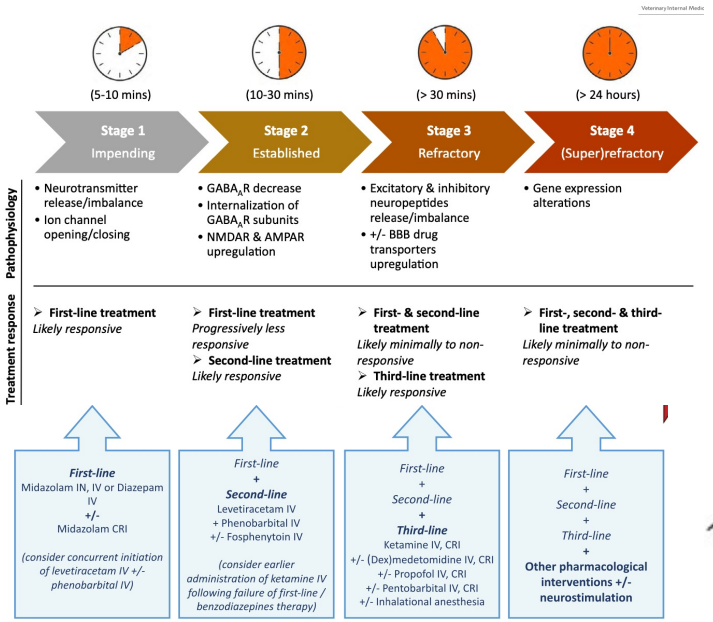
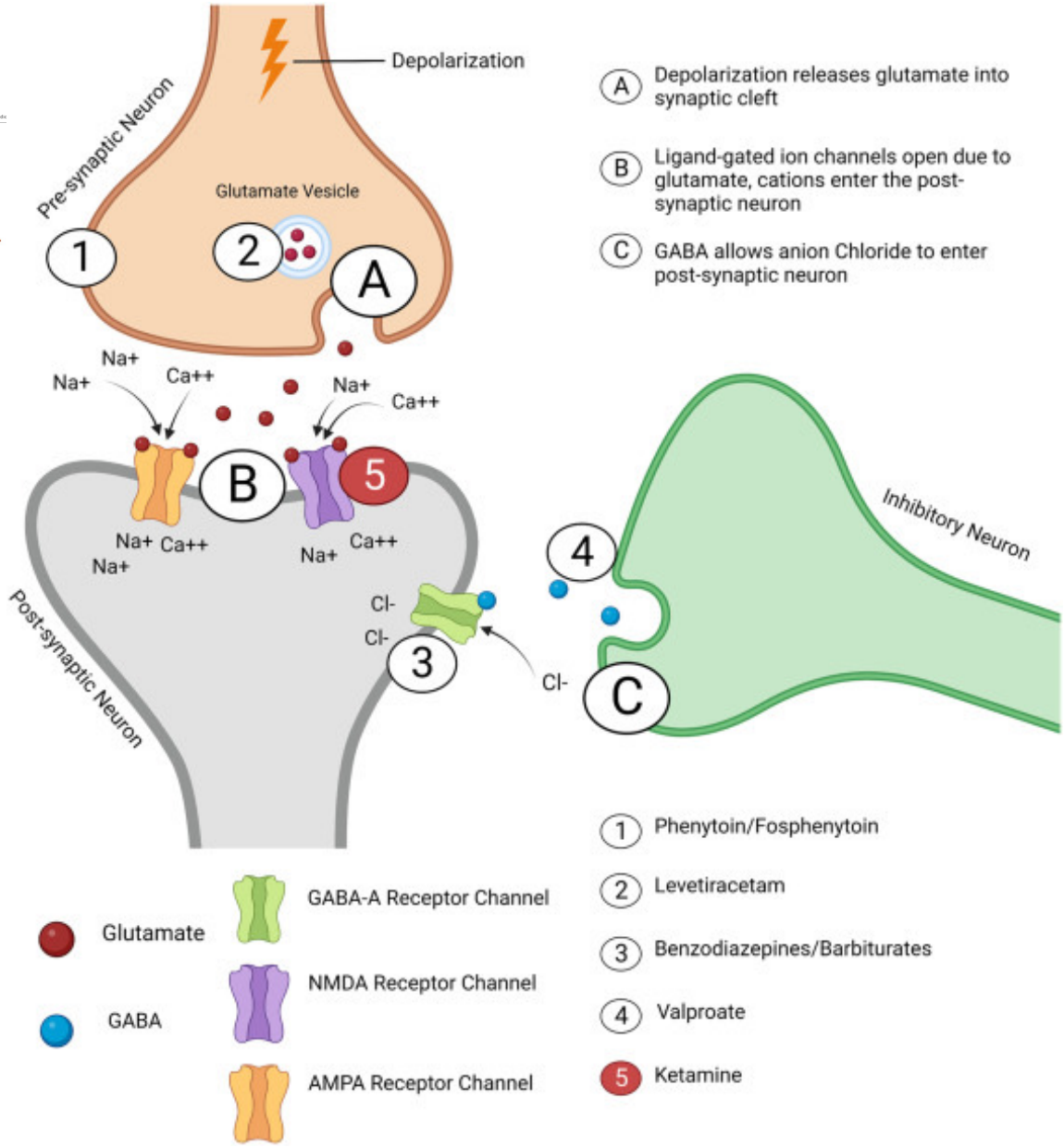


Figure 7 ACVIM therapeutic approach proposal in SE according to the stage







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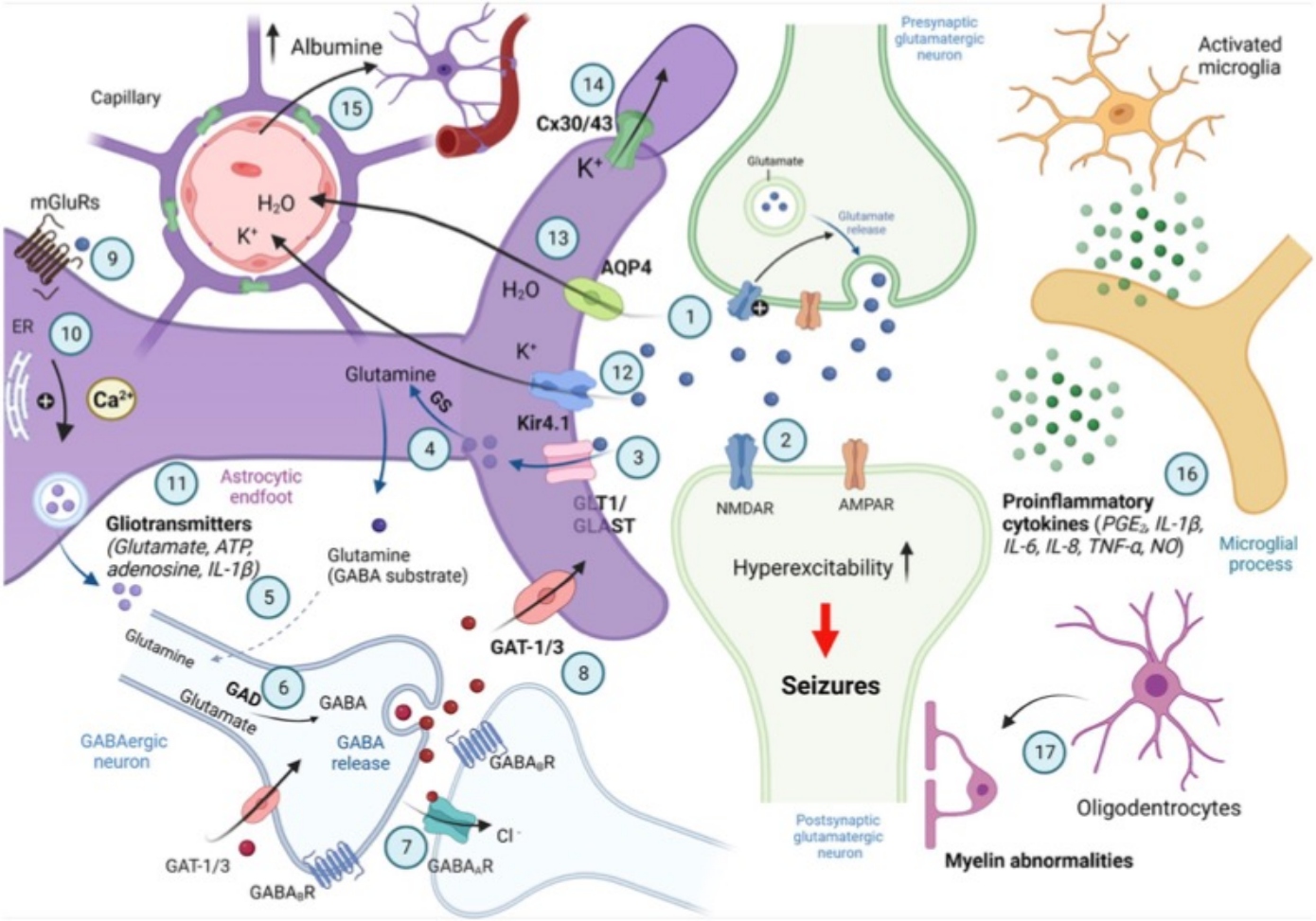
	Stage 1 Impending	Stage 2 Established	Stage 3 Refractory	Stage 4 (Super)refractory
Pathophysiology	• Neurotransmitter release/imbalance • Ion channel opening/closing	• $GABA_AR$ decrease • Internalization of $GABA_AR$ subunits • NMDAR & AMPAR upregulation	• Excitatory & inhibitory neuropeptides release/imbalance • +/- BBB drug transporters upregulation	• Gene expression alterations
Treatment response	➢ **First-line treatment** *Likely responsive*	➢ **First-line treatment** *Progressively less responsive* ➢ **Second-line treatment** *Likely responsive*	➢ **First- & second-line treatment** *Likely minimally to non-responsive* ➢ **Third-line treatment** *Likely responsive*	➢ **First-, second- & third-line treatment** *Likely minimally to non-responsive*



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Types and semiology

The clinical forms of SE in humans (ILAE)

- Based on 2 taxonomic criteria:

  Motor activity and impairment of consciousness

I. SE with prominent motor signs ie, convulsive SE (CSE), myoclonic SE, focal motor SE, tonic SE, and hyperkinetic SE

II. SE without prominent motor sings ie, non-convulsion SE (NCSE)

Types and semiology

The degree of impairment of consciousness

- Convulsive status epilepticus (CSE)
  - Impairment of consciousness with generalized or generalized with focal onset motor signs
- Non- convulsive status epilepticus (NCSE)
  - Comatose or non-comatose

