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Diagnostic approaches and pharmacological treatments for nonketotic hyperglycinemia: a 30-year scoping review

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Resumen

La hiperglicinemia no cetósica (HNC) es una enfermedad minoritaria autosómica recesiva del metabolismo de la glicina, caracterizada por un amplio espectro de manifestaciones neurometabólicas. A pesar de su gravedad clínica, aún no se han estandarizado su diagnóstico y terapéutica. Esta revisión exploratoria sintetiza 30 años de bibliografía científica con el objetivo de describir los enfoques diagnósticos actuales y los tratamientos empleados en la HNC. Se incluyeron un total de 56 artículos publicados entre 1992 y 2022, la mayoría de los cuales correspondían a casos clínicos (63%). La evaluación diagnóstica se basó principalmente en pruebas bioquímicas —niveles plasmáticos de glicina (75% de los artículos) y el cociente glicina en LCR/plasma (64%)—, seguidas de confirmación genética (50%). Las técnicas de neuroimagen se utilizaron de forma complementaria (RM 45%, ERM 25%). El tratamiento fue básicamente farmacológico, predominantemente con el benzoato sódico (80% de los artículos), mientras que antagonistas del receptor NMDA como el dextrometorfano (73%) y la ketamina (43%) se emplearon como coadyuvantes. El diazepam y el fenobarbital se utilizaron habitualmente para el control de las crisis epilépticas, mientras que el ácido valproico está sistemáticamente contraindicado. En conjunto, la evidencia refleja un consenso creciente en torno a los criterios diagnósticos, pero pone de manifiesto importantes lagunas en la evidencia terapéutica. Se requieren estudios colaborativos de calidad que permitan establecer algoritmos terapéuticos estandarizados y desarrollar terapias capaces de mejorar los resultados neurológicos a largo plazo en la HNC.

Palabras clave
Antagonista de los receptores NMDA, benzoato, dextrometorfano, diagnóstico, encefalopatía por glicina, hiperglicinemia no cetósica, tratamiento.

Summary

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive disorder of glycine metabolism characterized by highly heterogeneous neurometabolic manifestations. Despite its clinical severity, no standardized diagnostic or therapeutic pathways have been established. This scoping review synthesizes 30 years of scientific literature to map current diagnostic approaches and pharmacological treatments for NKH. A total of 56 peer-reviewed journal articles published between 1992 and 2022 were included; most (63%) were case reports. Diagnostic evaluation relied primarily on biochemical testing—plasma glycine concentrations (75% of articles) and the cerebrospinal fluid-to-plasma glycine ratio (64%)—followed by genetic confirmation (50%). Neuroimaging techniques were used as complementary tools (MRI 45%, MRS 25%). Treatment of NKH was predominantly pharmacological: sodium benzoate was the most frequently used agent (80% of the articles), and NMDA-receptor antagonists such as dextromethorphan (73%) and ketamine (43%) were frequently employed as adjunctive therapies. Diazepam and phenobarbital were commonly used for seizure control, but valproic acid was consistently contraindicated. Overall, the findings show a growing consensus on biochemical and molecular diagnostic criteria but also reveal substantial gaps in the therapeutic evidence base. High-quality collaborative studies are urgently needed to establish standardized treatment algorithms and to develop targeted therapies to improve long-term neurological outcomes in NKH.

Key words
Benzoate, dextromethorphan, diagnosis, glycine encephalopathy, NMDA-receptor antagonist, nonketotic hyperglycinemia, treatment.

INTRODUCTION

Nonketotic hyperglycinemia (NKH), also referred to as hyperglycinemic encephalopathy or glycine encephalopathy, is a rare autosomal recessive inborn error of glycine metabolism in which a defect in the glycine cleavage system (GCS) leads to the accumulation of glycine in plasma and cerebrospinal fluid (CSF), giving rise to a broad spectrum of neurometabolic manifestations (Perry et al., 1975; Selvanathan et al., 2026). Reported incidence estimates of NKH range from 1 in 12,000 to 1 in 76,000 live births, depending on the population studied (van Hove et al., 2002). In Spain, although no reliable registry-based data are available, seven cases of NKH are currently recognized.

The metabolic defect underlying NKH involves dysfunction of the GCS, a multienzyme complex composed of four proteins (P, H, T, and L). Impaired GCS activity results in excessive accumulation of glycine in all tissues, particularly in the brain and CSF, which is reflected in elevated glycine concentrations in blood and urine. The GCS complex is expressed primarily in the liver, brain, and placenta, with lower levels detected in Epstein–Barr virus (EBV)-transformed lymphoblasts (van Hove et al., 2002; Kanno et al., 2007; Beyoğlu & Idle, 2012). Disruption of glycine cleavage may also interfere with one-carbon metabolism and methyl group homeostasis, processes that are essential for normal brain development (Beyoğlu & Idle, 2012).

