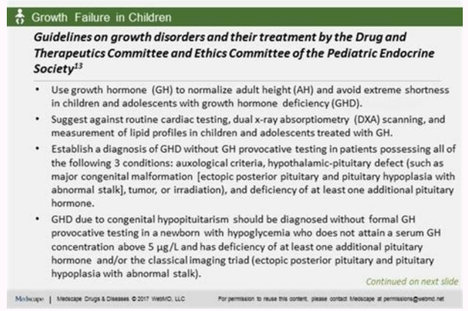
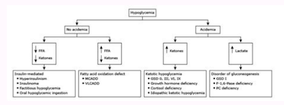
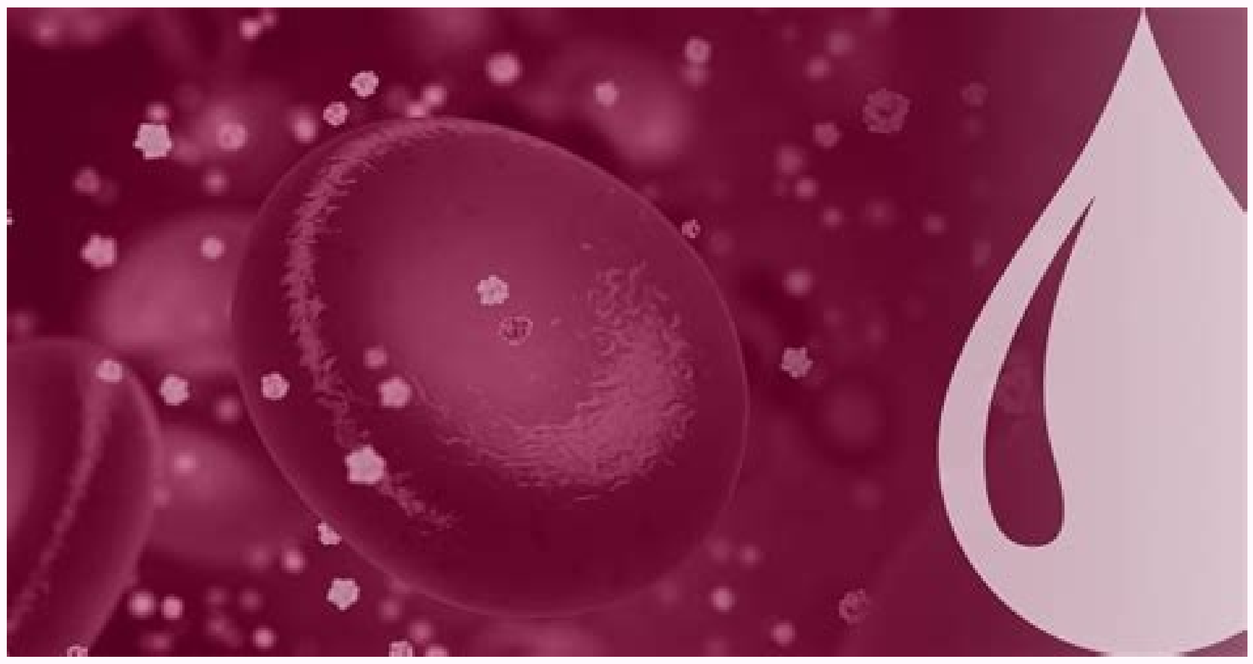
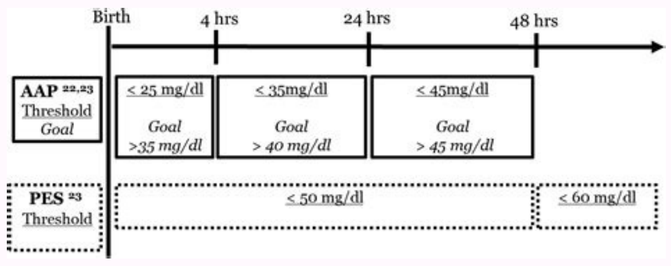
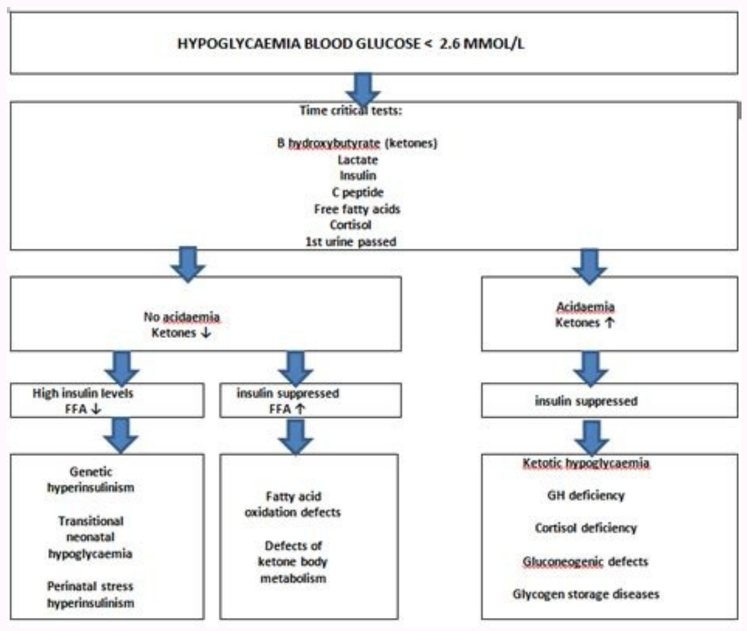
Pediatric endocrine society hypoglycemia guidelines











Hypoglycemia endocrine society guidelines. Pediatric hypoglycemia guidelines. Pediatric endocrine society guidelines. Pediatric endocrine society neonatal hypoglycemia guidelines. Pediatric endocrinology society guidelines.

