



Carglumic acid in hyperammonaemia due to organic acidurias: a profile of its use in the EU

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Abstract

Carglumic acid (*N*-carbamyglutamate; Carbaglu[®]), a structural analog of *N*-acetylglutamate, is an effective and generally well-tolerated option for the treatment of hyperammonaemia due to propionic, methylmalonic and isovaleric acidurias. These organic acidurias are linked to a group of autosomal recessive inherited disorders that are associated with secondary hyperammonaemia due to the inhibition of the urea cycle. Carglumic acid can be administered orally or through a nasogastric tube. In retrospective, observational studies and case series/reports, carglumic acid rapidly reduced plasma ammonia levels and improved clinical symptoms of hyperammonaemia. Carglumic acid is generally well tolerated, and, based on limited data, may be associated with fewer treatment-emergent adverse events when used in combination with ammonia scavengers than when either therapy is administered alone.

Adis evaluation of carglumic acid in the treatment of hyperammonaemia due to organic acidurias

Administered orally or through a nasogastric tube
Rapidly reduces plasma ammonia levels in patients with propionic, methylmalonic and isovaleric acidurias
Improves clinical symptoms of hyperammonaemia, including neurological symptoms and feeding difficulties
Generally well tolerated

What is the rationale for using carglumic acid in hyperammonaemia due to organic acidurias?

The main function of the urea cycle is to eliminate excess nitrogen as urea [1]. Five catalytic enzymes are required for ureagenesis: carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase and arginase 1. The first enzyme of

the urea cycle is CPS1, which catalyzes the conversion of ammonia, bicarbonate and adenosine triphosphate to carbamoylphosphate, the initial rate-limiting step of the urea cycle [1]. The urea cycle is also regulated by *N*-acetylglutamate (NAG), which is necessary for the activation of CPS1 [2]. Defects in any part of the urea cycle can cause nitrogen to build up as ammonia, resulting in hyperammonaemia [1].

Hyperammonaemia can be secondarily caused by organic acidurias [3], a group of autosomal recessive inherited disorders [4, 5]. Propionic, methylmalonic and isovaleric acidurias are inborn errors of metabolism characterized by the accumulation of the respective organic acids due to a deficiency of the enzymes propionyl coenzyme A carboxylase, methylmalonyl coenzyme A mutase or isovaleryl coenzyme A dehydrogenase, respectively. Secondary hyperammonaemia in patients with propionic and methylmalonic acidurias occurs when accumulated coenzyme A derivatives (propionyl coenzyme A and, to a lesser extent, methylmalonyl coenzyme A) inhibit NAG synthase [6]. Most organic acidurias become clinically apparent during the first days to weeks of life, with symptoms such as poor feeding, vomiting, seizures and decreased level of consciousness, progressing to coma and death [4]. Late-onset cases with a more heterogeneous clinical picture may present at any age [5].

Hyperammonaemia in organic acidurias can be life-threatening [3]. Conventional treatments for hyperammonaemia include glucose, dietary protein restriction, enteral nutrition, ammonia scavengers, dialysis and transplant [7].

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However, questions remain regarding the optimal and safe use of dietary protein restriction [8, 9] and ammonia scavenger therapy [5] to treat hyperammonaemia in patients with propionic and methylmalonic acidurias.

Carglumic acid (*N*-carbamylglutamate; Carbaglu®), a structural analog of human NAG, is the only drug approved for hyperammonaemia caused by organic acidurias. This review focuses on the use of carglumic acid for the treatment of hyperammonaemia due to propionic, methylmalonic and isovaleric acidurias, as approved in the EU (Table 1) [10]. A discussion of the use of carglumic acid in its other approved indication (hyperammonaemia due to primary NAG synthase deficiency) is beyond the scope of this article.

What are the pharmacological properties of carglumic acid?

