In Clinical Practice

Nedim Hadžić
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Liver Disease in Adolescence

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Preface

Medical practice of the twenty-first century has seen several significant changes. Alongside considerable progress in early diagnostics, use of molecular genetics in confirming rare diagnoses and development of specific medications directly targeting components of pathophysiological cascade—leading to patient-tailored specific treatments, there were also some novel organisational trends. Medicine has become more specialty-oriented with reduced interpersonal professional relations due to ever-increasing bureaucracy and administration, but also massive expansion of emerging social media networks, allowing instant access to medical knowledge practically without any individualisation or scrutiny.

These blurred boundaries have left adolescent age group particularly vulnerable. Traditionally, there was not much communication between paediatricians and adult physicians and the disease nuances related to the specific ages have not often been highlighted during medical handover of these patients, which in majority of countries occurs between 16 and 18 years of age. Their healthcare outcomes appear to be comparably inferior to younger and older age groups. Recent advances in neuroimaging confirm that adolescent brain development continues into the mid-20s. This concept challenges the existing distinct models of either more supportive, family-orientated, paediatric care, or patient-centred adult care for this vulnerable population. Typical behaviours such as rebellious attitudes, risky lifestyles, non-adherence to medications, or combination of those could thus be developmentally justified, but require multidisciplinary and holistic approach. This entails embracing the concept of 'meaningful' survival, a state of complete physical, mental, and social well-being and not merely the absence of disease. Young people are perceived to be difficult to manage, whilst their determination, resilience, and sense of humour are often overlooked. In addition, they are keen explorers of the global social media empires, where opinions and advice may not necessarily always be compatible with the conventional medicine.

Looking after young people is a challenge for health professionals both on paediatric and on adult side. Hepatology is no exception to this and children are occasionally growing up with the liver diseases that adult colleagues are not familiar with. Our primary aim in this book was to compile expert views and guidance both

from health professionals and young people for those affected by different chronic liver diseases during adolescence. Problem anticipation, as always in medicine, is a key strategy and gentle educational refresher in areas that are not often highlighted we believe would be timely and helpful. Therefore, we hope that this collection could provide assistance for professionals involved in both paediatric and adult hepatology while threading this complex period together with their adolescent patients.

London, UK

Nedim Hadžić
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The Impact of Liver Disease on Adolescent Development

Chapter 1
Impact of Chronic Liver Disease on Nutrition, Growth and Puberty in Adolescence

Eirini Kyrana

Introduction

The liver is responsible for several key functions: protein synthesis (e.g., albumin, insulin growth factor-1 (IGF-1), majority of clotting factors), removal of ammonia from the circulation by synthesis of urea, carbohydrate metabolism (glycogenesis, glycogenolysis and gluconeogenesis), synthesis of cholesterol, bile salts and phospholipids and detoxification of a wide array of endogenous and exogenous substances. Chronic liver disease (CLD) is the progressive destruction of the liver parenchyma leading to cirrhosis and end stage liver disease. As the disease progresses more of these functions are impaired having a detrimental influence on the patient's health. Many of the adolescents with CLD will have been diagnosed as infants or young children, whilst some of them may have been diagnosed in adolescence but their condition would have been progressing asymptomatically for many years prior to the diagnosis. Of course, not all children diagnosed with liver disease in childhood will suffer from CLD in adolescence. About 11% of children with biliary atresia will enter adolescence with no evidence of CLD [1], but 14–40% of patients with biliary atresia will develop complications of CLD like cholangitis and portal hypertension in adolescence [2]. In addition to this, adolescence is a demanding period of considerable physical and psychological change which is likely to complicate the effects of a failing liver.

In the last few decades advances in hepatology and in liver transplantation (LT) mean that many young patients with CLD are surviving for longer. The aim of the medical teams looking after these patients currently is for them to not only survive

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to adulthood, but to reach adulthood in an optimal state of physical and emotional health so that they can lead meaningful and fulfilling lives. For this to be achieved attention has turned to how liver disease affects nutrition, growth, and puberty and to how these effects can be mitigated. Not so much anymore for the shorter term effects e.g., how optimal nutrition can help the peri-transplant course of a patient, even though these strategies remain important, but for the longer term effects, e.g. how do we support optimal neurocognitive development, how do we encourage optimal metabolic health, etc.

Nutrition in Adolescence (Table 1.1)

Chronic Liver Disease

Patients with CLD and cirrhosis of all ages, adolescents included, are at risk for malnutrition. The reasons for this are multiple. The most important contributing factors are anorexia of chronic disease and fat malabsorption due to cholestasis [3, 4]. Additional factors are prescribed low salt diets and micronutrient deficiencies contributing to dysgeusia [5, 6]. The presence of organomegaly and ascites further contribute to feelings of fullness and discomfort whilst eating. CLD resulting in cirrhosis is a state of accelerated starvation and protein-energy malnutrition [7–9] where metabolism has switched from using glucose to using fatty acids. One reason for this are the reduced hepatic glycogen stores. In this situation protein synthesis is decreased and gluconeogenesis is increased. Gluconeogenesis involves muscle proteolysis and conversion of amino acids to glucose; a process leading to sarcopenia.

Multiple studies in adults and children with cirrhosis have shown significant changes to body composition when compared to healthy controls [10–13]. These changes are reduction of lean mass (comprised mainly of skeletal muscle),

Table 1.1 Nutrition in adolescence

A.	**Chronic Liver Disease**
	50% of young patients with CLD will be malnourished
	Macronutrient and micronutrient requirements need careful monitoring
	Fatty acid oxidation, gluconeogenesis with muscle proteolysis leading to sarcopenia and peripheral insulin resistance are common metabolic aberrations
B.	**Liver Transplant**
	Food allergies may develop post LT
	Obesity and metabolic syndrome are observed after LT
C.	**NAFLD**
	Weight loss is currently the only intervention proven to reduce or ameliorate liver steatosis
	Vitamin D is frequently low in adolescents with NAFLD
	Alcohol consumption may contribute to the liver disease in older adolescents

reduction of total body fat, reduction of bone mineral density and an increase in extracellular water. In addition, these patients have been shown to have abnormal metabolic profiles with hypermetabolism, insulin resistance and abnormal protein metabolism [14–17].

The reduction of skeletal mass and skeletal function is called sarcopenia. Sarcopenia has been described in male and female patients with cirrhosis but tends to be more common in males [11, 18, 19]. This should be kept in mind when looking after adolescents where some of these gender differences may be relevant. Sarcopenia has been linked to worse outcomes both before [19, 20] and after LT [21, 22]. Studies have shown that the presence of sarcopenia does not necessarily correlate with the disease severity [23–25] and may be present from the early stages of cirrhosis. Sarcopenic obesity is the term used to describe the presence of sarcopenia in an obese individual [26]. Two patients with the same body mass index (BMI) may have significantly different body composition. With the increasing prevalence of obesity in the population this may become relevant for the adolescents with liver disease.

Fluid retention presenting as ascites or as whole body fluid retention and oedema is a common complication of CLD. It is the main reason (together with the presence of organomegaly) that makes basic anthropometry like weight very difficult to use in these patients as it will underestimate the presence of malnutrition [27]. Measuring body composition in children and adolescents is challenging as the measurements have to be adjusted for age and the availability of normal data for comparison is not always possible.

Total energy expenditure and therefore energy requirements in patients with CLD depends on their energy expenditure at rest, their activity level, energy for thermogenesis and the degree of malabsorption they have. The equations used to calculate energy requirements for these patients have been shown to be inaccurate [28, 29]. Evaluating energy requirements in a way that we are not under- or overfeeding patients can be challenging. One can perform indirect calorimetry to help better assess difficult cases. If a child is growing, that is an indirect sign that their nourishment is adequate, but unfortunately with patients with CLD there is frequently a delay in growth associated with the anabolic resistance, which cannot be addressed by increasing caloric intake.

Requirements in fat will vary amongst adolescents with CLD depending on the degree of malabsorption they have, but generally they will be normal, and fat will provide 25% to 30% of their total caloric requirements [30]. Practices of using nasogastric tube to deliver supplemental nutrition tend to be less common in adolescents in comparison to younger children, mainly because older children may cooperate more in taking additional supplements. In cholestatic patients long chain fatty acids are poorly absorbed because the intraluminal bile salt concentrations in the gut are reduced and therefore the formation of mixed micelles which are important for the absorption of these fats is impaired. It is common practice to supplement the diet of these children with medium chain triglycerides, which are smaller molecules and can be more directly absorbed into the circulation and do not require bile salts. The fat malabsorption of long chain fatty acids may lead to a deficiency of essential fatty

acids (linoleic and linolenic acid) which can manifest with skin abnormalities like scaly dermatitis and alopecia, thrombocytopenia, and, in the longer term, with intellectual disability. It is important to consider essential fatty acid deficiencies in patients with severe fat soluble vitamin deficiency, particularly if they have symptoms like the ones described that are not responding to vitamin supplementation. Even though fat intestinal absorption, particularly in cholestatic patients, is reduced, fat metabolism has been shown to be normal [14].

Fat soluble vitamin deficiency is frequently described in CLD and needs to be considered in adolescents as well. The liver is implicated in the metabolism of vitamin D and its deficiency is common in patients with cholestatic CLD. It is likely involved in hepatic osteodystrophy, but also in liver disease of other aetiologies. Low vitamin D levels and suspicion of metabolic bone disease should result in more detailed studies including parathormone, calcium and phosphate levels. Other fat soluble vitamin deficiencies that need to be monitored for, particularly in cholestatic disorders, are vitamin K, vitamin A and vitamin E. Vitamin K is also important for its role in the γ-carboxylation of osteocalcin in bone and therefore has an important role in bone mineralisation aside its role in activating clotting factors and haemorrhagic disease. Vitamin A deficiency can cause dry skin, xerophthalmia and night blindness. Vitamin A is mostly stored in the liver and therefore serum levels are not reflective of body stores. Vitamin A has been found to be deficient in up to 62% of patients with cirrhosis [31]. When considering to supplement with vitamin A, one needs to consider that retinol binding protein is also low in cirrhosis, as the protein is synthesized in the liver and excess vitamin A is stored in stellate cells in the liver leading to fibrosis. Vitamin E may also be low in children with cholestasis, but may also be falsely normal. Therefore, the ratio of serum vitamin E to total serum lipids is the most reliable biochemical index of vitamin E status during chronic childhood cholestasis [32]. Vitamin E deficiency is associated with progressively reduced reflexes, ataxia, peripheral neuropathy and loss of vision. If absorption by the enteral route is significantly impaired, supplementation of these vitamins, particularly vitamin D and E, can be done intramuscularly. For patients who are in hospital and coagulopathic, intravenous preparations exist.

Other micronutrient deficiencies that are relatively common in patients with chronic liver disease are those of vitamin B6, vitamin C and zinc. They need to be considered in adolescents who potentially are not on any nutritional supplements [33]. Vitamin B12 is almost never found to be deficient, and in fact, for reasons unclear, vitamin B12 levels are higher with more advanced liver disease. Iron deficiency in patients with cirrhosis is not commonly described, as most patients will have a normocytic or macrocytic anaemia of chronic disease. If iron deficiency is suspected, detailed iron studies would be required, as ferritin can be falsely elevated in inflammation. After LT though iron deficiency anaemia becomes more common [34]. Magnesium and copper deficiency may occur in about 13–17% of cases.

