eTABLE 1. METABOLIC DERANGEMENTS THAT MAY CONFOUND BD/DNC EVALUATION

Laboratory Result	Value[a]
Metabolic	
Ammonia[b]	>75 µmol/L
Blood urea nitrogen	>75 mg/dL
Calcium (or ionized calcium)	<7 mg/dL or >11 mg/dL (or <1 mmol/L or >1.3 mmol/L)
Glucose	<70 mg/dL or >300 mg/dL
Magnesium	<1.5 mg/dL or >4 mg/dL
Potassium	<3 mmol/L or >6 mmol/L
Sodium	<130 mmol/L or >160 mmol/L
Acid-Base	
pH	<7.3 or >7.5
Endocrine	
Total T4	<3 mg/dL or >30 mg/dL
Free T4[b]	≤0.4 ng/dL or >5 ng/dL

[a]The exact values at which the laboratory abnormality could affect the clinical evaluation are uncertain, and the values listed in this table are practical thresholds based on consensus only.

[b]Routine measuring of these values may not be necessary unless clinically indicated.

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eTABLE 2. COMMON MEDICATIONS ADMINISTERED TO CRITICALLY ILL PATIENTS AND ESTIMATED HALF-LIVES[a]

Drug	Pharmacokinetics			Comments
Intravenous sedatives				
Dexmedetomidine[e32]	$t_{½}$	Infant ≤28d	3.2 hours	**Hepatic impairment** Compared to a baseline half-life of 2.5 hours in healthy adult patients, clearance in mild, moderate, and severe hepatic impairment was 3.9, 5.4, and 7.4 hours, respectively.[e33] Consider tapering rather than abrupt cessation for patients on >24 hours of therapy to avoid hemodynamic changes.
		Pediatric	<2 years: 2.3 hours 2–11 years: 1.6 hours	
		Adult	~3 hours	
	Metabolism		Hepatic	
	Excretion		Urine (95%)	
Etomidate[e34]	$t_{½}$	Infant ≤28d	2.6–3.5 hours	**Continuous infusion:** Plasma terminal half-life was found to be ~5.5 hours when administered as a continuous infusion.[e35] **Hepatic impairment:** In patients with cirrhosis, the terminal half-life of continuous infusion can be prolonged up to 2-fold (~9 hours).[e36]
		Pediatric		
		Adult		
	Metabolism		Hepatic; plasma esterases	
	Excretion		Urine (~75%), bile (10%)	
Ketamine[e37, e38]	$t_{½}$	Infant ≤28d	~2.5 hours	
		Pediatric[e39]		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine (91%)	
Midazolam[e40,b]	$t_{½}$	Infant ≤28d	4–12 hours	**Renal impairment:** With continuous infusions, half-life of the parent compound can increase up to 2-fold. Half-life of the active metabolite can increase significantly compared to control group.[e41] **Special populations with prolonged half-lives**: • Elderly: Increased 2-fold • Heart failure: Increased 2-fold • Hepatic impairment: Increased 2.5-fold • Obesity: increased 2-fold
		Pediatric	2.9-4.5 hours	
		Adult	~3 hours	
	Metabolism		Hepatic	
	Excretion		Urine (90%)	
Propofol[e42]	$t_{½}$	Infant ≤28d	Initial: 40 minutes Terminal: 4–7 hours	**Context sensitive half-time**: Prolonged infusions (>10 days) have been associated with a drug half-life of 1-3 days. **Elderly:** Clearance may be decreased.[e43]
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine (90%)	