As a synthetic structural analog of NAG, carglumic acid enhances the detoxification of ammonia by activating CPS1 in the liver [10, 11]. Although carglumic acid has a lower affinity for CPS1 than NAG, the mitochondrial membrane is more permeable to carglumic acid than NAG. Carglumic acid is also less prone to hydrolysis by cytosolic aminoacylase than NAG. In rats, carglumic acid stimulated CPS1 and protected against ammonia intoxication

to a greater extent than NAG. Carglumic acid decreased plasma levels of ammonia and increased plasma and urine levels of urea, while the liver content of CPS1 activators was significantly increased [10]. In healthy young adults aged 20–40 years, administration of a single dose of carglumic acid 50 mg/kg augmented ureagenesis, as measured by the *in vivo* synthesis of radiolabeled urea during an intravenous infusion of radiolabeled sodium bicarbonate [2]. The increased rate of urea production was rapid, occurring \approx 60 min after administration of carglumic acid. Carglumic acid also significantly decreased plasma levels of alanine, but not levels of glutamine and arginine [2].

Following a single oral dose of 100 mg/kg, \approx 30% of carglumic acid is absorbed, with maximum plasma concentrations being reached in 2–4 h [10]. Carglumic acid follows a biphasic elimination curve (i.e. a rapid initial phase followed by a slower phase), with a terminal half-life of up to 28 h. A proportion of carglumic acid may be metabolized by the intestinal bacterial flora. Carglumic acid metabolites are detectable in plasma, with a peak at 36–48 h and a half-life of \approx 100 h. One metabolite (glutamic acid) has been identified in the faeces. The primary route of excretion of carglumic acid metabolites is via exhaled carbon dioxide. Following oral administration of a radiolabeled dose of carglumic acid (100 mg/kg), 60% is excreted as unchanged drug in the faeces and 9% is excreted unchanged in the urine [10].

Table 1 Prescribing summary of oral carglumic acid (Carbaglu®) in the treatment of hyperammonaemia due to propionic, methylmalonic and isovaleric acidurias in the EU [10]

How is carglumic acid available and how should it be stored?	
Availability	Dispersible tablets containing 200 mg of carglumic acid
Storage	Prior to opening the tablet container, refrigerate at 2–8 °C
	After the first opening of the container, do not refrigerate and do not store above 30 °C
	Protect from moisture (i.e. keep the container tightly closed)
How should carglumic acid be administered?	
Recommended dosage	Initial daily dose 100 mg/kg, up to 250 mg/kg if necessary; individually adjust dosage in order to maintain normal plasma levels of ammonia
Administration	Divide total daily dose into 2–4 doses by breaking tablets into halves or quarters
	Administer before meals or feedings
	Disperse tablets in \geq 5–10 mL of water and ingest immediately <i>OR</i> administer by fast push via nasogastric tube using a syringe
How should carglumic acid be used in special populations?	
Pregnant women	Use with caution (lack of data)
Breastfeeding women	Use is contraindicated
What other special warnings/precautions pertain to the use of carglumic acid?	
Therapeutic monitoring	Maintain plasma levels of ammonia and amino acids within normal limits
	Monitor liver, renal cardiac functions and haematological parameters
Nutritional management	Protein restriction and arginine supplementation may be indicated in case of low protein tolerance

What is the clinical efficacy of carglumic acid?

Retrospective, observational studies

Oral carglumic acid, \pm ammonia scavenger therapy, reduced plasma ammonia levels and improved clinical symptoms of hyperammonaemia in patients with organic acidurias in the clinical practice setting [11, 12]. The efficacy population of a retrospective, phase 3b study included 41 patients with a confirmed diagnosis of organic aciduria with hyperammonaemia (i.e. plasma ammonia $> 60 \mu\text{mol/L}$) who had at least one metabolic decompensation episode that was treated with carglumic acid. A total of 48 episodes of hyperammonaemia were treated with carglumic acid, with 35 patients having a single episode, 5 having two episodes and 1 having three episodes [11].

Plasma ammonia levels decreased rapidly from baseline following initiation of carglumic acid (Table 2) [11]. The mean time to normalization of plasma ammonia (i.e. $\leq 60 \mu\text{mol/L}$) was ≈ 2 –3 days, and was generally similar in all patient subgroups. Carglumic acid reduced plasma ammonia levels to similar levels in both neonates and non-neonates, and in patients with propionic, methylmalonic and isovaleric aciduria (Table 2). The plasma ammonia levels reached at endpoint were similar with or without ammonia scavenger therapy [11].