Protein requirements in adolescents with CLD are increased above the standard requirements of 1.0–1.24 g/kg/day to 1.2–1.5 g/kg/day, because of increased protein loss, amino acid oxidation and poor nutrition [35–37]. Branched chain amino acids requirements in children with CLD are also increased [38]. Amino acids are the

primary source for gluconeogenesis and they are derived from proteolysis of skeletal muscle. The proteolysis generates aromatic and branched chain amino acids (BCAA), but only BCAA can be catabolized in the skeletal muscle as an energy source and therefore plasma BCAA concentrations are lower in cirrhotic patients. In contrast, aromatic amino acids are primarily metabolized in the liver, but due to both porto-systemic shunting and hepatocellular dysfunction their plasma concentrations are increased in CLD. Frequently, supplements to children with CLD will have more BCAA to help reverse this imbalance of a raised ratio of aromatic amino acids to BCAA, which is linked to sarcopenia and hepatic encephalopathy.

Requirements for carbohydrates are as per normal children; 50–65% of their daily caloric intake [30, 37]. Adolescents with advanced CLD are at risk of hypoglycaemia, because of reduced glycogen reserve and in addition to this periods of starvation should be kept short, because their metabolism shifts to catabolism a lot sooner than in healthy individuals. Therefore, in patients with cirrhosis 3–5 meals a day with a late evening snack are recommended [39]. Peripheral insulin resistance has been shown to be present in patients with cirrhosis and elegant studies by Müller et al. have shown its presence regardless of aetiology of the cirrhosis, the severity of the liver impairment and the clinical and nutritional state of the patients [15]. The implications of this metabolic phenomenon have drawn attention in recent years and are mostly related to anabolic resistance which can potentially contribute to sarcopenia and impaired growth in adolescence. The insulin resistance has been shown to reflect reduced glycogen synthesis and reduced insulin-dependent glucose transport into the muscle cells [15, 17] and not hepatic insulin resistance.

Even in the modern era where the importance of the nutritional management of children with CLD is accepted, a significant percentage of children with CLD are malnourished. In one cohort almost 50% of the children were malnourished with 5% being severely malnourished and 38% of them with growth failure. Almost two thirds of the children with normal nourishment were over 5 years of age [40]. Malnutrition is known to negatively impact neurocognitive development and growth and is associated with worse outcomes after LT [41]. It is pertinent that we gain a deeper understanding of the role of nutrition and metabolism in CLD and become more sophisticated and targeted in our approach to manage it. This would achieve the best outcomes for our patients not only for their immediate survival, but for their overall future [42].

Liver Transplant

After LT, nutritional interventions are frequently relaxed, but there are some key issues worth considering when reviewing these patients in the longer term. One issue is the development of food allergies post LT. About 5.7%–37% of paediatric recipients develop LT-induced food allergy [43]. The other issue is that obesity and metabolic syndrome have been increasingly reported after solid organ transplantation.

In adults, obesity and metabolic syndrome after LT have been described and unfortunately a similar situation has been seen in children. One study retrospectively reviewed 70 children, the majority of which had had LT when they were less than one year old. This study found that 44% of these children were overweight or obese 3 years after transplant and this percentage dropped to 26% at 5 years post-transplant [44]. The children who were overweight or obese at transplant were more likely to have been overweight or obese at 6 months after transplant and about a third of the more malnourished ones at transplant were overweight or obese at 3 and 5 years post LT [44]. It is useful to know that the children who are overweight/obese after LT tend to gain significant weight in their first year after transplant, which is when they are under the most intense follow up [44]. Another study looking at all children (6–20 years) recipients of LT in the US from 1987–2010, found that weight at transplant was not associated with obesity by 10 years after transplant. The prevalence of post-transplant obesity remained as high as 20%–50% in long-term follow-up [45].

Non-alcoholic Fatty Liver Disease (NAFLD)

Studies looking at nutritional interventions and their impact on NAFLD are difficult to assess, because they vary in how NAFLD is defined/diagnosed. Whereas the gold standard is liver biopsy for many of these studies the diagnosis is based on ultrasound, MRI and/or liver function tests. Vitamin E supplementation has been shown to improve histology in patients with NASH, whereas it does not seem to have an impact on liver function tests [46]. It may have a role in young patients that are finding it difficult to adhere to lifestyle changes, but more evidence in that direction is required [47]. Benefits from supplementation with probiotics have been inconsistent and in particular these studies tend to be of relative short duration and therefore do not assess for the potential of the microbiome variations once the probiotics have been stopped [48].

Other supplements that have been trialled are omega-3 fatty acids. Some of the trials done in children have shown a reduction in liver steatosis, but again the difficulty in comparing the studies is due to the different composition of omega-3 supplements used, the different dosing and the variation in time periods [48]. Studies comparing low fat to low glycaemic diets have shown similar benefits with both interventions [49] and do not favour one over the other. Currently the only dietary intervention with proven benefits for the reduction or resolution of NAFLD is that of weight loss, regardless of macronutrient composition of the diet. In spite of experimental data showing an association between fructose intake and the development of a fatty liver [50], reduction of fructose intake when compared to reduced glucose intake in children it did not have any effect on liver steatosis [51].

Low levels of vitamin D are quite common in patients with NAFLD, and vitamin D has been demonstrated to have an anti-inflammatory and anti-fibrogenic effect on the liver. One study in the UK has shown that only about 19% of children with

NAFLD had sufficient levels of vitamin D and certain genetic polymorphisms in the vitamin D metabolic pathway, including the vitamin D receptor, were independently associated with increased steatosis [52]. A similar study in adults, which included controls, did not find any association between vitamin D deficiency and expression of vitamin D-related genes and histological severity in patients with NAFLD [53].

In addition to the above, special mention needs to be made to alcohol intake. Alcohol is one of the commonest causes of end-stage liver disease with 50% of cirrhosis-related mortality is attributed in some way to alcohol. With the increasing prevalence of obesity in the general population, one needs to be aware that alcohol contributes to liver diseases of other aetiologies, including NAFLD. This may be relevant for older adolescents or young adults.

Growth in Adolescence (Table 1.2)

Chronic Liver Disease

Growth failure is commonly seen in children with chronic diseases and CLD affects growth significantly particularly when diagnosed in infancy. The factors contributing to the growth failure are multiple and ultimately result in malnutrition and anabolic resistance. Children with CLD are likely to have increased energy needs and increased energy losses due to malabsorption because of cholestasis and portal enteropathy, but also decreased energy intake due to anorexia and abdominal organomegaly and discomfort.

A state of growth hormone (GH) resistance has been very well described, with high GH levels and low IGF-1 levels, probably due to IGF-1 being synthesized by the liver [54]. GH replacement in CLD is unlikely to be successful, because in CLD

Table 1.2 Growth in adolescence

A.	**Chronic Liver Disease**
	Growth failure is common
	There is growth hormone resistance with insulin resistance resulting in anabolic resistance
	Hepatic osteodystrophy is very well described and is multifactorial
B.	**Liver Transplant**
	Impaired growth may persist post LT
	Sarcopenia is associated with slower growth
	Avascular bone necrosis, scoliosis and fractures may develop post LT
C.	**NAFLD**
	People that were small for age as babies are at higher risk of developing NAFLD if they become obese
	Upper body fat distribution is associated with NAFLD
	10% weight loss has a significant beneficial effect on liver steatosis

IGF-1 levels are low and do not increase in response to treatment with recombinant GH [55]. In one cohort 38% of the children had growth failure/malnourishment [40] and this percentage increases to 60% in children being assessed for LT [56]. As previously mentioned, patients with advanced CLD also have peripheral insulin resistance, which results in impaired anabolic function of insulin in their muscles and growth [15].

Liver disease is known to affect bone health. Patients with liver disease may suffer from hepatic osteodystrophy, a term used to describe the clinical manifestations of the metabolic bone disease. The pathogenesis of hepatic osteodystrophy is complex and includes deficiency in 25-hydroxylation of vitamin D by the liver, resulting in secondary hyperparathyroidism, deficiency of vitamin K required for making bone matrix protein, IGF-1 deficiency or insensitivity (which is involved in osteoblast differentiation and proliferation), hypogonadism, medications—particularly steroids, a sedentary lifestyle and poor nutrition [57–59]. Optimization of nutrition may prevent further stunting of growth before LT, but because of the anabolic resistance it is rarely successful. Hepatic osteodystrophy in children results in low bone mass and fractures. The vitamin D deficiency should be treated aggressively with cholecalciferol or ergocalciferol. The active vitamin D metabolites alphacalcidol or calcitriol can be used to increase calcium absorption from the gut but will do nothing to increase vitamin D stores. Children before LT have an increased prevalence of fractures of 10–13%. Most fractures are vertebral and related to low spine bone mineral density. Frequently, they are asymptomatic but may also cause chronic pain and later scoliosis. The main risk groups are infants with cholestatic liver disease and adolescents with later LT and greater BMI [56], but children with non-cholestatic liver disease may also suffer from low impact fractures unrelated to low bone mineral density [60].

Liver Transplant

It has been well described that post-LT children catch up in weight and subsequently in height [61, 62]. This may be because of the, at least in part, resolution of the growth hormone resistance state seen before surgery [54, 63]. For 20% of children that do not achieve their parental height potential after LT, it remains to be seen with randomised controlled trials if growth hormone supplementation would be suitable [56]. Height z-score at transplant is the most important predictor of linear growth post-LT. In a study that looked at linear growth for 10 years post-LT most of the catch up in height was noted in the first 2 years post-LT after which no significant increases in z-scores were noted [64]. Another study that compared children with biliary atresia that were transplanted before and after the age of 1 year, noted that at 3 years post-LT, the ones who were transplanted before the age of 1 year had a higher height gain even though eventually there were no significant differences in height z-score between the children transplanted before and after their first birthday [65]. A few studies have reported better growth with steroid-free immunosuppression regimes [56, 61, 66].

Sarcopenia has been noted in patients with CLD and particularly the ones that reach end stage liver disease requiring LT. Unfortunately, the operation does not always resolve the issue of sarcopenia and 41% of children post-LT have been found to remain sarcopenic [67]. Post-LT sarcopenia has been associated with slower growth [67]. This would have implications for children who are transplanted at a younger age, as they are the ones most at risk of being sarcopenic and this sarcopenia and poor growth would affect them during puberty.

Other issues related to growth after LT are risks for avascular bone necrosis (4%) and for development of scoliosis (13–38%) [56]. The risk for fractures that was there pre-transplant seems to persist after LT as well [56].

Non-alcoholic Fatty Liver Disease (NAFLD)

Individuals who are small during early childhood and then obese as adults are at the highest risk of having NAFLD as adults [68]. Intrauterine growth retardation (IUGR) at birth is associated with metabolic syndrome, insulin resistance and NAFLD later in life. Of 90 children with NAFLD in Italy almost 39% were small for gestational age in comparison to 6.7% in the controls. In the same study, being small for gestational age was independently associated with NAFLD after correction for age, sex, BMI z-score, and glucose homeostasis. Among children with NAFLD, small for gestational age was significantly associated with insulin resistance after correction for age, sex, and BMI z-score, and the association was maintained even after exclusion of type 2 diabetes cases [69]. Catch up growth reduction strategies may help mitigate this risks [70]. In the USA, it was found that children with NAFLD have an overrepresentation of low and high birth weight in comparison to the general population [71]. Interestingly, children with high birth weight were more at risk of having steatosis and steatohepatitis when they developed NAFLD and the ones with low birth weight more at risk of having fibrosis [71].