Excess glycine in NKH affects two major receptor systems in the central nervous system: inhibitory glycine receptors and excitatory N-methyl-D-aspartate (NMDA) receptors. Overactivation of glycine receptors contributes to hypotonia and apnea, whereas excessive stimulation of NMDA receptors is associated with excitotoxic neuronal injury (Vázquez Mora et al., 1995; van Hove et al., 2002). Clinical manifestations of NKH typically appear during the neonatal period and tend to worsen throughout childhood, although later-onset presentations have also been reported. Clinically, NKH is classified into severe and attenuated forms. Severe NKH is characterized by profound developmental delay and intractable epilepsy, whereas attenuated NKH presents with variable degrees of developmental impairment with seizures being absent or more or less controllable (van Hove et al., 2002). Severe NKH is the most frequent clinical phenotype, accounting for approximately 85% of neonatal cases. Attenuated NKH is further subdivided into attenuated poor (developmental quotient [DQ] < 20, invariably associated with epilepsy), attenuated intermediate (20 < DQ ≤ 50, without epilepsy or with controllable epilepsy), and attenuated mild forms (DQ > 50 without epilepsy). Patients with severe NKH often present with progressive lethargy, coma, seizures, and apnea, subsequently developing intellectual disability, persistent axial hypotonia, and spasticity. Congenital brain malformations, including agenesis of the corpus callosum or retrocerebellar cysts with hydrocephalus, have also been reported. Although not pathognomonic, neonatal hiccups are frequently described as an early sign preceding epileptic manifestations. Apnea, hypotonia, and neonatal hiccups may be explained by inhibitory overstimulation of glycinergic receptors in the spinal cord and brainstem (van Hove et al., 2002; García-Muñoz et al., 2004).

Prognosis is largely determined by the degree of residual enzymatic activity of the GCS complex. Most patients with neonatal or infantile onset have poor outcomes due to severe enzyme deficiency (Swanson et al., 2015). In some cases, apnea may result in death during the neonatal period. The progression and severity of epilepsy vary according to the timing of diagnosis and the initiation of treatment (van Hove et al., 2002).

The diagnosis of NKH is established through elevated concentrations of glycine in plasma and CSF, in combination with neuroimaging studies (magnetic resonance imaging [MRI]/computed tomography). The diagnosis is further supported by demonstration of reduced GCS activity in enzymatic assays or by the identification of pathogenic variants through molecular genetic testing (van Hove et al., 2002; Coughlin et al., 2017). To date, no formal evidence-based guidelines have been established for the treatment of NKH. Current management strategies primarily aim to reduce plasma glycine concentrations, antagonizing NMDA receptor activity, and controlling associated neurological symptoms (van Hove et al., 2002).

As with many rare diseases, limited knowledge remains a major challenge in NKH. There is no clear consensus regarding diagnostic criteria, and therapeutic approaches vary widely (Applegarth et al., 2002; Benoist et al., 2007). To our knowledge, no systematic reviews addressing diagnostic criteria and/or therapeutic interventions for NKH have been published. This paper aims to synthesize the available scientific evidence on diagnostic approaches and therapeutic interventions for NKH, with a particular focus on pharmacological treatments.

METHODS

Information on NKH is very limited; few scientific studies and no clinical trials have investigated it. Most articles on NKH report single cases or very small series of patients; thus, the scant available data are very heterogeneous. Thus, we reviewed the available literature to map current diagnostic approaches and pharmacological treatments for NKH. Following the methodology described by Arksey and O'Malley (2005), we developed this scoping review in the following five stages:

Stage 1: Identifying the research questions

After defining the objectives of the study, we posed two research questions: 1. How is NKH diagnosed? and 2. How is NKH treated?

Stage 2: Identifying relevant studies

To identify studies relevant to the two research questions, we elaborated a preliminary list of keywords to search the literature. We found that the first article with the keyword "nonketotic hyperglycinemia" was published in 1968 (Ziter et al., 1968), and a larger number of articles on NKH began to appear in the 1990s. Thus, we decided to focus this review on articles published during the last 30 years (1992-2022). To select the most suitable keywords and combinations of keywords with Boolean operators, we tried various strategies and lists of keywords. We identified and eliminated keywords that could be misleading. Finally, we simplified the search, using the same strategy for all the bibliographic databases: (nonketotic hyperglycinemia) AND (diagnosis) AND (treatment). The definitive searches were done on April 24, 2023 in the three main bibliographic databases: PubMed, Scopus, and Web of Science. Citations were loaded into Mendeley Desktop reference management software (version 1.19.8) for title and abstract selection as well as data characterization.

Stage 3: Selecting studies

Figure 1 outlines the results of the selection process. The searches initially yielded 175 records; 36 of these were duplicates and were therefore excluded. We analyzed the title, abstract, and full text of the remaining 139 records to ensure that they met the following inclusion criteria: having been published in Spanish or English and providing information on the diagnosis or treatment of NKH. We also excluded records published in formats other than articles in scientific journals (e.g., books or book chapters), those that did not focus on the neonatal or severe type of NKH or on the mild attenuated type without neonatal debut or without epilepsy, and those that focused on other diseases and other metabolic disorders where NKH was not the main object of study. Two authors (PM and FB) reviewed all the articles independently.

Stage 4: Charting the data

We entered the data from the selected articles into a spreadsheet (Microsoft Excel), registering information about the type of articles, authors, and the journals where the articles were published (see **Table S1** in Supplementary Material). All data were entered into worksheets to enable descriptive analyses, including the number of articles, means, ranges, and percentages for the evaluated variables. We also did a qualitative analysis of the contents of the articles and the data obtained from them. We decided to analyze the data on diagnosis separately from the data on treatment. As an indirect quality measure of the articles' impact, we categorized the number of citations the articles received into 4 levels based on the number of citations listed in WoS-JCR: low (<10 citations), medium (10-25 citations), high (26-35 citations), and very high (>35 citations).