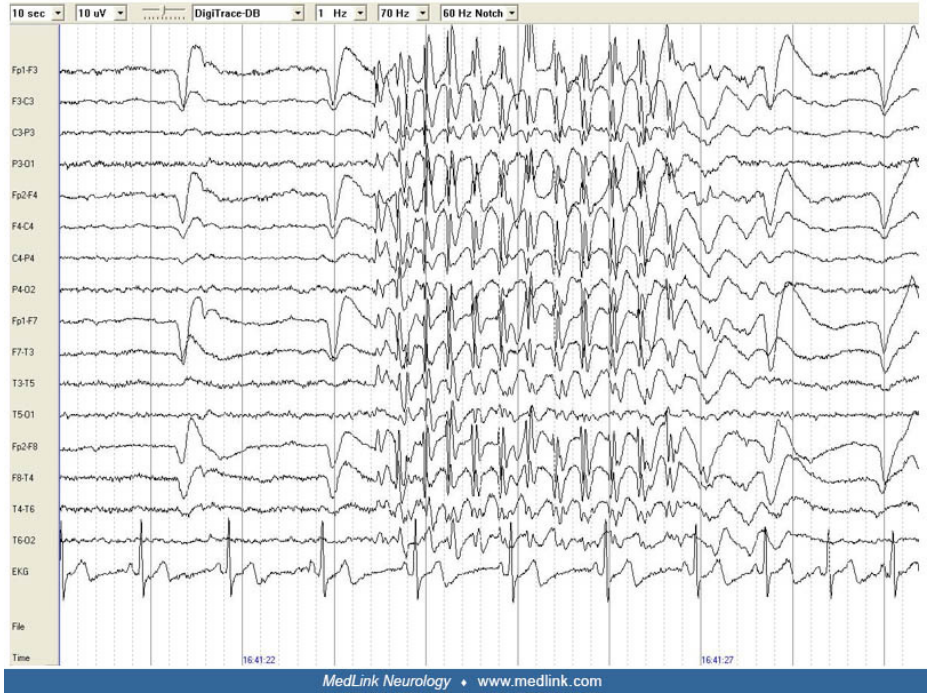
neuronal injury and apoptotic cellular mechanism, making early recognition and treatment as important as in CSE

Non- convulsive status epilepticus (NCSE)

- Comatose NCSE
  - Usually is observed after CSE
  - The absence of any motor activity, although subtle myoclonus or nystagmus
- 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 eyelid, perioral or upper limb area)
  - In the form of focal SE with impairment of consciousness

Ictal electroencephalography (EEG)

- a valuable tool in the diagnosis of all types of SE
- Most importantly for NCSE, because the clinical signs are often subtle and nonspecific



Methodology

- Consensus Panel

Aim

- I. perform a through assessment and systematic review of the listerature
- II. identify any gaps, and share knowledge and clinical expertise,
- III. introduced 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
  - Basic research studies
  - Guideline in human medicine

The procedure included
- a listerature search
- a screening of each study
- quality of evidence assessment (study design, study group sizes, assessment of methods for evaluating study treatment outcomes)
- treatment outcomes assessment
- drafting of recommendations

Drafting the recommendations

Based on the combination of 2 elements

1. Current evidence from published studies
2. Panel member's expert opinion

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Level of evidence

- 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.

The panel's recommendations

- 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.

Specific guidelines & recommendations for the treatment of status epilepticus

- The level of evidence and recommendations

  The pyramids of hierarchy

  .....Focus on the pharmacotherapy of SE
- Supportive treatment
- Search for a cause, which are equally important for achieving seizure cessation and providing further neuroprotection

Figure 2 Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **dogs**

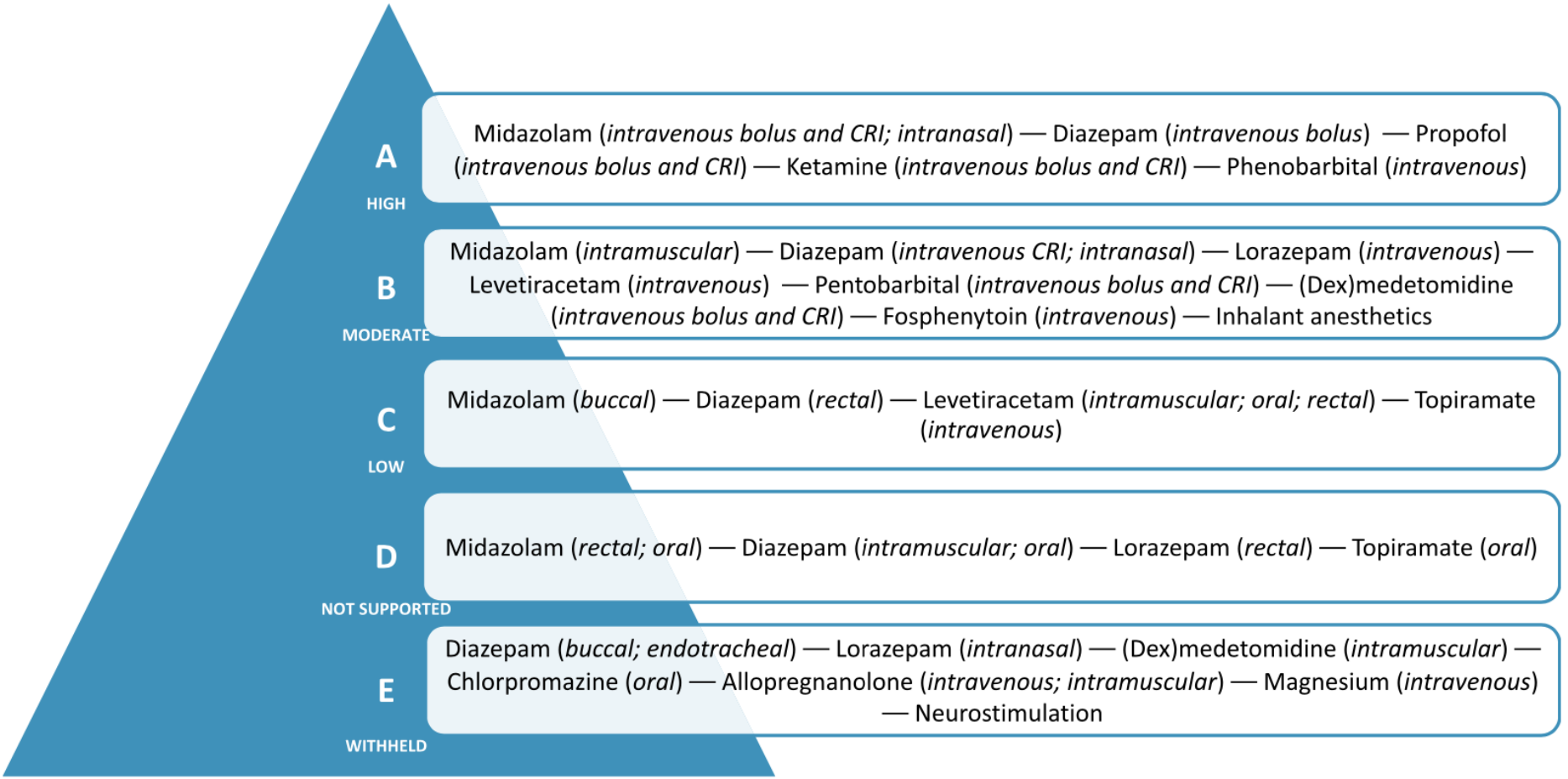


Figure 3 Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in cats

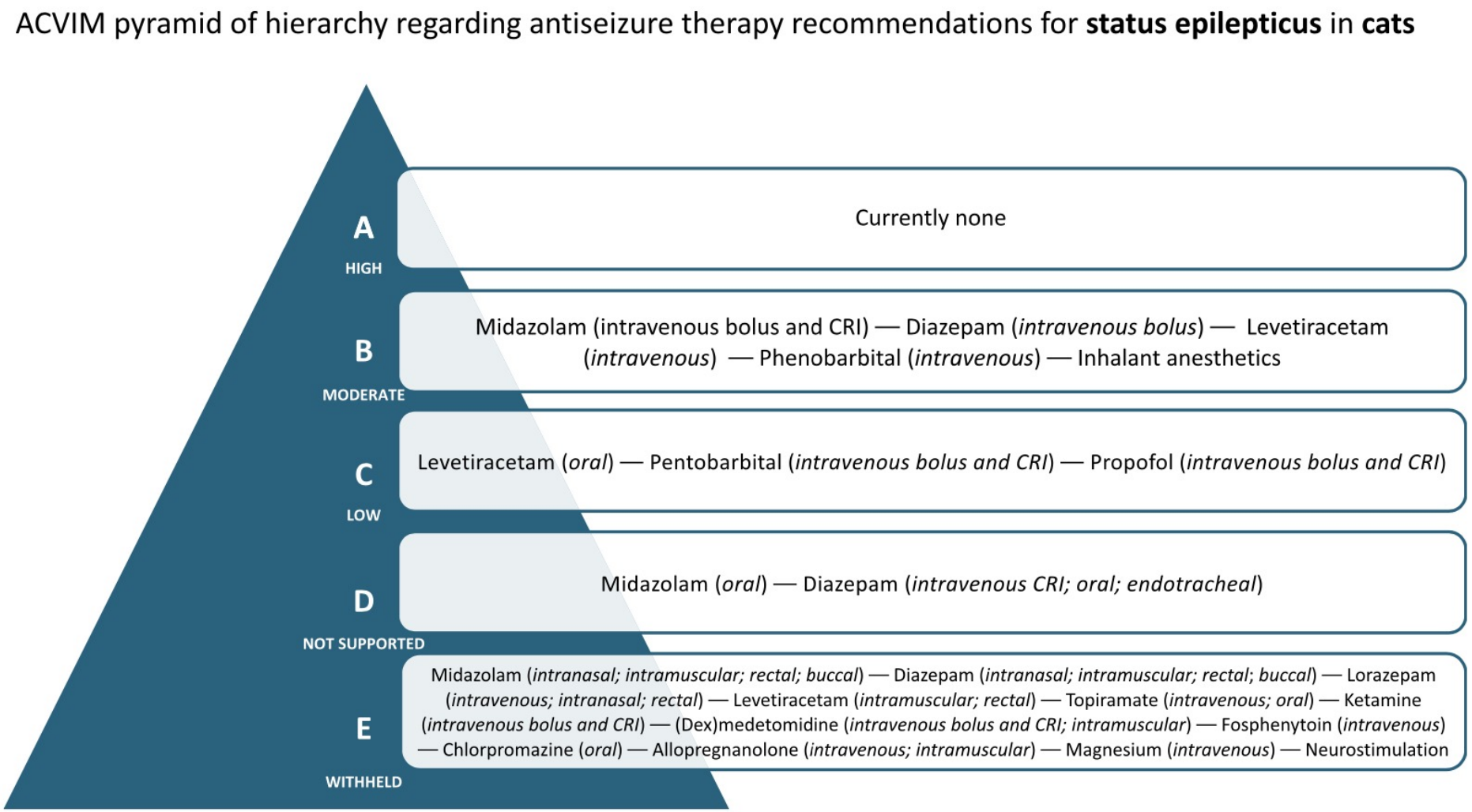


Figure 4 Pyramid of hierarchy regarding antiseizure therapy recommendations for CS in dogs

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **cluster seizures** in **dogs**