Hypoglycemia (HY) in pediatric age shows some peculiarities regarding its diagnosis and management, mostly linked to age dependent features in glucose homeostasis and to the broad spectrum of causes. Such causes can initially present with the same unspecific picture, but they require different treatment (1). While being frequent but hard to detect in neonatal age, it is less common in infants and toddlers, even rarer in older children (1–3). In childhood, HY is a common metabolic-endocrine emergency possibly causing permanent neurological consequences. It is therefore essential to promptly detect and treat children with HY as well as those at risk. It is crucial to appropriately investigate its specific etiology for providing adequate and specific therapy (3, 4). In this review, we present current knowledge on management of HY in neonates and children including difficulties in establishing thresholds for both definition and therapeutic intervention and providing a comprehensive overall diagnostic approach through the use of a simple practical flowchart (5–8).Controversies About Clinical and Biochemical Definition of HypoglycemiaGlucose is the primary energy source for central nervous system metabolism, independently from the feeding state (1). Several metabolic pathways cooperate to ensure normal blood glucose concentrations in the fasted state (Figure 1). Such pathways are tightly regulated by the hormonal (insulin, glucagon, cortisol, and growth hormone) and autonomic (catecholamines) response. In case of impaired metabolic pathways and/or altered hormonal regulation, glucose could become too low to satisfy neuronal demand, causing classical symptoms of HY. In pediatric age, both glucose homeostasis and clinical presentation of HY show peculiarities compared to adults. In newborns, the adaptation to extrauterine life, characterized by immature hormonal and enzymatic pathways, and the higher glucose requirement of the brain, lead to a higher HY risk compared to older children and adults (9). Infants and children, have less glycogen storage and a higher substrates demand.Figure 1 Schematic representation of the major metabolic pathways involved in glucose homeostasis during absorptive phase and fasting including exogenous carbohydrates (brown), glycogenolysis (red), gluconeogenesis (blue), fatty acid oxidation (green), ketogenesis and ketolysis (yellow). These mechanisms are tightly controlled by hormonal regulation. Defects in specific enzymes or transporters involved in those pathways as well as endocrine disorders may result in fasting intolerance and hypoglycemia. FFA, free fatty acids, KB, ketone bodies.HY definition remains controversial in neonates and children. Some approaches define HY on the basis of symptoms, others on the plasma glucose value. In adolescents and adults, HY definition is based on the so-called “Whipple triad” [(I) symptoms of HY, (II) blood glucose level below 60 mg/dl, (III) resolutions of symptoms after glucose intake]. This definition appears inadequate for neonates and children in which symptoms are often subtle, and with the child being unable to communicate them (10). In addition, it is difficult to identify a single plasma glucose (PG) value below which symptoms of HY appear: in fact, symptoms appearance depends on additional factors, including the availability of alternative energy substrates (e.g. ketone bodies) and the severity, duration, and recurrence of low PG (7). Neurogenic symptoms are secondary to the neuroendocrine response, while neuroglycopenic symptoms are due to the low glucose availability to the brain. In neonates and infants, neurogenic and neuroglycopenic symptoms are not specific for HY. Therefore HY can be defined as the individualized condition in which PG concentration is low enough to cause symptoms and/or signs of impaired brain function (11).Based on the above-mentioned considerations, three age-based different clinical scenarios exist:i. Neonates 48 h of life, infants, and younger children unable to communicate: HY is defined as PG 7 years). The fasting should be stopped at any time if glucose concentration is below 2.6 mmol/L (47 mg/dl). Since newer diagnostic strategies (biochemistry and molecular biology) are rapidly becoming available, fasting test is not performed routinely; however, it can be helpful in selected cases (96).Glucagon test explores the response of glucagon injection during HY to assess the availability of glycogen for compensation of low blood glucose. Typically, HY due to GSDI does not benefit from glucagon injection (with worsening hyperlactatemia) while an exaggerated glucose response to glucagon could be observed in case of CH. Due to its possible risks (prolonged HY) it has been largely superseded by enzyme or mutation analysis.Alternative causes of abnormality of the test results should always