Stage 5: Collating, summarizing, and reporting the results

Finally, we collected, summarized, and analyzed the results reported in the following section of this article.

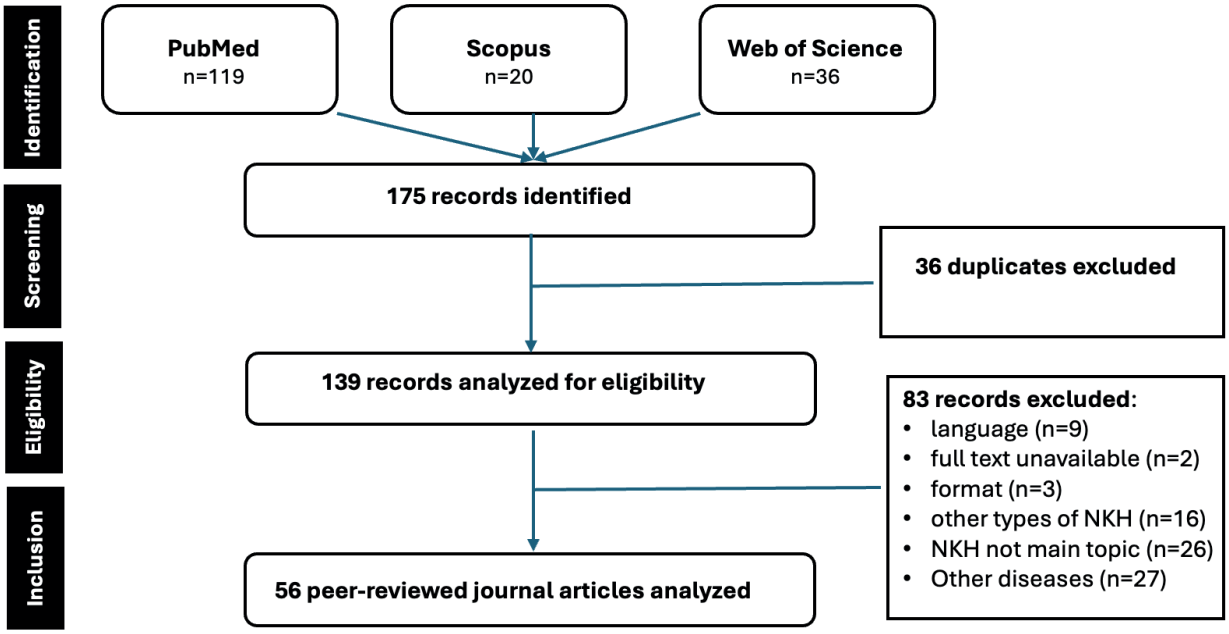

Figure 1. Flow diagram of the study selection process. The diagram shows how the articles in this scoping review were identified, screened, assessed for eligibility for inclusion. Records were identified through three bibliographic databases (PubMed, Scopus, and Web of Science). After eliminating duplicate records, we screened titles and abstracts and assessed the full text of identified records; we excluded records that were not published in English or Spanish (n=9); those whose full text was unavailable (n=2); those published in formats other than scientific journal articles (e.g., books, book chapters, or other non-peer-reviewed publications) (n=3); those that did not focus on the neonatal form of NKH (n=16); those in which NKH was not the main topic (n=26); and those that addressed other diseases (n=27). In total, 83 articles were excluded, and 56 articles were included in the final synthesis (see **Appendix** for the complete bibliographic details).

RESULTS

This review included 56 eligible articles identified through searches of three bibliographic databases (see **Appendix** for the bibliographic details of all the articles included). Of these, 53 (94.6%) were published in English and 3 (5.4%) in Spanish. **Table 1** summarizes the main characteristics of the studies included. Over the 30-year period (1992–2022), a mean of 1.8 articles on NKH were published per year, with peaks of four publications in 2004 and 2015 (**Figure S1A**, Supplementary Material). The most common type of publication was a case report (n=35; 62.5%), followed by original articles (n=16; 28.6%). The 56 articles received a total of 1,293 citations (mean, 25.9; range, 1–146). The level of the impact of the article according to the number of citations was very high (>35 citations) for 13 (23.2%) articles and low (<10 citations) for 22 (39.3%). A total of 325 authors contributed to these publications (mean, 5.8 per article; range, 1–32). Authors came from 22 countries, led by the United States and Japan, followed by Spain and Israel (**Figure S1B**, Supplementary Material). The articles included were published in 41 different journals, most frequently in the *Journal of Inherited Metabolic Disease* (n=4), followed by the *Journal of Child Neurology* (n=3), *Metabolic Brain Disease*, *Neuropediatrics* (n=3), and *Pediatric Neurology* (n=3) (**Table S2**, Supplementary Material). The journals were classified into 11 Journal Citation Reports subject categories, predominantly *Pediatrics* and *Clinical Neurology* (**Table S3**, Supplementary Material). Most articles were published in first- (Q1, 28.6%) or second-quartile (Q2, 26.8%) journals, and the mean journal impact factor was 1.1 (range, 0.08–3.26) (**Table 1**).

Table 1. General characteristics of the 56 articles included in the review.