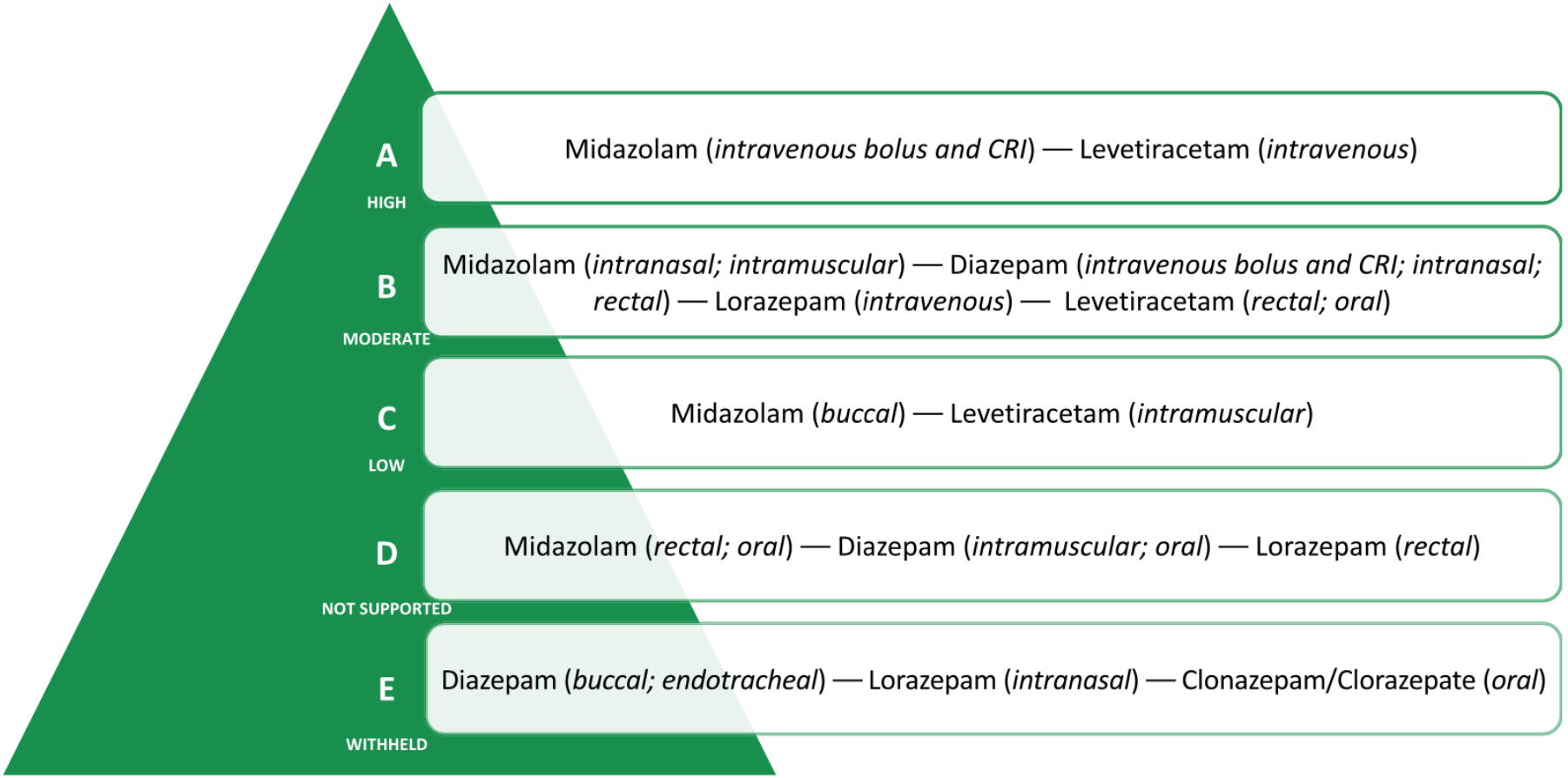
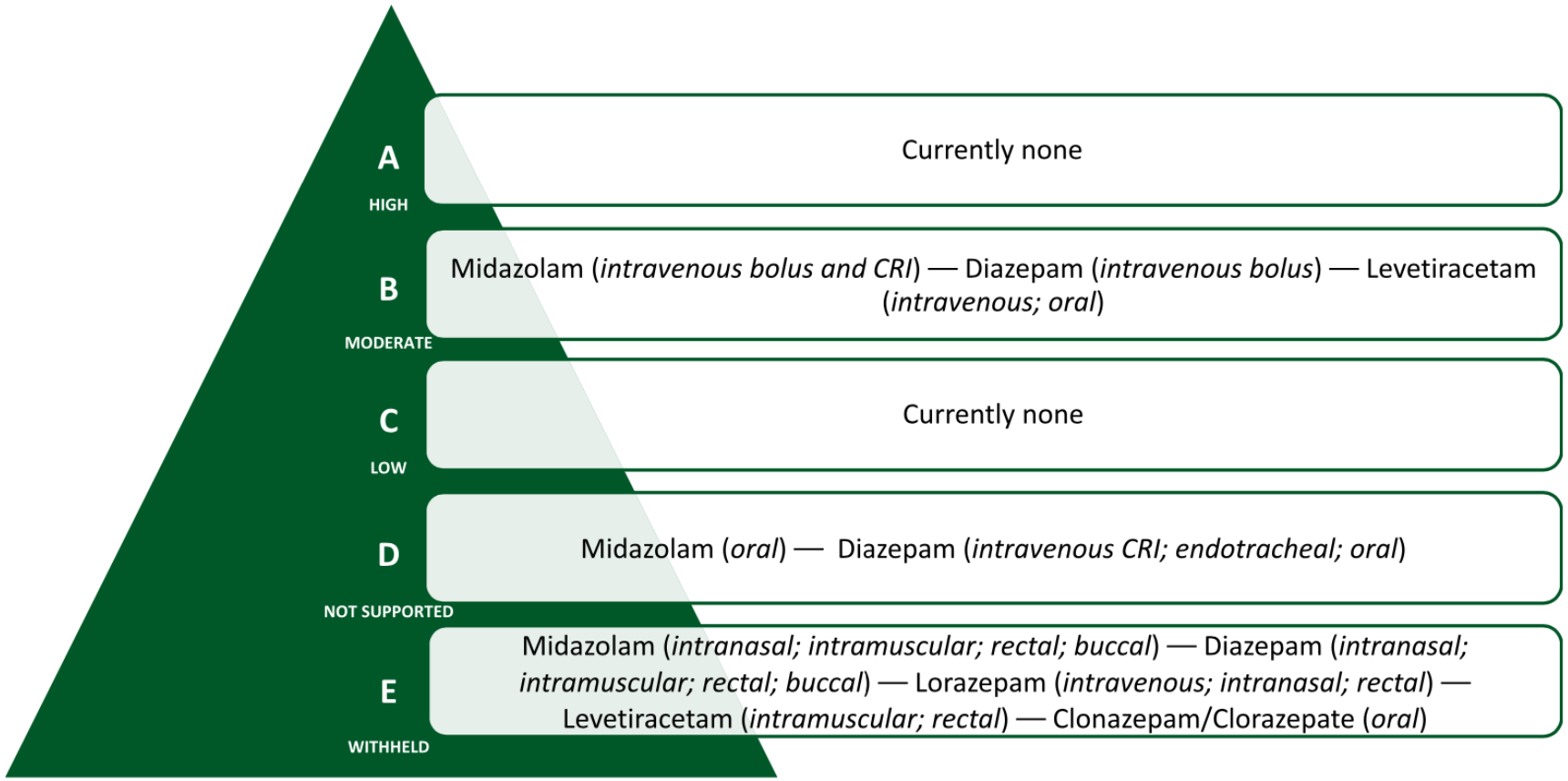
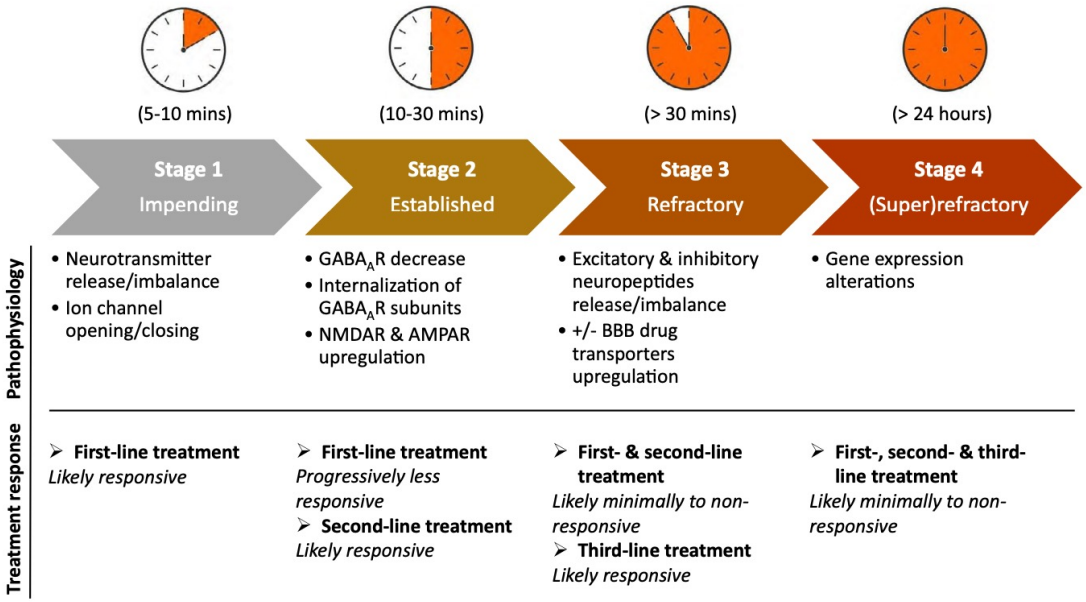


Figure 5 Pyramid of hierarchy regarding antiseizure therapy recommendations for CS in cats



Specific guidelines & recommendations for the treatment of status epilepticus



First-line treatment

(5-10 mins)