Aberrations in various hormones associated with growth have been described in young people with NAFLD. IGF-I was the major predictor of ballooning in 14 obese subjects with NAFLD and of NAFLD activity score. IGF-I/IGFBP-3 ratio was the major predictor of liver inflammation and IGF-II was the major predictor of liver fibrosis. Insulin-like growth factor-I and its receptor are upregulated in children with NAFLD. These findings are indicative of the possible use of insulin-like growth factor-I as treatment in paediatric NAFLD [72]. In a study looking at stimulated growth hormone response in obese children, with and without NAFLD, and normal controls, the obese group had significantly lower peak stimulated GH ($p < 0.001$) and lower insulin-like growth factor 1 (IGF-1) ($p < 0.001$) compared with the control group. Children with NAFLD had significantly lower peak stimulated GH ($p < 0.001$) and lower IGF-1 ($p = 0.022$) compared with non-NAFLD

group [73]. Peak stimulated GH was negatively associated with the homeostasis model assessment of insulin resistance (HOMA-IR); in other words, the higher GH was associated with better insulin sensitivity [73]. Children and adolescents with NAFLD have been shown to have higher TSH levels, which are associated with the degree of hepatic steatosis and therefore this mild thyroid dysfunction may contribute to an unfavourable metabolic profile in these children and adolescents [74].

Upper body fat distribution in adolescents, like in adults, is associated with the development of NAFLD [75]. Significantly higher BMI, BMI standard deviation score, waist circumference, and weight-to- height ratio were found in obese children with NAFLD compared to obese children without NAFLD, but only weight-to-height ratio was found to be an independent predictor for NAFLD [76]. Higher hepatic fat content in children with a mean age of 10 years has been shown to be significantly associated with lower bone mineral density regardless of confounders amongst others like age, sex, activity and vitamin D intake [77].

Achievement of 10% weight loss can have a significant effect of mitigating the effects of a fatty liver. Body composition and metabolic profiling of obese children with and without NAFLD has shown a decrease in total body mass, BMI, body fat, visceral and subcutaneous fat, insulin concentration, HOMA-IR, total cholesterol and an increase in lean body mass in both groups after weight loss therapy [78]. Bariatric surgery can decrease the grade of steatosis, hepatic inflammation, and fibrosis in non-alcoholic steatohepatitis (NASH). Roux-en-Y gastric bypass is considered a safe and effective option for adolescents with extreme obesity if an appropriate long-term follow-up is provided. Laparoscopic adjustable gastric banding and sleeve gastrectomy are still considered investigational for adolescents [79]. Uncomplicated NAFLD is not an indication for bariatric surgery.

Puberty (Table 1.3)

Table 1.3 Puberty in adolescence

A.	**Chronic Liver Disease**
	Puberty is delayed
	Males exhibit hypogonadism and females have menstrual irregularities
	Pregnancies are still possible; discussion about contraception is advised where appropriate
B.	**Liver Transplant**
	About 40% of adolescents have delayed puberty post LT
	Pubertal delay can affect final adult height attainment
	Menarche is delayed on average by a year
C.	**NAFLD**
	Obese boys with NAFLD have lower testosterone levels
	PCOS is associated with an increased risk to develop NAFLD
	Higher testosterone levels are associated with improved steatosis and fibrosis in boys, but are detrimental to girls

Chronic Liver Disease

Pubertal delay is defined by sexual maturation not being apparent by age 14 years in boys or age 13 years in girls. The same diagnosis applies if menarche is absent by age 16 years in girls or within 5 years of the onset of puberty [80]. Chronic disease is well known to be associated with delayed puberty and CLD is no exception. More specific to CLD, male hypogonadism is well described in cirrhotic males [81] with low testosterone levels resulting from hypogonadotropic hypogonadism and an additional contribution of increased oestrogen levels due to porto-systemic shunting and due to peripheral conversion of androgens [82, 83]. The reduction in testosterone, which is an anabolic hormone, is likely to contribute to the sarcopenia, osteoporosis, gynecomastia, and low libido reported in these males [82]. Trials in adults have shown benefit of intramuscular injections with testosterone, but this is not an established treatment and certainly not in adolescents [84]. Menstrual cycle irregularities, amenorrhoea and infertility are seen in females with cirrhosis mainly due to dysfunction of the hypothalamo-pituitary axis [85, 86]. In spite of this, pregnancies do occur even in advanced liver disease and therefore appropriate contraception needs to be discussed with all adolescents engaging in sexual activities. Excellent guidance exists for reproductive health in liver disease by the American Association for the Study of Liver Diseases [87].

Liver Transplant

Apart from linear growth impairment, delayed puberty has also been described in pubertal LT recipients, with pre-transplant growth impairment identified as potentially modifiable. Review of data collected prospectively through the Studies of Pediatric Liver Transplantation registry identified 353 children with Tanner stage data recorded. Thirty-nine percent of girls and 42% of boys aged 16–18 years had not reached Tanner stage 5, whereas in a normative population 100% would have reached Tanner stage 5 by this age [88]. Pubertal delay can have a negative effect on attainment of final adult height and therefore in this population catch-up growth by the end of puberty may be incomplete [88]. An older study of 35 patients (17 male and 18 female) with a mean age at transplant of 10.6 years demonstrated that pubertal scores decreased in the first 6 to 12 months after LT, but there was a catch up in the following 5 years [89]. Menarche was at 14.4 years, which is significantly delayed in comparison with the 13.3 years noted in the general population [89].

NAFLD

In adult studies, obese subjects with NAFLD have been shown to have poor sperm quality, and lower testosterone and luteinizing hormone levels. Kurku et al. studied pubertal status and gonadal function of obese boys with NAFLD by comparing obese boys with and without NAFLD to healthy controls. There was no difference between the groups regarding testicular size and pubertal status, or levels of gonadotrophins and anti-Mullerian hormone. Total testosterone levels were significantly lower in the obese-NAFLD group in comparison to the obese-non NAFLD group and the control group [90].

For women there is an inverse relationship between age at menarche and the development of NAFLD later in life [91, 92] independent of BMI and insulin resistance [93]. The timing of onset of menarche affects the development of NAFLD in the future as per diagnosis by CT; earlier onset by a year was associated with NAFLD with a relative risk of 1.15, but also with increase in visceral adipose tissue, intramuscular and subcutaneous adiposity [94]. A study that identified female patients with polycystic ovary syndrome (PCOS) from a national inpatient database concluded that patients with PCOS were younger and more likely to be obese than those without PCOS [95]. They were though less likely to have diabetes mellitus, hypertension, and dyslipidaemia, but had a four times higher risk of developing NAFLD [95]. Androgen excess is believed to be the most likely reason for this [96].

In a study of 573 children with NAFLD (median age at liver biopsy 13.1 years) the associations of circulating hormones with histological features of NAFLD were looked at. Lower sex hormone binding globulin was inversely associated with steatosis severity in both boys and girls, and with portal inflammation in girls only. Higher testosterone was related to improved features of steatosis and fibrosis in boys, but was detrimental in girls. In boys and girls, higher estrone, oestradiol and testosterone were associated with lower portal inflammation grade; higher oestradiol was positively associated with hepatic ballooning severity; dehydroepiandrosterone was inversely associated with hepatic ballooning and NASH severity. Androstenedione was not associated with NAFLD features. These findings were consistent with what has been observed in adults [97].

Another study has shown that steatosis, portal inflammation, and fibrosis are less severe during or after puberty than before puberty among subjects with NAFLD. It would be interesting to know, if the histological features seen in prepubescent patients with NAFLD, improve after puberty [98]. Differences in paediatric NAFLD when compared to adult NAFLD may be due to the occurrence of hepatic metabolic derangements typical of NAFLD during periods of active growth (infancy, mid-childhood and puberty) [99].

Key Points for Adult Hepatologists

In addition to the above, one needs to keep in mind that CLD frequently occurs in the context of other conditions that have their own implications for the nutrition, growth, and pubertal development of the adolescent patient. For example, it is not uncommon for children with autoimmune liver disease to have concomitant inflammatory bowel disease, sickle cell disease may be accompanied by a chronic cholangiopathy, and cystic fibrosis-related liver disease may be significant enough to require LT. Patients with NAFLD may have concomitant diabetes, hypertension and sometimes nephropathy.

The pathophysiology of CLD is similar for children, adolescents and adults, but in the younger patients there are two additional dimensions that can be affected—growth and neurocognitive development. The effects on growth and neurocognitive development can obviously be longstanding and may persist after the condition is treated or successfully managed with LT. After LT there may be ongoing issues with nutrition, growth and puberty and these will need to be optimally addressed as they could have a profound effect on how these young people integrate in society as adults. The prevalence of NAFLD in adolescents is increasing as overall levels of obesity increase and this could affect their growth and puberty as well.

CLD can affect the nutritional status, growth and pubertal maturation of adolescents and requires specialist and frequently individualised management to achieve optimal results. There are still many gaps in our understanding of the pathophysiology of these metabolic changes and more research is needed for the development of successful treatment strategies, particularly as these aberrations in nutritional status, growth and puberty are likely to exert their effects for the longer term future of these young people.

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Chapter 2
Neurodevelopment During Adolescence

Hester Velthuis and Grainne McAlonan

Puberty is a human neuroendocrinological developmental period (see Table 2.1). Individuals naturally enter puberty during adolescence. Adolescence is defined by the World Health Organisation as the timespan between the ages 10 to 19 years, although research on "young people" often also includes youth aged 15 to 24 years old [1]. The neuroendocrinological developments of puberty are accompanied by rapid physical, psychological and behavioural changes. As a result, health risks and the burden of disease can change rather abruptly [2]. Adolescence is, therefore, a critical brain maturation time with an important impact upon cognition, behaviour, and mental health, which will ultimately influence education, employment, and social outcomes. This makes knowledge of adolescent brain development for health-care professionals treating patients in this age group essential.

The investigation of brain development and maturation in the living human is challenging. To better understand and predict the effects on brain maturation when puberty is disrupted, we first need to have a clear picture of 'typical' brain development during this period. To map the trajectory of brain maturation, sizeable datasets of longitudinal data *in vivo* are needed. Advances in neuroimaging techniques allow

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Table 2.1 Endocrine events in puberty. Sex differences of endocrine events show that pubertal development in females starts on average earlier than in males

Endocrine event	Developmental period	References
Adrenarche: characterized by the increase in adrenal androgens (dehydroepiandrosterone (DHEA), DHEA-sulphites and androstenedione)	In females between 6 and 9 years, in males between 7 and 10 years	[3, 4]
Gonadarche: starting with the reactivation of the gonadotropin-releasing hormone neurons which stimulates the secretion of sex steroid hormones (testosterone and oestrogens) from the gonad	In females between 8 and 14 years (mean age 11), in males between 9 and 15 years (mean age 12)	[5, 6]
Activation of the 'growth axis' resulting in a linear growth spurt	In females around age 12, in males around age 14.	[7, 8]

us to obtain these datasets on a large and safe scale; and with the emergence of Magnetic Resonance Imaging (MRI) in particular, our knowledge of brain maturation has grown exponentially. This technique enables us to quantify structure, function, and neurochemical concentrations non-invasively in the living brain. However, there are many possible neuroimaging indices of neurodevelopment, including measures of neuronal integrity, structural and functional connectivity, or temporal change. This can make comparison between studies complex, and it can be difficult to interpret the underlying biological substrates of MR signals.