Type of information	Variables		Data
Article characteristics	Number of articles, n		56
	Evaluation period, years (range)[a]		30 (1992-2022)
	Type of article, n%		
	Case report	35	62.5%
	Original article[b]	16	28.6%
	Case series	3	5.3%
	Letter to the editor	1	1.8%
	Invited commentary	1	1.8%
	Citations:		
	Total, n		1,293
	Mean (range)		25.9 (1-146)
	Impact according to the number of citations, n%		
	Very high (>35)	13	23.2%
	High (26-35)	8	14.3%
	Medium (10-25)	7	12.5%
	Low (<10)	22	39.3%
	Not assessable	6	10.7%
Authorship	Number of authors, n		325
	Authors per article, mean (range)		5.8 (1-32)
	Number of corresponding authors, n		45
	Countries[c] represented, n		22
Journal characteristics	Number of journals, n		41
	JCR subject categories, n		11
	JCR impact factor, X̄ (range)		1.1 (0.08-3.26)
	JCR quartiles[d] by subject category, n%		
	Q1	16	28.6%
	Q2	15	26.8%
	Q3	10	17.8%
	Q4	9	16.1%
	Not assessable	6	10.7%

[a] Although this review includes only articles published between 1992 and 2022, a literature search on February 11, 2026 identified no additional relevant articles. See also, Figure S1A (Supplementary Material), which shows the number of articles published per year.

[b] The original articles encompassed a wide range of study designs, including genetic, biochemical, molecular, and animal studies, as well as various types of clinical research, such as studies involving the ketogenic diet, descriptive clinical studies, drug-diet interaction studies, therapeutic or clinical pharmacology studies, and diagnostic studies.

[c] See also Figure S2B (Supplementary Material) for information on the most represented countries according to the authors' affiliations.

[d] JCR quartiles (Q1–Q4), according to the Journal Citation Reports classification.

The most frequent diagnostic technique for NKH described in the 56 articles included was biochemical determination of glycine concentrations: 42 (75%) reported glycine measurement in plasma and 40 (71.4%) reported glycine measurement in CSF (**Table 2**). The CSF-to-plasma glycine ratio, considered the most specific biochemical marker in current clinical practice, was reported in 32 (64.3%) articles. Electroencephalography was mentioned as a complementary tool in 31 (55.3%) articles; these typically reported burst-suppression or hypsarrhythmia patterns. Genetic testing was reported in 28 (50.0%) articles; these primarily employed genetic testing for diagnostic confirmation and mainly identified biallelic variants in *GLDC* or *AMT*. Brain magnetic resonance imaging (MRI) findings were reported in 25 (44.6%) articles, including magnetic resonance spectroscopy findings, which enable in vivo detection of cerebral glycine accumulation, in 14 (25.0%). Enzymatic studies of GCS activity were reported in 24 (42.8%) articles, largely through liver biopsy or lymphoblast assays. Prenatal diagnosis by chorionic villus sampling was reported in 14 (25.0%) articles. Additional supportive tests included amino-acid chromatography, reported in 17 (30.3%) articles, and arterial blood gas analysis, reported in 13 (23.2%). Overall, the data reflect a progressive shift over the study period from predominantly biochemical and enzymatic approaches toward integrated biochemical and molecular diagnostic strategies. Together, these findings indicate that the current diagnostic gold standard consists of identifying elevated concentrations of glycine in plasma and CSF with an increased CSF-to-plasma glycine ratio, supported by molecular confirmation when available.

Table 2. Main diagnostic techniques for nonketotic hyperglycinemia (NKH) reported in the articles included, stratified by citation impact.

	Diagnostic technique and key features[a]	No. of articles (%) and citation impact[b]
1.	**Plasma glycine** Normal plasma glycine ≤450 μmol/L (age-dependent). Attenuated NKH: typically up to ~1,590 μmol/L. Severe NKH: values may reach >2,300 μmol/L.	42 (75%) articles 7 (16.6%) Very high 8 (19.0%) High 5 (12.0%) Moderate 17 (40.4%) Low 5 (12.0%) Not assessable
2.	**CSF glycine** Normal CSF glycine <20 μmol/L; NKH usually 40–510 μmol/L. Values ≤230 μmol/L suggest attenuated NKH. CSF must be free of blood/protein contamination.	40 (71.4%) articles 7 (17.5%) Very high 8 (20.0%) High 5 (12.5%) Moderate 16 (40.0%) Low 4 (10.0%) Not assessable
3.	**CSF-to-plasma glycine ratio** Normal CSF-to-plasma glycine ratio ≤0.02. Higher ratios are strongly suggestive of NKH.	32 articles [64.3%] 6 (18.7%) Very high 5 (15.6%) High 3 (9.4%) Moderate 14 (43.8%) Low 4 (12.5%) Not assessable
4.	**Electroencephalogram** Supportive tool; not diagnostic alone. Typical findings include burst-suppression, evolving to hypsarrhythmia or multifocal spikes. Burst-suppression and hypsarrhythmia are associated with poor prognosis.	31 (55.3%) articles 3 (9.7%) Very high 6 (19.4%) High 5 (16.1%) Moderate 13 (41.9%) Low 4 (12.9%) Not assessable