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Intravenous narcotics				
Fentanyl[e44,b]	$t_{½}$	Infant ≤28d	5.5 ± 1.2 hours[e45]	**Continuous infusion:** Half-life prolongs with infusion duration. In children aged 6 months to 14 years, half-life reported as ~21 hours in long-term continuous infusions. **Special populations with prolonged half-lives:** • Infants**:** half-life inversely proportional to gestational age • Elderly: Increased 5-fold[e46] • Transdermal route: 20-27 hours
		Pediatric	5 months-4.5 years: 2.4 hours	
		Adult	2-4 hours	
	Metabolism		Hepatic	
	Excretion		Urine (75%)	
Hydromorphone[e47,b]	$t_{½}$	Infant ≤28d	2.3 hours	**Renal impairment:** Increased terminal half-life seen in patients with severe renal impairment compared to controls after oral administration immediate release hydromorphone (40 vs 15 hours).
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	
Morphine[e48, e49,b]	$t_{½}$	Infant ≤28d[e50]	6.5 ± 2.8 hours	**Hepatic impairment:** 1. Children: extrahepatic metabolism may occur, minimal half-life changes 2. Adults with cirrhosis: delayed clearance **Elderly:** Reduced clearance
		Pediatric[e50]	2 ± 1.8 hours	
		Adult	2 hours	
	Metabolism		Hepatic	
	Excretion		Urine (90%)	
Remifentanil[e51, e52]	$t_{½}$	≤2 months	5.4 minutes	
		Pediatric	>2 months to <2 years: 3.4 minutes 2–6 years: 3.6 minutes 7–2 years: 5.3 minutes 13 to <16 years: 3.7 minutes 16–18 years: 5.7 minutes	
		Adult	10–20 minutes	
	Metabolism		**Blood and tissue esterases**	
	Excretion		Urine (90%)	

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Antiseizure Medications				
Clonazepam[e53,b]	$t_{½}$	Infant ≤28d	22–81 hours	**Hepatic impairment:** Clearance may be decreased **Elderly:** Hepatic clearance may be decreased
		Pediatric	28.7 hours	
		Adulte54	17–56 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Diazepam [e55,b]	$t_{½}$	Infant ≤28d	Parent: 33–45 hours Active metabolite: 87 hours	Terminal half-life prolonged with repeated dosing. **Hepatic impairment:** In mild and moderate cirrhosis, diazepam half-life is increased by 2-5 fold.[e56] **Elderly:** In healthy patients >60 years, half-life of parent compound was ~79 hours.[e57]
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	
Levetiracetam	$t_{½}$	Infant ≤28d[e58]	8.9 hours	**Renal impairment:** Renal clearance is directly proportional to creatinine clearance, reported half-lives[e59]: • Mild impairment: 10.4 hours • Severe impairment: 24.1 hours **Elderly:** Renal clearance may be decreased. • Reported increases in half-life by 2.5 hours.
		Pediatric	<4 years: 5.3 ± 1.3 hours 4–12 years: 6 ± 1.1 hours	
		Adult	6–8 hours	
	Metabolism		Plasma hydrolysis (~24%)	
	Excretion		Urine	
Lorazepam[e60,b]	$t_{½}$	Infant ≤28d	40.2 ± 16.5 hours	**Renal impairment**: Half-life slightly prolonged in end stage renal disease (~18 hours).[e61]
		Pediatric	5 months to <3 years: 15.8 hours 3 to <13 years: 16.9 hours 13 to <18 years: 17.8 hours	
		Adult	~14 hours	
	Metabolism		Hepatic	
	Excretion		Urine (88%)	
Pentobarbital[e62]	$t_{½}$	Infant ≤28d	26 ± 16 hours	
		Pediatric		
		Adult	22 hours	
	Metabolism		Hepatic	
	Excretion		Urine	