Stage 1
Impending

- Neurotransmitter release/imbalance
- Ion channel opening/closing

➢ **First-line treatment**
Likely responsive

- 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

Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs and cats

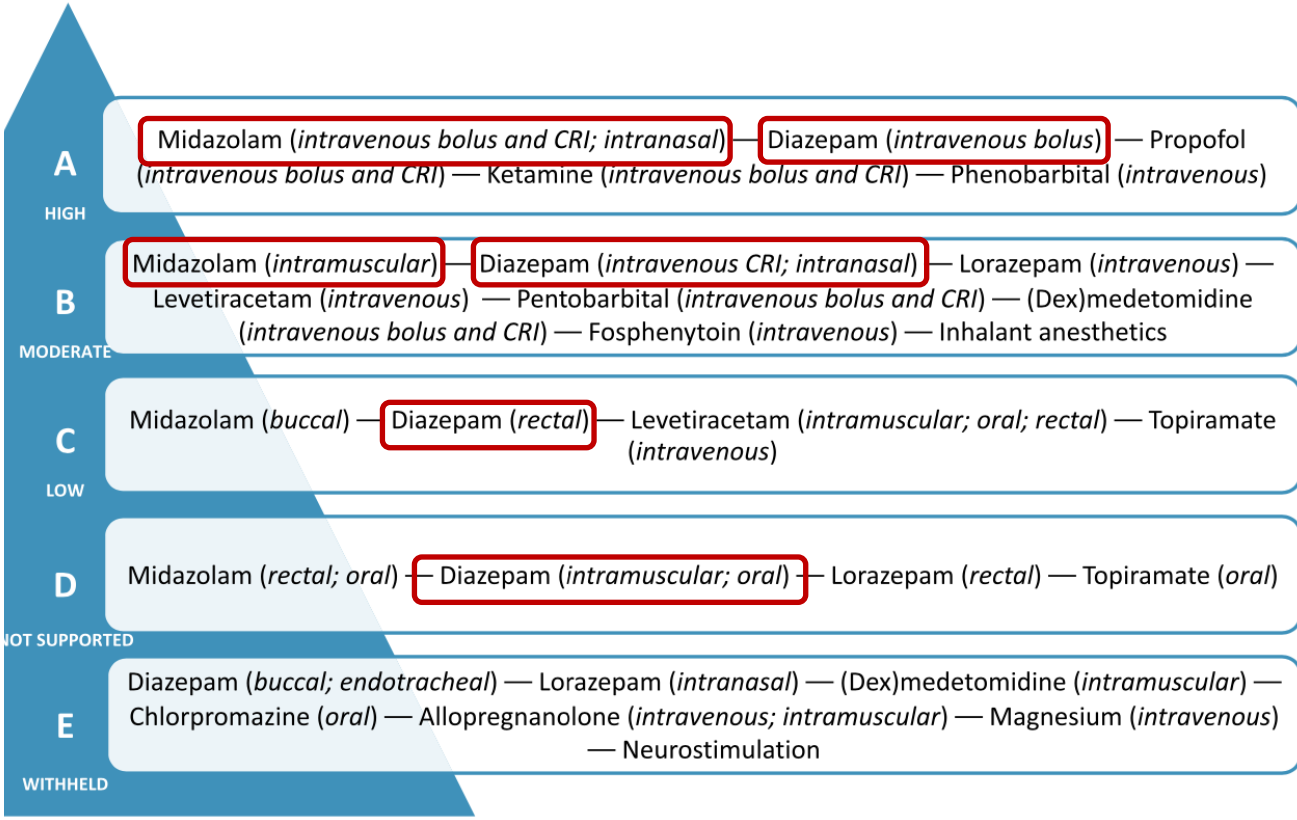
ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **dogs**

***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**).*



Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs and cats

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **cats**

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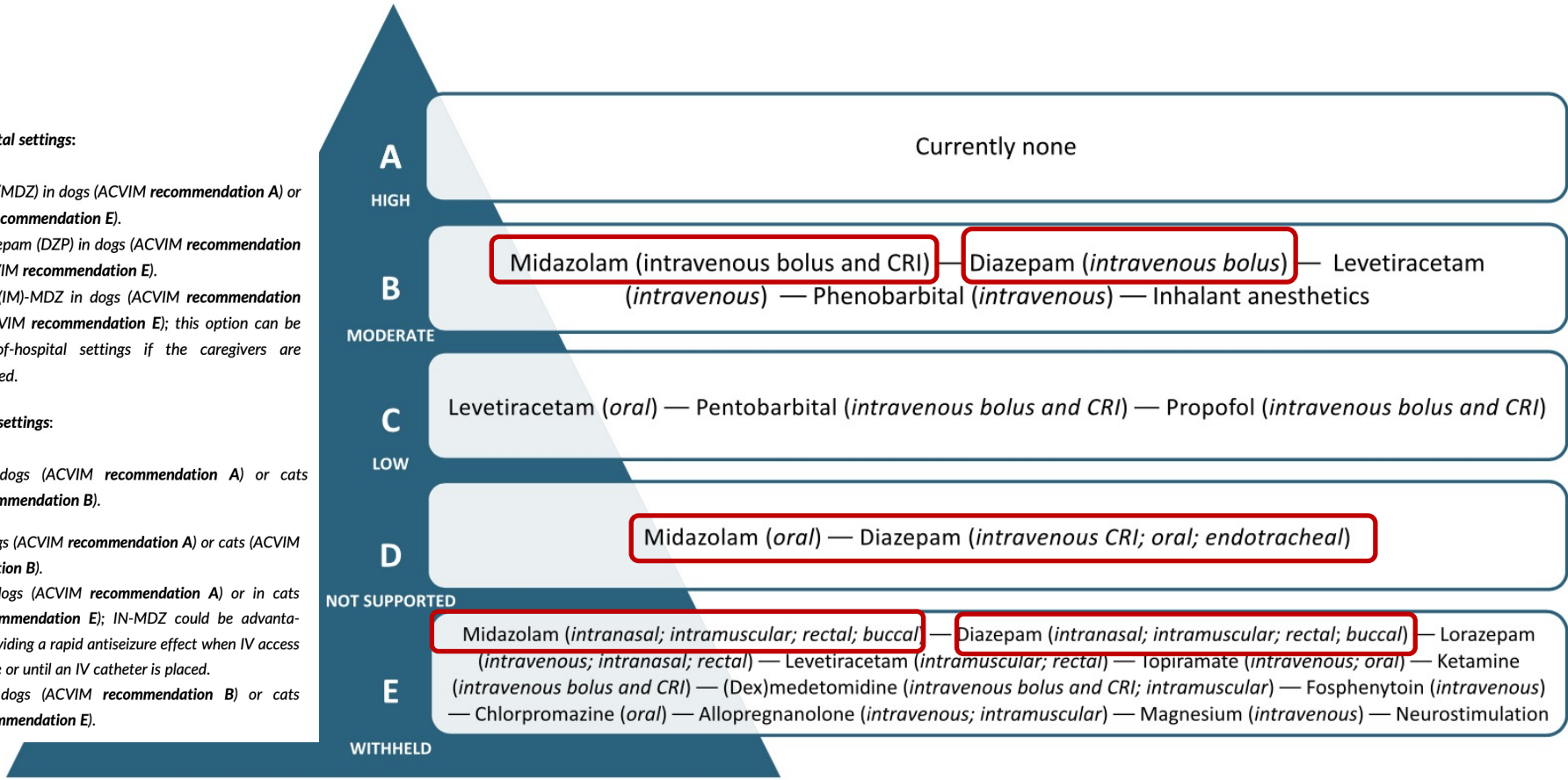

Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs and cats

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **cats**

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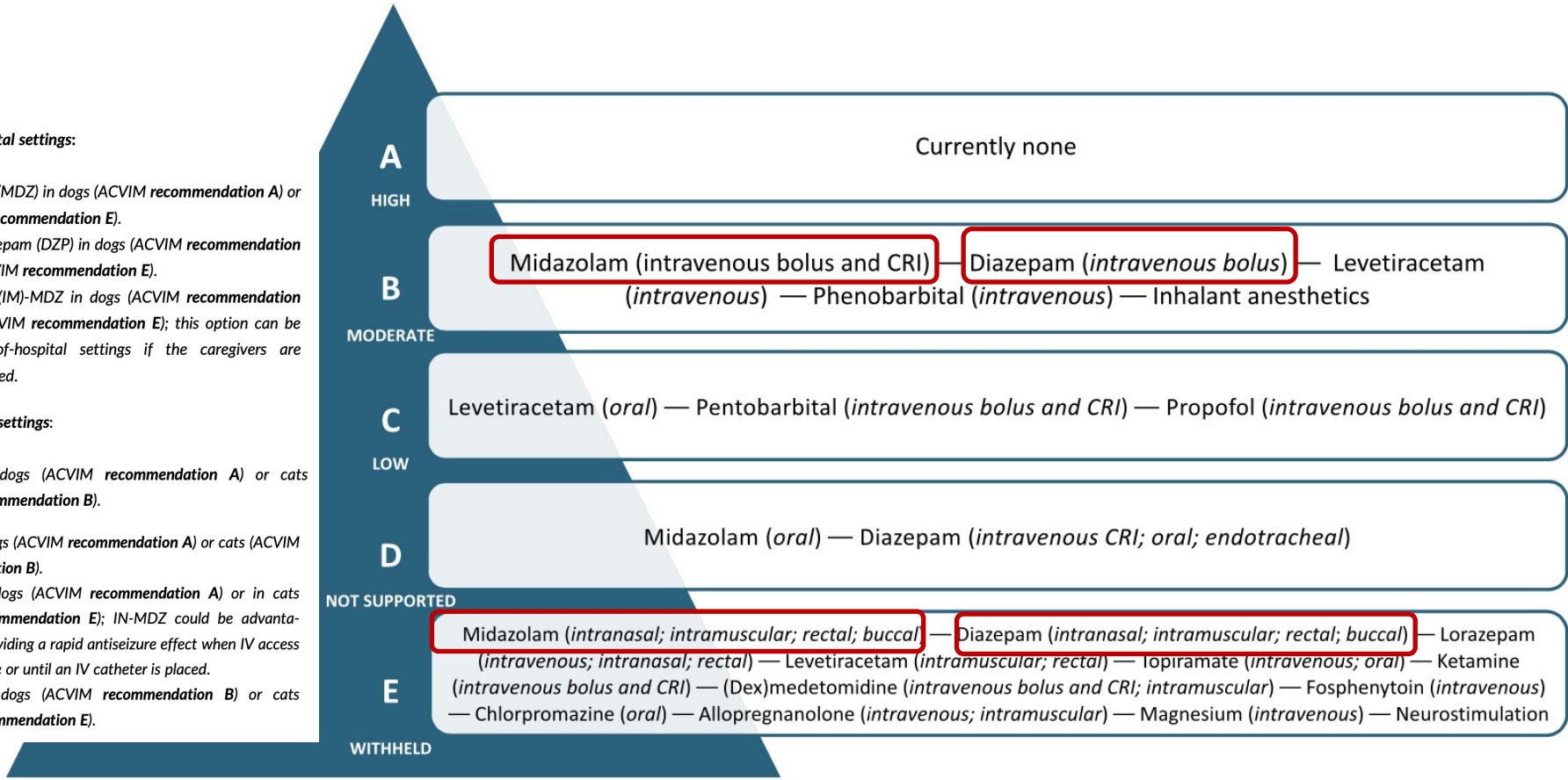


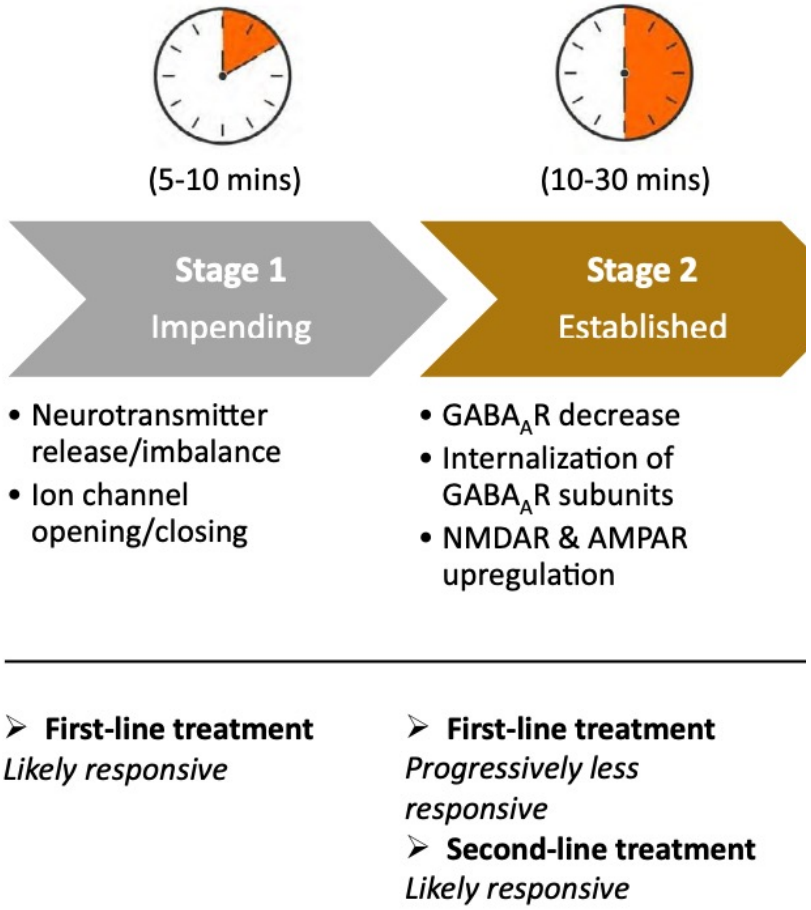
Midazolam or diazepam?