Diagnostic technique and key features[a]	No. of articles (%) and citation impact[b]
5. **Genetic studies** Confirmatory diagnostic tests for NKH. Biallelic variants in *GLDC* and *AMT* are most common; *GCSH* is less frequent. Multigene panels with CNV analysis are recommended.	28 (50%) articles 5 (27.8%) Very high 6 (21.4%) High 1 (3.6%) Moderate 14 (50.0%) Low 2 (7.2%) Not assessable
6. **Magnetic resonance imaging (MRI)** Early MRI shows diffusion restriction in internal capsule, brainstem, and cerebellum. Later progression may involve both infra- and supratentorial white matter. Corpus callosum abnormalities or retrocerebellar cysts may be present.	25 articles [44.6%] 3 (12.0%) Very high 4 (16.0%) High 4 (16.0%) Moderate 11 (44.0%) Low 3 (12.0%) Not assessable
7. **Enzymatic studies: by liver biopsy and in lymphoblasts** Liver biopsy assesses glycine cleavage system (GCS) activity; the enzyme complex is highly labile. Most NKH patients show absent or markedly reduced GCS activity. Lymphoblast assays are unreliable due to overlap with controls.	24 (42.8%) articles 6 (25.0%) Very high 6 (25.0%) High 2 (8.3%) Moderate 7 (29.2%) Low 3 (12.5%) Not assessable
8. **Amino acid chromatography** Performed on blood or urine to detect elevated glycine levels. Confirms absence of metabolic acidosis and normal anion gap. Helps differentiate NKH from organic acidemias.	17 (30.3%) articles 4 (23.5%) Very high 2 (11.8%) High 3 (17.6%) Moderate 6 (35.3%) Low 2 (11.8%) Not assessable
9. **Magnetic resonance spectroscopy** Glycine peak detected at 3.6 ppm at intermediate echo time (TE). Prominent in severe NKH; reduced or absent in attenuated forms. False positives may occur in cerebral hemorrhage.	14 (25%) articles 4 (28.6%) Very high 2 (14.3%) High 3 (21.4%) Moderate 5 (35.7%) Low 0 (0%) Not assessable
10. **Chorionic villus biopsy** Used for prenatal diagnosis once familial pathogenic variants are known. Can be performed by molecular testing or enzymatic GCS activity analysis. Enzymatic testing has ~1% false-negative rate.	14 (25%) articles 2 (14.3%) Very high 5 (35.7%) High 2 (14.3%) Moderate 3 (21.4%) Low 2 (14.3%) Not assessable
11. **Arterial blood gases** Used to exclude ketoacidosis and metabolic acidosis. Based on arterial or capillary pH and bicarbonate levels.	13 (23.2%) articles 0 (0%) Very high 0 (0%) High 3 (23.1%) Moderate 6 (46.1%) Low 4 (30.8%) Not assessable

[a] Other techniques for diagnosing NKH reported less frequently include urinary glycine (n=10 articles); computed tomography (n=9); transfontanellar ultrasound (n=9); next-generation sequencing (n=8); routine blood tests (n=7); whole-exome sequencing (n=6); amniocentesis (n=5); sepsis workup (n=5); urinalysis to exclude ketosis (n=4); electromyography and nerve conduction studies (n=3); increased frequency and intensity of seizures after valproate administration (n=3); ^{13}C-glycine breath test (n=3); multiplex ligation-dependent probe amplification (n=3); full gene nucleotide sequencing (n=2); umbilical cord blood glycine analysis (n=1); analysis of ventilator waveform suggesting hiccups and NKH diagnosis (n=1); metabolic screening (n=1); TORCH serology (n=1); and high-performance liquid chromatography to determine 5-hydroxyindoleacetic acid and homovanillic acid in CSF and urine (n=1).

[b] The number of articles reporting each diagnostic technique; percentages are calculated from the total of 56 articles included. Citation impact is categorized into 4 levels based on the number of citations listed in WoS-JCR: low (<10 citations), medium (10-25 citations), high (26-35 citations), and very high (>35 citations)

Most interventions were pharmacological, and sodium benzoate was the most frequently reported treatment, being mentioned in 45 (80.3 %) articles. Sodium benzoate remains the only pharmacological agent currently used in clinical practice to reduce plasma glycine concentrations, although it does not normalize glycine levels in the central nervous system (**Table 3**). Dextromethorphan, an NMDA-receptor antagonist, was mentioned in 41 (73.2%) articles, being mainly used for attenuated forms of NKH, although interindividual variability related to *CYP2D6* polymorphisms may influence the therapeutic response. Ketamine, another NMDA-receptor antagonist, was reported in 24 (43.0%) articles; it was generally described as an adjunctive option. Among other drugs administered for seizure management, diazepam was reported in 16 (28.6%) articles and phenobarbital in 15 (27.0%). Strychnine was mentioned in 13 (23.2%) articles; however, its use has largely been abandoned due to its toxicity. Although sodium valproate was mentioned in 11 (20.0%) articles, it is contraindicated in NKH because of its inhibitory effect on the GCS and its potential to increase cerebral glycine levels. In some reports, sodium valproate was used in the diagnostic process, because seizure exacerbation after administration has been considered suggestive of NKH. Overall, the data indicate that treatment strategies primarily target glycine reduction and NMDA-receptor modulation, with seizure control representing a major supportive component.

Table 3. Main treatments for nonketotic hyperglycinemia (NKH) reported in the included articles, stratified by citation impact.

