Lorenzo D'Antiga
Editor

Pediatric Hepatology and Liver Transplantation

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Lorenzo D'Antiga
Paediatric Hepatology, Gastroenterology and Transplantation
Hospital Papa Giovanni XXIII
Bergamo
Italy

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To Martina, the sun of my life,
and to our children Francesco, Mattia, Anna and Maddalena
who make our days full of joy, projects and hope for the future

To Mum and Dad†
so trustful and proud, since the very beginning

To my brothers
Luca, who, as a young employee, made my studies at the Medical School affordable,
Alvise† and Angelo, always supportive during my career,
and Maria Giovanna†, who passed away at 4 months of age from an unknown liver disease

To my mentors
Lucia, Giorgina, Anil
and many others I am still learning from

To all doctors who take tender care of the sick ones
and consider it a privilege

Foreword

Paediatric hepatology has gone from obscurity to a status of specialty in its own merit over the span of seven decades. Though jaundice in babies and children had been occasionally reported in the past, liver disorders in childhood were considered extremely rare and almost always lethal. The real burden of paediatric liver disease was first recognised in the late 1950s and became a focus of attention only in the 1960s and 1970s.

Visionary men, like Morio Kasai, Daniel Alagille and Alex Mowat, put paediatric hepatology firmly on the map of paediatrics by the 1970s, recognising the importance of concentrating expertise in specialised centres, in order to elucidate physiopathological mechanisms, with consequent improved management and outcome for children with liver disease. This has resulted over a relatively short period of time in a vortex of new information, including the discovery of several causes of juvenile liver disease, leading not only to successful specific managements, but also to a better understanding of the liver physiology, based on the discovery of the deleterious effect of genetic defects affecting synthesis, transport and function of proteins manufactured by the liver.

In parallel, grew the awareness that liver disorders of adulthood can affect children as well, but that in children they present important differences, which need to be taken into account for successful treatment, examples of these conditions being autoimmune liver disease, viral hepatitides and acute liver failure.

Despite improved knowledge, the prognosis of paediatric liver disease remained severe for decades, with mortality rates between 50 and 60% within a few years from diagnosis for many conditions, until the advent of liver transplantation as a standard mode of treatment for children with end-stage liver disease in the early 1990s, which rapidly led to long-term survival rates of over 95%.

Current tasks are to clarify the physiopathological mechanisms of those juvenile liver diseases that remain without a recognised cause, to perfect medical management to avoid transplantation—including isolated hepatocyte or gene therapy—and to overcome the problems of rejection and long-term complications for those patients who need a liver transplant.

D'Antiga's *Pediatric Hepatology and Liver Transplantation* stems from the Editor's ambitious aim to provide a comprehensive, practical and up-to-date description of paediatric liver disorders and their management, spanning from historical notes, liver anatomy and physiology, to the discovery of new conditions and their management, to liver transplantation, to the peculiarities in children and adolescents of liver disorders that affect also adults.

This textbook will be highly valuable not only to gastroenterologists, paediatric hepatologists and transplant surgeons, but also to medical students, residents and adult physicians looking after patients with liver disease, as improved knowledge and management of hitherto lethal paediatric liver conditions has led to survival into adulthood and transition to adult services.

Lorenzo D'Antiga's aim was ambitious: the result excellent.

Giorgina Mieli-Vergani
London, UK

Preface

The liver may be considered "a timid, clever and resilient organ", because of its circulation enclosed between two capillary beds and the hidden excretion in the middle of the digestive tract, its pivotal role in human metabolism and its resistance to suffering if not to the exhaustion of the reserves. These intrinsic features and the relative rarity of hepatic disorders in infancy make liver disease in children a narrow and rather unknown field.

The liver goes through a perinatal immaturity phase during which it is prone to insults of various kinds but then matures and acquires the silent and stable control of most of the functions of body homeostasis and intermediate metabolism. The reasons why the functions and the diseases of the liver are still little known, and the expertise is prerogative of few specialized centres, probably reside in the lack of non-invasive tests allowing to understand the punctual state of health of this organ.

The purpose of this book is to try shedding some light on this field, spreading the experience made in the major international centres of paediatric hepatology and transplantation. Indeed the strength of this work stands on the contribution of the greatest experts working in the field all over the world, who kindly agreed to grant their expertise preparing a chapter of this book. It has been a great pleasure and honour having a prompt acceptance from persons I consider the top experts in various hepatology subspecialties and from whom I keep learning. Once again I experienced that friendship and mutual respect is a key component of any team project.

I am also particularly grateful for having the chance to deepen my experience in the field of education I have always been very fond of. In that respect the attempt of this work is to give a comprehensive (although certainly incomplete) scenario of what a physician involved in the care of paediatric liver disease might face, opening the lens of the camera to a wide angle, and helping the reader place information within the broader topic of child health and global health. For this reason the first chapter, taking advantage of the World Health Organisation data, focuses on the relevance of liver disease worldwide, both in adults and in children. Part III is entirely devoted to paediatric liver disease in continents having different epidemiology and standards of care, appearing less frequently in the current literature but certainly taking care of the largest proportion of children with liver disease in the world. Another novelty of this book is the balanced examination of both paediatric liver disease and liver transplantation, discussed in the first two parts, since these topics are inherently related, given that most chronic liver disorders eventually require organ replacement. Several chapters are dedicated to emerging issues in the field, such as long-term graft dysfunction, quality of life and transition to adult care, but also to newly developed strategies to manage our patients, such as next-generation sequencing testing, cell and gene therapy.

My wish is to provide a helpful tool for a range of practitioners looking after children with liver disease, from residents making their first approach to paediatric liver disease through to specialists working in transplantation centres. I really hope this book can contribute to the care of children with liver disease.

Bergamo, Italy — Lorenzo D'Antiga

The Editor would be pleased to receive from the readers any suggestion aimed to improve the next edition of this book. Please send your precious comments to the following mailing address: dantiga.book@gmail.com.

Contents

Editor and Contributors

About the Editor

Lorenzo D'Antiga is a Paediatric Hepatologist and Gastroenterologist working in Italy. His current position is Director of Child Health and of the Paediatric Liver, GI and Transplantation Unit of the Papa Giovanni XXIII Hospital of Bergamo. He trained as a Paediatrician at the University of Padua and as a Paediatric Hepatologist in the United Kingdom at King's College Hospital London. He has worked as Consultant Gastroenterologist and Hepatologist as well as Paediatric Intensivist, specializing in organ failure and transplantation. ESPGHAN member for 15 years, he contributed to the field of paediatric hepatology with publications, scientific presentations and invited lectures. He has been member of the Council of the ESPGHAN as Education Secretary (till 2014) and Member of the Education Committee of the UEG (till 2014). He serves as Senior Associate Editor for *Journal of Pediatric Gastroenterology and Nutrition* and as Associate Editor of *Liver Transplantation*.

Contributors

R. Agazzi Interventional Radiology, Department of Diagnostic Radiology, Hospital Papa Giovanni XIII, Bergamo, Italy

Henrik Arnell Department of Paediatrics, Karolinska University Hospital and CLINTEC, Karolinska Institutet, Stockholm, Sweden

Alastair Baker Paediatric Liver Centre, King's College Hospital, London, UK

Ulrich Baumann Liver Unit and Small Bowel Transplant, Birmingham Women's and Children's Hospital, Birmingham, UK

Hannover Medical School, Hannover, Germany

Pietro Betalli Department of Paediatric Surgery, Papa Giovanni XXIII Hospital, Bergamo, Italy

Rishi Bolia Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Alberto Burlina Division of Inherited Metabolic Diseases, Reference Centre Expanded Newborn Screening, Department of Woman's and Child's Health, University of Padova, Padova, Italy

Stefania Camagni Department of Organ Failure and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Valeria Casotti Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Michele Colledan Department of Organ Failure and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Laura Cristoferi Division of Gastroenterology, Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy

International Center for Digestive Health, University of Milan-Bicocca, Milan, Italy

Daniel D'Agostino School of Medicine, USAL University, Buenos Aires, Argentina

Division of Pediatric GI and Hepatology, Pediatric Liver and Intestinal Transplantation Program, Hospital Italiano, Buenos Aires, Argentina

Department of Pediatric, Hospital Italiano, Buenos Aires, Argentina

Lorenzo D'Antiga Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Mark Davenport Department of Paediatric Surgery, King's College Hospital, London, UK

Dominique Debray Pediatric Liver Unit, Reference Center for Biliary Atresia and Cholestatic Genetic Diseases, Hôpital Necker-Enfants Malades, Paris, France

Andrea Dellostrologo Hepatology, Gastroenterology and Nutrition Unit, "Bambino Gesù" Children's Hospital, Rome, Italy

Anil Dhawan Paediatric Liver GI and Nutrition Center and Mowat Labs, King's College Hospital, London, UK

Fabiola Di Dato Department of Translational Medical Science, Section of Paediatrics, University of Naples Federico II, Naples, Italy

Angelo Di Giorgio Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Mortada H. F. El-Shabrawi Faculty of Medicine, Cairo University, Cairo, Egypt

Luca Fabris International Center for Digestive Health, University of Milan-Bicocca, Milan, Italy

Digestive Disease Section, Yale University, New Haven, CT, USA

Department of Molecular Medicine, University of Padua, Padua, Italy

Stefano Fagiuoli Gastroenterology, Hepatology and Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy

Sandy Feng Division of Transplantation, Department of Surgery, University of California San Francisco, San Francisco, CA, USA