- Both BZD 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

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.*

Second-line treatment

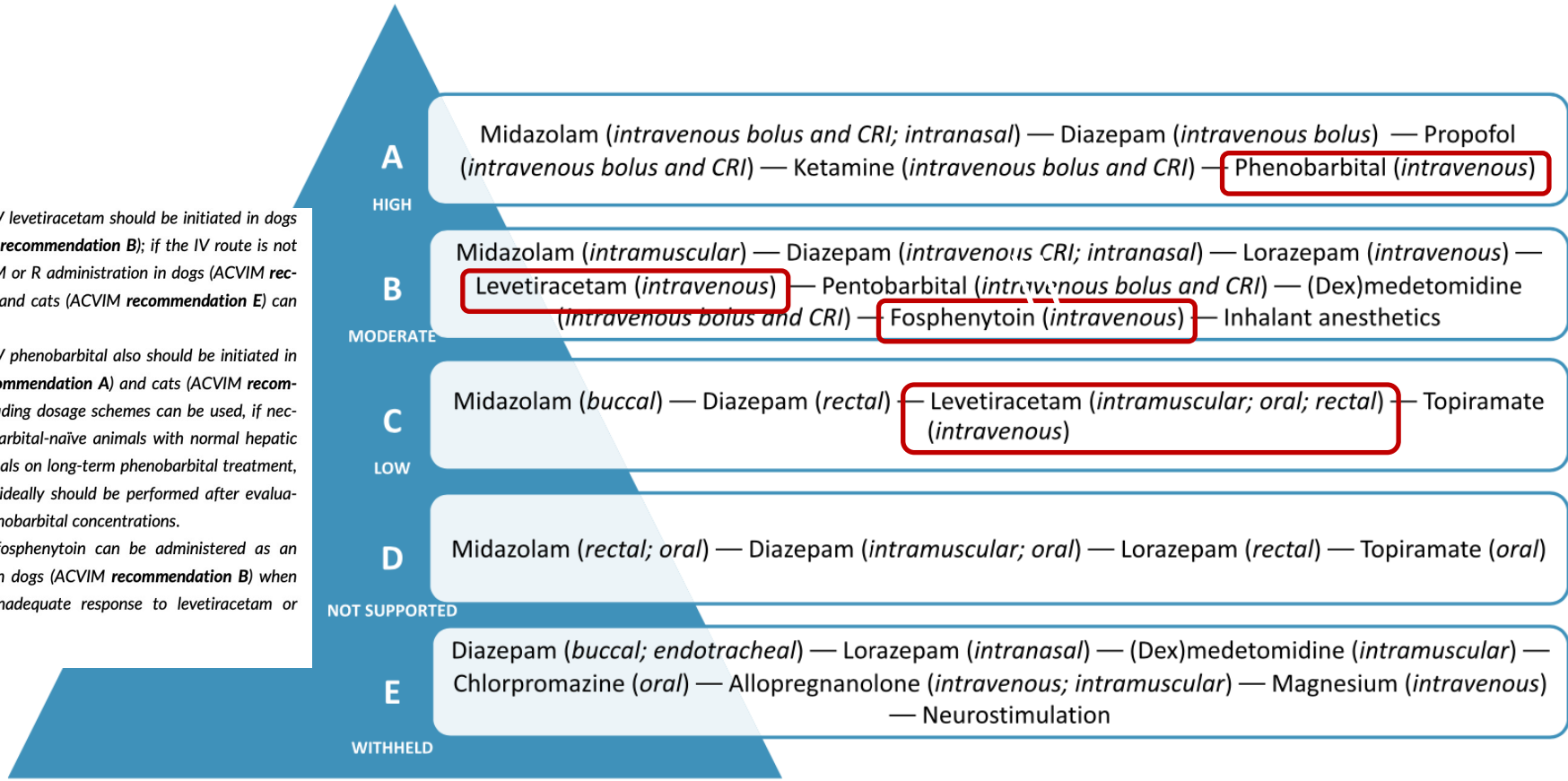


- Levitiracetam
- Phenobarbiturate
- Fosphenytoin

The aim to maintain adequate seizure control in the short- and long-term

Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs and cats

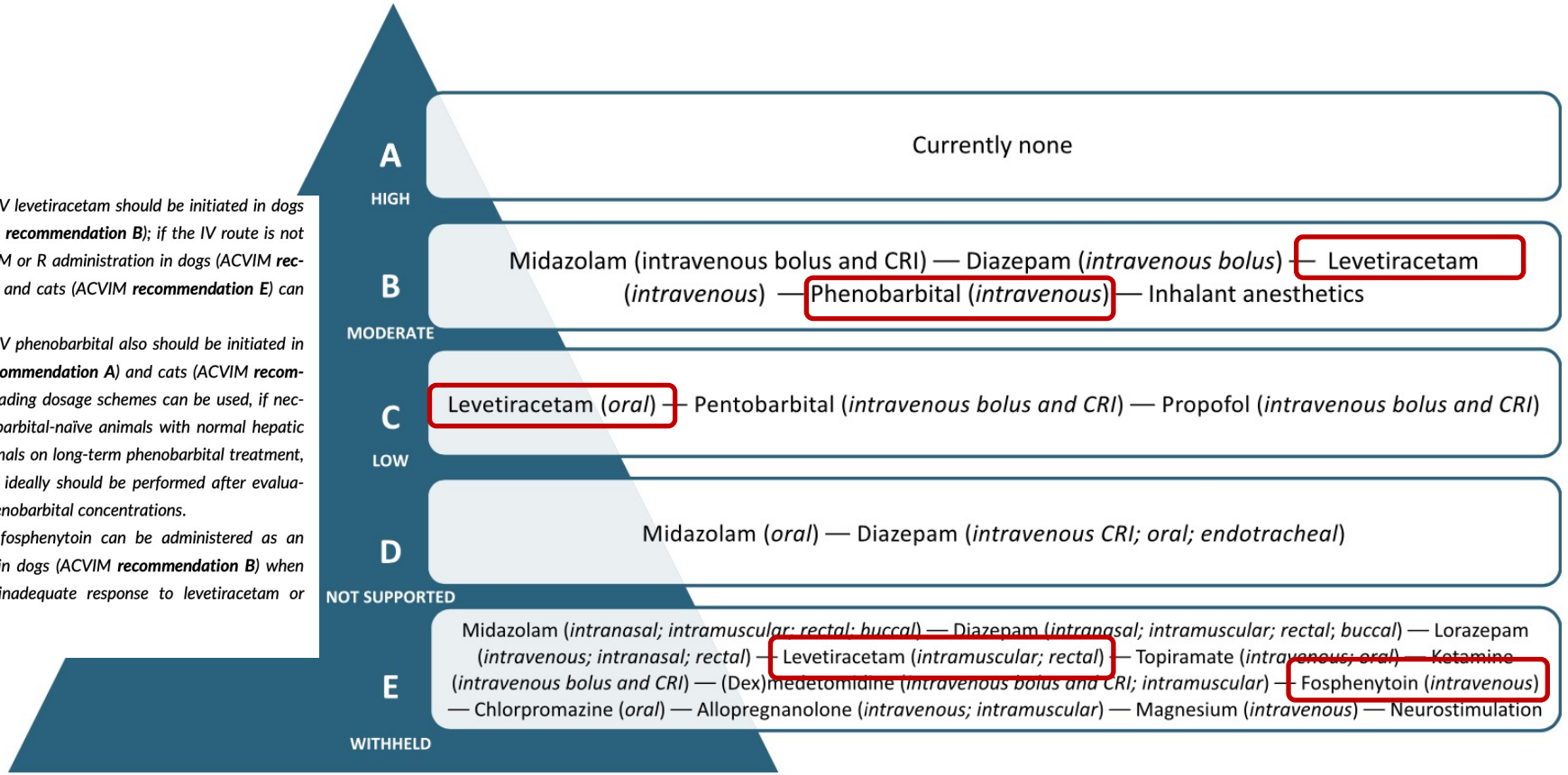
ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **dogs**



- *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.*

Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs and cats

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **cats**



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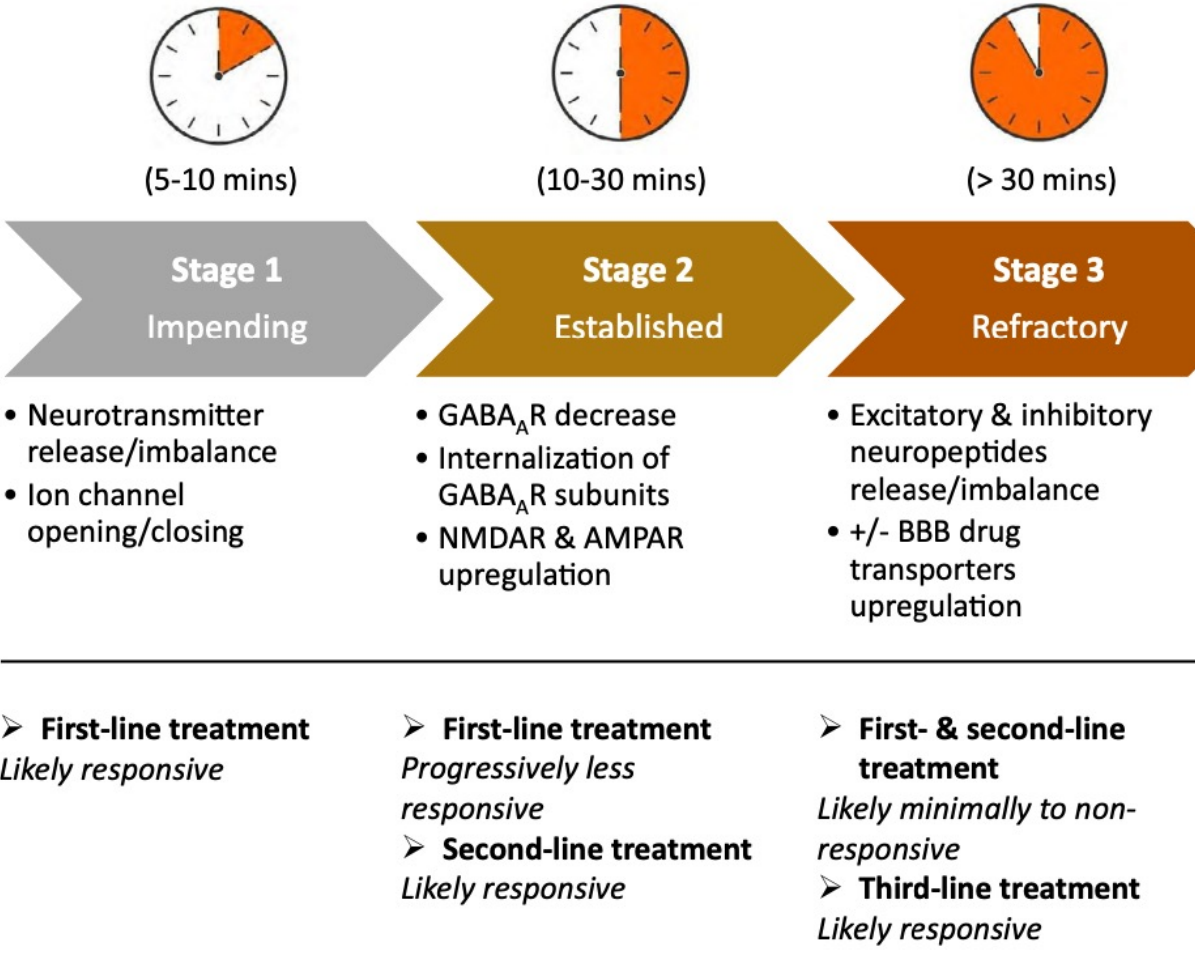
- *An IV bolus of fosphenytoin can be administered as an adjunctive ASM in dogs (ACVIM **recommendation B**) when there is no or inadequate response to levetiracetam or phenobarbital.*

