Inborn Errors of Metabolism in a Tertiary Pediatric Intensive Care Unit

Patrícia Lipari[1]   Zakhar Shchomak[1]   Leonor Boto[2]   Patrícia Janeiro[3]   Oana Moldovan[4]
Francisco Abecasis[2]   Ana Gaspar[3]   Marisa Vieira[2]

[1] Department of Pediatrics, Santa Maria's Hospital - Lisbon North University Hospital Center, EPE, Pediatric University Clinic, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

[2] Pediatric Intensive Care Unit, Department of Pediatric, Santa Maria's Hospital - Lisbon North University Hospital Center, EPE, Pediatric University Clinic, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

[3] Metabolic Diseases Unit, Department of Pediatric, Santa Maria's Hospital - Lisbon North University Hospital Center, EPE, Pediatric University Clinic, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

[4] Department of Medical Genetics, Santa Maria's Hospital - Lisbon North University Hospital Center, EPE, Pediatric University Clinic, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

Address for correspondence Patrícia Lipari Pinto, MD, Department of Pediatrics, Santa Maria's Hospital - Lisbon North University Hospital Center, EPE, Pediatric University Clinic, Faculty of Medicine, University of Lisbon, 1649-035 Lisboa, Portugal (e-mail: ppinto3@campus.ul.pt).

Abstract

Few studies exist describing resources and care of pediatric patients with inborn errors of metabolism (IEM) admitted to pediatric intensive care unit (PICU). This study aims to characterize the PICU admissions of these patients to provide better diagnostic and therapeutic care in the future. Retrospective analysis of pediatric patients with IEM admitted to the PICU of a tertiary care center at a metabolic referral university hospital from 2009 to 2019 was included. Clinical information and demographic data were collected from PICU clinical records. During this period, 2% ($n = 88$ admissions, from 65 children) out of 4,459 PICU admissions had clinical features of IEM. The median age was 3 years (range: 3 days–21 years) and 33 were male. Median age at diagnosis was 3 months; 23/65 patients with intoxication disorders, 21/65 with disorders of energy metabolism, 17/65 with disorders of complex molecules, and 4/65 with other metabolic diseases (congenital lipodystrophy, Menkes' disease, hyperammonemia without a diagnosis). From a total of 88 admissions, 62 were due to metabolic decompensation (infection—38, neonatal period decompensation—14, external accident—5, prolonged fasting—2, and therapeutic noncompliance—3) and 26 elective admissions after a scheduled surgery/elective procedure. The most frequent clinical presentations were respiratory failure (30/88) and neurological deterioration (26/88). Mechanical ventilation was required in 30 patients and parenteral nutrition in 6 patients. Extracorporeal removal therapy was required in 16 pediatric patients (12 with maple syrup urine disease and 4 with hyperammonemia) with a median duration of 19 hours. The median length of PICU stay was 3.6 days (3 hours–35 days). Eight patients died during the studied period (cerebral edema—2, massive hemorrhage—5, and malignant arrhythmia—1). Acute decompensation was the main cause of admission in PICU in these patients. The complexity of these diseases requires specialized human and technical resources, with an important impact on the recovery and survival of these patients.

Keywords
► inborn errors of metabolism
► pediatric intensive care unit
► referral center

Introduction

Inborn errors of metabolism (IEM) are an uncommon and widely assorted group of inherited diseases in childhood. However, these disorders are being increasingly identified, and are responsible for significant morbidity and mortality in intensive care units.[1–7] IEM can present as acute metabolic emergencies that require a significant amount of pediatric intensive care unit (PICU) resources. Prompt and adequate intensive care supportive management and specific metabolic crisis treatment play an important role in improving outcomes.[2,3]

From a physiological point of view, IEM diseases can be classified in three major groups: the intoxication disorders that results from defects in the intermediary metabolic pathway with an accumulation of toxic compounds proximal to the metabolic block manifested by metabolic crises (e.g., urea cycle disorders [UCDs], organic acidurias [OAs], and aminoacidopathies); disorders of energy metabolism that results from deficient energy production with compromised involvement of the organs with higher energetic demand such as the skeletal muscle, heart, and brain (e.g., fatty acid oxidation disorders, mitochondrial cytopathies), and finally, disorders of complex molecules that are due to the lack of an enzyme that degrades the accumulating metabolite leading to chronic and progressive symptoms with enlargement of solid organs and dysmorphic features (e.g., lysosomal and peroxisomal storage diseases).[4]

Because of the clinical, biochemical, genetic heterogeneity, and the increasing number of new disorders, updated data on the occurrence of IEM is lacking. Characterization of patients with IEM when admitted to PICU, the impact of specific therapeutic interventions together with mortality numbers, is all necessary to find out how to respond to these patients with correct diagnostic and efficient therapeutic modalities.[2,4] An earlier recognition of IEM followed by early and prompt therapeutic intervention[3,5] has the potential to reduce the mortality rate in children,[2] prevent progressive neurologic damage, and reduce morbidity.[6,8–12]

We report a retrospective analysis of pediatric patients with a suspected or confirmed diagnosis of IEM who were admitted over the past 10 years to a PICU at a metabolic disorder referral university hospital. We intended to describe the clinical profile and outcome of pediatric patients with IEM admitted to a tertiary PICU.