Björn Fischler Department of Paediatrics, Karolinska University Hospital and CLINTEC, Karolinska Institutet, Stockholm, Sweden

Laura Fontanella Department of Organ Failure and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Akinari Fukuda Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan

Maria Guido Department of Medicine—DIMED, Anatomic Pathology Unit, University of Padova, Padova, Italy

Gustavo Boldrini Division of Pediatric GI and Hepatology, Pediatric Liver and Intestinal Transplantation Program, Hospital Italiano, Buenos Aires, Argentina

Department of Pediatrics, Hospital Italiano, Buenos Aires, Argentina

Nedim Hadzic Kings College Hospital, London, UK

Steffen Hartleif University Children's Hospital Tübingen, Tübingen, Germany

A. Holvast Pediatric Hepatology, Beatrix Children's Hospital-UMCG, University of Groningen, Groningen, The Netherlands

Giuseppe Indolfi Meyer Children's University Hospital, Firenze, Italy

Raffaele Iorio Department of Translational Medical Science, Section of Paediatrics, University of Naples Federico II, Naples, Italy

Wojciech Janczyk The Children's Memorial Health Institute, Warsaw, Poland

Naglaa M. Kamal Faculty of Medicine, Cairo University, Cairo, Egypt

Mureo Kasahara Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan

Chayarani Kelgeri Liver Unit and Small Bowel Transplant, Birmingham Women's and Children's Hospital, Birmingham, UK

Deirdre Kelly The Liver Unit, Birmingham Womens and Childrens Hospital and University of Birmingham, Birmingham, UK

Florence Lacaille Pediatric Gastroenterology-Hepatology-Nutrition Unit, Hôpital Universitaire Necker-Enfants Malades, University Paris Cité Sorbonne Paris Descartes Medical School, Paris, France

Lisa Licini Department of Pathology, Papa Giovanni XXIII Hospital, Bergamo, Italy

Simon C. Ling Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, ON, Canada

Department of Paediatrics, University of Toronto, Toronto, ON, Canada

Ines Loverdos Unidad de Gastroenterología, Hepatología y Nutrición pediátrica, Corporació Sanitària Universitària Parc Taulí. Sabadell, Barcelona, Spain

Maria Grazia Lucà Gastroenterology, Hepatology and Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy

Kathrin Ludwig Department of Medicine—DIMED, Unit of Pathology and Cytopathology, University Hospital of Padova, Padova, Italy

George V. Mazariegos UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

Patrick McKiernan Division of Pediatric Gastroenterology Hepatology and Nutrition, Children's Hospital of Pittsburgh of UPMC and University of Pittsburgh, Pittsburgh, PA, USA

V. A. McLin Pediatric Gastroenterology, Hepatology and Nutrition Unit, Swiss Pediatric Liver Center, University Hospitals of Geneva, Geneva, Switzerland

Giorgina Mieli-Vergani MowatLabs, Paediatric Liver, GI and Nutrition Centre, King's College Hospital, London, UK

Federico Mingozzi Spark Therapeutic Inc, Philadelphia, PA, USA

Inserm, Évry, France

Genethon, Évry, France

Ellen Mitchell Division of Pediatric Gastroenterology Hepatology and Nutrition, Children's Hospital of Pittsburgh of UPMC and University of Pittsburgh, Pittsburgh, PA, USA

Giovanni Morana Division of Radiology, Treviso Regional Hospital, Treviso, Italy

Antonella Mosca Hepatology, Gastroenterology and Nutrition Unit, "Bambino Gesù" Children's Hospital, Rome, Italy

Andrès F. Muro Mouse Molecular Genetics Laboratory, International Center for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy

Vicky Lee Ng The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Emanuele Nicastro Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Valerio Nobili Hepatology, Gastroenterology and Nutrition Unit, "Bambino Gesù" Children's Hospital, Rome, Italy

Department of Pediatrics, Facoltà di Medicina e Psicologia, Sapienza University of Rome, Rome, Italy

Massimiliano Paganelli Pediatric Gastroenterology, Hepatology and Nutrition, Sainte-Justine University Hospital Center, Montreal, QC, Canada

Hepatology & Cell Therapy Laboratory, Sainte-Justine Research Center, Montreal, QC, Canada

Department of Pediatrics, Université de Montréal, Montreal, QC, Canada

Isabella Pellicioli Pediatric Intensive Care Unit, Hospital Papa Giovanni XXIII, Bergamo, Italy

Domenico Pinelli Department of Organ Failure and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

Giusy Ranucci Department of Translational Medical Science, Section of Paediatrics, University of Naples Federico II, Naples, Italy

Nathalie Marie Rock Pediatric Gastroenterology, Hepatology and Nutrition Unit, Swiss Pediatric Liver Center, University Hospitals of Geneva, Geneva, Switzerland

Diana Sacchi Department of Medicine—DIMED, Anatomic Pathology Unit, University of Padova, Padova, Italy

Seisuke Sakamoto Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan

Marianne Samyn Paediatric Liver, GI and Nutrition Centre, King's College Hospital NHS Foundation Trust, London, UK

Maria Camila Sanchez Division of Pediatric GI and Hepatology, Pediatric Liver and Intestinal Transplantation Program, Hospital Italiano, Buenos Aires, Argentina

Department of Pediatrics, Hospital Italiano, Buenos Aires, Argentina

Alberto Sanchez-Fueyo Institute of Liver Studies, King's College, London, London, UK

Mariateresa Sanseviero Hepatology, Gastroenterology and Nutrition Unit, "Bambino Gesù" Children's Hospital, Rome, Italy

Samantha Sarcognato Department of Medicine—DIMED, Anatomic Pathology Unit, University of Padova, Padova, Italy

Melanie Schranz Gastroenterology, Hepatology and Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy

Naresh Shanmugam Institute of Advanced Paediatrics, Dr. Rela Institute and Medical Centre, Chennai, India

Khalid Sharif Liver Unit and Small Bowel Transplant, Birmingham Women's and Children's Hospital, Birmingham, UK

S. Sironi Department of Diagnostic Radiology, Hospital Papa Giovanni XIII, Bergamo, Italy

Piotr Socha The Children's Memorial Health Institute, Warsaw, Poland

Aurelio Sonzogni Department of Pathology, Papa Giovanni XXIII Hospital, Bergamo, Italy

James E. Squires UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

Anshu Srivastava Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Mario Strazzabosco Division of Gastroenterology, Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy

International Center for Digestive Health, University of Milan-Bicocca, Milan, Italy

Digestive Disease Section, Yale University, New Haven, CT, USA

Ekkehard Sturm University Children's Hospital Tübingen, Tübingen, Germany

P. Tessitore Department of Diagnostic Radiology, Hospital Papa Giovanni XIII, Bergamo, Italy

Roshni Vara Paediatric Inherited Metabolic Disease, Evelina Children's Hospital, London, UK

Silvio Veraldi Hepatology, Gastroenterology and Nutrition Unit, "Bambino Gesù" Children's Hospital, Rome, Italy

Diego Vergani MowatLabs, Institute of Liver Studies, King's College Hospital, London, UK

H. J. Verkade Pediatric Hepatology, Beatrix Children's Hospital-UMCG, University of Groningen, Groningen, The Netherlands

Jessica Woolfson The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Part I

Paediatric Hepatology

"Cure the sick, raise the dead, cleanse the lepers, cast out devils.
You received without charge; give without charge"

(Matthew 10:8)

Liver Disease in Paediatric Medicine: An Overview

1

Valeria Casotti and Lorenzo D'Antiga

Key Points

- Aepidemiological studies of global mortality reveal that liver disease is the 11th cause of death in the world population, but only a minority relates to the paediatric age.
- Probably in children liver disease is the cause of global mortality in less than 1% of cases, and it is mainly due to viral hepatitis.
- In Western countries, liver disease is the 20th cause of death during childhood.
- Liver disease in children presents most often in the first 2 years of age and is mainly caused by biliary atresia and genetic cholestatic disorders.
- Chronic liver disease in children eventually requires liver transplantation in a large proportion of cases.

Research Needed in the Field

- To improve our knowledge on the aepidemiology of liver disease in different continents and at different latitudes, to better focus on specific needs of different populations
- To improve the prevention of HAV infection in developing countries
- To develop strategies able to achieve the global eradication of HCV infection
- To develop effective treatments to control HBV infection worldwide, including children vertically infected by the virus
- To improve our knowledge on pathophysiology of biliary atresia, the most common indication to liver transplantation, still orphan of an effective cure

V. Casotti (✉) · L. D'Antiga
Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy
e-mail: vcasotti@asst-pg23.it; ldantiga@asst-pg23.it

1.1 How It All Began: The Study of the Liver in the Third Millennium BC

1.1.1 The Liver of Mari in Mesopotamia

As far as we can go back to the history of human culture and tradition, the first information we gathered on examinations of the liver dates back to the third millennium BC. In the ancient Near East (the current Middle East), around the year 3000 BC, the practice of divination was widely diffused. In particular the Babylonians believed that the gods would manifest their answer in the healthy liver of a sacrificial animal. Such belief was connected with the production of liver clay models carrying inscriptions describing the meaning of the features the liver had, as shown in those excavated in 1935 in the Royal Palace of Mari, a city of Mesopotamia (Fig. 1.1).

This practice of slaughtering animals to observe the liver and predict the future is mentioned also in the *Book of Ezekiel* 21:21: 'For the king of Babylon stands at the split in the road, at the fork of the two roads, to practice divination: he shakes the arrows, consults the idols, and observes the liver'.