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Antiseizure Medications				
Phenobarbital[e63]	$t_{½}$	Infant ≤28d	<10 days: 114.2 ± 43 hours 11-30 days: 73.19 ± 24.17 hours	**Hepatic impairment:** Small changes in half-life are seen in patients with cirrhosis (130 ± 15 hours) compared with the control group (86 ± 3 hours). There is large interpatient variability seen in hepatic impairment.[e64] **Therapeutic Range:** 10–40 mcg/mL
		Pediatric	2-3 months: 62.9 ± 5.2 hours 4-12 months: 63.2 ± 4.2 hours 1-5 years: 68.5 ± 3.2 hours	
		Adult	~79 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Phenytoin[e65] and fosphenytoin[e66, e67]	$t_{½}$	Infant ≤28d	0–2 days: 80 hours 3–14 days: 15 hours 15–150 days: 6 hours[e68]	**Michaelis-Menten**: Half-life increases with increasing phenytoin concentrations. **Hepatic impairment:** Active metabolite undergoes enterohepatic circulation and may prolong duration of action.[e69, e70] **Renal impairment:** Total phenytoin serum concentrations should be interpreted with caution. If available, recommend the use of free phenytoin concentrations.[e65] **Obesity:** Half-life may be prolonged in obese patients compared to controls (19.9 vs 12 hours, respectively).[e71] **Elderly:** Clearance decreases with increasing age **Therapeutic Range:** Total Phenytoin 10-20mcg/mL; Free Phenytoin 1-2 mcg/mL
		Pediatric	10–12 hours	
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	
Valproic acid[e72, e73]	$t_{½}$	Infant ≤28d	First week of life: 40–45 hours <10 days: 10–67 hours	**Liver impairment:** 18 hours[e73] **Elderly:** 15 hours[e74] **Therapeutic Range:** 50–100 mcg/mL
		Pediatric	>2 months: 7–13 hours 2-14 years: 9 hours	
		Adult	9–19 hours	
	Metabolism		Hepatic	
	Excretion		Urine	

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Neuromuscular blocker agents				
Atracurium[e75, e76]	$t_{½}$	Infant ≤28d	Infants: 20 minutes Children: 17 minutes	
		Pediatric		
		Adult	20 minutes	
	Metabolism		Hofmann elimination and ester hydrolysis	
	Excretion		Urine (<5%)	
Cisatracurium[e77, e78]	$t_{½}$	Infant ≤28d	22-29 minutes	
		Pediatric		
		Adult		
	Metabolism		Hoffman elimination	
	Excretion		Urine (95%)	
Pancuronium[e79,b]	$t_{½}$	Infant ≤28d	89–140 min	**Renal impairment:** 257 minutes **Biliary obstruction:** 270 minutes **Hepatic cirrhosis:** 208 minutes **Hypothermia:** May prolong duration
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine (40%), Bile (11%)	
Rocuronium[e80,b]	$t_{½}$	Infant ≤28d	3–12 months: 1.3 ± 0.5 hours	**Hepatic impairment:** 4.3 hours **Renal impairment:** 2.4 hours **Elderly:** Duration prolonged in elderly patients compared with young adults (110 vs 78 minutes, respectively)[e81]
		Pediatric	1 to <3 years: 1.1 ± 0.7 hours 3 to <8 years: 0.8 ± 0.3 hours	
		Adult	1.4–2.4 hours	
	Metabolism		Minimally hepatic	
	Excretion		Urine (26%)	
Succinylcholine[e82]	$t_{½}$	Infant ≤28d	<1 minute	**Pseudocholinesterase deficiency:** Prolonged clearance[e83]
		Pediatric		
		Adults		
	Metabolism		Plasma pseudocholinesterases	
	Excretion		Urine (10%)	

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Neuromuscular blocker agents				
Vecuronium[e76, e84,b]	$t_{½}$	Infant ≤28d	Infants: 65 minutes	**Hepatic impairment:** Half-life is prolonged in patients with cholestasis compared to controls (58 vs 98 minutes, respectively)[e85] **Hypothermia:** Clearance may be reduced[e86]
		Pediatric	Children: 41 minutes	
		Adult	65–75 minutes	
	Metabolism		Hepatic	
	Excretion		Urine (30%)	

[a]The duration of time that medications should be held before neurologic examination to determine brain death is patient and medication specific. Providers should be aware that the metabolism and clearance of pharmacologic agents can be affected by patient-specific factors, including but not limited to hypothermia, organ dysfunction, obesity, and concomitant drug therapies. Typically, 3 to 5 half-lives will allow for adequate clearance of pharmacologic therapy; however, elimination half-life does not guarantee clearance of medications with active metabolites or enterohepatic recirculation. This table includes terminal half-life, which takes into account both volume of distribution and elimination rate, as well as information on specific populations that experience deviations in standard clearance when clinically significant data are available. Context-sensitive half-time was included when shown to be prolonged compared with reported half-life values. Whenever possible, providers should obtain drug levels to ensure that the levels are in a low to mild therapeutic range before neurologic examination.

[b]Reversal agents can be considered after evaluating the risk vs benefit of their use.

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