Methods

This retrospective descriptive study was conducted from January 1, 2009, to December 31, 2019, in a tertiary care center at a metabolic disorder referral university hospital, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal.

Centro Hospitalar Universitário Lisboa Norte is the largest center for management and treatment of inherited metabolic disorders in Portugal, which has cared for more than 4,700 patients.[10] Centro Hospitalar Universitário Lisboa Norte was named Inherited Metabolic Disorders Portuguese Referral Unit for the southern region and islands in 1984, and since

2016, it is a National Referral Center and member of the European Reference Network for Hereditary Metabolic Disorders (MetabERN). A global assistance, 24/7, is assured by pediatric emergency department (with continuous and priority support of all specialties including neonatology, intensive care, and access to specific techniques such as mechanical ventilation, hemodynamic support, dialytic techniques, and extracorporeal membrane oxygenation) supported by highly specialized and qualified teams. Hospital pharmacy has the technical experience and specific equipment for cofactors, scavengers, enzymatic therapy, and orphan drugs management.[10]

The clinical charts of children and adolescents admitted to the PICU with a diagnosis of IEM were reviewed, regardless of whether the diagnosis was previously known or made during the PICU stay. Diagnosis of IEM was based on biochemical, molecular analysis, and newborn screening for inherited metabolic disorders. In Portugal, newborn screening using tandem mass spectrometry tests 24[a] treatable biochemical disorders.

Charts with incomplete data were excluded. Data were collected retrospectively from the PICU electronic registry. Clinical parameters collected included the age at presentation, whether the disease was known at the time of admission, age at diagnosis, gender, consanguinity, relevant family history, decompensation cause, clinical manifestations during the presentation, treatment, and outcome in terms of mortality or discharge. Decompensation management details were collected, including substrate reduction specific measures, cofactors supplementation, toxic metabolites removal, and supportive measures. The pediatric patients were categorized as intoxication disorders, disorders of energy metabolism, and disorders of complex molecules.

Categorical data were expressed as number and numerical data as a median. Statistical analysis was performed in Microsoft Excel 2013 and in IBM SPSS Statistics 25. We have used chi-square nonparametric test to compare mortality and the need of continuous venovenous hemodiafiltration (CVVHDF) between the different types of IEM, and to compare the length of stay, we have used Kruskal–Wallis' H test.

Results

There was a total of 4,459 admissions in our PICU during the study period; out of which, 88 admissions had IEM, representing 2%. These 88 admissions corresponded to 65 different patients, 33/65 were male, 12/65 were born from consanguineous marriage, and 10/65 had a positive family history. Out of 65, 54 of the patients had been diagnosed before PICU admission, 20 of which were diagnosed by newborn screen. The median age at diagnosis was 3 months (range: 3 days–9 years) and the median age at PICU admission was 3 years (range: 3 days–21 years).

The spectrum of IEM presenting in PICU was as follows (►**Tables 1** and **2**): 23/65 patients with intoxication

---

[a] http://www2.insa.pt/sites/INSA/Portugues/DiagnosticoPrecoce/Paginas/DoencasRastreadas.aspx

Table 1 Demographic characteristics ($n = 65$, 88 admissions)