Carglumic acid was also associated with improvement in clinical symptoms of hyperammonaemia [11]. All 48 episodes of hyperammonaemia were accompanied by clinical symptoms at baseline (e.g. poor sucking, vomiting,

hyperventilation, muscle hypotonia, recurrent ketoacidosis, lethargy and coma). After treatment with carglumic acid, there were no clinical symptoms in 8 of 30 (27%) episodes with available baseline and endpoint data. Normal psychiatric, hepatic, respiratory and psychomotor status was seen in 88, 84, 84 and 64% of episodes, respectively, at study endpoint, compared with 71, 75, 61 and 64% of episodes at baseline [11].

In a pooled analysis of two retrospective, observational studies (including the phase 3b study [11]), plasma ammonia levels were reduced to a significantly greater extent with carglumic acid + ammonia scavengers than with ammonia scavengers alone at all timepoints during the first 72 h of treatment, except 12–24 h (Table 3) [12]. Significantly greater reductions in plasma ammonia levels were also observed at 24–48 h with carglumic acid alone than with ammonia scavengers alone. In the carglumic acid group, reductions in plasma ammonia levels were similar among neonates and non-neonates. However, in the combination therapy group, neonates had a greater reduction in plasma ammonia than non-neonates. Reductions in plasma ammonia levels over 72 h of treatment with carglumic acid \pm ammonia scavengers were similar for patients with propionic, methylmalonic and isovaleric acidurias. The time to success in 25% of episodes was numerically shorter in the combination therapy group, while the median time to halve baseline levels of plasma ammonia was similar in all treatment groups. The time to halve baseline plasma ammonia levels was shorter when a higher average dose of carglumic acid ($\geq 100 \text{ mg/kg}$) was administered (Table 3) [12].

Most clinical symptoms of hyperammonaemia were markedly reduced from baseline to study endpoint in all

Table 2 Efficacy of carglumic acid in treating hyperammonaemia episodes in patients with organic aciduria in a retrospective study [11]

Efficacy population	No. of episodes	Mean change in plasma ammonia from BL to study endpoint ^a (BL value) [$\mu\text{mol/L}$]	No. of episodes	Mean change in plasma ammonia from BL to normalized plasma ammonia ^b ($\mu\text{mol/L}$)	Mean time to normalized plasma ammonia ^b (days)
All patients	48	– 292.2 (350.7)	42	– 272.8	2.4
Methylmalonic aciduria	25	– 229.2 (296.9)	20	– 233.1	1.9
Propionic aciduria	19	– 307.3 (355.0)	19	– 310.5	3.0
Isovaleric aciduria	4	– 614.3 (666.8)	3	– 299.0	2.3
Neonates	29	– 407.6 (468.3)	24	– 392.6	2.0
Non-neonates	19	– 116.1 (171.3)	18	– 113.2	3.1
With concomitant ammonia scavengers	15	– 366.0	14	– 344.7	2.3
With concomitant haemofiltration (\pm ammonia scavengers)	6	– 521.8	6	– 529.3	1.5
Without concomitant treatment	27	– 200.2	22	– 157.2	2.8

BL baseline

^aPrimary outcome; study endpoint defined as end of treatment (no more than 18 h after the last intake of carglumic acid) or the last available value under treatment up to a maximum of 15 days

^bNormalized plasma ammonia defined as plasma ammonia level of $\leq 60 \mu\text{mol/L}$

Table 3 Efficacy of carglumic acid ± ammonia scavengers^a in treating hyperammonaemia episodes in patients with organic aciduria in a pooled analysis of two retrospective, observational studies (*n* = 83) [12]

Endpoint	Treatment (no. of episodes)		
	Carglumic acid (38)	Ammonia scavengers ^a (33)	Combination therapy (27)
Median plasma ammonia level (µmol/L)			
Baseline	199	122	271
0–12 h	132	115	200
12–24 h	99	90	96
24–48 h	78	84	84
48–72 h	65	84	53
Mean change from baseline in plasma ammonia level (%)			
0–12 h	– 13	+ 12	– 27*
12–24 h	– 47	– 22	– 52
24–48 h	– 44*	– 5	– 61** [†]
48–72 h	– 66	– 16	– 76**
Time to success^b in 25% of episodes (h)			
	34	37	29
Median time to a 50% decrease in baseline plasma ammonia levels (h)			
All episodes	18.2	19.7	18.0
Episodes with first 24-h dose ≥ 100 mg/kg	16.9		8.3
Episodes with average dose ≥ 100 mg/kg	15.7		8.0
Episodes with an average dose of < 100 mg/kg	19.7		18.8