In this introduction, we provide an overview of typical neurodevelopment in adolescence based on evidence from MRI research. We further address common morbidities and 'neurodivergence' emerging from atypical neurodevelopment.

Anatomy and Brain Functions

Brain tissue is differentiated into 'relatively unmyelinated' grey matter and 'myelinated' white matter. Grey matter is the major component of the cerebral cortex and subcortical structures. In the deep part of the cerebrum lays the white matter, composed of bundles that connect the different grey matter areas to each other. The cerebrum is divided into four lobes: frontal, parietal, occipital, and temporal (See Table 2.2 for their main functional involvement); and subcortical structures including e.g. amygdala, thalamus, hippocampus, and basal ganglia.

The basal ganglia are a group of subcortical 'nuclei' in the cerebrum comprising the striatum (consisting of the caudate nucleus, nucleus accumbens and putamen), globus pallidus, substantia nigra, and subthalamic nucleus. The basal ganglia have strong connections with the thalamus and cortex and coordinate the signal transmission between these regions. The thalamus makes up a central part of basal ganglia-thalamic-cortical connections [18, 19] and acts as mediator in sensory processing and sleep-arousal state regulation. With the amygdala, essential for emotion processing [20], and the hippocampus a key memory hub (Per [21]), correct signalling across these subcortical-cortical pathways is essential for appropriate behavioural control, movement regulation, and reward processing [22].

Table 2.2 Lobes of the cerebrum

Lobe	Function	References
Frontal lobe	Cognitive and executive functions (e.g. control of voluntary movement or activity)	[9–11]
Parietal lobe	Processing information about temperature, taste, touch, and movement	[12, 13]
Occipital lobe	Processing of visual information	[14, 15]
Temporal lobe	Processing memories and integrating sensations (e.g. smell, taste, sound, sight, touch) in memory	[16, 17]

Neuronal Maturation

Neural Structure

As the brain ages, neurons become more connected and specialized, and their function matures. Neural connections (synapses) undergo modifications in response to the internal and external environment. Synapses are removed in a process called "synaptic pruning" or adapt as a result of long-lasting neuronal activation or inactivation [23]; respectively, long-term potentiation (LTP) or long-term depression (LTD). These mechanisms increase synaptic efficacy and hence the efficiency of connections between brain regions. Myelin sheaths are formed around neuronal axons, which increases the signalling speed from neuron to neuron. Synaptic pruning continues into adolescence [24–26], while neuronal myelination continues even longer, up to the 2nd or 3rd decade of life [27, 28]. When the trajectory of brain maturation is disrupted, the resulting developmental outcomes can be atypical.

Brain Chemistry

Alongside structural maturational changes, neurotransmitter systems undergo alterations throughout development. Neurotransmitters mediate the signal transmission between neurons via a cycle of neurotransmitter 'release > binding > signal generation > reuptake' taking place in the synapse [29]. Functional neurotransmission is essential for synaptic pruning, and synaptic pruning is essential for a healthy neurotransmitter circuitry. Disrupted pruning predominantly impacts upon the glutamatergic neurotransmission system [30], which is the brain's most abundant 'excitatory' neurotransmitter. The GABAergic system, the brain's most abundant 'inhibitory' neurotransmitter, is predominantly comprised of GABAergic interneurons that are critical for the regulation of the glutamatergic system [25]. The interplay of glutamate and GABA, which regulates the 'excitation-inhibition' balance in the brain, is responsible for shaping synaptic and hence network connectivity [31].

There are periods in development which are especially 'sensitive' to influences on neuronal growth; very early childhood is one and adolescence another [32, 33]. Many synaptic changes occur during these sensitive periods, with glutamatergic and GABAergic neurotransmitters essential for delimitation of these time windows. Prior to and after these sensitive periods, synaptic adaptation is limited [25]. During adolescence, glutamatergic and GABAergic systems underpin the maturation of excitation-inhibition balance, but also the endocannabinoid system, which is critical for the regulation of the glutamatergic system, also has a key impact [25]. It has been suggested that not only are adolescents more prone to experimentation with substances because of the maturation status of their brain [34], this experiment may then have a substantial effect on the finely balanced neurochemical processes in the brain needed for behaviour control. For example, this age group shows a particular 'sensitivity' to THC, an active compound of cannabis [32]. THC transiently disturbs the endocannabinoid neurotransmitters system and its regulation of glutamate and GABA release. As a result, the maturation of (predominantly frontal) neural circuitries may be affected adversely [32]. Increasing the sensitivity of the brain further [25]. This may lead to more experimentation (i.e. with substances) and subsequently more harm (i.e. neural damage), spiralling into a vicious circle of disrupted neuronal maturation.

Brain Volumetric Changes

Timing and Time Course

The greatest expansion in brain size occurs during pregnancy up to 2 years after birth [24, 35]. Brain growth continues and reaches a peak in adolescence [36]. On average, puberty happens earlier in females compared to males [37]. This is also the case for brain maturation during adolescence; onset is in females at around 10.5 years and later in males at 14.5 years of age on average. [38].

The same pattern is observed for grey matter volume (in frontal and parietal cortices); peaking in females at 11 years and in males at 12 years of age [38, 39]. This peak thus coincides with gonadarche in each sex, suggesting a possible interaction between grey matter development and levels of sex steroid hormones. (Further explained in section "sex-steroid hormones and brain development") Subsequently, grey matter volume declines throughout and after adolescence. This decline is thought to be the result of ongoing synaptic pruning [38], which has been shown to have a direct effect on (reducing) grey matter volume [40].

In contrast, white matter volume increases over the course of childhood throughout adolescence [41, 42], reaching its peak during the 4th decade of life [43]. During adolescence, the volume of white matter in many different tracts (e.g. association tracts) and brain regions (e.g. callosum, putamen, caudate) increases [44–46]. This volume increase has been attributed to ongoing axonal myelination [47] or axonal

enlargement [48]. The sharp increase in white matter volume seen in males is thought to be largely explained by axonal enlargement, which is directly testosterone-related. Studies using diffusion MRI, a technique capable of measuring white matter microstructure (e.g. structural organisation and density), confirm this white matter volume increase in adolescent males is accompanied by advancing (micro) structural organisation and myelination density over the course of adolescence [44, 49, 50]. This maturation trajectory of white matter microstructure is more prolonged in males—*for a review* [27]. Thus, for both grey and white matter, maturation during adolescence peaks on average later in males [37].

In sum, the maturational trajectories of grey matter and white matter in both sexes go hand-in-hand up to adolescence, but deflect in different directions thereafter [51]. Total volume of grey matter in both sexes peaks in mid-childhood to early adolescence and then decreases along with cortical thickness in a U-shaped developmental trajectory [52] *for a review*—[27]. White matter volume expands, and microstructure matures throughout adolescence, but this trajectory is extended in adolescent males compared to females.

It is very important to note that most of the findings of sex differences in the timing of brain changes reported during adolescence were not controlled for 'pubertal timing'. Although it has been assumed that the timing of neuronal maturational changes is linked to the timing of puberty, this has not always been directly examined. In those studies that do control for pubertal timing, there are inconsistencies in approach [53–55]. It is generally accepted that the trajectory of brain maturation in adolescence may be influenced by both pubertal development stage (e.g. Tanner stage,[1] pubertal development score[2]) and related endocrinological changes [51]. However, a recent review highlights a role for additional components of brain development during adolescence, such as the intra-individual 'tempo' of pubertal development and the temporal dynamics of hormone levels, and these can be overlooked when focussing on 'coarse' descriptions of stages or levels [51].

Sex Differentiation

As noted above, sex influences bulk measures of brain; indeed across development, females have smaller average brains than males relative to body size—*for a review* [56]. However, throughout development, sex also has differential impact at a brain regional level. To illustrate; for cortical grey matter, cortical thinning in adolescent males occurs predominantly in the limbic (posterior cingulate), prefrontal (Megan M. [57]) and parietal cortices [58]. Whereas in adolescent females, the most

[1] Tanner stages are divided into five sexual maturation stages, from the pre-pubertal form to the adult form. The Tanner scale provides a rating of sexual maturity [87].

[2] Pubertal development score (PDS) is a self-report measure of pubertal status for young adolescents [88].

pronounced volumetric changes are seen in the parietal (somatosensory) [59], limbic [58], and temporal [57] cortices.

Sexually dimorphic development also occurs in subcortical grey matter. Similar to the cortex, the volumes of the amygdala and thalamus are significantly smaller in adolescent females compared to males [60–62]. In addition, amygdala volume becomes even smaller over the course of puberty in females, whereas it gets larger in males [58]—*for a review* [51]. In contrast, volumes of the basal ganglia and hippocampus are disproportionately larger in adolescent females compared to males [60], but their volumes subsequently increase in females (hippocampus) and decrease in males (basal ganglia) [38, 58]. Precisely how these sex differences in brain regional growth link to cognition, emotion and behaviour in the sexes is not yet understood.

To conclude, cortical and subcortical grey matter exhibit sexually dimorphic volumetric trajectories. For subcortical structures, volume differences between the sexes increase throughout adolescence (Megan M. [63]). It is suggested that the observed dimorphism may be underpinned by a sex-specific propensity for change among these brain regions. Yet we should be cautious before fully accepting that there are very strong sex differences in specific brain regions [51]. There are subtleties we likely do not appreciate, and again, pubertal development stage and/or "tempo" (further explained in section "timing and time course") is thought to impact on neurodevelopment sometimes more than sex per se [51].

Sex-steroid Hormones and Brain Development

Sex steroid hormones are produced by the gonads and adrenal glands and include androgens (e.g. testosterone, dehydroepiandrosterone (DHEA)), oestrogens (e.g. oestradiol), and progestogens. During the perinatal period, the first time window for steroid-dependent changes in neural organisation, these hormones produce sexually differentiated brain circuits [64, 65]. Gonadarche signals the second time window for steroid-dependent changes in neural organisation [66]. Sex steroids cause irreversible structural changes to neuronal systems called "organisational effects". The time windows for these effects to have an impact are limited to sensitive periods for neuronal plasticity (e.g. perinatal, puberty)—*for a review* [51]. Sex steroids can also have 'activational effects' which instead lead to temporary changes in the activity of the neural systems [67]. (Further explained in section "Functional changes".)

It is important to note that different sex steroids play a role in different periods of adolescent development. Testosterone is implicated in late pubertal stages in males only, whereas its 'pro-hormone' DHEA is involved in early puberty in both males and females [68, 69]. Equally, each sex steroid has a distinct pattern of association with structural brain development. Rising testosterone levels are associated with grey matter volume reduction (i.e. cortical thinning) and structural changes in white matter [50, 55, 70]. These effects are most pronounced in males, as is the rise/levels of testosterone across puberty [71]. Less consistent associations are found for

oestradiol levels, although higher oestradiol levels may limit cortical thinning in females [51, 55]. These results indicate that sex steroids relate to sex-specific changes in cortical development across adolescence [57].