Third-line treatment



- Anesthetic medicine

A four-step approach

First step:

- Ketamine, dexmedetomidine

Second step:

- Propofol

Third step:

- Anesthetic barbiturates

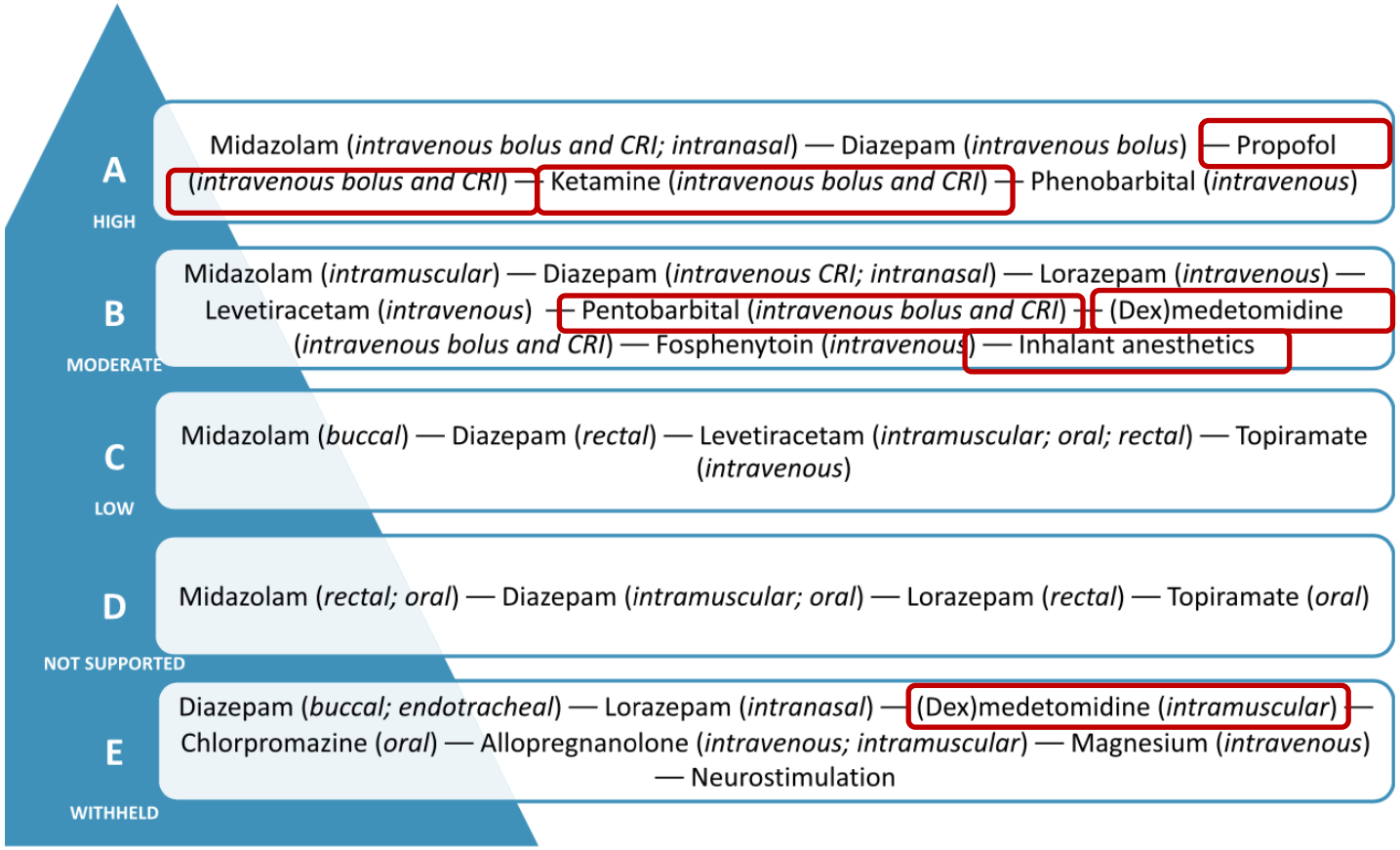
Fourth step:

- Inhalational anesthesia

Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs and cats

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **dogs**

- *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.*



Pyramid of hierarchy regarding antiseizure therapy recommendation for SE in dogs and cats

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **status epilepticus** in **cats**

- *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.*
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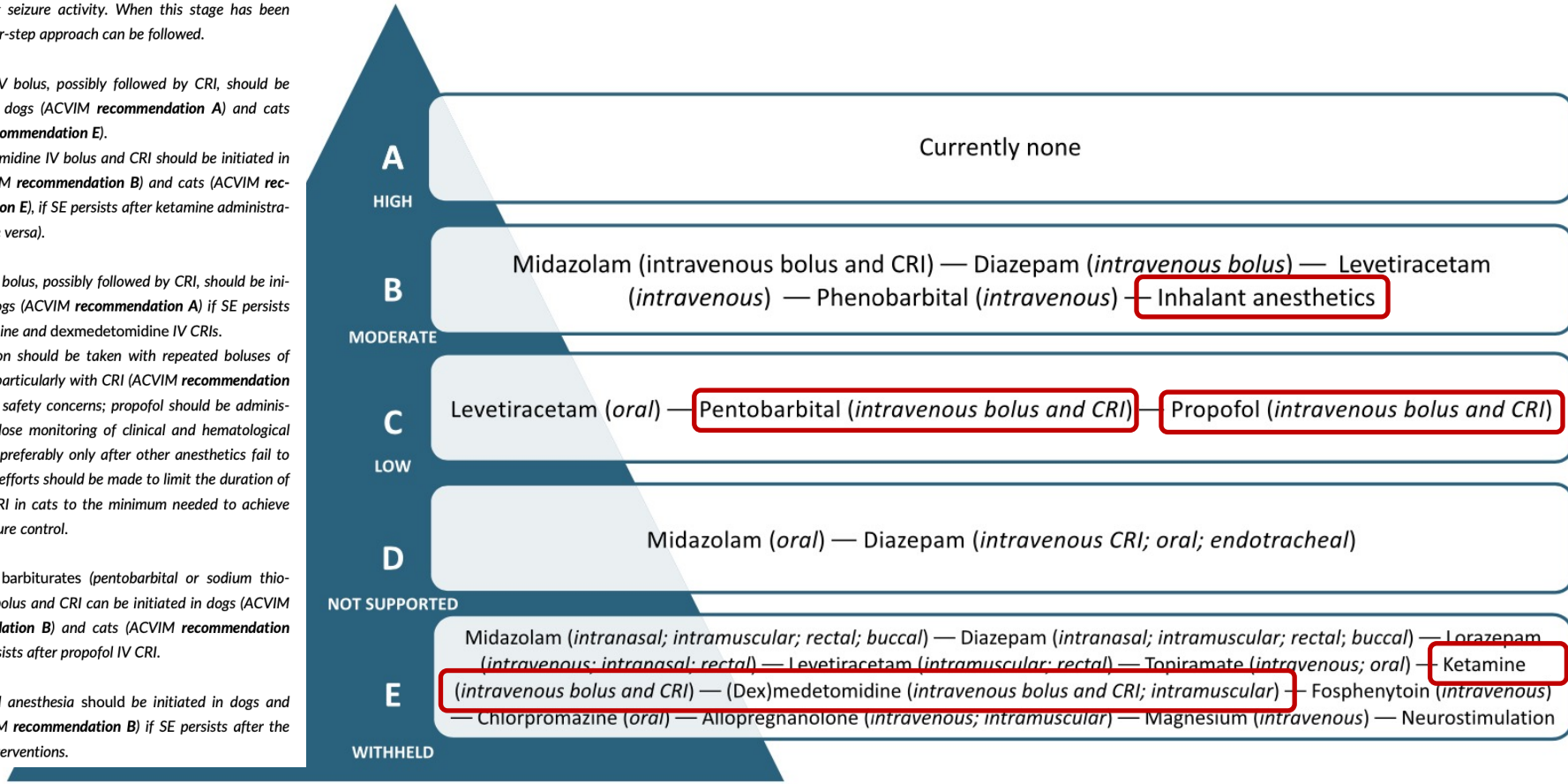

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What if the combine measures with first-,second- and third- line treatment as well as supportive care still fail to terminate seizure activity?