* *p* < 0.05, ** *p* < 0.01 vs ammonia scavengers alone; [†]*p* < 0.05 vs carglumic acid alone

^aAmmonia scavengers included sodium benzoate and sodium phenylbutyrate

^bDefined as the time to first of two consecutive measurements of plasma ammonia ≤ 60 µmol/L without initiation of extracorporeal detoxification, death or study withdrawal

treatment groups [12]. At baseline, 86–100% of episodes were associated with neurological symptoms and/or feeding difficulties. At study endpoint, normal neurological status was reported for 50, 36 and 45% of episodes in the carglumic acid, ammonia scavengers and combination therapy groups, respectively. The greatest improvements were seen in symptoms of somnolence/asthenia, lethargy and muscle hypotonia. There was also a shift towards normal feeding in 58, 75 and 80% of episodes treated with carglumic acid, ammonia scavengers and combination therapy, respectively [12].

Other reports in the clinical practice setting

The benefits of carglumic acid therapy in treating acute (Table 4) [13–29] and chronic (Table 5) [30–32] hyperammonaemia due to organic acidurias have also been reported in case reports/series. In almost all acute cases, plasma ammonia levels decreased (and often normalized) within a few hours of treatment initiation (Table 4). Other benefits of carglumic acid therapy included increased protein intake and metabolic stabilization. Some patients experienced developmental delays and other long-term sequelae (e.g. seizures, hepatomegaly, hypotonia) after recovery.

When used for the long-term treatment of organic acidurias, carglumic acid decreased/normalized ammonia levels, increased protein intake, increased bodyweight and/or improved bone mineral density (Table 5) [30–32].

What is the tolerability profile of carglumic acid?

Oral carglumic acid was generally well tolerated in patients with secondary hyperammonaemia due to organic acidurias in the retrospective phase 3b study [11]. Twenty-five of 57 patients in the safety population experienced a total of 74 treatment-emergent adverse events (TEAEs), including 24 treatment-related adverse events, 6 of which were serious. Most TEAEs were from one of the following system organ classes: general disorders and administration site conditions (16%), blood and lymphatic system disorders (14%), metabolism and nutrition disorders (12%) or infections and infestations (12%). Seven patients experienced fatal TEAEs; however, none of these were considered likely to be related to carglumic acid [11].

Combination therapy with carglumic acid + ammonia scavengers was better tolerated than either treatment alone,

Table 4 Efficacy of carglumic acid in the treatment of acute hyperammonaemia due to organic acidurias in case reports/series ($n = 1-10$)