Treatments[a] and key features[b]	No. of articles (%) and citation impact[c]
1. **Sodium benzoate** This benzoic acid salt is widely used as an antimicrobial preservative (E211) in foods, cosmetics, and medicines, and combined with salicylic acid as a topical antifungal agent. Derived from dietary sources and gut microbiota metabolism, it regulates glycine through amino acid conjugation. Clinically, it treats hyperammonemia in urea cycle disorders by enhancing nitrogen excretion. In NKH, it lowers plasma glycine via mitochondrial conjugation with glycine to form hippuric acid, excreted renally, although cerebrospinal fluid levels remain elevated. It is administered orally or intravenously (3–15 mg/kg/day). Adverse effects include gastrointestinal symptoms and irritability. Newborns risk toxicity, metabolic acidosis, kernicterus, and carnitine depletion	45 articles [80.3%] 9 (20.0%) Very high 7 (15.6%) High 5 (11.1%) Moderate 19 (42.2%) Low 5 (11.1%) Not assessable
2. **Dextromethorphan** This codeine analogue antitussive acts as an NMDA-receptor antagonist independently of opioid receptors. In NKH, it counteracts NMDA overstimulation caused by elevated glycine, implicated in early brain injury. In attenuated NKH, combined with sodium benzoate, it improves neurocognitive outcomes and reduces seizure risk, although its benefit in severe forms remains controversial and may increase pneumonia risk. Administered orally (3–15 mg/kg/day), its effects vary according to CYP2D6 metabolism. It is generally well tolerated, without addictive potential, though high doses may cause central nervous system depression and histamine-mediated reactions.	41 articles [73.2%] 7 (17.1%) Very high 7 (17.1%) High 5 (12.2%) Moderate 18 (43.9%) Low 4 (9.7%) Not assessable
3. **Ketamine** This NMDA-receptor antagonist has traditionally been used as a rapid-onset anesthetic, particularly in hemodynamically unstable patients and children. In NKH, its NMDA antagonism supports use in attenuated forms, often combined with sodium benzoate. It can be administered intravenously (1–2 mg/kg bolus or 0.5–2 mg/kg/h infusion), intramuscularly (4–5 mg/kg), orally (6–10 mg/kg), or intranasally (3–6 mg/kg). Adverse effects include drowsiness, agitation, amnesia, and involuntary movements; rapid intravenous administration may cause respiratory depression or apnea. Drug interactions are frequent and may increase hypotension, sedation, plasma levels, or seizure risk.	24 articles [43%] 4 (16.7%) Very high 6 (25.0%) High 3 (12.5%) Moderate 8 (33.3%) Low 3 (12.5%) Not assessable
4. **Diazepam** This long-acting benzodiazepine enhances GABA-mediated inhibition in the central nervous system and is widely used for seizure control and status epilepticus. In NKH, it provides anxiolytic, sedative, anticonvulsant, and central muscle relaxant effects without extrapyramidal symptoms. Other benzodiazepines, such as clonazepam, clobazam, lorazepam, nitrazepam, and midazolam, have also been used. Administered orally or rectally with weight-based pediatric dosing, its efficacy may decrease with enzyme inducers. Adverse effects include sedation, cognitive changes, incoordination, amnesia, paradoxical reactions, and, rarely, respiratory depression.	16 articles [28.6%] 2 (12.5%) Very high 3 (18.8%) High 1 (6.2%) Moderate 7 (43.7%) Low 3 (18.8%) Not assessable

