Therapie bei BZD-Resistenz

- Phenytoin
- Phenobarbital
- Paraldehyd
- Valproat
- Levetirazetam
- Lacosamid

Phenytoin

- **Standard first-line Behandlung benzodiazepin-resistenter Anfälle bei Kindern >1 Jahr**
  - Evidenz: unkontrollierte Studien mit geringen Fallzahlen
- **nicht atemdepressiv**
- **sehr ungünstiges NW Profil (Nekrosen, kardiotoxische NW)**
  - limitierte Dosierungsrate (1 mg/kg/min)

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Intravenous Sodium Phenytoin

- Recommended dosage: 18–20 mg/kg (maximum dose 1 g);
- Must not be injected faster than 1 mg/kg/min (i.e., usually at least 20 min);
- Must be diluted in saline because it does not dissolve in glucose solution;
- Should be diluted to a concentration not exceeding 10 mg/ml
- Should be infused using an independent venous access in a large caliber vessel (if possible) to reduce the risk of phlebitis (depending on the child's age);
- Heart rate and blood pressure should be monitored;
- Can cause side effects such as sedation (rare), hypotension, cardiac arrhythmias, "purple glove syndrome," and skin reactions of varying severity up to Stevens-Johnson syndrome;
- Respiratory depression is possible, but very rare;
- Is contraindicated in patients with grade II atrioventricular block or severe hypotension;

Phenobarbital

- **PB nach wie vor Mittel der Wahl bei Neugeborenen und Säugligen**
  - extensive klinische Erfahrung
  - günstigeres NW-Profil als PHT
  - weniger komplexe Pharmakokinetik als PHT
- **keine repetitiven Gaben nötig, da lange HWZ (Loading Dose 20 mg/kg)**
  - Leviterazetam wahrscheinlich überlegen => in Hinkunft Ersatz für PB?

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Intravenous Phenobarbital

- Recommended dosage: 15–20 mg/kg (maximum dose 1 g);
- Must not be injected faster than 1 mg/kg/min (i.e., usually at least 20 min);
- Must be diluted to a concentration not exceeding 10 mg/ml with water for injections;
- Can cause side effects such as sedation, respiratory depression, or hypotension;
- In spontaneously breathing patients it should be administered with a resuscitator and/or trained medical personnel available to support advanced ventilation (through ventilation with Ambu and mask and oral or nasotracheal intubation) and treat hypotension;
- Heart rate should be closely monitored with a monitor including, electrocardiography, and blood pressure.

Paraldehyd

- **Evidenz = Fallberichte:**
  - inakzeptables NW-Profil bei IV oder IM Gabe
  - instabil
- **rektale Alternative, wenn kein Zugang möglich**
  - kaum mehr verwendet, seit Möglichkeit schneller/verbesserter IO Applikation

Curless RG, Holzman BH, Ramsay RE. Paraldehyde therapy in childhood status epilepticus. *Arch. Neurol.* 2008; **40**: 477–80.

Valproat

- **erwiesen effektiv in der Behandlung von CSE bei Kindern**
  - Induktion von Encephalopathien
    - Vorsicht bei jungen Kindern =>
  - Potentiell hepatotoxisch =>
    - Leberversagen bei Kindern <2 Jahren
    - Kindern mit metabolischen und mitochondrialen Erkrankungen

Yu KT, Mills S, Thompson N, Cunanan C. Safety and efficacy of intravenous valproate in pediatric status epilepticus and acute repetitive seizures. *Epilepsia* 2003; **44**: 724–6.

Intravenous VPA

- bolus 30–45 mg/kg (maximum dose 1.5) as a 15-min intravenous infusion (some protocols suggest more rapid infusion but the rate should always be less than 200 mg/min);
- the bolus can be followed by continuous infusion of 1–2 mg/kg/h depending on clinical course;
- VPA has the advantage of rarely inducing hypotension, respiratory depression, or excessive sedation (occasional hypotension/respiratory depression may be seen during infusion);
- VPA is contraindicated in cases with liver disease, or suspected metabolic disease, and must be avoided or used with extreme caution in children, especially those younger than 3 years, if the SE etiology is not known

Levetirazetam

- **Attraktive Alternative in der Behandlung kindlicher CSE**
- **Studien im Gange**
  - Neuer, nicht gut definierter Wirkmechanismus
  - Günstiges NW-Profil (i.e. keine Atemdepresion)
  - Effektiv bei unterschiedlichen Anfallstypen
  - Keine nennenswerten Interaktionen

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Intravenous Levetiracetam

may be a therapeutic option in SE, especially if other drugs are contraindicated and/or the SE is refractory, but it is not yet registered in Italy for this indication (Level 4, Grade C).

- Dosage: bolus of 13–70 mg/kg (maximum dose 4 g), typical starting dose 30 mg/kg in 15-min intravenous infusion (from 5 to 60 min) for a total of 100 ml (but at high concentration and low volume: 50 mg/ml);
- The drug can be administered through a nasogastric tube; In cases where it was effective, seizures stopped in 25–30 min after intravenous injection and in 1.5 days when given through a nasogastric tube;
- This drug can be used for continued oral therapy, does not cause significant side effects, and needs no preliminary check of renal function;

Lacosamid

- Anektodische Berichte bei CSE im Kindesalter
- Notwendige Bolusdosis nicht bekannt
- LCM 25 mg x 2/Tag effektiv in 1Fallbericht (Kind mit CSE)
- Zugelassen nur für fokale Anfälle bei Patienten > 16 Jahre
- LCM kann das PR Intervall prolongieren, daher bei Patienten mit Herzerkrankungen nur mit äußerster Vorsicht zu verwenden