Gender	No. of admissions	Age at admission	Diagnosis	Diagnosis by NBS (yes/no)	Motif of hospitalization	Length of stay (d)	Outcome
F	2	16 d/17 y	MSUD	No	Neonatal period decompensation/therapeutic noncompliance	3/4	Recover
M	2	6 y	MSUD	Yes	Therapeutic noncompliance/infection	3/3	Recover
M	3	9 d/17 d/6 mo	MSUD	No	Neonatal period decompensation (2x)/infection	1/4/3	Recover/recover/deceased
M	1	13 y	MSUD	Yes	After scheduled surgery	1	Recover
M	1	5 y	MSUD	Yes	Infection	3	Recover
M	1	2 y	MSUD + MCAD	Yes	Prolonged fasting	1	Recover
M	1	20 d	MSUD	Yes	Neonatal period decompensation	8	Sores
M	1	11 d	MSUD	Yes	Prolonged fasting	6	Recover
F	2	6 d/3 y	MSUD	Yes	Neonatal period decompensation/infection	7/2	Recover
F	2	10 mo/2 y	MSUD	No	Infection (2x)	3/16	Recover
F	1	7 d	MSUD	No	Neonatal period decompensation	4	Recover
F	3	7 d/y 1y/17 y	MSUD	No	Neonatal period decompensation/infection (2x)	4/2/1	Recover
F	1	6 d	MSUD	Yes	Neonatal period decompensation	8	Recover
M	1	12 y	3-Hydroxy-3-MA	Yes	After scheduled surgery	1	Recover
M	1	17 y	GA type 1	No	After scheduled surgery	1	Recover
M	1	8 mo	GA type 1	No	Infection	1	Recover
M	1	14 d	OTC	Yes	Neonatal period decompensation	1	Deceased
F	1	18 mo	Propionic aciduria	No	Infection	4	Recover
F	1	4 y	Propionic aciduria	Yes	Infection	10	Recover
F	1	8 y	Propionic aciduria	Yes	Infection	1	Recover
F	1	8 y	Propionic aciduria	Yes	Infection	10	Recover
F	1	3 d	Citrullinemia	No	Neonatal period decompensation	1	Deceased
F	1	6 d	Methylmalonic aciduria	Yes	Neonatal period decompensation	1	Deceased
F	1	3 mo	PDH deficiency	No	Infection	19	Recover
F	1	21 y	PDH deficiency	No	External accident	1	Recover
M	1	3 y	PDH deficiency	No	Infection	1	Recover
F	1	18 d	PDH deficiency	No	Neonatal period decompensation	5	Recover
M	1	11 mo	CPT II deficiency	Yes	Infection	3	Recover
F	1	10 mo	MCAD deficiency	Yes	Infection	1	Recover
F	1	16 mo	MCAD deficiency	Yes	Infection	1	Recover
M	1	14 d	MCAD deficiency	Yes	Neonatal period decompensation	2	Recover
M	1	20 mo	GSD 1A	No	Infection	5	Recover
F	1	11 y	GSD 1A	No	After scheduled surgery	1	Recover

(Continued)

Table 1 (*Continued*)

Gender	No. of admissions	Age at admission	Diagnosis	Diagnosis by NBS (yes/no)	Motif of hospitalization	Length of stay (d)	Outcome
F	1	17 y	GSD 1A	No	Therapeutic noncompliance	1	Recover
M	1	5 y	GSD IV	No	Elective procedure	1	Recover
M	2	13 y/14 y	Mitochondrial cytopathy	No	After scheduled surgery (2x)	1/1	Recover
F	1	16 y	Mitochondrial cytopathy	No	Infection	1	Recover
F	3	10 y/10 y/10 y	Mitochondrial cytopathy	No	Elective procedure /infection (2x)	1/3/13	Recover
M	1	4 y	Mitochondrial cytopathy	No	After scheduled surgery	1	Recover
F	1	3 y	Mitochondrial cytopathy	No	Infection	<1	Recover
F	2	5 y/7 y	Leigh's syndrome	No	External accident/after scheduled surgery	1/1	Recover
M	1	3 y	Fumaric aciduria	No	Infection	3	Recover
F	1	2 y	LCHAD deficiency	Yes	After scheduled surgery	3	Recover
M	2	2 y/2 y	GA type 2	Yes	After scheduled surgery (2x)	1/1	Recover/deceased
F	1	10 mo	Peroxisome disorder	No	Infection	7	Recover
M	1	7 y	Lipofuscinosis	No	Infection	1	Recover
M	2	1 y/2 y	MPS type I	No	After scheduled surgery/external accident	1/1	Recover
M	1	3 y	MPS type I	No	Infection	3	Recover
F	1	3 y	MPS type I	No	Infection	1	Deceased
M	2	11 y/11 y	MPS type II	No	After scheduled surgery (2x)	1/15	Recover/deceased
M	1	14 y	MPS type II	No	After scheduled surgery	1	Recover
M	1	15 y	MPS type II	No	Infection	25	Recover
M	1	16 y	MPS type VI	No	After scheduled surgery	1	Recover
F	1	13 y	MPS type VI	No	External accident	2	Sores
M	3	2 mo/2 mo/3 mo	Gaucher's disease	No	Infection (3x)	1/1/6	Sores
M	3	13 mo/15 mo/16 mo	Gaucher's disease	No	Infection/elective procedure /external accident	6/1/1	Recover
F	1	2 y	Pompe's disease	No	Infection	35	Sores
F	2	7 mo	Pompe's disease	No	After scheduled surgery (2x)	3/6	Recover
F	1	7 y	NCL 2	No	Infection	1	Recover
M	1	7 mo	SLOS	No	After scheduled surgery	1	Recover
M	1	4 mo	Zellweger's syndrome	No	Infection	1	Recover
M	1	11 mo	Hyperammonemia	No	Infection	1	Recover
F	1	4 d	Hyperammonemia	No	Neonatal period decompensation	3	Deceased
F	2	14 y/15 y	Congenital lipodystrophy	No	After scheduled surgery (2x)	4/3	Recover
M	3	2 y	Menkes' disease	No	After scheduled surgery/infection/after scheduled surgery	1/3/1	Recover

Abbreviations: CPT, carnitine palmitoyltransferase; GA, glutaric aciduria; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase; MCAD, medium-chain acyl-coenzyme A dehydrogenase; MPS, mucopolysaccharidosis; MSUD, maple syrup urine disease; NCL, neuronal ceroid lipofuscinosis; OTC, ornithine transcarbamylase; PDH, pyruvate dehydrogenase; SLOS, Smith–Lemli–Opitz's syndrome.