Treatments[a] and key features[b]	No. of articles (%) and citation impact[c]
5. **Phenobarbital** This long-acting barbiturate enhances GABAergic inhibition, reduces glutamate- and acetylcholine-mediated excitation, and inhibits calcium channels, decreasing excitatory neurotransmitter release. In NKH, it is used for its sedative and anticonvulsant effects in focal and generalized seizures as well as status epilepticus. Administered orally or parenterally with age-adjusted dosing, its narrow therapeutic window requires plasma level monitoring. The risk of respiratory depression increases with benzodiazepines, and gradual tapering is needed to avoid dependence. Adverse effects include cognitive and behavioral impairment; when administered intravenously rapidly, it can cause severe respiratory complications and significant drug interactions.	15 articles [27%] 1 (6.7%) Very high 3 (20.0%) High 0 (0%) Moderate 9 (60.0%) Low 2 (13.3%) Not assessable
6. **Intensive care** The management of patients with NKH is complex and requires continuous 24-hour clinical surveillance. Close collaboration with pediatric intensive care units is essential to ensure appropriate monitoring and intervention. Specialized expertise is needed in respiratory support, including mechanical ventilation as well as in administering intravenous medications via infusion pumps and in enteral feeding through nasogastric tubes and gastrostomies.	15 articles [27%] 1 (6,7%) Very high 3 (20.0%) High 3 (20.0%) Moderate 5 (33.3%) Low 3 (20.0%) Not assessable
7. **Strychnine (historical)** This plant-derived compound was formerly used as a medical stimulant and as a pesticide and doping agent. Its use was abandoned due to its high toxicity. Strychnine competitively antagonizes glycine receptors in spinal cord neurons, disrupting chloride channel function and blocking inhibitory glycinergic signaling. This increases neuronal excitability, exaggerates reflexes, and may trigger seizures. Despite its toxicity, it has been used in selected NKH cases to counteract the effects of elevated glycine. Rapidly absorbed, its effects appear within 10–20 minutes. It is mainly metabolized in the liver. Poisoning mimics tetanus, causing severe spasms and respiratory failure. The lethal dose in humans is between 15 mg in children and 30-100 mg in adults.	13 articles [23.2%] 4 (30.7%) Very high 2 (15.4%) High 3 (23.1%) Moderate 3 (23.1%) Low 1 (7.7%) Not assessable
8. **Valproic acid (contraindicated)** This broad-spectrum anticonvulsant enhances cortical inhibition and neuronal stabilization, mainly by reducing GABA metabolism, increasing GABAergic neurotransmission, and suppressing voltage-gated sodium channel activity. It also has neuroprotective effects in epilepsy, migraine, and bipolar disorder. Although historically used in NKH as an anticonvulsant, valproic acid has proven harmful in this condition, being associated with increased seizure frequency and clinical deterioration. These adverse effects are attributed to secondary inhibition of the glycine cleavage system, leading to reversible elevation of cerebrospinal fluid glycine levels. Consequently, valproic acid is contraindicated in NKH and should not be used for diagnostic or therapeutic purposes in this disorder.	11 articles [20%] 2 (18.2%) Very high 0 (0%) High 2 (18.2%) Moderate 6 (54.5%) Low 1 (9.1%) Not assessable
9. **Ketogenic diet** The precise mechanisms underlying the therapeutic effects of the ketogenic diet in NKH remain unclear. This dietary intervention shifts cerebral energy metabolism away from carbohydrates toward fat-derived substrates, inducing broad changes in cellular and biochemical pathways. These metabolic adaptations contribute to the restoration of brain energy and metabolic homeostasis. The resulting molecular and cellular effects reduce glycine availability, normalize neuronal excitability, and promote neuroprotection. However, despite these benefits, the ketogenic diet does not modify the hypsarrhythmic pattern observed on electroencephalography.	10 articles [20%] 0 (0%) Very high 1 (10.0%) High 1 (10.0%) Moderate 6 (60.0%) Low 2 (20.0%) Not assessable
10. **Low-protein diet** Dietary glycine restriction is based on limiting the intake of foods containing the amino acid glycine. In NKH, the contribution of exogenous dietary glycine is minimal compared to excessive endogenous glycine production and impaired catabolism. Consequently, dietary restriction may help control plasma glycine levels only in selected patients with severe NKH. Low-protein infant formulas with reduced glycine content are available and may be used during early feeding stages. Transition to a solid diet increases glycine intake slightly; a modest increase in sodium benzoate dosage can usually compensate for this increase. Excessive dietary glycine restriction carries a risk of protein malnutrition and is therefore not recommended as a first-line measure.	10 articles [20%] 3 (30.0%) Very high 1 (10.0%) High 2 (20.0%) Moderate 3 (30.0%) Low 1 (10.0%) Not assessable

[a] These ten treatments, each reported in ≥ 10 of the articles included in this scoping review, are described in detail. Other NKH treatments reported in < 10 articles include additional amino acids, anticonvulsants, benzodiazepines, dietary interventions, supportive measures (e.g., enteral feeding, physiotherapy), and other pharmacological and non-pharmacological approaches.

[b] The table summarizes the key characteristics of each treatment—mechanism of action, indications, route of administration, and major limitations—based on the articles analyzed and complementary literature.

[c] The number of articles reporting each treatment is presented, with percentages calculated from the total of 56 studies included. Citation impact is categorized into 4 levels based on the number of citations listed in WoS-JCR: low (<10 citations), medium (10-25 citations), high (26-35 citations), and very high (>35 citations).

DISCUSSION

This scoping review synthesizes and critically appraises the available evidence on the diagnosis and pharmacological management of NKH. Although some authors, most notably van Hove et al. (2002) in a reference chapter updated in 2019, have described the clinical and molecular features of NKH, to our knowledge no previous systematic or scoping review has specifically examined diagnostic criteria and/or therapeutic strategies. The rarity of NKH has resulted in a limited body of literature over the past three decades, largely restricted to case reports and small case series, thereby generating substantial heterogeneity in the evidence base. Across studies, measurement of glycine concentrations remains the cornerstone of diagnosis, and sodium benzoate aimed at reducing systemic glycine levels is the most frequently reported therapeutic approach.

Our findings indicate that currently available tools can diagnose NKH with reasonable reliability. Diagnosis is based primarily on the detection of elevated glycine concentrations, particularly an increased cerebrospinal fluid–to–plasma glycine ratio, supported by characteristic neuroimaging findings, and confirmed by molecular genetic testing (van Hove et al., 2002). Amino acid analysis and basic metabolic investigations remain essential for raising initial clinical suspicion and guiding differential diagnosis in neonatal encephalopathy, as described in early clinical series (Koepp et al., 1973). Neuroimaging, especially magnetic resonance imaging, frequently demonstrates structural abnormalities consistent with impaired neurodevelopment, and magnetic resonance spectroscopy provides noninvasive evidence of glycine accumulation in the brain (Rite Gracia et al., 1999; van Hove et al., 2002). Although enzymatic assays of the GCS were historically used, their invasiveness and limited reproducibility have reduced their clinical applicability. Consequently, molecular analysis of *GLDC, AMT*, and *GCSH* has become the preferred confirmatory approach, despite challenges related to variants of uncertain significance and interpretation of residual enzymatic activity (Kanno et al., 2007; Coughlin et al., 2017). Nevertheless, nonuniversal access to specialized diagnostic techniques and the absence of standardized diagnostic pathways remain relevant challenges.