be ruled out (e.g. lactate elevation secondary to laborious sampling or increased pCO2 secondary to apnea during blood collection).Additional InvestigationsImaging tests can provide additional information. Abdominal ultrasound and Magnetic Resonance Imaging (MRI)/Computed tomography/Scintigraphy scan can define liver, spleen, pancreas, and kidneys morphology and structure (e.g. liver steatosis, liver adenomas, focal hyperplasia). Left hand and wrist X-ray can be helpful in patients with growth retardation. Specific additional investigations may be performed based on the accompanying clinical features (e.g. cardiac ultrasound, brain MRI).HY Comprehensive FlowchartThe combination of the aforementioned information enables reaching a working diagnosis in most of the children presenting with HY. To date no consensus exists on a standardized diagnostic flowchart. Several algorithms with various starting points and workflow have been proposed (5, 7, 8). Although such algorithms can provide metabolic or endocrine specialists with specific pathophysiological insight, the two main groups of causes (namely endocrine and metabolic) may appear not clearly suited to the understanding and use of generalist pediatricians, which, on the other hand, are often the first level of observation of HY phenomena. Our center has a long-standing experience of cooperation between metabolic and endocrine experts in the management of childhood HY. In this respect, a comprehensive diagnostic flowchart is proposed (Figure 2). The major advantage of such flowchart is the ability to orient the diagnose, distinguishing both (main) metabolic and endocrine causes of childhood HY by using simple, routinely available tests such ketone bodies, emogas analysis, and lactate. As a matter of fact, data included in this flowchart can be easily implemented by physicians in a hospital setting, to obtain biochemical findings at the time of hypoglycemia, that should not be missed and that could be very useful to hypothesize the diagnosis. In order to provide adequate information, physicians should be aware that the flowchart applies to results collected on a “critical sample.” Possible limitations include the lack of rarer disorders (e.g. PEPCK deficiency, GKD, CDG) and the inability to diagnose uncommon presentations of common disorders.Figure 2 Hypoglycemia diagnostic flowchart.Only the main diagnostic features that guide bedside diagnosis about the most common causes of pediatric HY are shown in the flowchart (e.g., hyperlactatemia is also found in OXPHOS defects and GSD I; hepatomegaly is also found in FBPase deficiency and GSD I). Firstly: the timing of HY is the starting point; the patients fasting tolerance can provide an essential clue to the diagnosis in children with fasting HY (e.g. HY after a short fast suggests hepatic GSD, HY after moderate to long fast suggests gluconeogenesis defects or FAOD/KB defects). Secondly: laboratory investigations play a pivotal role to reach a working diagnosis. In this respect, assessing the presence of (un) detectable ketones (as well as metabolic acidosis, hyperlactatemia and, if possible, FFA) on a “critical sample” is of paramount importance. Thirdly: the presence of hepatomegaly can help differentiating disorders causing fasting ketotic HY.So far, the resultant flowchart seems to facilitate the logical process leading to the diagnostic suspicion and help to address the biochemical and clinical elements that need to be sought. The subsequent diagnostic process is up to the specialists of the two endocrine and metabolic sectors.In case of HY in otherwise healthy children and/or with no recognizable pattern, intoxications/factitious causes should always be ruled out by toxicological tests on blood and urine (most common drugs include insulin, sulfonylurea, beta-blockers, salicylates).Diagnosis can be confirmed through enzymatic and/or molecular testing for IMD and CH and challenge tests for endocrine disorders. Enzyme diagnostics is generally performed on blood cells or skin fibroblast (e.g. debranching enzyme or very-long chain acetyl-CoA dehydrogenase activity). However, some enzymes (e.g. G6Pase) are not expressed in these mediums and require a liver biopsy. Since liver biopsy is invasive, it has been largely superseded by DNA analysis.The Recent Role of NGSDNA analysis has become increasingly sophisticated and rapid in recent years. Various techniques are used to search for mutations in IMD/CH genes; single gene analysis (Sanger sequencing) has been traditionally used to confirm a specific diagnostic suspicion, after a traditional work-up. When a group of disease is considered, the traditional diagnostic approach would involve a long process with subsequent gene-by-gene molecular analyses. The gene-by-gene technique has now been superseded and replaced by the analysis of panels with