Pt age at treatment initiation	Carglumic acid dosage	Effect of carglumic acid on hyperammonaemia, plasma ammonia levels and other outcomes
Case reports in pts with propionic aciduria		
2 d [13]	150 mg/kg → 100 mg/kg/d	Ammonia levels ↓ within 6 h and normalized after 12 h; slow but constant neurological improvement; diffuse cerebral hypotrophy, axial hypotonia, poor head control at 2 mo of age
3 d [14]	115 mg/kg → 150 mg/kg/d	Ammonia levels ↓ within 14 h and normalized within 72 h; protein intake ↑ to 1.2–1.4 g/kg
8 d [15]	100 mg/kg → 70 mg/kg/d	Ammonia levels normalized within 36 h; methylcitrate excretion remained ↑
4 mo [16]	100 mg/kg/d	Ammonia levels ↓ on d 1 and normalized by d 6; no invasive procedures or hospitalization
6 y [17]	2.2 g/m ² /d	Almost 3-fold ↑ in radiolabeled urea; plasma glutamine, alanine and glycine levels ↓
22 y [18] ^a	3.5 g/d	Ammonia levels controlled despite the development of sepsis due to <i>Klebsiella pneumoniae</i>
Case series in pts with propionic aciduria		
2 or 11 d (2 pts) [19]	250 or 25 mg/kg	Ammonia levels ↓ over 6–10 h (250 mg/kg in pt aged 2 d) or ↑ over 2.5 h (25 mg/kg in pt aged 11 d)
3 d (2 pts) [20]	400 mg → 200 mg every 6–12 h	Ammonia levels ↓ after 4–8 h and stabilized after 8–22 h; motor developmental delays in 2 pts; feeding delays in 1 pt
2–9 d (4 pts) [21]	30–200 mg/kg → 115–300 mg/kg/d	Ammonia levels ↓ within 2 h in 3 pts and normalized within 12–29 h in 4 pts; 2 pts died during an initial episode of hyperammonaemia; 1 pt died after third episode (aged 46 d); 1 pt survived with well-controlled seizures, mild hepatomegaly and mild developmental delay at 3 y of age
7 or 10 d (2 pts) [22]	200 mg/kg	Ammonia levels ↓ within 2.5–3 h and normalized within 6 h; metabolic acidosis normalized within 20–24 h
1 d to 4 y (3 pts) [23]	17–53.5 mg/kg every 6–12 h	Ammonia levels ↓ over 3–15 h and normalized within 8–47 h; protein intake gradually ↑ in 1 pt
15 mo to 13 y (7 pts) [24]	100 mg/kg/d or 2.2 g/m ² /d	Peak radiolabeled urea ↑; ammonia and glutamine levels ↓
Case reports in pts with methylmalonic aciduria		
2 d [15]	200 mg/kg/d	Ammonia levels ↓ within 12 h and normalized within 3.5 d; methylmalonic acid excretion ↓ more slowly
4 d [13]	150 mg/kg → 100 mg/kg/d	Ammonia levels ↓ within 2 h; protein intake gradually ↑; progressive improvement of clinical condition; complete motility and immaturity of axial control at 24 d of age
6 d [25]	70 mg/kg → 100 mg/kg/d	Ammonia levels ↓ within 1 h and normalized within 3 h
9 d [26]	80 mg/kg/dose → 40 mg/kg/dose	Ammonia levels ↓ within 90 min and subsequently normalized; improvement of clinical condition; protein intake gradually ↑; normalization of liver size and function
3 weeks [27] ^a	100 mg/kg/d	Able to tolerate up to 2.25 g/kg/d of protein; normal ammonia levels maintained; physical and developmental growth; only mild episodes of hyperammonaemia during intercurrent illness
Case series in pts with propionic or methylmalonic aciduria		
0.75–7.2 y (10 pts) [28] ^a	Not reported	Ammonia levels ↓; no pts required dialysis
Case report in pt with isovaleric aciduria		
3 d [29]	150 mg/kg/d	Ammonia levels normalized over 6 h; normal neurology/good metabolic control at 2 mo of age

d day(s), mo months, pt(s) patient(s), y years, ↓ decreased, ↑ increased, → then

^aAvailable as an abstract

according to the pooled analysis of two retrospective studies [12]. There were fewer TEAEs with carglumic acid + ammonia scavengers than with carglumic acid alone or ammonia scavengers alone (18, 54 and 85 TEAEs, respectively). Similar results were seen with regard to the number of serious TEAEs (7, 13 and 31). However, it should be noted that the patient numbers are relatively small, and the number of patients affected by TEAEs is not specified - only the number of episodes. Most TEAEs were related to metabolic decompensation rather than to drug toxicity. The most frequent ($\geq 10\%$ incidence in any treatment group) TEAEs were thrombocytopenia (4% of episodes with carglumic acid + ammonia scavengers vs 5% with carglumic acid alone and

21% with ammonia scavengers alone), hyperglycaemia (4 vs 3 and 15%), hypokalaemia (0 vs 3 and 18%), coagulopathy (0 vs 3 and 15%), hypocalcaemia (0 vs 3 and 12%) and respiratory distress (0 vs 0 and 12%). In one patient treated with carglumic acid alone, thrombocytopenia, coagulopathy and hypocalcaemia were considered to be drug-related [12].

Further evidence of the safety of carglumic acid is available from the case series/reports in patients with hyperammonaemia due to organic acidurias. Where reported, carglumic acid was well tolerated and no TEAEs were observed [13, 23, 25, 28–30, 32]. The slightly acidic taste of the carglumic acid suspension [10] may explain the strong, non-offensive, aromatic urinary odour observed in one case report [25].