The liver was the organ used to hand down the practice of predicting the future not only among the Babylonians but also by the Etruscans, Greeks and Romans. The liver was considered the site of the soul, the vital organ and the central place of all forms of mental and emotional activity. Only much later the heart began to serve this function in these civilisations.

The association between divination and anatomy came from the interest of the priests in locating the souls of men and animals. Therefore, the former theologians became the first students of human and comparative anatomy. Priests realised that, although the basic configuration remained, two livers never looked the same. Prediction of the future was therefore based on specific findings of the liver surface. These priests developed sheep liver clay models that were used to instruct those aspiring to the priesthood. Wooden

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Fig. 1.1 The liver tablet—clay model of a sheep liver, Old Babylonian 1900–1600 BC. British Museum, London—BM92668. Reproduced with permission

pegs were placed in the holes of the clay tablet to record features found in a sacrificed animal's liver, to predict the outcome of a person's concern.

From the translation of the inscriptions, we know that the right and left lobes were designated as 'right and left wings'. The gallbladder fossa was called 'the river edge of the liver' and the umbilical fissure, 'River of the liver'. The caudate lobe was identified as the 'middle of the liver', and the gallbladder was given the name 'bitter part'. The hepatic duct was known as 'output' and the common bile duct as 'the junction'. The *porta hepatis* was called 'the gate'; the secondary hepatic ducts were named 'branches', and the portal triads were represented as 'holes' or 'passages'. The most important feature of the liver, namely, the groove found on the left lobe of the liver of the sheep, was called 'the left split' but also 'the presence', indicating that this is a mark left by the presence of the deity during the ritual. Modern liver anatomical terminology finds its roots in the nomenclature used by Babylonians.

Omens and liver models depict popular beliefs, state religion and how ancient inhabitants of Mesopotamia saw their relationship with the gods. The conception of the future, and the fact that men could act to prevent negative outcomes, is the reason for the long life of this practice and its presence in almost every aspect of life. In the light of what has been considered so far, the Mari liver models, dated around 1900–1600 BC, offer a fascinating insight into ancient Mesopotamian life and testify that the interest for the liver anatomy characterised their culture and religious tradition.

1.1.2 The Liver of Piacenza in Etruria

The practice of hepatoscopy survived for millennia and spread to other Mediterranean cultures, as attested by various liver omens and models from different periods, found in Mari (Mesopotamia, the current Middle East), Hattusa (Hittite city, the current Turkey) and Etruria (the current Italy).

In Hattusa, some 40 liver models have been excavated. In Etruria, a sculpture of a liver, known as the 'Liver of Piacenza', was discovered in 1877 near the town of Piacenza in Northern Italy. The Liver of Piacenza is a real-size bronze model of a sheep liver covered by Etruscan inscriptions, dated to the late second century BC. It is divided into 16 sections inscribed with names of Etruscan deities, among which the most famous are Neptune, Bacchus, Mars and Hercules (Fig. 1.2).

1.1.3 The Myth of Prometheus

Religions and myths always overlapped or even merged over the centuries. Indeed Hercules is also the protagonist of a Greek myth well known also by the Roman tradition: the myth of Prometheus. This mythological figure is often mentioned when it comes to discuss the regenerative capacity of the liver. What is less known of this myth is that Prometheus is presented as a sort of a saviour of the humankind, who created the men, took tender care of the human beings and defended them against all odds and against the gods of the Olympus.

According to Aeschylus, the ancient Greek playwright, Prometheus was a titan very faithful to Zeus, who, as a reward, gave him the opportunity to freely access the Olympus. Zeus, for the estimation he put in Prometheus, gave him the task of forging man. Prometheus moulded it

Fig. 1.2 The Liver of Piacenza: bronze model of a sheep liver indicating the seats of the deities. From Decima di Gossolengo, Piacenza, Italy. Etruscan, late second to early first century BC

from the mud and animated it with the divine fire. The 'man of forethought' (this is the meaning of *Προμηθεύς* in ancient Greek) felt a deep friendship for men and distributed to them several good qualities he received from Athena, including intelligence and memory. Besides, the titan closed in a vase all the evils that could torment men, such as fatigue, sickness, old age, madness, passion and death. Zeus did not approve Prometheus' kindness for his creatures, considering the titan's gifts too powerful for the mankind. Moreover Prometheus demonstrated to prefer men to Zeus, who therefore decided to destroy the humanity taking away the fire from men and hiding it. The men, without fire, were dying of cold. Prometheus went secretly to the Olympus, lit a torch and brought the fire back to the men. Zeus decided to punish the titan fiercely. He got Prometheus chained up in the highest and most exposed rock and sent an eagle that would pierce his abdomen and tear out pieces of his liver, which grew back during the night (Fig. 1.3).

Meanwhile, as reported in Hesiod's *Theogony* and *Works of the Days*, Pandora found the vase that was jealously guarded by Prometheus' brother and opened it, so that all the evils were spread to the mankind; only the hope remained in the vase and served as consolation for the humanity. Eventually, after several years, Hercules passed near the rock where Prometheus was chained, pierced with an arrow the eagle that tormented Prometheus and freed him, breaking the chains. Nevertheless the men remained affected by fatigue, sickness, old age, madness, passion and death, and the commitment to take care of the suffering mankind was so passed on to the human beings (Fig. 1.4).

Fig. 1.3 *Prometheus Bound.* Oil painting, completed by Peter Paul Rubens in 1618. Philadelphia Museum of Art, Pennsylvania

Fig. 1.4 *Pandora.* Oil on canvas, completed by Alexandre Cabanel in 1873. The Walters Art Museum, Online collection

1.2 Liver Disease Aepidemiology in the Twenty-First Century

Liver disease occurs throughout the world irrespective of age, sex, region or race. Many conditions are acute, but cirrhosis is a common end result of a variety of liver diseases and can have different clinical manifestations and complications. According to the World Health Organization (WHO), about 46% of global diseases and 59% of the mortality are because of chronic illnesses, and almost 35 million people in the world die of chronic diseases. In the following section, we present the burden of liver disease worldwide, to include the following discussion on paediatric hepatology and liver transplantation in the context of the global health situation.

1.2.1 The Global Causes of Death and a Focus on Liver Disease

In adulthood, it is reported that 29 million people are affected by liver diseases; moreover, cirrhosis and end-stage liver diseases are responsible for around 170,000 deaths every year.

Looking at the WHO Global Health Estimates data updated in 2015, liver cirrhosis and liver cancer are included in the 20 leading causes of deaths in adulthood, as shown in Table 1.1 [1].

In a study performed in the USA, looking at the burden of digestive diseases in the general population, the authors found that liver disease was the ninth leading digestive disease diagnosis at ambulatory care visits; however, if visits with liver disease are combined with the 3.5 million visits for viral hepatitis, then liver disease would have been the third leading diagnosis. Among all digestive diseases, liver disease was the second leading cause of death in adulthood, after colorectal cancer. In this study, also data from patients <15 years are reported, showing a prevalence of 14:100,000 of liver disease diagnosis at hospital discharge, a mortality rate of 0.2:100,000 and a number of years of potential life loss of 10,700 years for all patients (Figs. 1.5 and 1.6) [2].

Table 1.1 Leading causes of death in 2015

2015: Global health estimates: 20 leading causes of death per year				
Rank	Cause	Deaths (000s)	% of total deaths	CDR (per 100,000 population)
0	All causes	56,441	100,0	768,5
1	Ischaemic heart disease	8,756	15,5	119,2
2	Stroke	6,241	11,1	85,0
3	Lower respiratory infections	3,190	5,7	43,4
4	Chronic obstructive pulmonary disease	3,170	5,6	43,2
5	Trachea, bronchus, lung cancers	1,695	3,0	23,1
6	Diabetes mellitus	1,586	2,8	21,6
7	Alzheimer's disease and other dementias	1,542	2,7	21,0
8	Diarrhoeal diseases	1,389	2,5	18,9
9	Tuberculosis	1,373	2,4	18,7
10	Road injury	1,342	2,4	18,3
11	Cirrhosis of the liver	1,162	2,1	15,8
12	Kidney diseases	1,129	2,0	15,4
13	HIV/AIDS	1,060	1,9	14,4
14	Preterm birth complications	1,058	1,9	14,4
15	Hypertensive heart disease	942	1,7	12,8
16	Liver cancer	788	1,4	10,7
17	Self-harm	788	1,4	10,7
18	Colon and rectum cancers	774	1,4	10,5
19	Stomach cancer	754	1,3	10,3
20	Birth asphyxia and birth trauma	691	1,2	9,4

Modified from WHO: Global Health Estimates 2015 summary tables
CDR crude death rate

Paediatric liver disease aepidemiology is poorly studied, and the exact prevalence of these diseases is unknown. The available data reported that each year approximately 15,000 paediatric patients are hospitalised for liver diseases in the USA, but liver disease is not cited in the first 15 causes of death in children. It is possible that the relative lack of aepidemiological research studies leads to underestimate the true prevalence of chronic liver disease in children; it is known that incidence and prevalence is lower compared to adults, but the impact of these conditions is high. In fact, chronic hepatobiliary diseases have significant effects on health and quality of life, on the family unit or disruption, on the number of years of life gained or lost, on mortality and need for liver transplantation and finally on health-care expenditure. Overall lack of awareness of the varied manifestations of hepatobiliary diseases in children often delays their diagnosis, thus contributing to increased morbidity and mortality, as a result of progression to end-stage liver disease. Paediatric liver disorders are particularly important because several paediatric conditions are precursors for adult chronic liver diseases, cirrhosis and hepatocellular carcinoma [3, 4].