Non-steroid hormones (e.g. cortisol, luteinizing hormone) also play a role in pubertal development and may affect the neurodevelopment during adolescence. However, it is beyond the scope of the present review to discuss these further here.

Functional Changes

There is broad agreement that the sensitive period for neuroplastic changes in the brain extends into adolescence [32, 66]. Such changes in neural structure can impact upon functional neural networks such as the social, emotional, and higher-order cognition networks [25, 67]. All of these higher-order networks incorporate the frontal cortex and its targets, and frontal functional maturation continues until or after late adolescence [72, 73]. This predominantly frontal functional maturation can partly explain the wide variations in behaviour seen in this age group. That is, because the frontal lobe contributes to a multiplicity of higher-order processes, frontal maturational changes across adolescence are reflected in marked alterations (and variations) in cognition and behaviour. We present below a brief sample of the neurodevelopmental changes occurring in adolescence that underly some of these behaviours.

Social Cognitive Emotions

The prefrontal and temporal cortical regions associated with emotional processing become gradually more active over the course of adolescent development [74]. Similarly, subcortical brain structures that support emotional processing (i.e. amygdala and ventral striatum) show increasing neural activity by the middle of adolescence [75, 76]. Overall, neural activation during emotional processing increases with advancing metrics of pubertal development. A recent meta-analysis concludes that with advancing pubertal development, processing social information improves [76].

Reward Processing

Nucleus accumbens (striatum) activation is associated with reward processing (e.g. winning in a gambling task). The level of brain activation of the nucleus accumbens during reward-processing peaks by mid-adolescence [77]. This heightened activity

is linearly associated with (saliva) testosterone concentration [78]. These findings are in line with the increase of testosterone levels toward later pubertal stages.

However, despite the relatively large amount of literature focussing on the nucleus accumbens with regards to reward processing, a recent meta-analysis concludes "no convergence" in region or directionality [76]. Note that this is possibly due to the meta-analytical method used, which attaches equal weight to each finding regardless of, for example, sample size in a study. Thus, one should be cautious with the generalization of findings, even from meta-analyses.

Emotional Faces

Facial recognition improves steadily during the first decade of life but shows a decline around age 12 [79]. Specifically, young adolescents (10–11 years in females and 11–12 years in males) seem to have more difficulty with the recognition of emotion-expression, but their abilities improve/return to prepuberty levels by age 16–17 [80]. This has been suggested to be caused by a temporary relative inefficiency in frontal circuitry prior to the pruning of excess (mostly glutamatergic) synaptic contacts [80]. Recent meta-analysis also suggests changes in amygdala activation during face processing are associated with pubertal development [76], though the directionality of the neural activation changes are inconsistent across the constituent studies.

Key Findings

While we have a lot to learn about brain maturation during adolescence, there is reasonable consensus that the following key changes occur:

- Total brain volume peaks in early/mid-adolescence and declines thereafter. This decline is thought to be a result from ongoing neural pruning, which ultimately decreases grey matter volume.

Sex differences: The average age for total brain volume to decline is 4 years later in males than females. The 'deflection point' of increasing difference in total brain volume between males and females is probably a result of the later decline in grey matter volume in males, and continuous increase in white matter volumes that is augmented in males compared to females.

- Total grey matter volume peaks in early adolescence and declines thereafter.

Sex differences: Throughout adolescence, thinning of cortical grey matter is more pronounced in males. This is associated with the exponential increase in testosterone levels in males—showing a positive correlation with cortical thinning, and the exponential increase in oestradiol in females—showing a negative correlation with

cortical thinning [55]. There are differences in grey matter maturation among subcortical structures. Amygdala and thalamus volumes are smaller in adolescent females and decreasing throughout adolescence in females only, whereas the basal ganglia and hippocampus grey matter volumes are smaller in males and decreasing in males only. These structure-dependent sex differentiations are thought to have clinical relevance, considering the involvement of these structures in 'gender-disparate' mental health conditions. For instance, affective disorders (e.g. mood and anxiety disorders) incidence increases sharply in females toward late adolescence and beyond [81–83]. These disorders are known for the implication of the amygdala [84]. This can be linked with the findings of smaller volumes in adolescent females compared to males, which decreases in females away from the volumes found in males.

- Total white matter volume rises during childhood and continues to increase throughout adolescence.

Sex differences: The increase in white matter volume throughout adolescence is augmented in males compared to females. This is thought to be potentially a result of testosterone-related changes to myelinated axons, which predominantly occur in males [48].

- The microstructure of white matter shows increasing organisational maturation during adolescence and a growing myelination density.

Longitudinal studies have contributed to the investigation of potential sex differences in the 'timing' of neurodevelopmental changes during adolescence. Overall, these studies report that indices of neural maturation occur later in males compared to females. However, the findings of sex differentiation are controversial and may be better explained by the generally *later onset* and *longer* pubertal period in males. One explanation for this sex difference could be that different sex steroids affect different brain regions. This has clinical implications because it means that different sexes have a different predisposition for mental health conditions or the development of psychological problems. For example, the (predominantly male) increase in testosterone levels over the course of puberty are positively correlated with nucleus accumbens (part of the basal ganglia/striatum) activation during reward-processing [78]. This suggests that adolescent males may be relatively more responsive to rewards than females. In turn, it is possible that sex-difference in accumbens development in adolescence contributes to, and increase, in risk-seeking behaviours observed mostly in male teens. Adolescents also have an elevated risk for experimentation with substances (i.e. cannabis) as well as an increased vulnerability for neuronal changes during this development period [34]. There is suggested that the increase of sex steroids (both testosterone and oestradiol) in adolescence is associated with increased vulnerability for neurobiological changes during this period [85]. There is a clear sex differentiation, however, concerning the timing of onset, which is typically between 15 and 25 years old, compared to two onset peaks in females at 20 to 29 years, and 45 to 49 years old [86]. Ultimately, the use of substances may lead to the development of mental health conditions (i.e. psychosis or

schizophrenia), depending on the dose used, the exact time window, and the duration of exposure [32]. It is extremely important to supervise the adolescent patient population closely in order to minimize these risks and provide adapted care.

Conclusion

The rising levels of pubertal sex-steroid hormones induce a period of increased neuroplastic sensitivity in the adolescent brain [51, 66]. Neural pruning [24], myelination [27], and maturation of neural circuitries continue into adolescence [66]. With the induction of the 'sensitive' period during adolescence, these processes become more susceptible to influence or disruption. Functional neurochemical systems, and especially the glutamatergic and GABAergic systems [30], which are key regulators of the excitation-inhibition balance in the brain, are essential for delimitation of the 'sensitive' time window in adolescence [25]. An excitation-inhibition imbalance can compromise the maturation of grey and white matter tissue. Thus, physical conditions which disrupt the sex-steroid hormone axis and/or influence brain biochemistry and hence neurotransmitter levels may well have an important impact on the neurodevelopmental trajectory of adolescence. This trajectory provides the foundations for psychological development and shapes adult outcomes, as described in the next chapter.

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Chapter 3
Impact of Liver Disease on Cognitive and Psychosocial Development

Jemma Day

Introduction

Treatment advances have resulted in children consistently surviving liver conditions that were fatal in infancy (e.g. [1]). However, despite these improvements in survival and morbidity, young people with chronic liver disease (CLD) continue to report lower health-related quality of life (HRQOL) than their peers. There is some evidence that a large portion of this relates to poorer cognition and school performance. For example, Ohnemus et al. [2] found adolescent liver transplant recipients reported HRQOL similar to healthy peers in all domains except psychosocial, school, and cognitive functioning. Furthermore, these results indicated no reported improvement in cognitive functioning over time, suggesting transplant does not 'fix' this problem. The causal factors for poorer cognition in young people with CLD are therefore beginning to attract research attention. Research in the healthy population suggests that our cognition in childhood influences socioeconomic and health outcomes in later life [3]. In order to support our young people as they navigate education and embark upon employment, there is a need for improved understanding of the relationship between CLD and the brain, including consensus regarding how the presence of CLD during childhood affects brain structure and development, and the implications of this for cognitive function.

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Why Cognition?

Hepatic encephalopathy (HE) is a spectrum of neuropsychological problems caused by an accumulation of toxic substances that are normally removed by the liver. It is well studied in adults with CLD, with validated methods of identification, monitoring and treatment available. It is widely accepted that the human brain undergoes considerable development in the first years of life, but the potential impact of HE on the developing brain is unknown. The systemic inflammation implicated in the pathogenesis of conditions such as biliary atresia may also play a role. Systemic inflammation is a well-documented risk factor for neurodevelopment conditions such as Attention deficit Hyperactivity Disorder and Autism Spectrum Conditions.

Intellectual functioning and motor skills develop rapidly during the first years of life, and there is considerable evidence that this is influenced by environmental factors [4] such as severe disease, hospitalization, and surgery during early childhood [5]. Nutritional problems [6], poor growth [7] and delayed pubertal development are also common in young people with CLD. Puberty involves a number of social and emotional developments, as discussed in Chap. 10, and this period of maturation may be further delayed in these young people, alongside impaired physical development and growth.

It is currently unknown whether earlier liver transplant would limit early neural dysfunction and improve cognitive outcomes in our young people. Given studies demonstrate the reversible nature of HE after transplantation in other cohorts [8], the timely detection of (and prevention of) factors affecting brain development could greatly benefit this population. Timely detection of neural consequences, new treatment targets and informed approaches to management of both peripheral and central pathology could bring about a step-change in the quality of life of children and young people, and optimize their long-term occupational and educational potential.

Summary of Available Literature

Collectively, the literature indicates that cognition is poorer in children and young people with CLD (e.g. [5]) but there is insufficient data to determine whether cognitive development differs between young people surviving with their native livers and young people undergoing liver transplantation. Studies tend to focus on early childhood rather than adolescence or young adulthood, and disproportionately on those already post-transplant rather than those with their native liver [9–11]. Studies are also heterogeneous due to sample size, age, condition, areas examined and tests used. A recent systematic review of the available literature [5] identified a total of 25 studies which have investigated cognition in children and young people with liver conditions (n = 1913). The majority of these (nineteen of the twenty five studies) described individuals after liver transplantation (n = 1372 children). Of those

surviving with their native livers, four out of six studies found low average or impaired scores on cognitive and behavioral measures [12–17]. Poorer cognition seems to persist into adolescence, with approximately 50% of young people scoring below 85 for IQ tests (compared to expected rates of around 15% in the general population; [18]). There is also evidence of poorer educational attainment, a probable consequence of poorer cognition, which appears to be over and above those with comparable school absence due to hospitalisation for other forms of chronic illness [19]. Many children and young people with CLD required special educational support and with poor quality of life and job performance seen into adulthood, the importance of interventions to target these impairments becomes increasingly clear.

Factors Relating to Poorer Cognition

As the literature develops, factors associated with poorer cognition are emerging.