Table 5 Efficacy of carglumic acid in the treatment of chronic hyperammonaemia due to organic acidurias in case reports/series ($n = 1-22$)

Pt age at treatment initiation	Carglumic acid dosage	Effect of carglumic acid on hyperammonaemia, plasma ammonia levels and other outcomes
Case report in pt with propionic aciduria		
9 y [30]	100 → 50 mg/kg/d	Ammonia levels ↓; only 2 acute episodes of decompensation in 6 y; ammonia scavengers gradually discontinued; protein intake ↑ to 1.2 g/kg/d; bone mineral density improved
Case series in pts with propionic or methylmalonic aciduria		
6 d to 2.2 y (22 pts) [31] ^a	15–177 mg/kg	Total of 81 episodes of hyperammonaemia treated with dosage adjustment; only 15 episodes required hospitalization
2–20 y (8 pts) [32]	50 mg/kg/d	Few decompensation episodes (none in 3 pts); ammonia levels ↓ in 5 pts and were maintained in the normal range in 3; protein intake ↑ by 20–50%; bodyweight ↑ by 0–6.5 kg

d day(s), *pt(s)* patient(s), *y* years, ↓ decreased, ↑ increased, → then

^aAvailable as an abstract

Patient care guidelines

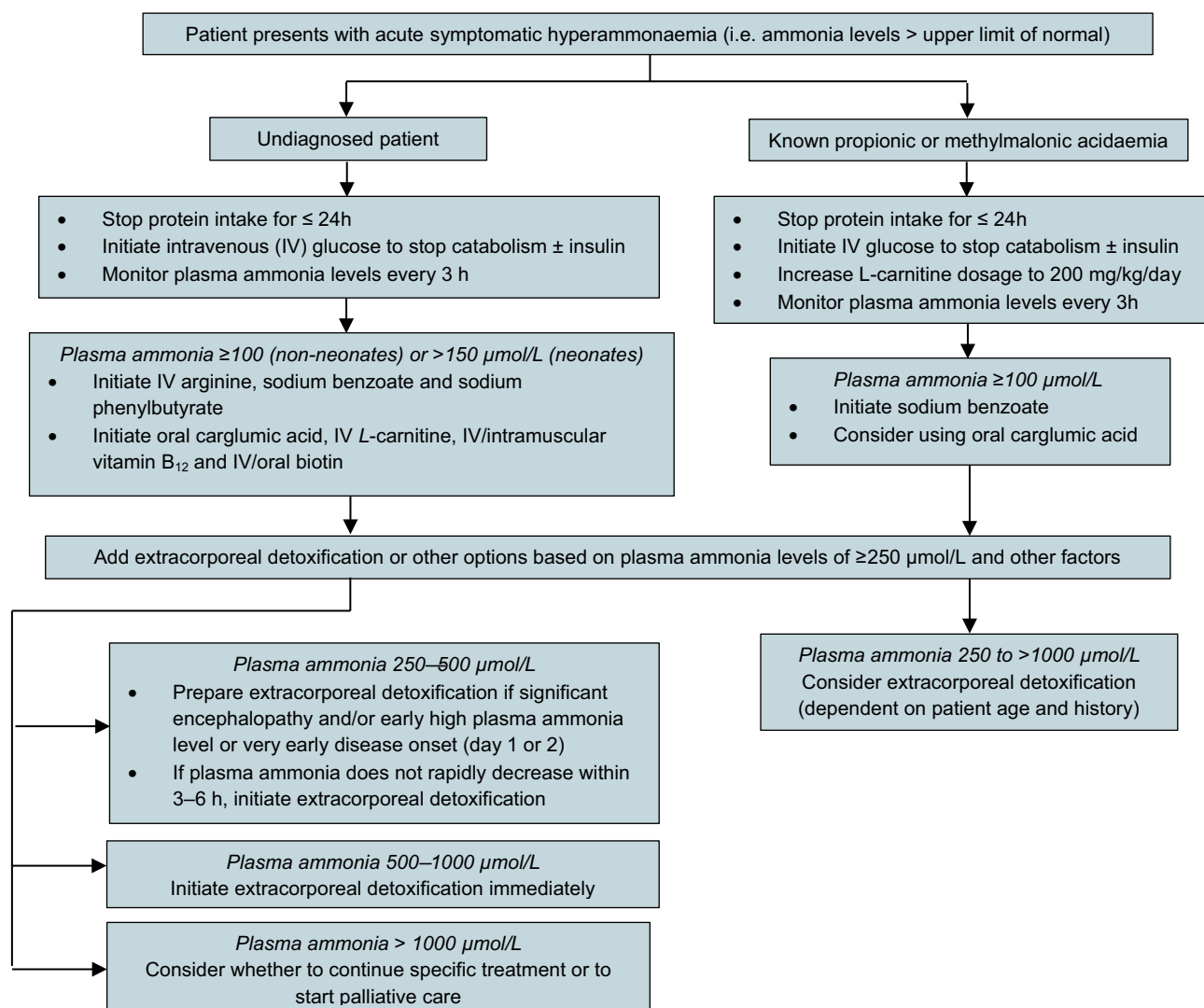


Fig. 1 Management of symptomatic hyperammonaemia in undiagnosed patients and patients with known propionic or methylmalonic acidurias, as recommended in a proposed European consensus guideline [5]

What is the current clinical position of carglumic acid in hyperammonaemia due to organic acidurias?

Carglumic acid represents an effective and generally well-tolerated treatment option for patients with secondary hyperammonaemia due to organic acidurias. Carglumic acid rapidly reduces plasma ammonia levels and improves clinical symptoms of hyperammonaemia in both neonates and non-neonates with organic acidurias, including propionic, methylmalonic and isovaleric acidurias. Of note, plasma ammonia levels are reduced to a significantly greater extent with carglumic acid + ammonia scavengers than with ammonia scavengers alone. Carglumic acid is effective for the treatment of both acute and chronic organic acidurias, an important observation as long-term usage is increasingly employed in treating patients with organic acidurias in clinical practice. In some case series/reports, long-term use of carglumic acid had beneficial effects on other outcomes (e.g. increased protein intake, increased bodyweight and improved bone mineral density). The drug is easy to administer orally or through a nasogastric tube. Carglumic acid is generally well tolerated, and, based on limited data, may be associated with fewer TEAEs when used in combination with ammonia scavengers than when either therapy is administered alone.