1.2.2 Global Causes of Death in Children

From the more recent data by the United Nations International Children's Emergency Fund (UNICEF) ('2017 Revision on Levels and Trends in Child mortality'), children under 15 years of age represent around 26% of the world's inhabitants, with 9% under age 5. In the last years, there was a substantial improvement in life expectancy, and a significant progress in reducing child mortality, in particular the under-five mortality rate, an important indicator of development and children's well-being. The total number of under-five deaths dropped from 12.6 million in 1990 to 5.6 million in 2016—15,000 every day compared to 35,000; the global under-five mortality rate declined by 56%, from 93 deaths per 1,000 live births in 1990 to 41 in 2016. Children face the highest risk of dying in their first month of life, at a rate of 19 deaths per 1,000 live births. By comparison, the probability of dying after the first month but before reaching age 1 is 12, and after age 1 but before turning 5 is 11 deaths per 1,000 live births.

Disparities in child survival exist across regions and countries, with about 80% of under-five deaths occurring in two regions, sub-Saharan Africa and Southern Asia.

Most under-five deaths are caused by diseases that are readily preventable or treatable with proven, cost-effective interventions.

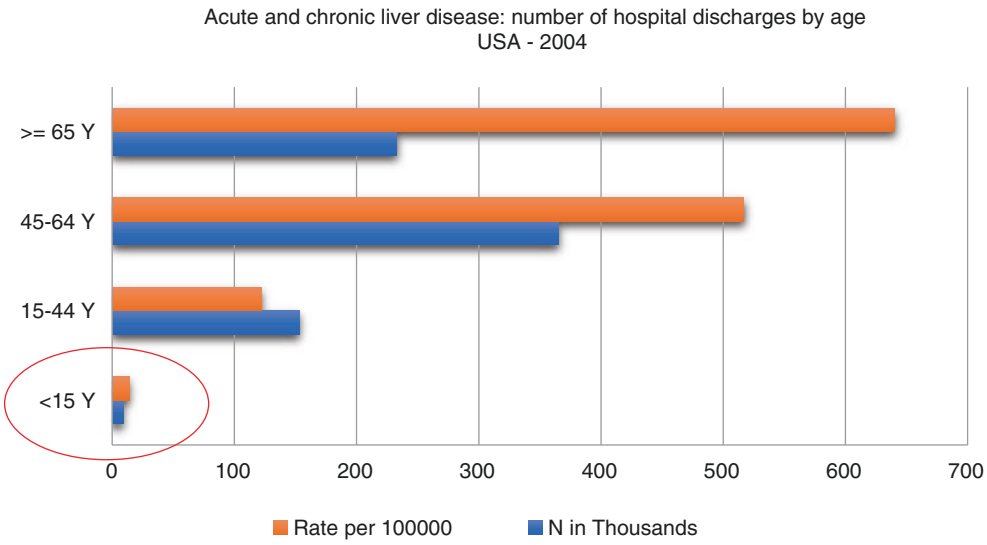

Fig. 1.5 Liver disease impact in hospitalised patients by age. Data referring to the paediatric age are circled. Data extracted from Everhart et al. Gastroenterology 2009 (see [2])

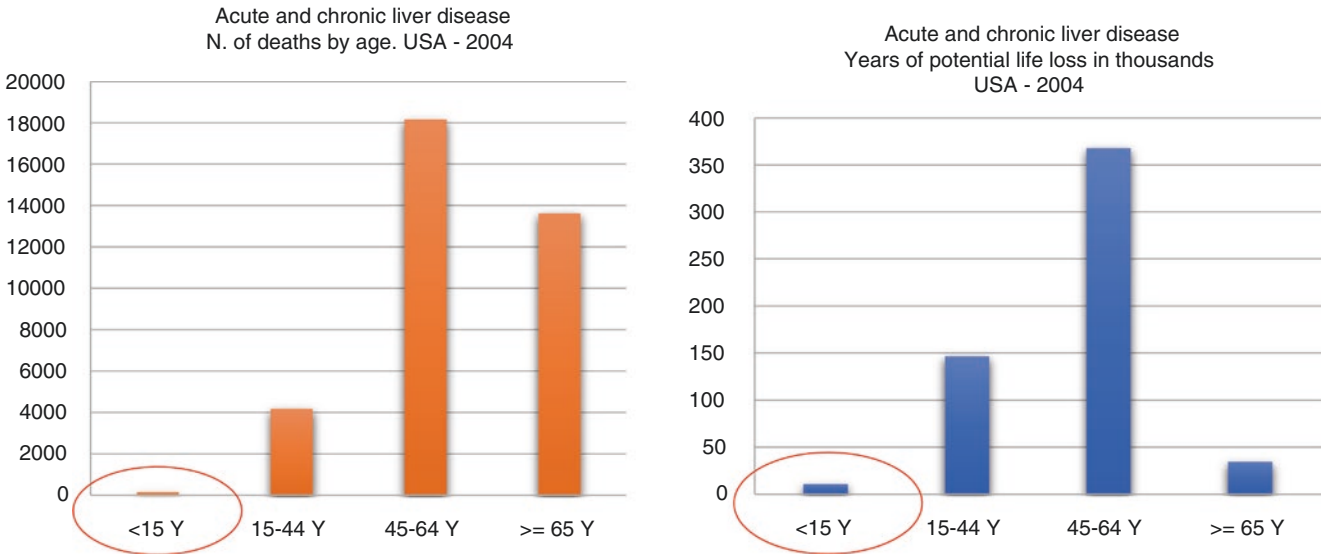

Fig. 1.6 Liver disease impact in mortality and life loss by age. Data referring to the paediatric age are circled. Data extracted from Everhart et al. Gastroenterology 2009 (see [2])

In particular, the WHO disease classification distinguishes three main categories:

- Group 1: Communicable, maternal, perinatal and nutritional conditions, including:
  - Infectious and parasitic diseases
  - Respiratory infections
  - Neonatal conditions
  - Nutritional deficiencies
- Group 2: Non-communicable diseases, including:
  - Malignant neoplasms
  - Other neoplasms
  - Diabetes mellitus
  - Endocrine, blood, immune disorders
  - Mental and substance use disorders
  - Neurological conditions (epilepsy)
  - Sense organ diseases
  - Cardiovascular diseases
  - Respiratory diseases
  - Digestive diseases
  - Genitourinary diseases
  - Skin diseases
  - Musculoskeletal diseases
  - Congenital anomalies
  - Sudden infant death syndrome
- Group 3: Injuries

In the next figures (from Figs. 1.7, 1.8, and 1.9), the WHO data, referred to the childhood mortality at the last Global Health Estimates (updated in 2015), are represented for the

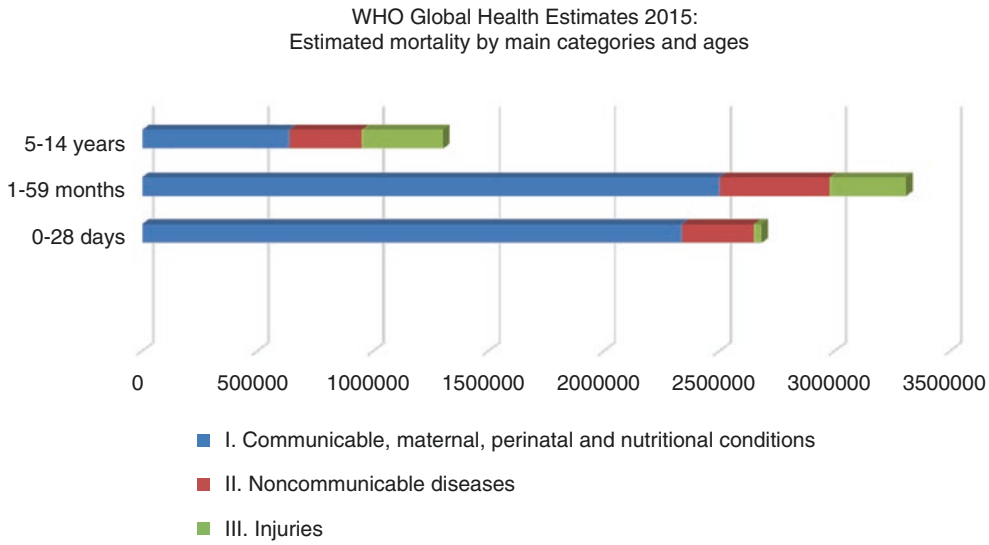

Fig. 1.7 Communicable diseases are the main mortality cause in all age groups, but their relative impact decreases in older ages, where injuries and non-communicable diseases (including all liver diseases except hepatitis) become more important. I, II and III refer to the three categories of communicable, non-communicable disease and injuries