FAZIT

- **Evidenz für Guidelines generell unzureichend**
  - DPH => PB (PB bei Kindern < 1 Jahr) für benzodiazepin-resistente Anfälle empfohlen(Level 2B, Grade B)
  - VPA potente Alternative, obwohl nicht zugelassen (Level 1B, Grade A)
    - Vorsicht bei jungen Kindern und wenn STW Diagnostik inkomplett

FAZIT

- **Evidenz für Guidelines generell unzureichend**
  - kontrollierte randomisierte Studie DPH versus LEV im Gange
  - Paraldehyd wenn kein Zugang vorhanden

Refraktärer SE

- **Transfer => ICU, Intubation, EEG Monitoring (Level 4, Grade C)**
- **Keine randomisierten Studien. Mittel der Wahl: Midazolam oder Propofol**
  - Beide Substanzen GABAerg
- **Ketamin als nicht-GABAerge Alternative**
  - Wirkung via N-methyl-D-aspartat Rezeptor
    - ungenügende Evidenz

Intravenous Sodium thiopental

- Induction of barbiturate coma: bolus of 3 mg/kg, repeated after 2 min, followed by maintenance (1–15 mg/kg/h) to control seizures and/or achieve “suppression-burst “EEG activity (increasing 1 mg/kg/h every 2 min);
- The subsequent maintenance infusion should continue for 12–48 h;
- During the infusion, continuous EEG monitoring should be maintained;
- Usually causes respiratory depression when induction is carried out in intubated and ventilated patients; can also induce hypotension and heart failure, and sometimes pharmacologic support for pressure and circulation is necessary;
- Contraindicated in the presence of hypotension, cardiogenic shock, sepsis.

Intravenous Propofol

- 1–5 mg/kg bolus (repeatable) followed by continuous infusion up to a maximum of 5 mg/kg/h;
- Requires continuous EEG monitoring;
- Can cause hypotension and arrhythmias, so heart rate and rhythm and blood pressure must be monitored to implement compensatory pharmaceutical measures;
- When used at high doses and for prolonged periods, may cause “propofol syndrome” involving metabolic acidosis, rhabdomyolysis, arrhythmias, heart failure, kidney failure, hepatomegaly, and possible death (Harrison et al., 1997; Riker et al., 2009);
- Liver problems may arise (Rason & Ko, 2009), either isolated (hypertriglyceridemia) or together with systemic problems.

high-dose phenobarbital

- In cases of contraindications to the use of sodium thiopental and propofol (Level 4, Grade C).
- Dosage: bolus of 20 mg/kg followed by maintenance to achieve plasma levels at least higher than 100 μg/ml (maximum daily dosage 80–120 mg/kg);
- In patients intubated and ventilated after failure of firstand second-line drugs;
- Possible side effects: hypotension, respiratory infections;
- Possible prolonged sedative effect on discontinuation.

Intravenous midazolam

- Bolus of 0.2 mg/kg; if clinical and/or electrical seizures cease continue with maintenance of 0.06 mg/kg/h;
- If there is no response after 15 min, inject a second bolus of 0.2 mg/kg and start infusion at 0.5 mg/kg/h;
- If there is no response after another 15 min, increase infusion to 1 mg/kg/h and assess response;
- Requires continuous EEG monitoring to assess response and decide tapering;
- Can lead to respiratory depression in spontaneously breathing patients;
- Can lead to metabolic acidosis, reversible on discontinuation, and hypotension.

	Mechanism of Action	Metabolism	Active Metabolite	Half-Life (Hours)	Half-Life Considerations	Drug Interactions	Examples of Drug-Drug Interactions	Adverse Reactions
Midazolam	GABA agonist	Hepatic	1-hydroxy-midazolam (renally eliminated)	2–7	Duration prolonged in renal failure and with extended duration of use	CYP 3A4 substrate	Phenytoin and phenobarbital (CYP 3A4 inducers) → lower midazolam concentrations	➢ Hypotension ➢ Respiratory depression
Propofol	GABA agonist; NMDA antagonist properties	Hepatic	N/A	0.5–7	Duration may be prolonged with extended duration of use	N/A	N/A	➢ Hypotension ➢ Respiratory depression PRIS ➢ ↑ Triglycerides
Pentobarbital	GABA agonist; Barbiturate	Hepatic	N/A	15–50	Duration may be prolonged with extended duration of use	CYP 2A6 inducer	Valproate (decreases barbiturate metabolism) → May increase pentobarbital concentrations Lamotrigine (CYP 2A6 substrate) → pentobarbital lowers lamotrigine concentrations	➢ Hypotension ➢ Respiratory depression ➢ Paralytic ileus ➢ Immune suppression ➢ Hepatic/pancreatic dysfunction ➢ ↓ Body temperature ➢ Propylene glycol toxicity
Ketamine	NMDA antagonist	Hepatic	Norketamine (hepatically eliminated)	2.5	N/A	CYP 2C9 & 3A4 substrate	Phenytoin and phenobarbital (CYP 2C9 inducers) → lower ketamine concentrations	➢ Hypertension ➢ Hypersalivation ➢ Hallucinations ➢ Emergence reaction

PRIS = propofol-related infusion syndrome.

FAZIT

- SE ist ein häufiger Notfall auch im Kindesalter
- Frühe Intervention begünstigt Behandelbarkeit und Outcome
- Verwendung von “Consensus Guidelines highly recommended”
- Benzodiazepine weiterhin “Gold-Standard”
- Zunehmende Auswahl an alternativen Substanzen bei Diazepin-Resistenz
  - Studien zu Effektivität und Sicherheit bei Kindern im Gange

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Treatment of convulsive status epilepticus in childhood: Recommendations of the Italian League Against Epilepsy

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SPECIAL REPORT

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

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