NGS techniques. The introduction of NGS represents a major advancement in the diagnostic approach, allowing in parallel sequencing of millions of small fragments of DNA. Given the difficulties in the diagnostic workup in HY and due to the overlapping of clinical manifestations in several disorders of glucose metabolism, patients showing recurrent undiagnosed HY could be further investigated with an NGS-based approach. This modern technique has the potential to identify underrecognized rare disorders in the wide group of children with ketotic hypoglycemia, clinically diagnosed in the past as affected by benign hydiopatic hypoglycemia. In addition to a targeted approach with gene panels, the NGS technology can be used through untargeted strategies based on whole-exome sequencing, having this approach also the potential to identify new genes involved in disorders of glucose metabolism (97).Discussion and Conclusive RemarksDespite being a common emergency in pediatrics (3, 4), there are still controversies on the definition and management of HY in neonates and children. Neither the standard diagnostic PG threshold nor the operative threshold are defined. Also, no consensus on the definition of at–risk neonates exists. Such uncertainties together with the broad spectrum of causes, make the approach to HY in childhood complex and time consuming. Irrespective of its cause, prompt recognition and treatment of acute HY are critical to prevent its complications (namely brain damage). Bolus administration of dextrose (either intravenously or orally) is the cornerstone of the treatment. Glucose requirements may vary depending on the patient’s age (e.g. higher in neonates) and disease (e.g. up to 10–15 mg/kg/min of glucose or more can be required in children with CH). Since additional treatments can be necessary for specific disorders (e.g. specific dietetic approach, drugs and cofactors in OA and FAOD or DZX in CH) a timely etiological diagnosis is crucial. Once acute HY has been managed, pending the results of confirmatory tests (e.g. enzyme/DNA diagnostics) specific actions should be taken in order to prevent HY relapse. As a general recommendation, fasting must be avoided and adequate carbohydrate intake must be maintained during any metabolic stress. Tailored dietary treatment plan with frequent feedings and UCCS and/or tube feeding are the most common interventions, such a plan aims at ensuring glucose concentrations as stable as possible and is generally sufficient in patients with ketotic HY, hepatic GSD, and disorders of KB metabolism. Additional dietary interventions may be required for specific IMD (e.g. life–long fructose–, sucrose– sorbitol–restricted diet regimen in HFI, or low–protein diet in OA). Irrespective of their final diagnosis, in acute situations (e.g. intercurrent illness, prolonged fasting) patients can become catabolic, due to (the combination of) high fever, a reduced intake, and/or increased losses. Therefore, it is important to know what to do in emergency situations. An emergency protocol is designed at this purpose (98). Patients (and caregivers) should be encouraged to always carry an emergency protocol with them and follow its instructions. As HY can be secondary to a variety of different disorders, a systematic multidisciplinary approach is ideal in caring for neonates and children with HY. Interestingly, there is no consensus on standardized diagnostic algorithms for childhood HY. Therefore, a comprehensive practical diagnostic flowchart (including the main endocrine and metabolic causes) is proposed to guide the diagnostic suspicion, highlighting a minimal set of clue clinical and biochemical findings at the time of HY, that can be easily investigated in any hospital, at any time of the day. In fact, it is of paramount importance that samples are collected during HY (i.e. “critical sample”), otherwise the diagnosis can be missed (biochemical investigations might result normal when euglycemia has been reached). As shown in the proposed diagnostic flowchart, the minimal set of biochemical findings in children presenting with of HY includes ketones, lactate (both in blood and urine), and blood gases (i.e. metabolic acidosis). Such findings can help reaching a provisional diagnosis, which can be confirmed with additional (biochemical and/or genetic) tests. In this respect, collecting (and store adequately) additional samples at the time of HY is crucial. Laboratory data must also be appropriately integrated with anamnestic, dietary, clinical, and imaging information. The proposed flowchart aims at guiding the diagnostic management of a such common manifestation in pediatric age that can be due to a wide spectrum of causes. A double level usefulness is expected for the proposed flowchart: the first one is addressed to general pediatrician by providing the