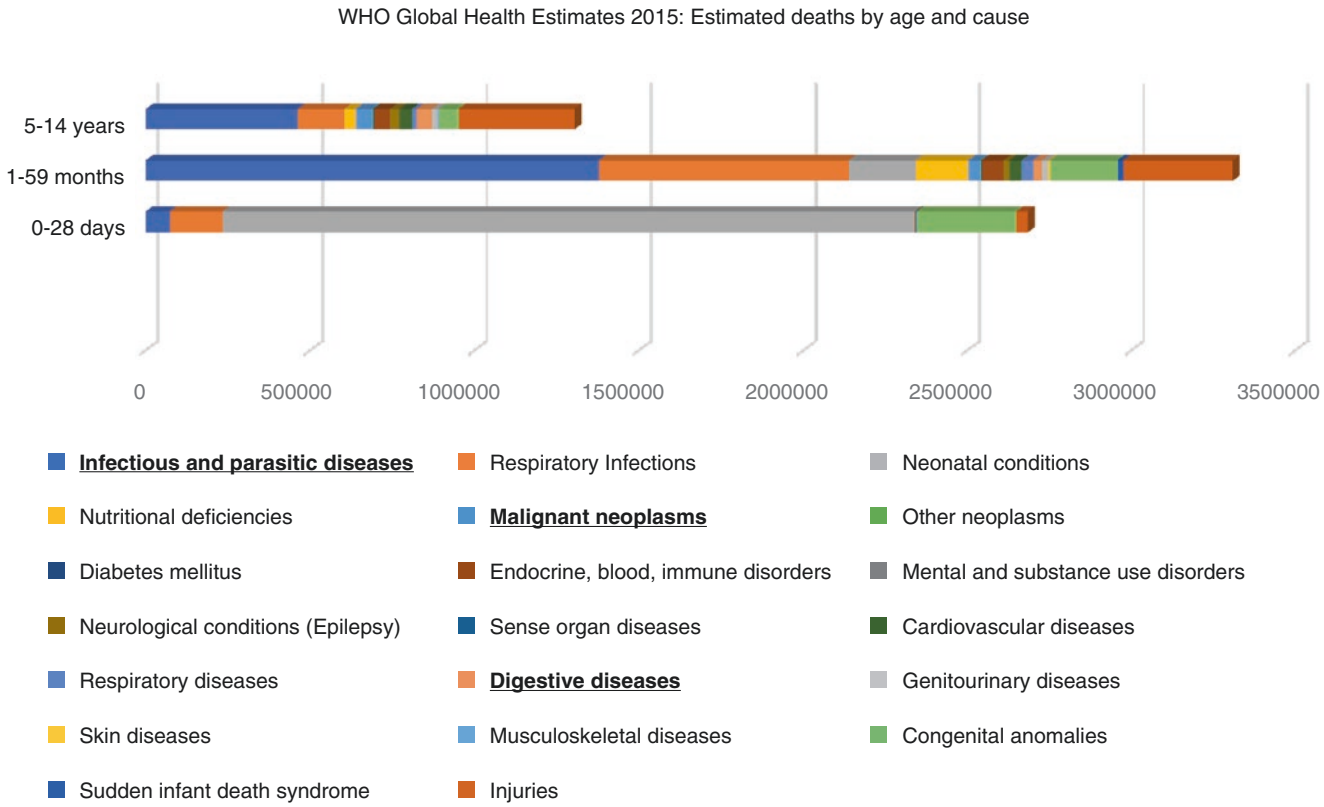

Fig. 1.8 The mortality by main causes and age is shown in this figure; the underlined categories are those including the different liver diseases

main categories. From these data, it is possible to derive information about the impact of liver disease in this global scenario [5–8].

Based on this classification, the WHO in 2016 reported the cause-specific estimates of deaths for children under age 5. These are expressed by distinguishing the causes of death during the neonatal (0–27 days) and postneonatal (1–59 months) periods (Table 1.2).

As shown in this table, the leading causes of death among children under age 5 (accounting for almost a third of global under-five deaths and about 40% of under-five deaths in sub-Saharan Africa) included preterm birth complications (18%), pneumonia (16%), intrapartum-related events (12%), diarrhoea (8%), neonatal sepsis (7%) and malaria (5%). Liver diseases are included in the group of 'other diseases' in neonatal period and in the

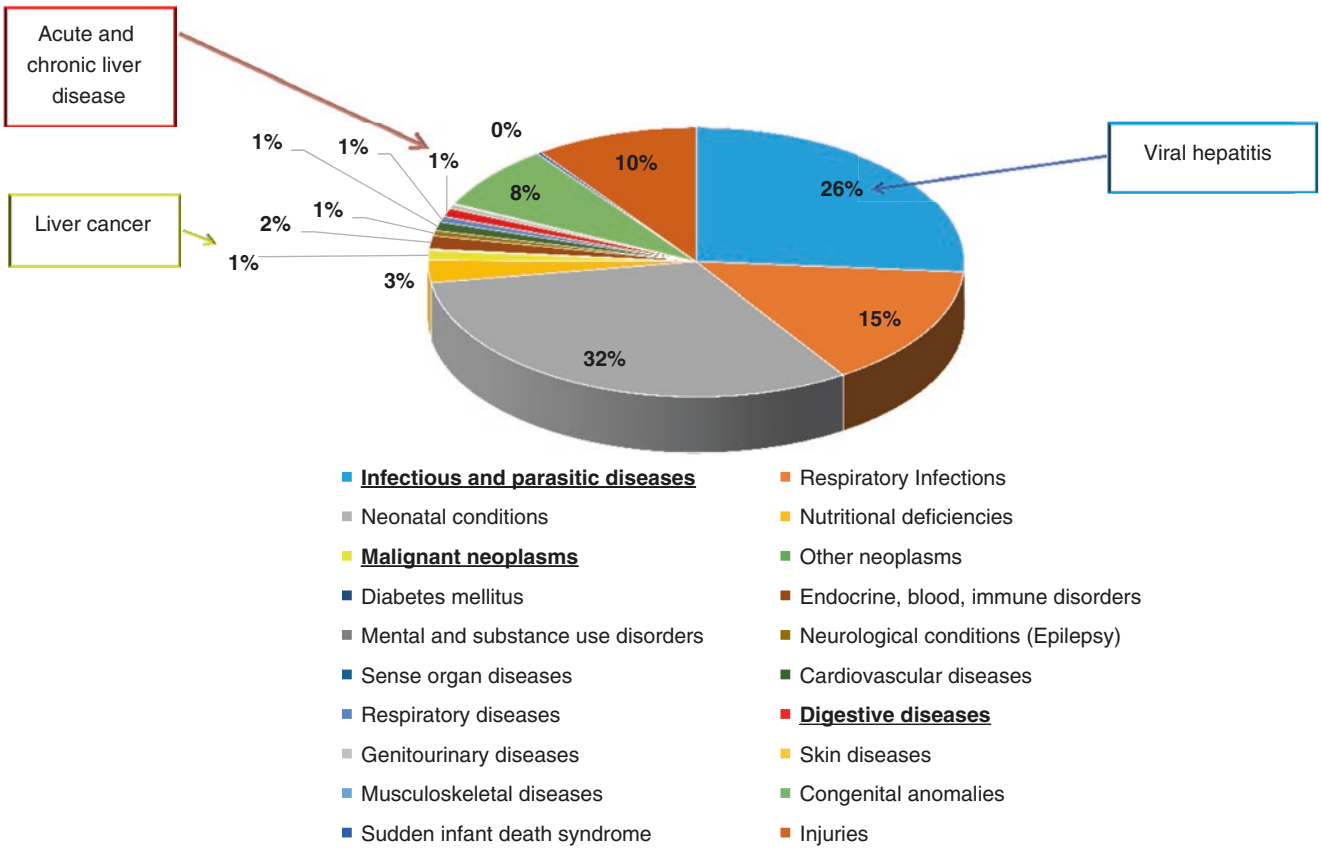

Fig. 1.9 WHO Global Health Estimates 2015: 0–14 year mortality by cause

Table 1.2 Causes of death among children under 5 years of age

Neonatal deaths 0–27 days (46%)		Postneonatal deaths 1–59 months (54%)	
Prematurity	16%	Pneumonia	13%
Intrapartum complications	11%	Other group 1 conditions	10%
Neonatal sepsis	7%	Diarrhoea	9%
Congenital anomalies	5%	*Congenital anomalies*[a]	*8%*
Pneumonia	3%	Injuries	6%
Other	*3%*	Malaria	5%
Neonatal tetanus	1%	Prematurity	2%
		Measles	1%
		HIV/AIDS	1%

Data are extracted from the Global Health Estimates technical paper, WHO-MCEE methods and data sources for child causes of death 2000–2015

[a]Includes other non-communicable diseases. Categories reported in italic include liver diseases

group of 'congenital anomalies' among children 12–59 months.

Looking at the older ages, the WHO data show that the probability of dying among children aged 5–14 was 7.5 deaths per 1,000 children; mortality in this age group is low, but 1 million children still died in 2016. The communicable diseases are a less prominent cause of death than among younger children, and other causes including injuries and non-communicable diseases become important.

In particular, injuries account for more than a quarter of the deaths, non-communicable diseases for about another quarter and infectious diseases and other communicable diseases, perinatal and nutritional causes, for about half of the deaths.

In this context, the liver disease aepidemiology includes:

- In the group of communicable diseases: viral hepatitis (HAV, HBV, HCV, HEV)
- In the group of non-communicable diseases: haemochromatosis, Reye's syndrome, Wilson's disease, alcoholic liver disease, toxic liver disease, hepatic failure, chronic hepatitis (not elsewhere classified), fibrosis and cirrhosis of liver, other inflammatory liver diseases, other diseases of liver, liver disorders in diseases classified elsewhere and metabolic disorders

These conditions are subcategorised within the groups of infectious, malignant and digestive diseases, as shown in Fig. 1.8.

In particular, the group of infectious diseases include the different forms of hepatitis; the group of malignant neoplasms include the liver and biliary tract cancers, the group

of digestive diseases include all forms of other liver disease and cirrhosis (Fig. 1.9).