The distribution of citation impact across diagnostic approaches suggests the progressive consolidation of current practice. Techniques that now constitute the diagnostic core—particularly CSF-to-plasma glycine ratio determination and molecular genetic testing—were consistently represented among highly cited publications. In contrast, older enzymatic or invasive approaches were more frequently reported in lower-impact articles. Although citation counts cannot be equated with methodological quality or clinical validity, this pattern likely reflects sustained scientific recognition and broader dissemination of contemporary biochemical–molecular diagnostic standards.

By contrast, therapeutic management remains less clearly defined, with no formal evidence-based clinical guidelines and a paucity of data from comparative or randomized studies (van Hove et al., 2002; Selvanathan et al., 2026). Most reported interventions are pharmacological, aiming to reduce systemic glycine concentrations or to counteract the neurotoxic effects of elevated glycine concentrations. Sodium benzoate is the most consistently reported therapeutic agent, and it remains the cornerstone of treatment. Sodium benzoate effectively lowers plasma glycine concentrations and is therefore widely used, particularly in severe phenotypes; however, it does not normalize cerebrospinal fluid glycine levels (van Hove et al., 2002). NMDA-receptor antagonists constitute the principal adjunctive strategy. Dextromethorphan is frequently administered, especially in attenuated forms of NKH, although interindividual variability related to *CYP2D6* polymorphisms may influence the therapeutic response (Beyoğlu & Idle, 2012; van Hove, 2024). Ketamine, metabolized via alternative pathways and less affected by such polymorphisms, has emerged as an alternative option with potentially more predictable pharmacokinetics in selected patients (van Hove, 2024). Other treatments such as strychnine (Koepp et al., 1973; Ziter et al., 1968) have been abandoned because of unacceptable toxicity.

Epilepsy in NDK is often refractory and may progress to status epilepticus, and seizure control remains a major therapeutic challenge. Benzodiazepines, particularly diazepam, are commonly used for acute management; however, their narrow therapeutic index and excipient-related risks demand caution in their off-label use in neonates (Koepp et al., 1973; Rite Gracia et al., 1999). When benzodiazepines are insufficient, phenobarbital is often administered, although combination therapy requires careful monitoring due to additive sedative effects (Koepp et al., 1973; García-Muñoz et al., 2004). Importantly, although

sodium valproate was occasionally used during the diagnostic process, it is contraindicated in NKH, as it may increase cerebral glycine concentrations and exacerbate neurological deterioration (Vázquez Mora et al., 1995; van Hove et al., 2002, Nowak et al., 2022).

As we observed with respect to diagnostic strategies, the distribution of citation impact across therapeutic approaches also suggests the progressive consolidation of current practice. The therapeutic agents that form the backbone of current management, sodium benzoate and NMDA-receptor antagonists, predominate in the articles that have been cited most frequently, and discontinued or contraindicated treatments appeared more frequently in publications with fewer citations. Again, while citation metrics do not directly measure clinical efficacy or methodological rigor, this distribution may reflect the gradual convergence of the field toward mechanism-based and consensus-driven therapeutic approaches.

Adjunctive non-pharmacological strategies have also been explored. Ketogenic diets may improve seizure control and quality of life when used alongside pharmacological treatment, although supporting evidence remains limited and the mechanisms involved are incompletely understood (Shelkowitz et al., 2022). In contrast, low-protein diets are generally discouraged, as excessive glycine restriction may result in protein malnutrition without clear neurological benefits.

Future therapeutic perspectives include the development of novel pharmacological approaches aimed at stabilizing defective enzymes or modulating glycine metabolism. Strategies currently under investigation in other inherited metabolic disorders, such as Fabry disease, may represent promising avenues for NKH, particularly if effective blood–brain barrier penetration can be achieved (Selvanathan et al., 2026; CSIC, 2020).

This review has several limitations. The predominance of descriptive studies, absence of comparative or randomized trials, and heterogeneity of reported outcomes preclude robust conclusions regarding treatment efficacy. The search strategy was restricted to articles published between 1992 and 2022, which may have limited capture of earlier or very recent data, although a more recent search in February 2026 identified no additional relevant evidence. Finally, our assessment of article impact was based primarily on citation counts, an approach inherently subject to bias, as citations do not necessarily reflect methodological quality, rigor, or clinical validity. Nevertheless, the consistency of diagnostic and therapeutic patterns across the literature underscores both the progressive standardization of clinical practice and the substantial unmet needs that persist.

In conclusion, while the diagnostic framework for NKH is relatively well established, therapeutic management remains largely empirical. Sodium benzoate is the mainstay of treatment, and NMDA-receptor antagonists such as dextromethorphan and ketamine serve as important adjuncts. High-quality collaborative studies are urgently needed to standardize treatment algorithms and to develop targeted therapies capable of improving long-term neurological outcomes.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest. FB serves as a member of the Editorial Board of AFT; however, he was not involved in the editorial handling, peer-review process, or decision-making regarding this manuscript. All publication decisions were made independently by the Editor-in-Chief and the remaining members of the Editorial Board.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at:

https://docs.google.com/document/d/1_B9u55zkseXL7MBG9AsM7xnTArmz0XzX/edit

PROTOCOL REGISTRATION

The protocol for this study was prospectively registered in the Open Science Framework (OSF) on January 17, 2023. See the following link: osf.io/5ah3p.

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Appendix. Chronological list of articles included in the scoping review (n=56).

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