Table 2 Classification of diagnosis ($n = 65$)

		N	Consanguinity (n)	Positive family history (n)	Mortality
Intoxication disorders ($n = 23$)	MSUD	13	6/13	3/13	1/13
	Propionic aciduria	4	0	0	0
	Methylmalonic aciduria	1	0	0	1/1
	Glutaric aciduria type 1	2	0	0	0
	OTC deficiency	1	0	0	1/1
	Citrullinemia	1	0	0	1/1
	3-Hydroxy-3-methylglutaric aciduria	1	0	0	0
Disorders of energy metabolism ($n = 21$)	Mitochondrial cytopathy	5	1/5	1/5	0
	PDH deficiency	4	1/4	0	0
	MCAD deficiency	3	3/3	2/3	0
	Glycogen storage disease 1A	3	1/3	1/3	0
	Glycogen storage disease IV	1	0	0	0
	Glutaric aciduria type 2	1	0	1/1	1/1
	Fumaric aciduria	1	0	0	0
	LCHAD deficiency	1	0	0	0
	CPT II deficiency	1	0	0	0
	Leigh's syndrome	1	0	0	0
Disorders of complex molecules ($n = 17$)	MPS type VI	2	0	0	0
	MPS type II	3	0	1/3	1/3
	MPS type I	3	0	0	1/3
	Gaucher's disease	2	0	0	0
	Pompe's disease	2	0	0	0
	NCL 2	1	1/1	0	0
	Zellweger's syndrome	1	0	0	0
	Lipofuscinosis	1	0	0	0
	Peroxisome disorder	1	0	0	0
	Smith–Lemli–Opitz's syndrome	1	0	0	0
Other diagnosis ($n = 4$)	Menkes' disease	1	0	1/1	0
	Congenital lipodystrophy	1	0	0	0
	Hyperammonemia without a diagnosis	2	0	0	½

Abbreviations: CPT, carnitine palmitoyltransferase; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase; MCAD, medium-chain acyl-coenzyme A dehydrogenase; MPS, mucopolysaccharidosis; MSUD, maple syrup urine disease; NCL, neuronal ceroid lipofuscinosis; OTC, ornithine trans-carbamylase; PDH, pyruvate dehydrogenase.

disorders, 21/65 with disorders of energy metabolism, 17/65 with disorders of complex molecules, and 4 with other metabolic diseases (congenital lipodystrophy, Menkes' disease, hyperammonemia without a diagnosis). There is also a table (►**Table 3**) describing all fatalities.

The intoxication disorders (►**Tables 1** and **4**) accounted for 31 admissions, corresponded to 23 different patients. Almost half (10/23) had been diagnosed in the neonatal period (median age at diagnosis 6 days), 14/23 by newborn screen, and 8 had no diagnosis before admission. Ten out of the 31 admissions were neonates. The median age at admission was 1.5 years (range: 3 days–12 months). The most frequent

clinical presentation on admission was coma (10/31). The main causes of decompensation were infection (13/31) and metabolic stress during the neonatal period (11/31). This was the group with more mortalities, 4/23 (1 due to cerebral edema and 3 due to massive hemorrhage, ►**Table 3**), and with more severe complications: 7/31 with neurological repercussions, 5/31 with neuroimaging abnormalities, and 5/31 with coagulopathy. Concerning supportive and specific treatments: 11/31 patients required respiratory support (invasive ventilation in 9), and 14 needed CVVHDF. This group of intoxication disorders also showed the longest median of PICU stay, which was 2 days (range: 1–16 days).

Table 3 Clinical presentation, management, and cause of mortality of the deceased patients ($n = 8$)