1.2.3 The Global Burden of Liver Disease in Children

Among the category 'infectious and parasitic diseases', liver diseases correspond to viral hepatitis. Of a total of 1,915,434 deaths due to infections in paediatric age, 21,328 (=1%) are due to the different forms of viral hepatitis, as shown in Fig. 1.10.

Among the category 'non-communicable diseases', the liver is involved in the group of malignant diseases and in that of digestive diseases.

On a total of 86,769 death in paediatric age because of malignancy, 1,983 (2.2%) are due to different forms of liver cancer, as shown in Fig. 1.11.

Finally, looking at the digestive diseases, on a total of 74,391 deaths in paediatric age, 27,882 (37%) were due to the different forms of cirrhosis, and 3,064 (4%) to gallbladder and biliary diseases, as shown in Fig. 1.12 [5–8].

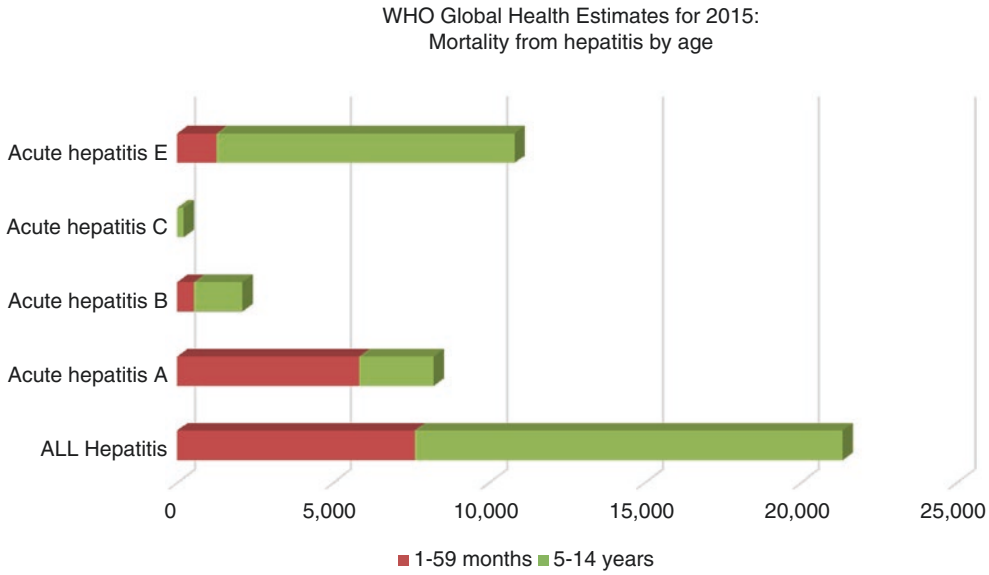

Fig. 1.10 The mortality for hepatitis is distinguished by different age groups (1–59 months, 5–14 years). No deaths were observed for this cause in the age group 0–28 days

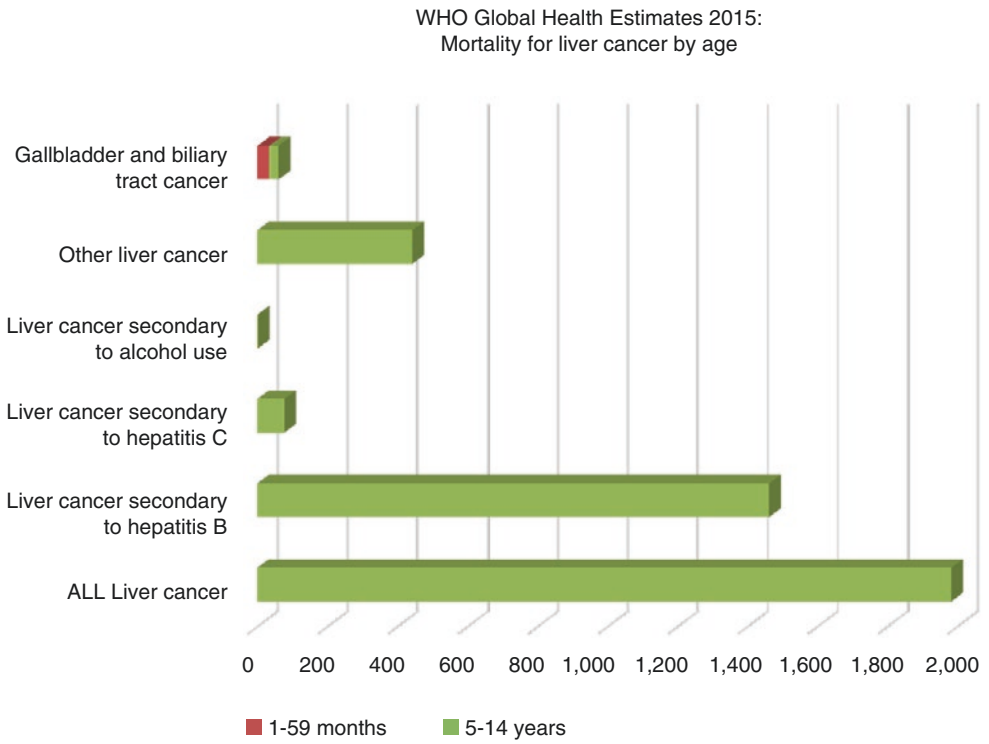

Fig. 1.11 The mortality for liver cancer is distinguished by different age groups (1–59 months, 5–14 years). No deaths were observed for these causes in the age group 0–28 days

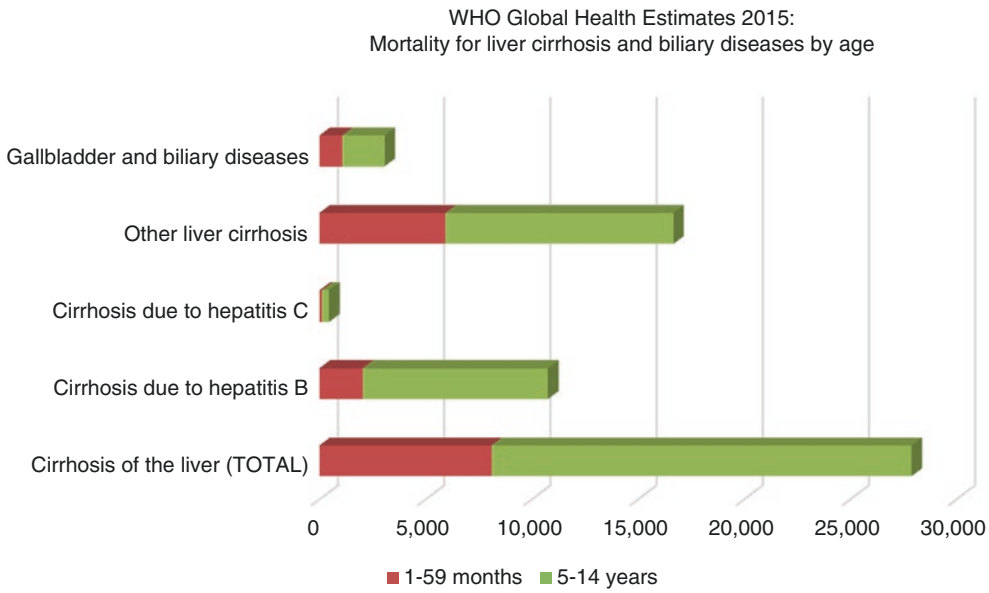

Fig. 1.12 The mortality for liver cirrhosis and biliary diseases is distinguished by different age groups (1–59 months, 5–14 years). No deaths were observed for this cause in the age group 0–28 days

1.2.4 Causes of Death in Western Countries (USA and Europe)

Besides the WHO reports, several recent studies in the USA and Europe focused the attention on mortality and morbidity by selected causes in paediatric population.

A recent paper by National Vital Statistics Reports represents final 2015 data on US number of deaths, death rates, life expectancy, infant mortality and trends, by selected characteristics such as age, sex, state of residence and cause of death. A total of 2,712,630 deaths were reported in the USA; the age-adjusted death rate was 733.1 deaths per 100,000 US standard population. Life expectancy at birth was 78.8 years. Looking at these data, it is possible to focus the attention on childhood mortality and on the low impact of liver diseases in this scenario, as shown in Table 1.3 [9].

More recently, an aepidemiological study was conducted in European regions, including data from 51 countries, assessing the distribution and trends of the main causes of death among children aged 5–9 years and 10–14 years from 1990 to 2016.

For children aged 5–9 years, all-cause mortality rates (per 100,000 population) were estimated to be 46.3 in 1990 and 19.5 in 2016, reflecting a 58% decline. For children aged 10–14 years, all-cause mortality rates (per 100,000 population) were 37.9 in 1990 and 20.1 in 2016, reflecting a 47.1% decline.

In 2016, 10,740 deaths in children aged 5–9 years and 10,279 deaths in those aged 10–14 years were estimated. The leading causes of death were similar between the two age groups. Liver cirrhosis is the 20th cause of death among children aged 5–9 years and the 16th cause in the group 10–14 years.

These data are shown in Figs. 1.13 and 1.14 [10].

1.3 Aepidemiology of Paediatric Liver Disease in Western Countries

In the last few decades, paediatric hepatology has developed from a newborn discipline to a highly specialised field in which unexpected progresses in genetics, molecular biology and pathophysiology of liver disease have been achieved. Liver disease in children is considered rare, and the care and follow-up of paediatric patients with hepatopathies are demanded to specialised centres. The opening of the frontiers has favoured immigration of people to the Western countries, changing the ethnical and cultural composition of our societies and consequently also the incidence of diseases once unfamiliar. For instance, inborn errors of metabolism are more frequent in communities having the tradition of consanguineous marriage, whereas viral hepatitis is common in children of Asian or African origin, where such infections are highly prevalent.