Left untreated, high levels of ammonia in the brain as a result of hyperammonaemia are associated with significant neurological dysfunction [33]. Long-term neurodevelopmental outcomes in patients with hyperammonaemia due to organic acidurias are also strongly influenced by the duration of coma and the plasma ammonia level [5]. Therefore, proposed European guidelines for the management of acute hyperammonaemia in patients with propionic or methylmalonic aciduria recommend that initial treatment should be started without delay, at the same time as the diagnostic workup. Following stabilization of the patient, protein intake should be discontinued and intravenous glucose should be initiated (Fig. 1). First-line treatment options include L-carnitine, arginine, ammonia scavengers (e.g. sodium benzoate or sodium phenylbutyrate), vitamin B₁₂ (preferably in the form of hydroxycobalamin), biotin and carglumic acid (Fig. 1) [5].

All currently available evidence for the efficacy and tolerability of carglumic acid in the treatment of secondary hyperammonaemia due to organic acidurias comes from the clinical practice setting. To date, no randomized controlled trials have investigated the use of carglumic acid for the treatment of hyperammonaemia in patients with organic acidurias, presumably because of the rarity of the disorder. A randomized, double-blind, placebo-controlled, phase 2 trial is currently underway to evaluate the efficacy and tolerability of

carglumic acid for the treatment of acute hyperammonaemia in patients with propionic aciduria, methylmalonic aciduria or other urea cycle disorders (NCT01599286). Also underway is a randomized, open-label, phase 3b trial comparing the efficacy of carglumic acid + standard therapy (dietary protein restriction, L-carnitine, metronidazole and vitamin B₁₂) versus standard therapy alone in patients with propionic or methylmalonic aciduria (CAMP; NCT02426775). In addition, two trials assessing the long-term use of carglumic acid in patients with propionic or methylmalonic acidurias are currently underway (PROTECT and LOTUS) [34]. Results from these trials are awaited with interest.

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Compliance with ethical standards

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