- Liver disease from birth
- Unsuccessful Kasai portoenterostomy for patients with biliary atresia
- Failure to thrive in early childhood
- Longer duration of decompensated liver disease OR symptomatic CLD
- Cognitive impairment prior to transplantation
- Prolonged intensive care stay post-transplantation

An increasing body of evidence suggests that cognitive impairments originate *prior* to transplant in this population. In those requiring liver transplantation at a young age, *the presence of cognitive impairment prior to transplantation* is associated with lower cognitive assessment scores post-transplant [20]. Indeed, in another study conducted before the widespread availability of transplantation, Stewart et al. [21] reported that children with CLD scored lower than typically developing children of the same age on both IQ scores and physical variables (particularly height). Ng et al. [22] also reported an association between height measured at 18 months and a set of subsequent cognitive variables assessed at 24 months, and Talcott et al. [23] found a relationship between pre-transplant percentiles for height, and IQ measured at long-term follow-up: suggesting *impaired growth in early childhood* is also a related risk factor. *Duration of symptoms due to liver decompensation* also appears to relate to the level of developmental delay and long-term IQ scores measured post-operatively (e.g. Talcott, Kaller et al. [19, 23]). Talcott and colleagues found lower IQ scores most frequently in those with CLD as compared to with acute liver failure (ALF). This finding remained despite transplantation status. Similarly, cognitive outcomes have been linked to

longer duration spent in intensive care post-transplant [19]. A crucial advancement from these studies was that chronically 'asymptomatic' children had altered brain biochemistry (consistent with sub-clinical HE) and poorer cognition, whereas those presenting with ALF did not. In line with this, neurometabolic profiles associated with ALF have been shown to normalise within a time span as little as 22 weeks [15] and outcomes from Magnetic Resonance Imaging (Myoinositol and glutamate/glutamine concentrations in cortex) have been linked to disease duration. Although much of the literature relates to individuals post-transplant, there is some evidence that children surviving with their native livers (e.g. babies with biliary atresia) also have developmental delay at 12 and 24 months [22]. *Children with biliary atresia with unsuccessful hepatoportoenterostomy* (possibly reflecting more severe liver disease in the early days of childhood) were more than four times as likely to have developmental impairment, compared with those with successful surgery, defined by clearance of jaundice. *The presence of liver disease from birth* as well as the duration of deteriorating liver function prior to intervention were the two main clinical factors associated with poorer cognition in the recent review [5], and are likely to be related. Together, these analyses suggest that any adverse cognitive outcomes associated with liver disease relate to the duration of symptomatic disease rather than the effects of transplantation itself. *No differences were found between groups of children stratified by transplant history*, suggesting that transplantation is not a 'fix' for poorer cognition, particularly undertaken 'too late'—i.e. after prolonged CLD, even when the CLD is not considered severe.

It is of note here that most studies within the literature measure inteligence quotient (IQ). However, there is also evidence of impaired executive functioning (mental skills including working memory, flexible thinking, and self-control) scores, even in individuals with normal general cognition [24], which is also reflected in the adult literature. For example, Talcott and colleagues found that despite IQ scores which fell into the 'normal range', children transplanted at less than 2 years of age (which likely reflects greater illness severity in the early days of childhood) had greater executive dysfunction (inattention and inhibition) than children alive with their native liver [23].

Collectively, this suggests that children with prolonged liver disease or severe liver disease in very early childhood had the poorest cognitive outcomes despite successful transplantation, reinforcing the need for timely interventions. Until research establishes the nature of such impairment in our children and young people, and thus highlights the profile of patients at risk, cognition and development should be considered in all young people with a diagnosis of CLD. The final section of this chapter will outline some of the ways of addressing, monitoring and managing the cognitive and developmental needs of our patients.

The Wechsler Intelligence Scale for Children	General Cognitive Ability
The California Verbal Learning Test (CVLT)	Verbal Memory
Symbol Digit Modalities Test (SDMT)	Oral Processing Speed
The Delis-Kaplan Executive Function System (D-KEFS) • *Verbal Fluency/Category Fluency* • *Color Word Interference* • *Trail Making Test (1-5)*	Executive Functioning
The Wechsler Individual Attainment Test	Scholastic Attainment
The Graphic Speed subtest of the DASH	Graphic Speed
The Beery VMI Module	Motor Skills
Digit Span	Working Memory
Rey-Osterrieth Copy	Visual Memory
Hospital Anxiety and Depression Scale	Mood and Anxiety
PedsQL™ Cognitive Functioning Module	Perceived Cognition

Fig. 3.1 Example Battery for detecting difficulties in CLD

Monitoring Cognition in Our Population

An ideal assessment protocol for all young people with CLD would include routine, comprehensive, longitudinal assessment of physical and cognitive development from the point of diagnosis. In order to determine the developmental course, assessment should be repeated at regular intervals and intervention considered in the event of lagging trajectory. For example, a cognitive assessment, neurological review (and assessment of pubertal status in adolescence) scheduled at the start of each Key Stage here in the United Kingdom (e.g. 5 years, 7 years, 11 years, 14 years and 16 years). An example of a comprehensive cognitive assessment battery is presented in Fig. 3.1.

It will be important to evaluate mood at the time of assessment as well as the young person's view on whether they have any problems with their cognitive functioning. The influence of fatigue should also be reviewed, during both the process of assessment as well as the perceived daily impact on functioning. The use of a measure such as the PedsQL™ Multidimensional Fatigue Scale (a generic symptom-specific instrument to measure fatigue across pediatric populations) evaluates cognitive fatigue (which focuses on problems with memory and attention) which assists with the interpretation of poorer performance across these domains.

The results of cognitive assessments will provide a learning profile (including strengths and difficulties) for each individual, compared to a standardization

sample, which gives a marker of performance relative to peers. Recommendations resulting from these assessments will guide personalized learning including identification of areas in which individuals require additional educational support or environmental modification (e.g. extra time for examinations, sitting at the front of the classroom, access to a keyboard for extended periods of writing), tailored revision and memory aids. The advantage of repeating these assessments is that any areas of development which are failing to progress at the normal rate will be identified, prompting intervention and increased surveillance.

In the absence of embedded clinical psychology provision, such assessments may be accessible through local neuropsychology or community paediatric pathways. An alternative form of these assessments may also be accessible via educational psychology provision embedded within schools. However, cognitive assessments such as those described above are incredibly labour-intensive, taking a full day to administer and many more hours of preparation, scoring, writing up and liaison with professionals to disseminate findings. For example, offering one assessment per year to a cohort of 80–90 patients will require the employment of a full-time neuropsychologist/clinical psychologist. Administering these at regular intervals for each patient is will almost certainly exhaust capacity of any psychology provision, which will likely need to prioritise mental health support. Until a clear evidence is established regarding which children and young people are vulnerable to cognitive impairments, the areas of cognition affected and which measures are sensitive to detect such difficulties, routine evaluation in this manner is unlikely to be possible. We suggest that children and young people reported to have: ongoing difficulties with reading or writing, memory, processing information, paying attention/concentrating or significantly struggling academically are prioritized for cognitive assessment. Other ways in which the multidisciplinary team may be able to support them children and young people to reach their academic and employment potential are considered in the final section of this chapter.

Suggestions for Clinicians

In the absence of extended clinical psychology provision, integrating brief evaluation of young people's performance with education or employment into routine clinical practice can help identify those who would benefit from extended cognitive assessment, or at least serve as a marker for those needing extra monitoring or support. This can take the form integrating school, education and employment information into routine clinical practice, and can include a brief screening instrument.

For example, the PedsQL™ (Pediatric Quality of Life Inventory™) is a modular instrument designed to measure health-related quality of life and disease-specific symptoms. The PedsQL™ Cognitive Functioning Scale is one of these modules; a brief generic symptom-specific instrument to measure cognitive functioning. The questionnaire has 6 items and takes less than a minute to complete and can help identify young people who feel their cognitive functioning is problematic for them. This tool is available from https://www.pedsql.org/. High scores on this questionnaire can prompt clinicians to enquire more about cognition.

As described further in Chap. 10, the HEEADDSS tool can be extremely useful in clinical practice with adolescents, and includes a review of young people's Education and Employment as one of the key areas. As part of the HEEADDSS interview, we find it helpful to review where young people are at in their education, including which school year/grade they are in and how they feel they get on in lessons, with exams and homework. We ask young people if there is any additional support they access at school, and indeed if there is any further support they feel they need. Some example questions are given below in Fig. 3.2.

- ☐ Which year/grade are you in at school?
- ☐ What do you like best and least about school?
- ☐ What is your favourite/least favourite subject(s)?
- ☐ Do you have any extra support at school? Do you feel you need any extra help with anything?
- ☐ How were your most recent grades? Are these the same or different from the past?
- ☐ What is your concentration like at school?
- ☐ What is your attendance like?
- ☐ Have you ever repeated any years?
- ☐ What do you want to do when you finish school/college/University? Any future plans/goals?
- ☐ How do you get along with teachers?
- ☐ What are the other students at your school like? (prompt: ask about bullying if response is not positive)
- ☐ How is your sleep?
- ☐ How is your mood?

Fig. 3.2 Example Questions (part of HEEAADDS interview) for Assessing Cognition

If young people or their parents mention any difficulties with learning (such as problems with concentration or a deterioration in grades) it can be helpful to determine whether they feel this has been a longstanding issue or is relatively new (particularly if their condition is newly diagnosed or only presented itself in later childhood or adolescence). Whilst new issues may be transient and reflect the 'ups and downs' of adolescent development, longstanding issues may require further investigation and monitoring, particularly if there has been a deterioration in school grades or attainment scores.

We know that young people with CLD report problems with both sleep and fatigue, and the impact of these on cognition cannot be overstated. It is therefore important to review these alongside any reported cognition problems and where possible, make tailored recommendations (e.g. sleep hygiene as described in Chap. 10). Low mood can also impact upon school attendance, motivation and concentration at school, and memory and therefore the potential contribution of mood difficulties should also be considered, which is also described in Chap. 10.

What to do When Concerns Are Identified?

In addition to encouraging young people and their families to discuss their concerns with school, it can be very helpful for clinicians to liaise directly with school staff (with patient and parental consent). Many schools will detect these difficulties independently and provide support, but some may assume difficulties only reflect periods of absence due to hospitalization (and will thus improve), and therefore not provide any additional support.

If patients themselves report concerns, sometimes simply alerting young people to the potential link between their liver condition and reduced concentration/heightened fatigue can be reassuring as well as reminding both parents/carers and school staff that the individual is not simply 'being lazy'. For example, the adult subclinical encephalopathy literature (i.e. the presentation of those whose difficulties would be otherwise undetectable without psychometric testing) indicates that many patients experience slower processing speed and slower motor/graphic speed. In a classroom environment this may present as an increased amount of *time* for young people to understand information, process it and respond and increased time to carry out a pen-and-paper tasks, such as writing notes. A few of our young patients have reported that having a conversation with their multidisciplinary team in which the potential link between liver disease and slower processing speed/reduced concentration/poorer motor speed was highlighted, prompted them to initiate some small changes at school, such as sitting at the front of the class, asking the teacher for a lesson summary or taking more frequent short breaks.