The discipline of paediatric hepatology has recently seen many advances in the understanding, diagnosing and treating paediatric liver diseases. At the same time other areas of paediatrics have improved leading to the emergence of new disorders caused by the complications of children who once would not have survived. This is, for instance, the case of the increasing number of newborn and infants treated for severe prematurity and presenting with liver disease. The field of liver diseases in ex preterm babies, still rather unknown, is expanding and will probably represent a new important area of interest for the paediatric hepatologist. The same can be stated for diseases following the use of chemotherapy and radiotherapy for the treatment of malignancies.

Table 1.3 Childhood mortality in the USA in 2015 by age and cause

Cause	<1 year	1–4 years	5–14 years	Total 0–14years
Septicaemia	180	54	64	298
Viral hepatitis	1	0	1	2
HIV disease	2	2	1	5
Enterocolitis due to Clostridium difficile	2	2	3	7
Malignant neoplasms total	53	354	865	1272
Malignant neoplasms of liver and biliary tract	2	14	19	35
Anaemia	17	25	33	75
Diabetes mellitus	3	5	23	31
Nutritional deficiencies	9	4	1	14
Obesity	0	1	4	5
Cardiovascular diseases	400	196	300	896
Influenza and pneumonia	174	88	83	345
Chronic lower respiratory diseases	26	40	173	239
Aspiration pneumonia	8	10	16	34
Chronic liver disease and cirrhosis	3	2	1	6
Nephritis, nephrotic syndrome and nephrosis	85	16	17	118
Perinatal conditions	11,613	50	21	11,684
Congenital malformations and genetic disease	4825	435	337	5597
Accidents (unintentional)	1291	1235	1518	4044
Intentional self-provoked injuries (suicide)	0	0	413	413
Assault (homicide)	263	369	298	930
Complications of medical and surgical care	12	18	17	47
All causes	23,455	3965	5411	32,831

Modified by Murphy 2015, National Vital Statistics Reports

The spectrum of diseases diagnosed at a centre depends on many factors. One is the diagnostic capacity of the centre itself, in terms of professional skills and resources; another is the composition of the population living in the area, and a third is the type and amount of referrals from other centres. For these reasons it is not possible to consider a single centre as representative of the changing spectrum of liver diseases in a country, and even less in the global community.

Nonetheless all children with rare conditions need high-quality service programmes that have sufficient patient volume to guarantee the clinical expertise, and ancillary services necessary to address their specialised needs. Although their impact in global children survival is low (mainly because the global prevalence is low), these diseases are heterogeneous and may have a significant impact on morbidity and quality of life of affected patients [11].

The overall incidence of liver diseases in neonates (neonatal cholestasis) in the USA is approximately 1 in every 2500 live births, with extrahepatic biliary atresia, metabolic disorders and neonatal hepatitis being the most common causes; in older children, common causes of chronic liver disease (CLD) include metabolic disorders, chronic intrahepatic cholestasis, obesity-related steatohepatitis, drug- and toxin-induced disorders and autoimmune liver disease (Table 1.4).

In Australia, the most common cause of CLD starting in the neonatal age in children is biliary atresia, occurring in approximately 1 in 8,000 live births, with other common causes being alpha-1-antitrypsin deficiency and Alagille syndrome. Similarly, in Brazil, biliary atresia is the most common cause of CLD in children. In contrast, a study in Pakistan found viral hepatitis to be the most common cause of neonatal onset CLD, followed by metabolic disorders and biliary atresia, while a study in India found metabolic disorders to be the most common cause of CLD in children [12].

In a study performed at King's College Hospital of London, patients referred to a tertiary centre for suspected hepatopathies in the period 1985–2000 were collected and classified according to the diagnoses:

1. Hepatitis of infancy ('idiopathic neonatal hepatitis' 'neonatal giant cell hepatitis')
2. Alpha-1-antitrypsin deficiency
3. Extrahepatic biliary atresia
4. Alagille syndrome
5. Autoimmune hepatitis and sclerosing cholangitis
6. Wilson disease
7. Cystic fibrosis
8. Progressive familial intrahepatic cholestasis

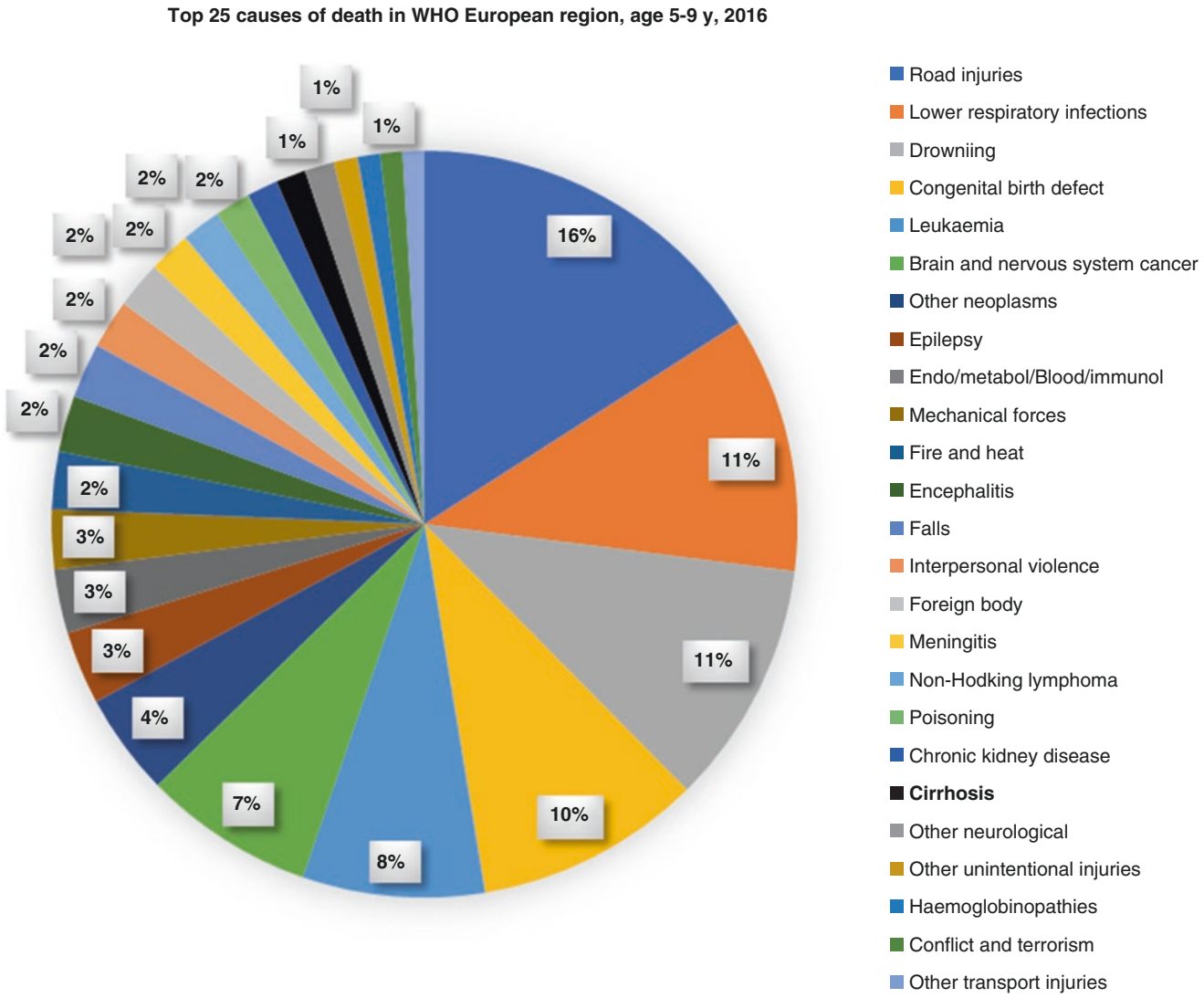

Fig. 1.13 Mortality by cause in the WHO European region, in the age group 5–9 years (data extracted by Kyu et al. systematic analysis for the Global Burden of Disease Study 2016)

9. Metabolic disorders (including all the inborn errors of metabolism involving the liver and not described singularly in other categories)
10. Cryptogenic cirrhosis
11. Prematurity-related liver disease
12. Ductal plate malformation
13. Viral hepatitis
14. Biliary anomalies (including choledochal cyst, inspissated bile syndrome, unspecified dilatation of the bile ducts, cholelithiasis, spontaneous perforation of the bile ducts)
15. Tumours (including primary and metastatic malignancies presenting with liver disease)
16. Septo-optic dysplasia (including any midline abnormalities causing hypopituitarism and liver disease)
17. NonA-NonB acute liver failure
18. Portal vein thrombosis and Budd-Chiari syndrome
19. Others (including other cases with less common diagnosis).

The database counted 3276 children who were described in this study (D'Antiga, unpublished data).