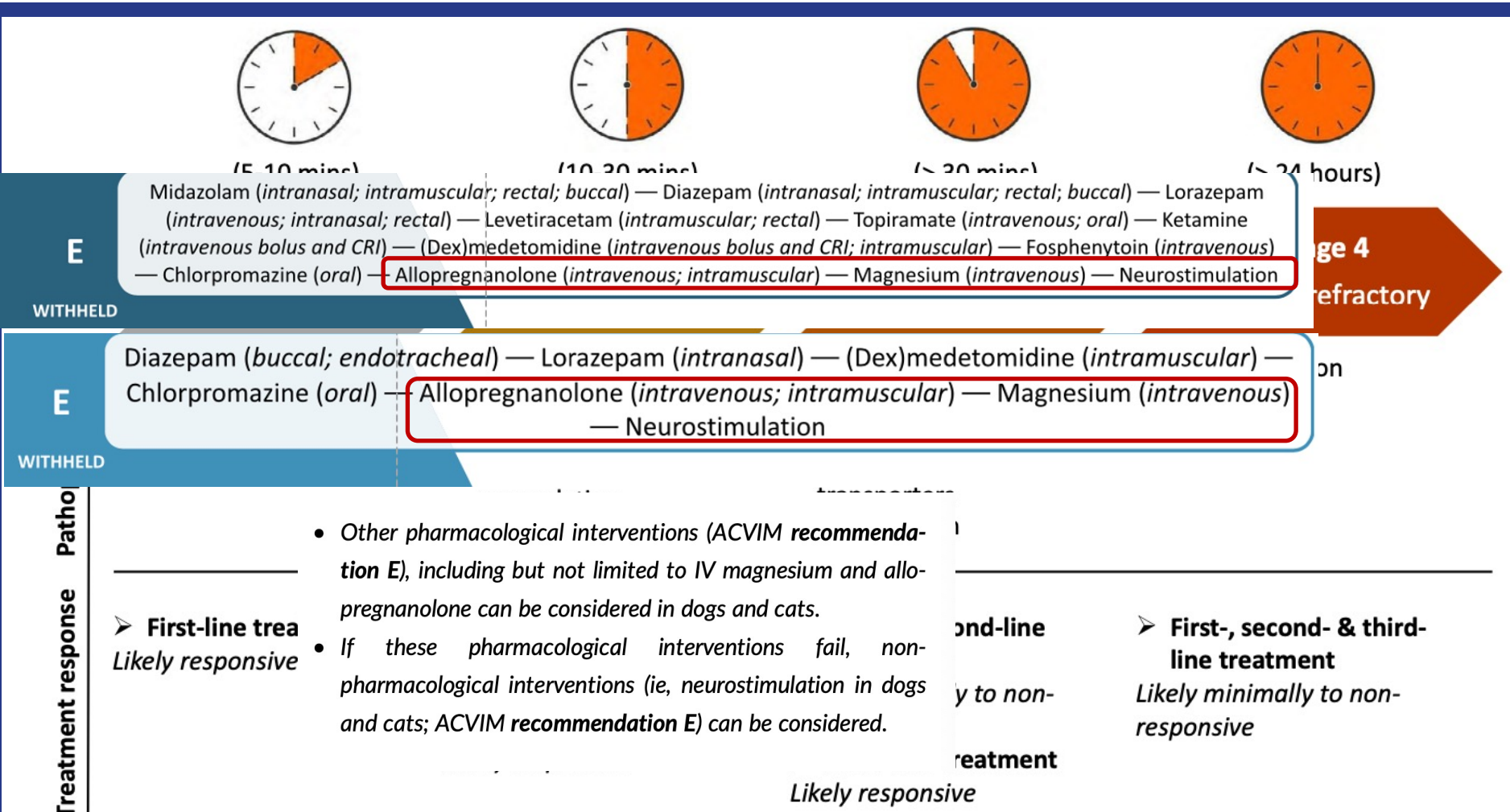
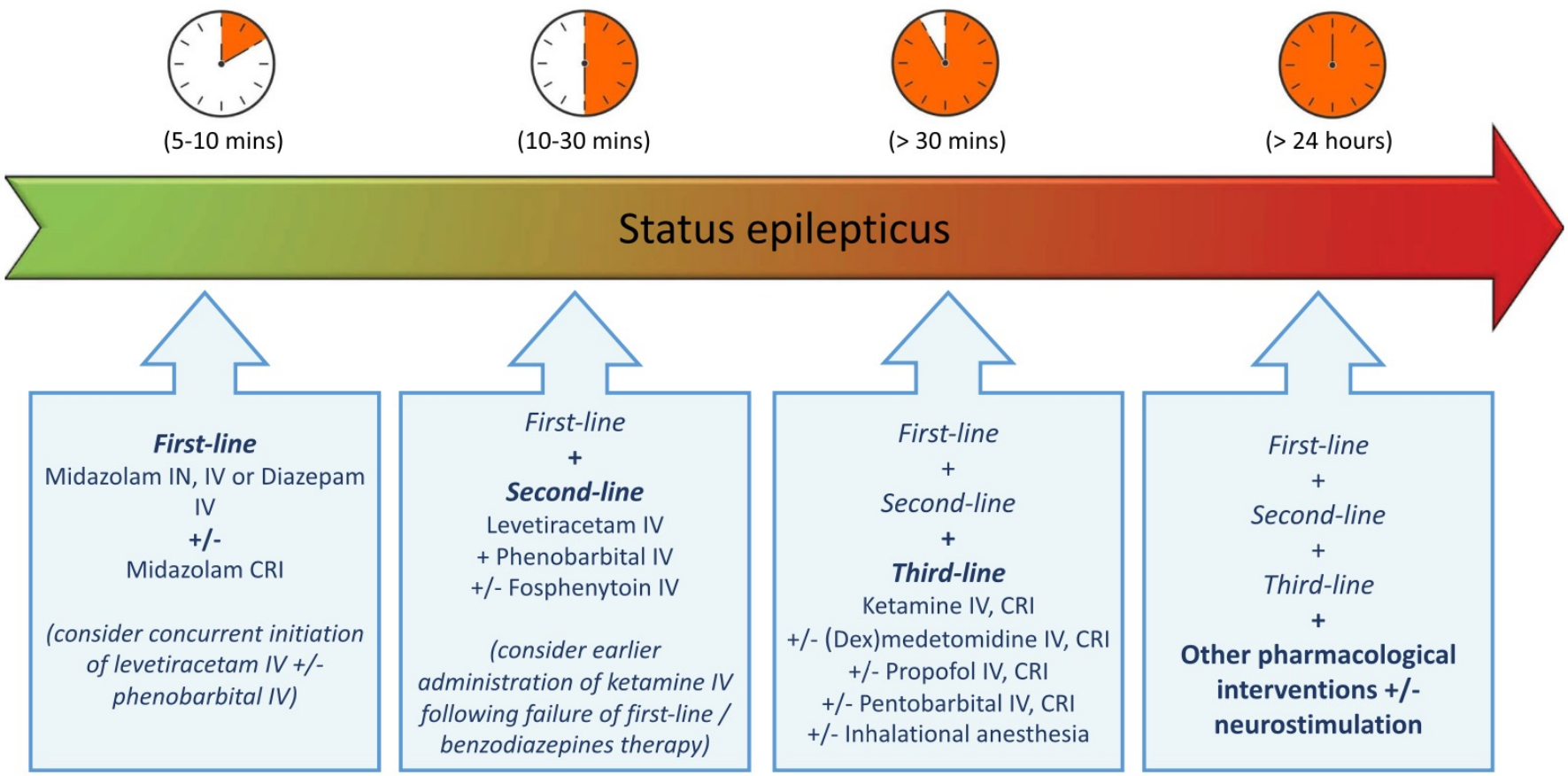
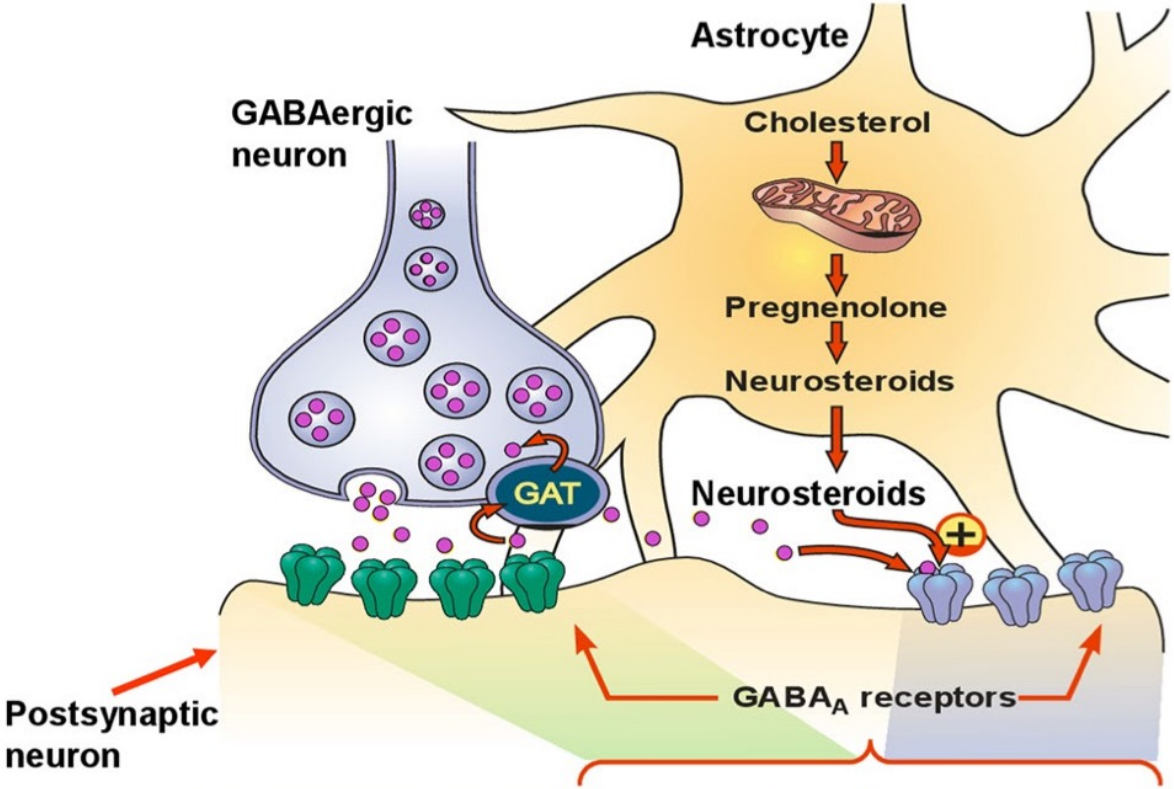


Figure 7 ACVIM therapeutic approach proposal in SE according to the stage





Localisation	Synaptic	Extrasynaptic
Function	Phasic inhibition	Tonic inhibition
Positive allosteric modulators	Anaesthetics Barbiturates Benzodiazepines Cenobamate Felbamate Ganaxolone Stiripentol Topiramate	Alcohol Anesthetics Cenobamate Ganaxolone

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.*

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.*

If SE has been successfully terminated, How should I taper polytherapy?