Case no. Year of mortality	Diagnosis	Age	Clinical presentation	Medical Management	Intervention	Cause of mortality
1 (2010)	MSUD (Homozygous mutation c.117delC in *BCKDHA*)	6 mo	Neurological dysfunction with leukoencephalopathy Leucine: 1,100 µmol/L	Thiamine	CVVHDF (heparin) Invasive ventilation	Massive pulmonary bleeding and complications related to the technique
2 (2013)	MMA (Homozygous mutation c.1877_1889del13 in *MMA*)	Neonatal period	Hyperammonemic coma Ammonia: 984 µmol/L	Cyanocobalamin L carnitine, sodium benzoate, carglumic acid	CVVHDF (heparin) Invasive ventilation	Massive intracranial bleeding
3 (2012)	Citrullinemia (Homozygous mutation c.1168G > A in *ASS1*)	Neonatal period	Seizures, hypotonia, neurological dysfunction Ammonia: 1,994 µmol/L	Sodium benzoate, carbaglumic acid	CVVHDF (heparin) Invasive ventilation	Massive bleeding due to disseminated intravascular coagulation and complications related to the technique
4 (2019)	OTC deficiency (Hemizygous mutation c.686T > A in *OTC*)	Neonatal period	Hyperammonemic coma, respiratory distress, jaundice Ammonia: 898 µmol/L	Sodium benzoate, carbaglumic acid	CVVHDF (citrate) Invasive ventilation	Cerebral edema and refractory intracranial hypertension
5 (2012)	Hyperammonemia	Neonatal period	Intracranial hypertension, neurological dysfunction Ammonia: 1,675 µmol/L	Hyperosmolar therapy, sodium benzoate, carbaglumic acid	CVVHDF (heparin) Invasive ventilation	Cerebral edema and refractory intracranial hypertension
6 (2017)	MPS I (Compound heterozygous mutations c.1205G > A / c.1598C > G in *IDUA*)	3 y	Respiratory distress	Antibiotics	Invasive ventilation	Lymphoproliferative syndrome with pulmonary infarction and bilateral subpleural hemorrhages
7 (2017)	MPS II (Hemizygous mutation c.241C > T in *IDS*)	11 y	Respiratory distress after an elective gastrostomy feeding tube insertion and Nissen fundoplication	Antibiotics	Invasive ventilation	Sepsis with severe thrombocytopenia and alveolar hemorrhage
8 (2019)	Glutaric aciduria type II (Compound heterozygous mutations c.463A > G/c.34_607del in *ETFDH*)	2 y	Severe dehydration, acute kidney failure, and metabolic acidosis after elective surgery	L carnitine, riboflavin, antibiotics, insulin, sodium bicarbonate, inotropic drugs		Malignant arrhythmia and cardiac arrest

Abbreviations: CVVHDF, continuous venovenous hemodiafiltration; IV, invasive ventilator; MMA, methylmalonic aciduria; MPS, mucopolysaccharidosis; MSUD, maple syrup urine disease; OTC, ornithine transcarbamylase.

Table 4 Characterization by type of disease

Classification of diagnosis	Diagnosis	N	Infection	Decompensation in neonatal period	Therapeutic noncompliance	Prolonged fasting	Accident	Respiratory failure	Coma	Septic shock	Seizure	Lethargy + metabolic acidosis	Blood dyscrasia	Cardiac abnormality[a]	Postcardiac arrest hypoxic-ischemic encephalopathy	Intracranial hypertension	Cerebral edema	Intraparenchymal hemorrhage	Deceased (n)
Intoxication disorders	MSUD	1	8	8	2	2		3	8		3	3	3			3	4		1
	PA	3	4					1		1		1							
	MMA	4		1					1										1
	GA-1	1	1									1	1	1					
	OTC deficiency	2	1	1					1		1	1	1					1	1
	Citrullinemia	1		1									1						1
	3-H3MGA	1																	
Disorders of energy metabolism	Mitochondrial cytopathy	5	3	1			1	1	2	1	1	1	1	1					
	PDH deficiency	4	2				1	2	1		1	1		1					
	MCAD deficiency	3	3		1			1				2							
	GSD 1A	1	1																1
	GSD IV	1	1																
	GA-2	1	1									1							
	Fumaric aciduria	1	1				1	1	1				1						
	LCHAD deficiency CPT II deficiency	1																	
	Leigh's syndrome																		
Disorders of complex molecules	MPS type VI	2					1	1	1	1	1		1	1	1		1		1
	MPS type II	3	1					1		1	1		1	1					1
	MPS type I	3	2				1				1			1					
	Gaucher's disease	2	4				1	6			1			3					
	Pompe's disease	2	1								1			1					
	NCL 2 disease	1	1								1								
	Zellweger's syndrome	1	1					1											
	Lipofuscinosis	1	1																
	Peroxisome disorder	1	1																
	SLOS	1						1											

Abbreviations: 3-H3MGA, 3-hydroxy-3-methylglutaric aciduria; CPT, carnitine palmitoyltransferase; GA, glutaric aciduria; GSD, glycogen storage disease; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase; MCAD, medium-chain acyl-coenzyme A dehydrogenase; MMA, methylmalonic aciduria; MPS, mucopolysaccharidosis; MSUD, maple syrup urine disease; NCL, neuronal ceroid lipofuscinosis; OTC, ornithine transcarbamylase; PA, propionic aciduria; PDH, pyruvate dehydrogenase; SLOS, Smith–Lemli–Opitz's syndrome.

[a]Hypertrophic cardiomyopathy, pericardial effusion, perimembranous ventricular septal defect, aortic and mitral regurgitation, left ventricular dysfunction, tachydysrhythmia with heart failure.