Regarding arrangement of further evaluation, some schools have embedded Educational Psychology or other provision to evaluate additional learning needs and it can be helpful to explore these referral pathways. For those under 18 years, a

- *Being given extra time for tasks (including examinations), to compensate for periods of distraction, inattention and weaker oral and motor processing speed.*
- *Incorporating short breaks for physical activity into lessons involving long periods in seats (e.g. short walks/ stretches).*
- *Recognition that the students ability to concentrate may fluctuate, depending on the task (e.g. when stimulating, they are motivated to do so and not fatigued), and not punishing this.*
- *Recognition that concentration is much more effortful for them than their peers (and that periods of inattention do not reflect laziness).*
- *Bringing awareness of student's own vulnerability to distraction- suggesting re-reading responses to questions (and permitting extra time in order to do so)*
- *Permitting the use of a keyboard for students with particularly slow graphic speed*
- *Creatively asking the student to repeat information back to you to check they have understood/paid attention (as well as to facilitate encoding and storage of the information)*
- *Support to catch up with any work missed, such as a mentoring/buddy system and 'catch up sessions' with teaching staff*
- *Prioritising key subjects*

Fig. 3.3 Common Recommendations from Cognitive Assessment

referral to a Community Paediatrician is likely to be the most appropriate as they are best placed to evaluate their developmental progress and link in with any necessary support. Community Paediatricians are also able to assess for neurodevelopmental disorders, discussed in the final section of this chapter.

In terms of adaptations, it can be tricky to provide a clear context for difficulties without a more robust evidence base, however, mentioning to schools that difficulties with learning are often seen in young people with liver conditions (up to 50% require additional educational support) can be very helpful for young people and schools are usually very receptive to support. Figure 3.3 illustrates a series of recommendations, which have helped some of the young people we look after. These should not be recommended without the appropriate assessment, but illustrate some examples of adaptations which young people have found helpful.

Finally, for a small group of patients, difficulties with processing information or struggling academically may reflect a diagnosable neurodevelopmental condition, such as autism spectrum conditions or attention deficit disorder. The characteristics of these conditions carry from person to person, but for a diagnosis to be made, the child or young person will be identified as having persistent difficulties (starting in early childhood) with social communication and social interaction, as well as a restricted range of behaviours, activities or interests. The National Autistic Society highlight some of the main signs that a child or young person may have autism, which are described below. Families keen to pursue an assessment should be signposted to their GP/Primary Care Physician, who will be able to action according to local pathways. It can be helpful to include a summary of your discussion with families in clinic letters, including a list of the described behaviours and characteristics, which may indicate an autism spectrum condition. Families can use this as a starting point for discussions with their GP/Physician.

- not drawing their parents' or others' attention to objects or events, for example not pointing at a toy or a book, or at something that is happening nearby (or a child may eventually do this, but later than expected)
- carrying out activities in a repetitive way, for example always playing the same game in the same way, or repeatedly lining toys up in a particular order
- resistance to change or doing things differently
- emerging difficulties with social interaction and social communication
- behaviour such as biting, pinching, kicking, pica (putting inedible items in the mouth), or self-injurious behaviour.

General practitioners or primary care providers may carry out their own screening assessments in order to determine whether a referral is indicated. We would caution against the use of such screening tools with children with CLD (other than professionally), as there are many factors affecting a child's development and many other factors (physical, mental health conditions, sensory needs) and this will require specialist evaluation. It will also be helpful to liaise with staff at the child's school in order to determine whether the difficulties are observed in multiple settings and to determine any support they may need in the interim.

Summary

There is an increasing body of evidence of impaired cognitive development in children and young people with CLD, and emerging evidence indicating which individuals may be particularly at risk. Whilst routine cognitive assessment would help establish the needs of this population, this is unlikely to be available for every patient. There are a number of things professionals working with this population can do to raise awareness of any potential difficulties and help ensure that support is in place at the earliest opportunity. The majority of studies indicate that CLD in childhood and adolescence negatively affects cognitive development; however, the factors associated with more significant impairment are now being explored. Longitudinal studies which assess a broad range of cognitive functions (including general cognition or 'intelligence quotient', memory and executive functioning) in our heterogeneous pool of patients are required, starting in infancy and progressing through childhood, adolescence and early adulthood. The influence of medical factors (such as disease severity and duration) could be delineated by examining children and young people with a range of different liver conditions and presentations, which will inform treatment and management plans. Timely detection and management may even result in reversal of this effect, and a significant improvement to quality of life, enabling young people to grow into independent and successful adults.

Key Points for Hepatologists

- There is growing evidence that general cognition is poorer and academic attainment is lower in children and young people with chronic liver disease.
- Children with congenital conditions, those with an unsuccessful Kasai portoenterostomy (for patients with biliary atresia), those with failure to thrive in early childhood and those with a long duration of decompensated liver disease appear to be particularly at risk.
- Hepatologists can monitor cognition as part of routine clinical practice by asking parents/young people if they have any concerns about their/their child's development, and asking how they are getting along at school. Specialist cognitive assessments can be used to assess these areas thoroughly as well as monitor change over time.
- Timely detection and management may help minimise these negative effects, and result in a significant improvement to quality of life.

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Part II
Specific Liver Diseases

Chapter 4
Biliary Atresia in Transition Hepatology

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Abbreviations

AFP	Alpha fetoprotein
AUROC	Area under the receiver operating characteristics
BA	Biliary atresia
BASM	Biliary atresia splenic malformation
CT	Computed tomography
HCC	Hepatocellular carcinoma
HPS	Hepatopulmonary syndrome
HRQoL	Health-related quality of life
KPE	Kasai portoenterostomy
LT	Liver transplantation
MELD	Model for end-stage liver disease
NLS	Native liver survival
PELD	Pediatric end-stage liver disease
PHT	Portal hypertension
PPH	Portopulmonary hypertension
SIBO	Small intestinal bacterial overgrowth
UK	United Kingdom
UKELD	UK model for end-stage liver disease
WHO	World Health Organisation

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Introduction

Biliary atresia (BA) is an idiopathic, progressive obliterative disease of the extrahepatic biliary tree that presents in infancy with features of biliary obstruction [1]. The incidence of BA markedly varies worldwide, ranging from about 1 in 5–10,000 live births in Taiwan and Japan, to about 1 in 15–20,000 in UK, Europe and North America. BA is currently considered a clinical phenotype with aetiological heterogeneity rather than one disease *per se.* The two largest clinical groups that have been characterised based on shared similarities, are known as *isolated BA* (70–80%) and *Biliary Atresia Splenic Malformation (BASM)* syndrome (15–20%) [2]. In isolated BA, aetiopathogenesis remains speculative, with evidence alluding to an unknown exogenous factor (e.g., virus/toxin) initiating an exaggerated inflammatory response, targeting the bile duct epithelium. BASM is a developmental defect, characterised by a constellation of unusual anomalies affecting multiple organs, most commonly the spleen (with polysplenia, asplenia) and occasionally with cardiac anomalies, situs inversus and portal vein anomalies. After BA diagnosis, a surgical procedure, known as Kasai portoenterostomy (KPE) is performed, in which a 'Roux-en-Y' loop of jejunum is anastomosed to the hilum of the liver, creating a new conduit for biliary drainage, aiming to restore bile flow and alleviate jaundice [1].

Overall, jaundice clearance is achieved in around 60% of infants post-KPE, but due to the progressive nature of BA, even with a good bile flow, chronic liver disease with its associated complications will develop, eventually necessitating liver transplant (LT) in the majority of patients [1]. In the UK, 46% and 40% of BA patients survive with their own liver (native liver survival; NLS), five and ten-years post-KPE, respectively [3] (See Fig. 4.1). Hence, a significant cohort of patients will enter adolescence, defined by World Health Organisation (WHO) as 10–19 years of

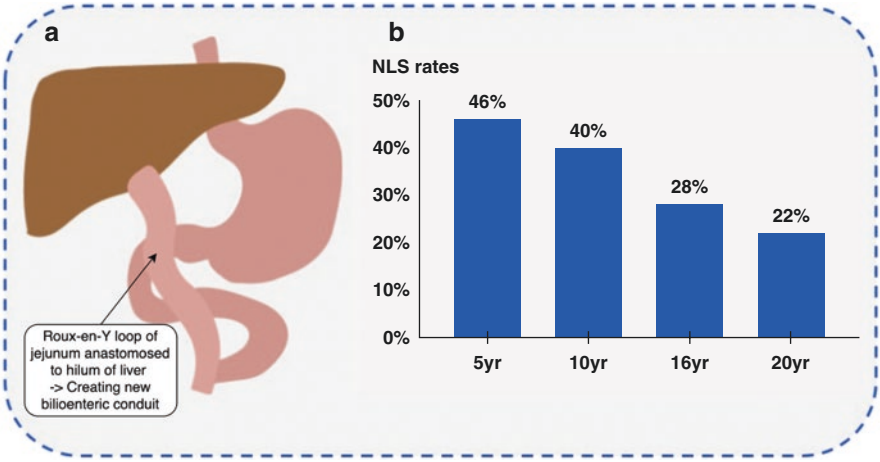

Fig. 4.1 (**a**) Diagrammatic representation of Kasai Portoenterostomy (KPE) (**b**) UK short-term (5 yr-, 10 yr-) and international long term (16 yr-, 20 yr-) BA native liver survival (NLS) rates

age [4], with their own liver. Longer term studies within UK and Europe have revealed 16-year and 20-year NLS rates as 28% and 21–25%, respectively [5–8] (See Fig. 4.1), with Japanese studies revealing higher overall long term NLS [9], largely due to differences in transplantation practice and lack of readily available grafts. Transition is an active and evolving process, incorporating a multi-disciplinary team, that addresses the medical, psychosocial, and educational needs of young people as they prepare to move from paediatric- to adult-centered health care [10]. As patients typically enter adult services by 18 years of age, adult hepatologists are increasingly managing this substantial long-term BA NLS cohort, with its distinct differences to adult-onset chronic liver disease. In this chapter, we will discuss the medical, psychosocial and educational issues facing adolescent/young adult BA native liver survivors, and their corresponding paediatric or adult hepatology teams. We will also discuss issues surrounding indications and timing of LT for this cohort. We will subsequently refer to the adolescent/young adult cohort as 'young people' [4], as per the WHO definition, which encompasses individuals between the ages of 10 and 24.

Medical Complications in Young People with BA

BA infants and children post-KPE are regularly monitored for complications of chronic liver disease and cholestasis, by the paediatric hepatologist. Although the same complications exist in young people with BA, their prevalence and relevance can vary compared to the younger cohort.

Cholangitis

Cholangitis is the inflammation of the biliary system, post-KPE [11]. Presenting symptoms are often non-specific, including fever, worsening jaundice, pale stool and/or worsening liver function tests. The incidence is reported as high as 40–60% within the first 2 years post-KPE, and has been associated with increased transplantation rates [12]. Reflux of gut bacteria via the Roux loop into the liver has been hypothesised as the most likely mechanism (ascending cholangitis). Cholangitis in adolescence is less common, although the incidence is not well documented. Interestingly, up to 60% of 20-year BA native liver survivors subsequently suffer with cholangitis in young adulthood [13]. Although the bacterial reflux is the most likely cause, Roux loop obstruction related to adhesions and/or its progressive shortening over time has been reported in adolescence [14, 15], particularly in the context of normal liver biochemistry. Biliary anatomical abnormalities, such as bile lake formation and hepatolithiasis, have been reported in a high proportion of adult cholangitis episodes [7, 14] and could predispose to recurrent infections.