clinical–anamnestic and laboratory findings to be sought in order to refer the patient to the most appropriate Tertiary Center (Endocrinological/Metabolic/Genetic disease), the second level is for specialists in pediatric endocrine–metabolic diseases in order to remind them the wider etiological spectrum of pediatric HY by giving the essential elements of the differential diagnosis involving different areas (genetic, endocrine, and metabolic). In other word our flowchart aims to be a quick scheme to help pediatricians of every setting in managing HY, attempting to be comprehensive of the main disorders and differential diagnosis. Of course, mostly compared to the current available flowcharts focused on peculiar fields (metabolic or endocrinological), some rare conditions or rare presentations cannot be included. Sometimes, clinicians are not able to reach a final diagnosis, despite multiple efforts, due to the lack of specific biochemical pattern or atypical presentation of some disorders. In such cases, innovative diagnostic techniques can be considered. Even if much progress has been made over past years, many things remain to be discovered and clarified for diseases causing HY in childhood. Advances in diagnostic techniques (e.g. NGS) will identify specific defects or even new entities in a subgroup of patients who have been diagnosed with ketotic HY, likely resulting in a change in the disease epidemiology or in the discovery of new conditions (97).In conclusion, future studies are also needed to optimally define normal glucose thresholds in neonates and children (10). In addition, irrespective of the specific diagnosis prompt recognition and treatment of acute HY are critical to prevent its complications, the diagnostic work–up should start at the emergency hospital, collecting critical sample at the time of HY and providing specialists the clued results from simple tests that are available at any hospital at any time and that are very useful to address the clinical suspicion.Based on the recognized risks of some tests the traditional diagnostic process, including fasting or dynamic tests, is presently controversial and probably superseded by modern molecular diagnostic techniques. NGS approach has also the potential to diagnose disorders with mild biochemical abnormalities or atypical presentations or even to identify new diseases, changing the epidemiology of many disorders. In this respect, the development of extended collaboration networks for rare diseases is worthy (43).Author ContributionsAC, AR and EM wrote the manuscript. EM, AF, SF and GP reviewed the manuscript. FMR, CM and FDC edited the manuscript and collected data. EM and SF are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for drafting the article and revising it critically for important intellectual content. All authors contributed to the article and approved the submitted version.Conflict of InterestThe authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.Publisher’s NoteAll claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.AcknowledgmentsThe authors are grateful to the European Reference Network dedicated to Rare Endocrine Conditions (Endo–ERN) for useful discussions.Supplementary MaterialThe Supplementary Material for this article can be found online at: American Academy of Pediatrics; ACTH, Adreno–CorticoTropic Hormone; AI, Adrenal Insufficiency; BAPM, British Association for Perinatal Medicine; CAH, Congenital Adrenal Hyperplasia; CAI, Central Adrenal Insufficiency; CDG, Congenital Disorders of Glycosylation; CH, Congenital Hyperinsulinism; CoA, Coenzyme A; CPT, Carnitine Palmitoyl–Transferase; CRH, Corticotropin–Releasing Hormone; DZX, Diazoxide; FAOD, Fatty Acid Oxidation Disorders; FBPase, Fructose 1,6 bisphosphatase; FFA, Free Fatty Acids; G6Pase, Glucose–6–Phosphatase; GALT, Galactose–1–phosphate uridyltransferase; GDH, Glutamate Dehydrogenase Enzyme; GH, Growth Hormone; GHD, Growth Hormone Deficiency; GHRH, Growth Hormone–Releasing Hormone; GKD, Glycerol Kinase Deficiency; GLP–1, Glucagon–Like Peptide–1; GSD, Glycogen Storage Disease; HFI, Hereditary Fructose Intolerance; HY, Hypoglycemia; IGF1, Insulin Growth Factor1; IMD, Inborn Metabolic Disorder; IVA, Isovaleric Acidemia; KB, Ketone Bodies; LGA, Large for Gestational Age; MMA, Methylmalonic Acidemia; MRI, Magnetic Resonance Imaging; NBS, Newborn Screening; NGS, Next Generation Sequencing; OA, Organic Acidemias; OXPHOS, Oxidative Phosphorylation; PA, Propionic Acidemia; PAI, Primary Adrenal Insufficiency; PC, Pyruvate Carboxylase; PEPCK, Phosphoenolpyruvate Carboxykinase; PES, Pediatric Endocrine Society; PET, Positron Emission Tomography; PG, Plasma Glucose; SGA, Small for Gestational Age; UCCS, Uncooked cornstarch; UDP, Uridine Di–Phosphate; UOA, Urine Organic Acids.References 3. 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