The second most common IEM was the group of disorders of energy metabolism (►**Tables 1** and **4**).[5] In our study, 2 of the 21 patients were neonates and the median age at diagnosis was 12 months (range: 6 days–3.5 years); 6/21 were diagnosed by newborn screen, 2/21 had no diagnosis before admission. The median age at admission was 3 years (range: 14 days–21 years). The most frequent clinical presentations were lethargy with severe dehydration (5/21), respiratory failure (4/21), and coma (4/21), whereas the main cause of decompensation was infection (11/21). Eight were elective admissions after a scheduled surgery (gastrostomy feeding tube insertion [two], central venous catheter insertion [one], ventriculoperitoneal shunt revision [one], orthopaedic surgery [one], cholecystectomy [one], orchidopexy [one], and Nissen fundoplication [one]). Regarding associated complications: two had seizures, two had coagulopathy, and three had cardiac abnormalities. Five patients needed mechanical ventilation and one needed CVVHDF (mitochondrial cytopathy with hyperammonemia). All of them received highly concentrated dextrose intravenous infusion. One mortality was recorded after elective gastrostomy feeding tube insertion due to malignant arrhythmia and cardiac arrest in a glutaric aciduria type 2 patient (►**Table 3**). The median length of PICU stay was 1 day (range: 1–19 days).

In the group of disorders of complex molecules (►**Tables 1** and **4**), consisted of 17 patients, there were no neonates, 2/17 had no diagnosis before admission, and the median age at diagnosis was 21 months (range: 1 month–2.5 years). The median age at admission was 3 years (range: 3.5 months–16 years). The most frequent clinical presentation on admission was respiratory failure (12/17), 11 due to infection. Eight were elective admissions after a scheduled surgery (gastrostomy feeding tube insertion [three], central venous catheter insertion [four], and ventriculoperitoneal shunt placement [one]). Concerning repercussions in different organs, six had seizures, two showed neuroimaging abnormalities, and seven had cardiac abnormalities. Regarding organ support treatment, 11 pediatric patients needed mechanical ventilation. Two patients died (►**Table 2**), both with mucopolysaccharidosis types I and II, respectively, one concomitantly had a lymphoproliferative syndrome after bone marrow transplant and died from massive pulmonary hemorrhage. The second mortality case was related to sepsis with severe thrombocytopenia and alveolar hemorrhage after an elective gastrostomy feeding tube insertion and Nissen fundoplication. The median length of PICU stay was 1 day (range: 1–35 days).

Comparing statistically the three groups, mortality was higher in the admitted patients with intoxication disorders (four deceased patients with intoxication disorders vs. one with disorders of energy metabolism vs. two with disorders of complex molecules), $p < 0.0001$. Patients with intoxication disorders needed CVVHDF more than the ones with disorders of energy metabolism and disorders of complex molecules (12 vs. 0 vs. 0), $p < 0.0001$. There was not statistically significant difference in hospitalization length of stay between the different types of IEM (mean hospitalization length of stay: intoxication disorders 4.6 days vs. disorders of energy metabolism 3.4 days vs. complex molecules 4 days, $p = 0.085$).

Considering nutrition therapy, specific nutritional care was performed and 80/88 of the patients received only enteral nutrition. Parenteral nutrition (PN) was used in 8/88 of the pediatric patients.

Regarding CVVHDF, 16 patients (12 with maple syrup urine disease, 1 with hyperammonemia without defined etiology, 1 with methylmalonic aciduria and hyperammonemia, 1 with citrullinemia, and 1 with mitochondrial cytopathy and hyperammonemia) underwent 18 sessions, 11 in the newborn period. The median duration of CVVHDF was 19 hours (5–72 hours). Anticoagulation was performed with unfractionated heparin (11) and citrate (7), and bleeding complications were present in three sessions with heparin anticoagulation. The median leucine and ammonia levels were, respectively, 1,675 µmol/L (900–4,000 µmol/L) and 1,834.4 µmol/L (898–4,758 µmol/L) before and 400 µmol/L (30–505 µmol/L) and 350 µmol/L (29.9–1,000 µmol/L) at the end of treatment. In 12 sessions, there was a good response to treatment with neurological improvement. Five patients died (►**Table 2**), three due to bleeding complications related to the technique and the underlying disease (citrullinemia and methylmalonic aciduria); two due to disease progression with cerebral edema and refractory intracranial hypertension.