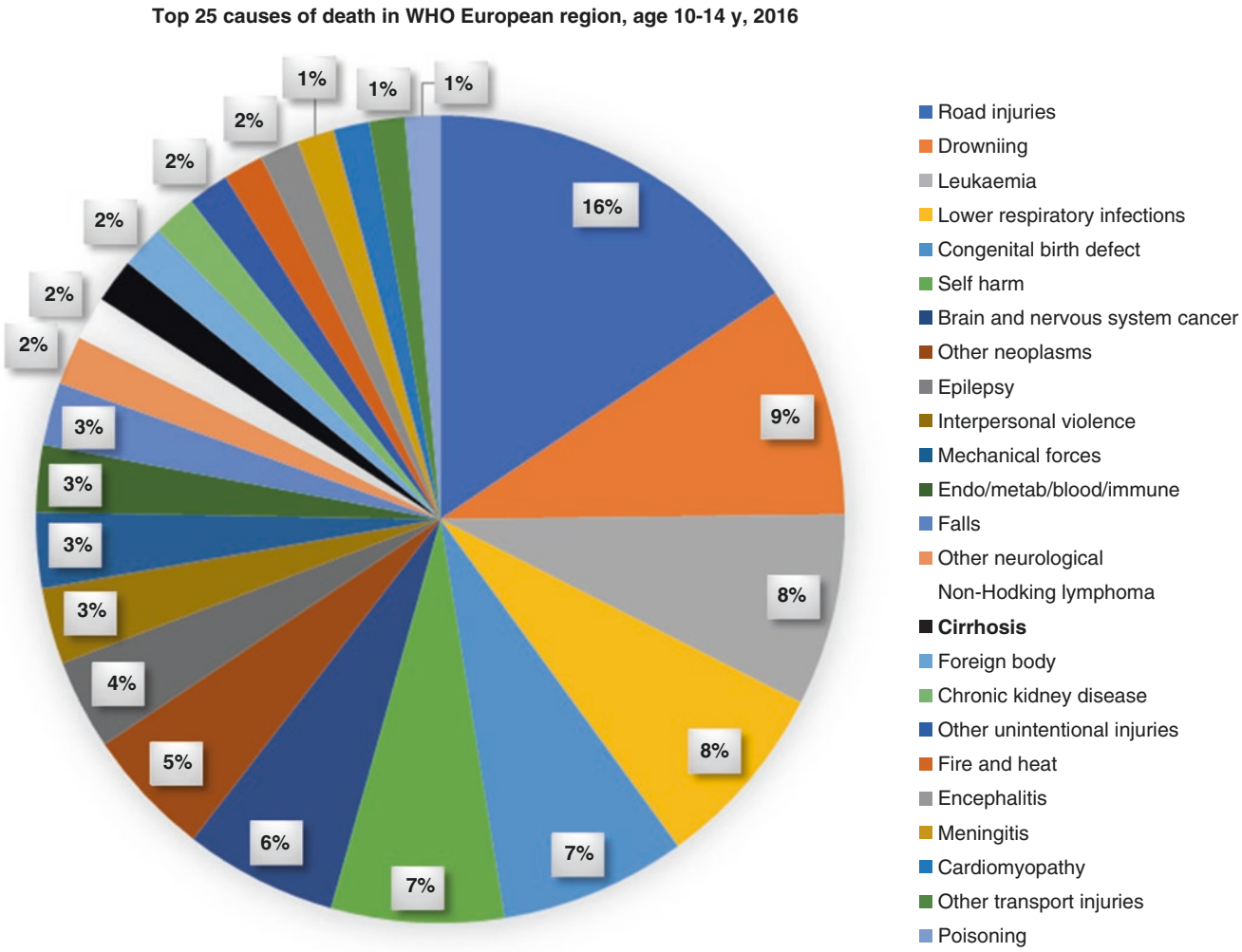

Fig. 1.14 Mortality by cause in the WHO European region, in the age group 10–14 years (data extracted by Kyu et al. systematic analysis for the Global Burden of Disease Study 2016)

The results show that liver disease in childhood presents mostly between 1 and 2 years of age (Fig. 1.15).

At the time of data collection (year 2000), in newborns and infants, the most common cause of liver disease was hepatitis of infancy, whereas between 1 and 10 years of age, it was viral hepatitis. After the tenth year, autoimmune hepatitis and sclerosing cholangitis were the most common diagnoses. In this study the data analysis did not include children affected by NAFLD, which is currently one of the most frequent causes of liver diseases in adolescents. This was due to the lack of referrals of these patients to the tertiary centre in which the study was conducted.

The impact of different liver diseases and the age at presentation are synthesised in Figs. 1.16 and 1.17. The hypothetical number of NAFLD/NASH cases, according to the known prevalence in Western countries, is reported aside. Figure 1.18 shows the different diagnoses divided by age group [19].

However, with the introduction of high-throughput genetic testing, the aepidemiology of liver disease in children is rapidly changing, especially for the definitions of many cases formerly classified as 'neonatal hepatitis' or 'cryptogenic liver disease' (see also chapters on cholestatic disorders and next-generation sequencing, Chaps. 13 and 42 respectively) (Fig. 1.19).

Table 1.4 Incidence/prevalence of different causes of liver disease in the paediatric population

Disease	Incidence/prevalence
Cholestatic diseases	1:2,500 live birth (l.b.)
Biliary atresia	1:8,000–1:21,000 l.b.
Alagille syndrome	1:70,000 l.b.
PFIC/BRIC	1:7,000 l.b.
Caroli disease/congenital hepatic fibrosis	1:6,000–1:40,000
Neonatal haemochromatosis	<1:1,000,000 l.b.
Idiopathic neonatal hepatitis	1:4,800–1:9000 l.b.
Wilson disease	1:30,000–1: 50.000 l.b.
Cystic fibrosis	1:2,000 l.b.
Alpha-1-antitrypsin deficiency	1:1,800 l.b.
Metabolic diseases	1:1,800 l.b.
Disorders of carbohydrate metabolism	– Fructosaemia 1:20,000 l.b. – Galactosaemia 1:63,000 l.b. – GSD I–III and IV: 1:100,000–1:1,000,000
Tyrosinemia	1:100,000–1:120,000 l.b.
Peroxisomal disorders	1:25,000 l.b.
Urea cycle disorders	1:30,000 l.b.
Organic acidosis	1:1,000 l.b.
Lysosomal storage disorders	– Gaucher disease: 1:5,700 l.b. – Niemann-Pick A/B: 1:1,000,000 l.b – Niemann-Pick C: 1:130,000–1:150,000 l.b. – CESD: 1:300,000 l.b. – Wolman disease: 1:500,000 l.b.
Congenital disorders of glycosylation	1:10,000–1:100,000 l.b.
Mitochondrial hepatopathies	1:20,000 children under 16 years of age
Tumours	1,8:1,000,000
NAFLD/NASH	Prevalence 5–17% in general paediatric population, up to 70–90% in young obese
Autoimmune liver disease (including AIH/ASC and PSC)	Prevalence 1:200,000
Infections	
Hepatitis A (HAV)	1.4 million cases occur annually
Hepatitis B (HBV)	Global prevalence 2–20%. Horizontal transmission responsible for 37–52%; perinatal transmission 13–26%
Hepatitis C (HCV)	Prevalence from 1:500 (age 6–11 years) to 1:250 (age 12–19 years)

PFIC progressive familial intrahepatic cholestasis, *BRIC* benign recurrent intrahepatic cholestasis, *GSD* glycogen storage disease, *CESD* cholesteryl ester storage disease, *NAFLD* non-alcoholic fatty liver disease, *NASH* non-alcoholic steatohepatitis, *AIH* autoimmune hepatitis, *ASC* autoimmune sclerosing cholangitis, *PSC* primary sclerosing cholangitis. Extracted from [13–18]

1.3.1 Prevalence of Liver Disease Among Children Presenting to an Emergency Department

Many acute systemic conditions may present with transient, benign raise of transaminases. Previous studies looking at children coming to the emergency department with an acute illness, who had liver function tests (LFTs) tested, showed that some 30% had raised transaminases. LFTs remained abnormal in 8%. At the end, excluding those lost to follow-up, 5% had a chronic liver disease, including NAFLD/NASH. The others normalised liver enzymes, and it can be hypothesised that, in many children, common viral infections play a role in the transient increase in transaminases during acute illnesses (Fig. 1.20).

Despite extensive investigation, the cause of elevated transaminases may remain unknown in 10–15% of cases [20–22].

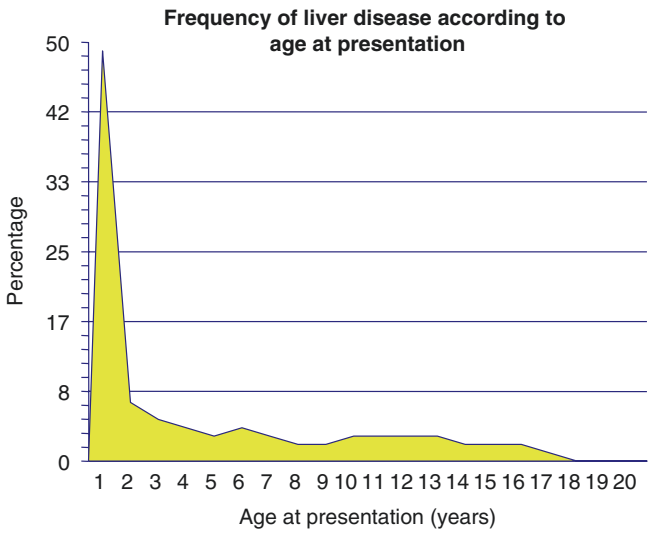

Fig. 1.15 Distribution of liver diseases in childhood at different presentation ages. The higher percentage of hepatopathies occurs in the first 2 years of age