- *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.*

Specific guidelines & recommendations for the treatment of cluster seizure

Specific guidelines and recommendations for the treatment of cluster seizures (CS)

- The appropriate management of CS consists

  A long-term and short-term plan

- Long term treatment focuses mainly on prevention of CS and is achieved with the appropriate implementation of antiseizure treatment of epilepsy
- Short-term treatment
  - Short-acting interventions (MDZ, BDP)
  - Long-acting interventions (Levetiracetam)

Cluster seizure management

A 3-step short-term plan can be followed:

First step:

- Out-of-hospital settings:
- Short-acting medications:
  - MDZ, DZP
- Long-acting medication
  - Levitracetam

- In-hospital settings:
- Short-acting medications:
  - MDZ, DZP
- Longer-acting medication
  - Levitracetam
- Second step:
- Longer-acting BZDs (clonazepam or clorazepate)
- Antiseizure medications (PB)
- Third step:
- Stage III SE

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

ACVIM pyramid of hierarchy regarding antiseizure therapy recommendations for **cluster seizures** in **dogs**

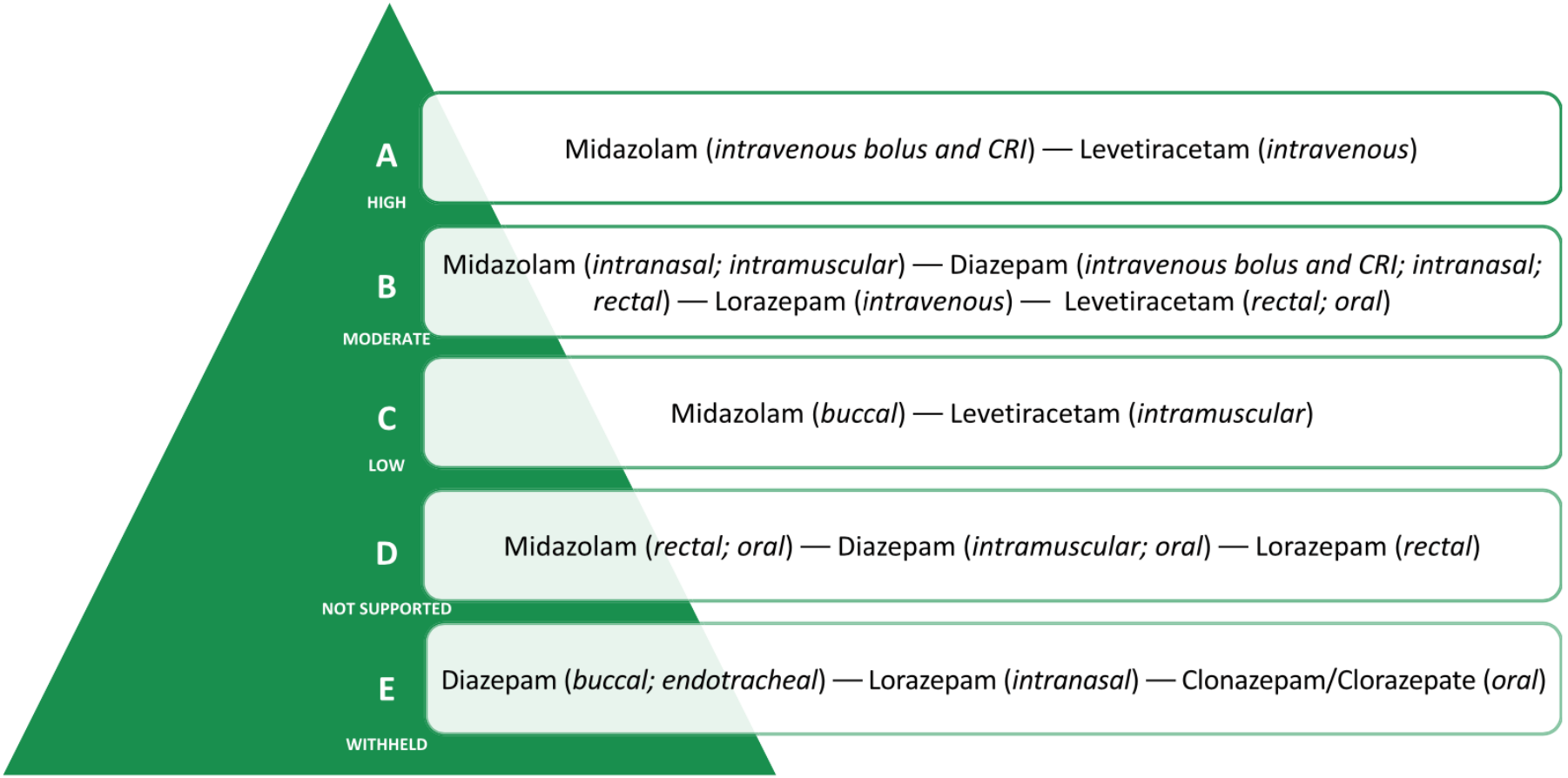


Figure 5 Pyramid of hierarchy regarding antiseizure therapy recommendations for CS in cats

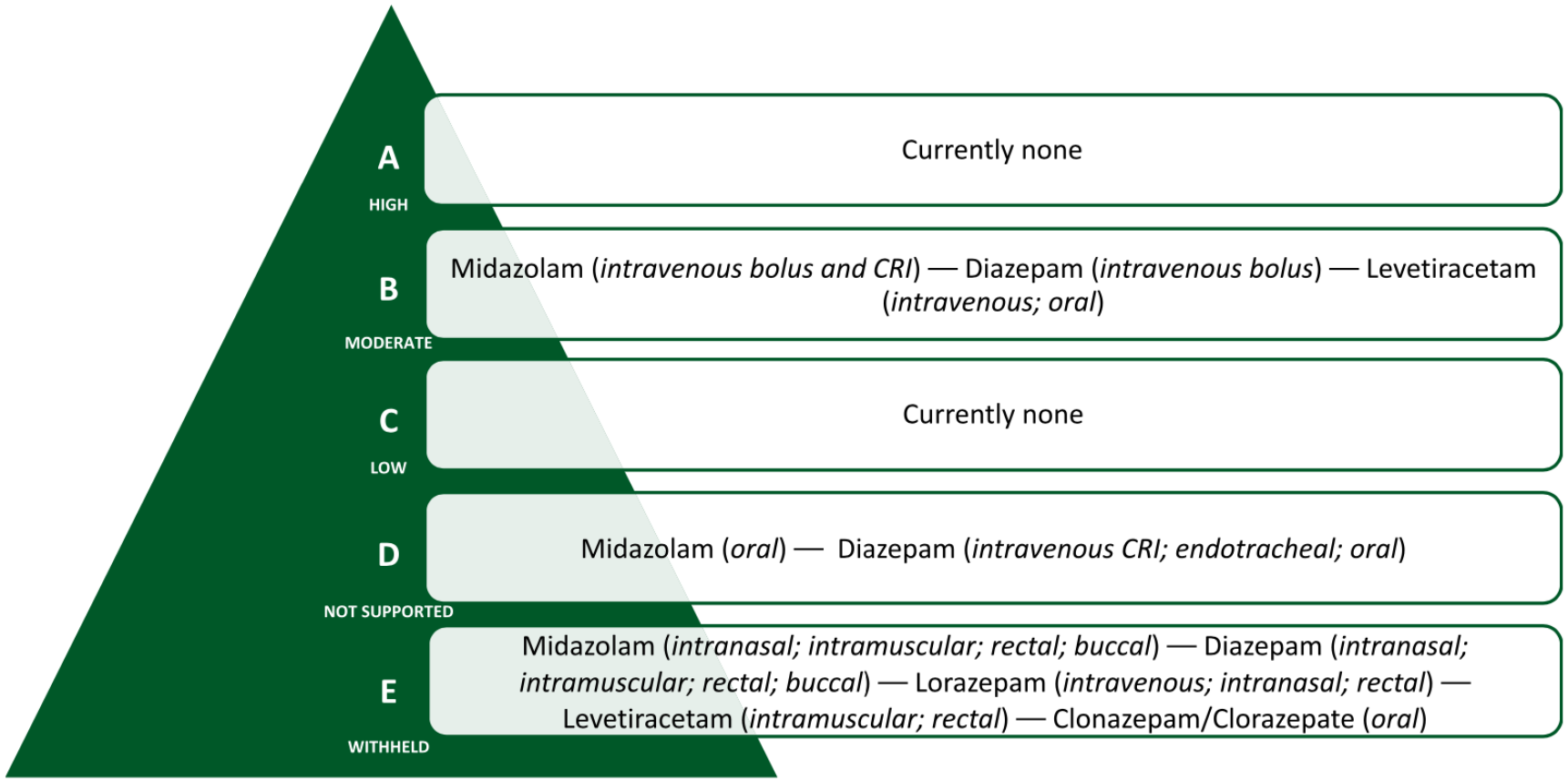
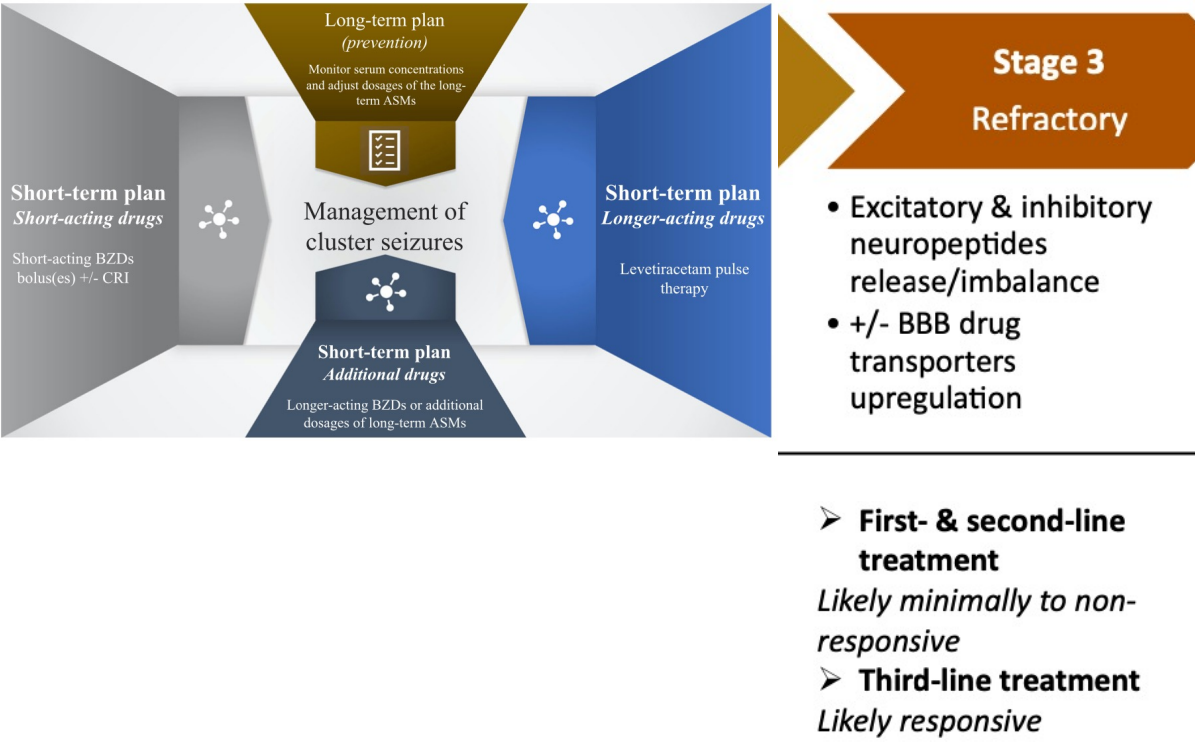


Figure 6 The long- and short-term plan for the management of CS in dogs and cats

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



- Anesthetic medicine

A four-step approach

First step:

- Ketamine, dexmedetomidine

Second step:

- Propofol

Third step:

- Anesthetic barbiturates

Fourth step:

- Inhalational anesthesia

Specific guidelines & recommendations for the treatment of status epilepticus

- The level of evidence and recommendations

  The pyramids of hierarchy

  .....Focus on the pharmacotherapy of SE
- Supportive treatment
- Search for a cause, which are equally important for achieving seizure cessation and providing further neuroprotection

Conclusions

Successful management includes

i. A stage-based treatment approach comprised of interventions with moderate to preferable high ACVIM recommendations

ii. addressing the pathophysiologically-based treatment obstacles and prevention of the refractory stages by following an early and rapid therapeutic approach

iii. Management of the complications and underlying causes related to the seizure emergencies

Thank you for your attention