Discussion

In this study, we report that, in a referral hospital in Portugal, the incidence of IEM in the population of patients admitted to our PICU was 2%, a figure quite similar to that previously reported by Jouvet et al[13] from Montreal, Canada (referral center for metabolic disorders) and higher than the figure reported by Sivaraman et al[1] from South India (accredited level III referral PICU) and by Ruttimann et al[14] from 16 different PICUs in the United States, where IEM constituted in both < 1% of admissions. We also report that the most common type of IEM is intoxication disorders, and overall mortality was 12% (8/65). As in our results, in the studies by Sivaraman et al[1] and Kamate et al,[2] intoxication disorders were also the most common group of IEM present as a metabolic crisis. Additionally, the median length of PICU stay in our study was similar to that described in the literature,[1,2,13,15] but the mortality in our study was lower (20/70[13]–7/11[15] vs. 8/65). Lower mortality is probably due to the higher percentage of diagnosis by newborn screen in our study, when compared with other geographic locations where newborn screen does not exist or includes fewer diseases.[1,2,15] In our study, an important percentage of pediatric patients was diagnosed with newborn screen. Only one with severe hyperammonemia died without a conclusive diagnosis. When a child with undiagnosed IEM dies, the postmortem findings are crucial to the diagnosis of an IEM.[16] So, it is important to consider IEM in advance, to collect DNA and skin and/or hepatic biopsies for accurate diagnoses in the future genetic counseling for parents. It is consistent in the literature that aggressive and immediate management is essential in these disorders.[1,2]

Related to our specific results, about the age at PICU admission, exceptionally, there was included one single patient with more than 17 years and 364 days (21 years old) due to his long follow-up in the pediatric department of this hospital with very poor weight and height (<third percentile). Regarding the intoxication disorder group, the usual clinical presentation is a metabolic crisis and that could be one of the reasons for being the most common disorder requiring PICU assistance.[1,2] In our study, newborn screen played a major role in the early identification of these patients. The neonatal period might be considered the front line of the clinical manifestations because, before delivery, the neonate has the advantage of maternal support via the placenta to clear certain metabolites along with reduced change through many pathways.[17] Central nervous system was the main and severely affected organ, with a high incidence of coma in this group. Apart from being the group with the most severe clinical spectrum and with the highest mortality, it was the group with the highest need for supportive and specific treatments. We can conclude that for those disorders associated with acute metabolic toxicity, such as OAs and UCDs, extracorporeal procedures to remove toxins are necessary when less invasive methods prove insufficient.[4,18] In our study, 16 patients needed CVVHDF (14 with intoxication disorders), for reduction of neurotoxic metabolites, as quickly as possible (ammonia and leucine) in metabolic decompensations, to prevent irreversible brain damage. Indeed, we noted a rapid decrease of neurotoxic metabolites with clinical improvement (12/18 sessions), decisive for the suspension of the technique. Like any extracorporeal technique, CVVHDF includes a major risk of bleeding, which was the cause of mortality in three of the patients. It is important to highlight that, after the introduction of citrate as preferred anticoagulation, there was a reduction in bleeding complications. Citrate seems safer because it provides only regional anticoagulation of the circuit, while heparin causes systemic anticoagulation, with increased risk of bleeding. On the contrary, considering the number of filters used, jugular vein access allowed longer filter life and less technical interruptions. Additionally, with the help of a bedside ultrasound device, the safety and ease of insertion of the internal jugular line has increased, making the technique safer and more effective. In our hospital, CVVHDF is available only in PICU, so neonatal patients who need this technique are transferred from the neonatal intensive care unit to our PICU. Analyzing our results, and according to the literature, it is obvious that these patients suffered from a more severe spectrum within the IEM, with longer PICU stay.

In the group of disorders of energy metabolism, metabolic decompensation may be provoked by poor caloric intake, emesis, prolonged fasting, and intercurrent illness/infection.[9] However, frequent critical metabolic decompensations and neonatal presentations were not as frequent as in the first group. Additionally, the group of intoxication disorders was diagnosed earlier than the disorders of energy metabolism, with a median age at diagnosis of 6 days versus 12 months. The median length of PICU stay was shorter than in the first group.

These patients needed less aggressive organ support. Besides the involvement of central nervous system, heart is also a major target organ in these diseases. In fact, it should be noted that, although this is a heterogeneous group of metabolic disorders, any patient with a disorder of energy metabolism is at risk of sudden death if not treated promptly.

In the third group—disorders of complex molecules— clinical manifestations are cumulative, independent of external events, and are not related to diet.[16] Due to the cumulative nature, repercussions in different and multiple organs are expected. Less aggressive organ support treatment was used in the management of these patients. However, the mortality of two patients in this group shows the need for specific care and close clinical monitoring, despite rare decompensations.

Regarding nutritional support, in our study, almost all patients underwent specific nutritional care. Critically ill patients have a high risk of malnutrition because of stress-induced changes in intermediary metabolism. These facts result in an amplified basal metabolic percentage and severe protein catabolism.[19] Nutrition care studies have proposed that timely nutritional intervention can prevent or minimize the complications of malnutrition.[19,20] Although the consensus is that nutrition therapy is essential in the care of critically ill patients, especially during the acute phase of stress, its implementation remains the major challenge in IEM due to dietary specificities that vary depending on the disease. It is important to highlight the challenges that exist in adapting PN, considering the nutritional requirement of each of these diseases.

While it is true that our hospital is a referral center for metabolic disorders, which may have contributed to an increase in the number of patients with inherited metabolic disorders admitted to our PICU, there is almost no information available on the exact incidence of inherited metabolic disorders in national PICUs. A large national multicentric approach would be necessary to obtain precise knowledge.

Conclusion

Clinical presentation of acute decompensations of IEM is generally multisystemic and unspecific. It is crucial for IEM, to be identified and treated in the early phase of decompensation, especially in the intoxication disorders. The disorders of energy metabolism are a heterogeneous group of metabolic disorders, in which it is important to pay attention to complications such as neurological deterioration in situations such as illness and perioperative period. In the group of disorders of complex molecules, metabolic decompensations are rare, but we must consider the associated comorbidities in "stress periods," like after surgery. We believe that the concentration of patients in a major center, where highly specialized human and technical resources are available 24/7 for their treatment, contributed to the high survival rate. But we also believe that multidisciplinary approach and retrospective review of bad outcome cases lead to innovation in therapies and techniques, which meant major achievements in the management of these patients.

What Is New in This Study?

- We present the largest Portuguese series of pediatric patients with IEM admitted to a tertiary PICU.
- Newborn screen allows the possibility of prompt treatment for many diseases that otherwise are characterized by severe morbidity and high risk of fatality.
- Good intensive care supportive management and specific metabolic crisis treatment play an important role in improving the outcomes of these patients.
- The concentration of highly specialized human and technical resources in the treatment of patients with IEM contributed to a high survival rate.

Conflict of Interest
None declared.

References

1 Sivaraman RP, Balakrishnan U, Chidhambaram S, Tarikare S, Sankaranarayanan S. Profile and outcome of children with inborn errors of metabolism in a tertiary pediatric intensive care unit in South India. Indian Journal of Child Health 2019;6(03):104–109

2 Kamate M, Chetal V, Kulgod V, Patil V, Christopher R. Profile of inborn errors of metabolism in a tertiary care centre PICU. Indian J Pediatr 2010;77(01):57–60

3 Dionisi-Vici C, Rizzo C, Burlina AB, et al. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr 2002;140(03):321–327

4 Agana M, Frueh J, Kamboj M, Patel DR, Kanungo S. Common metabolic disorder (inborn errors of metabolism) concerns in primary care practice. Ann Transl Med 2018;6(24):469–469

5 Champion MP. An approach to the diagnosis of inherited metabolic disease. Arch Dis Child Educ Pract Ed 2010;95(02):40–46

6 Dias Costa F, Moinho R, Ferreira S, et al. [Acute liver failure related to inherited metabolic diseases in young children]. An Pediatr (Barc) 2018;88(02):69–74

7 Chapman Kimberly A. Practical management of organic acidemias. Transl Sci Rare Dis 2019;4(3-4):121–131

8 Frazier DM, Allgeier C, Homer C, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab 2014;112(03):210–217

9 Aldubayan SH, Rodan LH, Berry GT, Levy HL. Acute illness protocol for fatty acid oxidation and carnitine disorders. Pediatr Emerg Care 2017;33(04):296–301

10 European Reference Network for Hereditary Metabolic Disorders. Available at: https://metab.ern-net.eu/centro-hospitalar-lisboa-norte-e-p-e/. Accessed April 2020

11 Narkewicz MR, Olio DD, Karpen SJ, et al. Pattern of diagnostic evaluation for the causes of pediatric acute liver failure: an opportunity for quality improvement. J Pediatr 2009;155(06):801–806

12 Saudubray JM, Baumgartner M, Walter J. Inborn Metabolic Diseases: Diagnosis and Treatment. Germany: Springer; 2016

13 Jouvet P, Touati G, Lesage F, et al. Impact of inborn errors of metabolism on admission and mortality in a pediatric intensive care unit. Eur J Pediatr 2007;166(05):461–465

14 Ruttimann UE, Patel KM, Pollack MM. Relevance of diagnostic diversity and patient volumes for quality and length of stay in pediatric intensive care units. Pediatr Crit Care Med 2000;1(02):133–139

15 Isabel I-G, Cynthia F-L, Diana R-G, et al. Inborn errors of intermediary metabolism in critically ill Mexican newborns. J Inborn Errors Metab Screen 2014;2:2

16 Martins AM. Inborn errors of metabolism: a clinical overview. Sao Paulo Med J 1999;117(06):251–265

17 Rennie JM. Rennie & Roberton's Textbook of Neonatology. Churchill Livingstone, UK, 2012

18 Celik M, Akdeniz O, Ozgun N, Ipek MS, Ozbek MN. Short-term results of continuous venovenous haemodiafiltration versus peritoneal dialysis in 40 neonates with inborn errors of metabolism. Eur J Pediatr 2019;178(06):829–836

19 Zamberlan P, Delgado AF, Leone C, Feferbaum R, Okay TS. Nutrition therapy in a pediatric intensive care unit: indications, monitoring, and complications. J Parenter Enteral Nutr 2011;35(04):523–529

20 Stratton RJ, Elia M. Who benefits from nutritional support: what is the evidence? Eur J Gastroenterol Hepatol 2007;19(05):353–358