Suspicion of cholangitis in a young person with BA should prompt appropriate laboratory tests, in particular liver function, inflammatory markers and blood cultures, followed by prompt treatment with antibiotics. Evidence for type, duration or mode of antibiotic administration for cholangitis and the benefit of prophylaxis, is currently limited. Ultrasound imaging is essential, in particular looking for anatomical biliary abnormalities, but also signs of advanced liver disease, which may have been triggered by cholangitis, both of which are poor prognostic features. Furthermore, a low threshold should be held for investigating the anatomic and functional patency of the Roux loop with hepatobiliary scintigraphy or enteroscopy, particularly for those presenting with their first episode and/or unremarkable liver biochemistry. In the case of suspected Roux loop obstruction, urgent transfer to a paediatric liver disease centre is warranted, where further imaging including magnetic resonance cholangiopancreatography (MRCP) and enteroscopy will be considered to characterise any obstruction and to culture the bile. Endosopic retrograde cholangiopancreatography (ERCP) is not feasible via Roux-en-Y loop. The development of cholangitis in young people with BA is often associated with deterioration of liver disease and an increased likelihood of subsequent LT [5].

Portal Hypertension

Portal hypertension (PHT) is the term used for increased pressure within the portal venous system, and in BA is a reflection of progression of liver fibrosis and cirrhosis [16]. Clinical features include splenomegaly with associated hypersplenism (low peripheral blood cell counts) and the development of oesophageal and gastric varices (dilated submucosal blood vessels), which have the propensity to bleed. Further complications associated with PHT include the development of portopulmonary hypertension, extrahepatic portosystemic shunts, ascites and hepatic encephalopathy [17].

In view of the progressive nature of BA, even with a good bile flow the majority of patients will develop cirrhosis and PHT. At the time of KPE, 50% of infants already have evidence of bridging fibrosis and elevated portal pressure [18]. By 10 years of age, over two thirds of BA native liver survivors have evidence of PHT, with 80% and 50% of this portal hypertensive cohort demonstrating varices and variceal bleeding, respectively [19]. By young adulthood, over 70% display features of PHT, and case series revealed nearly 20% experiencing a variceal haemorrhage in adulthood [7, 13]. Crucially, even if there are no clinical or laboratory signs of PHT, cirrhosis will be present in the majority of long term BA native liver survivors [20]. The presence of PHT or gastroesophageal varices is associated with a 7-fold and 8.6-fold increased risk of LT, respectively [5].

Consequently, the high incidence of PHT and its complications in young people with BA requires a vigilant follow up. Several non-invasive predictors for the development of varices in children exist, but splenomegaly with platelet count <100 x 10^9/L is the most used marker for defining the ‘at risk’ PHT group. In adults,

surveillance endoscopy is widely used for primary prophylaxis of variceal haemorrhage [21] in this 'at risk' cohort. In paediatrics, due to a lack of rigorous clinical studies assessing safety and efficacy of endoscopic prophylaxis, there is no agreed consensus for the surveillance. Duche et al. reported eradication of varices in 70% children with chronic liver disease undergoing primary endoscopic prophylaxis, following a mean of 4.2 procedures [22]. Administration of pharmacologics (e.g. non-selective beta blockers) to reduce the pressure within the portal system, is common practice in adult hepatology, but due to a lack of evidence is less commonly used in paediatrics.

When a young person presents with suspected variceal bleeding, urgent admission and emergency management should be instigated [23]. Intravenous access, blood sampling (for cross-match, haemoglobin, coagulation profile, electrolytes) and fluid management (saline and blood products) based on haemodynamic status, should be ensured. Over-transfusion should be avoided (due to risk of rebound bleeding and thrombosis) and any coagulation/platelet abnormalities actively corrected. Vasoactive drugs, such as octreotide, have been shown to be effective and safe in early control of active bleeding, and should be commenced at presentation. Other pharmacological agents include antibiotic prophylaxis and antacids. Endoscopy should be carried out ideally within 24–36 hours after the bleeding episode, once the patient is haemodynamically stable, in a unit with therapeutic PHT experience. Regular follow-up endoscopies (at 2–4 weekly intervals) are initially recommended, due to the high risk of re-bleed, and when varices have been suitably ablated, frequency of endoscopies can be reduced. Uncontrolled symptomatic PHT is an indication for LT.

Cholestasis and Pruritus

Although jaundice is a common indication for LT in infancy and childhood, it remains present in a large proportion of young people with BA. Reports suggest that up to 50% of 10-year BA native liver survivors and 70% of 20-year BA native liver survivors [7, 19, 24] have elevated bilirubin levels, although the severity spectrum is not clearly stated. Interestingly, over 2/3 of the jaundiced long-term native liver survivors had previously achieved a normal bilirubin, highlighting the risk of jaundice relapse in young people. Whether the jaundice is predominantly due to progressive liver disease and/or cholangitis is unclear. A recent study has highlighted that mild hyperbilirubinemia at 16 years of age is an independent predictor for subsequent LT [5]. Hence, vigilant monitoring of bilirubin levels in adolescence/young adulthood is important and its presence should be considered a significant risk factor when assessing young people for transplantation. Fat soluble vitamin malabsorption remains a complication common in young people with chronic cholestasis, necessitating regular supplementation (vitamins A, D, E and K) [25], with frequent monitoring of vitamin levels and tailoring of doses. Input from the specialist

pharmacist regarding suitable vitamin preparations, including combination therapy, can be helpful to minimise the number of medications.

Pruritus, a clinical manifestation of cholestasis, is a recognised complication in BA. It can have a deleterious effect on quality of life and, depending on its severity, can be a *bona fide* indication for LT [26]. The prevalence of pruritus in young people with BA is not well documented. One series reports approximately 20% of young BA adults experiencing pruritus, but data regarding severity and management are limited [7]. Although the exact pathogenesis is unknown [27], pruritus driven by certain substances known as 'pruritogens' is a popular theory. Bile salts, which accumulate with the impairment of bile flow, are considered one type of pruritogen [28, 29]. Measurement of bile acids in young people with pruritus can potentially be informative, but does not necessarily correlate with severity. Anti-pruritic therapeutic agents, such as ursodeoxycholic acid, oral bile acid resins (e.g. cholestyramine), antihistamines and rifampicin have been the mainstay of treatment by promoting choleresis or altering the bile acid pool.

Synthetic Function

Decompensated liver disease and synthetic failure, with hypoalbuminemia and/or coagulopathy, are common indications for LT in young children with BA [30]. In adolescent/young people with BA, synthetic failure remains an indication for LT [31], related to progression of PHT, or triggered by an acute event (cholangitis, variceal bleed). Ascites and hypoalbuminemia can be supported with diuretics (e.g. spironolactone) and intravenous albumin infusions [32]. A peritoneal tap may be indicated, if respiratory complications from abdominal distension are present, or in the case of unexplained fever, where a diagnosis of spontaneous bacterial peritonitis (acute bacterial infection of ascitic fluid, defined by presence of >300 cells/ml and not attributable to an intra-abdominal, or surgically treatable source [33]) should be excluded. LT is usually the only treatment for young people who develop chronic liver synthetic failure.

Hepatocellular Carcinoma

BA, like any chronic liver disease, has the potential for development of malignancies [34–39]. However, it is a rarer complication in BA than in other chronic liver diseases (particularly in adult liver diseases). A case series from King's College Hospital, revealed malignant transformation in 5/387 BA cases, with one case being an adolescent (17 years old) [34]. Routine ultrasonography identified a large focal lesion in this adolescent BA patient, who had normal AFP levels. Histology on the

explanted liver revealed a well-differentiated hepatocellular carcinoma (HCC). Further case reports have diagnosed HCC at explant in young adults with BA, following on from the identification of suspicious lesions on computed tomography (CT), whilst being investigating for shunts [35] and abdominal pain [37]. Hepatoblastoma [39] and cholangiocarcinoma [36] have also been identified in explanted BA livers of BA, but only during childhood. Screening for malignancy with ultrasonography and AFP levels (6 monthly) is recommended in all young people with BA. Any suspicious nodule on ultrasound should be further characterised by dynamic scanning, such as, contrast-enhanced CT, magnetic resonance or contrast-enhanced ultrasound. Typical characteristics of HCC include hyperenhancement in the arterial phase and washout in the venous phase. AFP levels should be interpreted cautiously, as levels can be normal even in the presence of large tumours [34, 36]. Biopsy is not recommended for suspicious lesions with coexistent cirrhotic liver disease, due to risks of dissemination. LT represents the only curative treatment for smaller HCCs.

Extrahepatic Medical Complications

Pulmonary

Further complications of cirrhosis and PHT include hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH). HPS is characterised by intrapulmonary vascular dilatation and abnormal pulmonary arterial oxygenation, leading to chronic hypoxia (shunting). PPH, conversely, results from increased pulmonary vascular resistance, vascular remodelling and increased pulmonary arterial pressures [40]. Both conditions, although rare, have been reported in young people with BA, with PPH being more prevalent [41, 42]. LT can reverse both conditions, however, pulmonary artery pressure > 35 mmHg in patients with PPH is associated with very high perioperative mortality risks, contraindicating LT [43]. In a retrospective series of 320 BA patients [42], two developed PPH at a median age of 15.5 years. Both patients had the disease progression that led to death, one after cardiac arrest post-procedure (aged 13.5 years) and the other in hospice care (aged 29 years). In another series of 88 BA patients [41], three adolescents developed PPH; two underwent LT and one died whilst awaiting LT. Hence, pulmonary complications, although rare, are associated with a significant morbidity and mortality. Any cardiorespiratory symptoms or signs, such as dyspnoea, lethargy, syncope or cyanosis in young people with BA, should prompt oximetry and arterial blood gas examination for hypoxia. Demonstration of intra-pulmonary shunting (bubble echocardiography, lung perfusion scanning with macro-aggregated albumin) for HPS and increased right ventricular and pulmonary arterial pressures (echocardiogram, cardiac catheterisation) for PPH are required. LT can revert both conditions, depending on their severity.

Small Intestinal Bacterial Overgrowth

Gastrointestinal complications are commonly reported in young people with BA. Small intestinal bacterial overgrowth (SIBO), is one such complication, associated with a wide range of nonspecific intestinal symptoms (e.g., abdominal bloating, diarrhoea, vomiting) [44, 45]. Pathogenesis in SIBO is unclear, but commensal gut bacteria (gut microbiota) and structural and functional intestinal abnormalities in BA, in particular the Roux loop, will be major players. Although it is defined as an increased quantity (10^5 or more CFU per mL) of small bowel gut microbiota, its diagnosis is challenging [46]. Quantitative microbiological analysis of jejunal aspirate at endoscopy is currently the gold standard, but due to its invasive nature, alternative tests are preferred. The hydrogen breath test, which measures the concentration of gaseous products of bacterial fermentation in expired air, is more appropriate in young people, but interpretation of results and false negatives, preclude its broader use. Therefore, SIBO is usually diagnosed empirically, with the response to oral gut microbiota-directed antibiotics (e.g., metronidazole, ciprofloxacin) contributing to the diagnosis. Sequencing of the genes harboured by the gut microbiota are increasingly revealing pathogenic patterns in BA [47], shedding more light on the intricate gut-liver link in BA, potentially making way for newer treatments, such as probiotics or faecal microbiota transplantation.

Others

Major extrahepatic anomalies are found in approximately 16% patients with BA [48], including cardiac, vascular, gastrointestinal and urogenital defects. Although there will be a lower proportion that survive into adolescence/young adulthood with their native livers, ongoing assessment and management of these extrahepatic features is mandatory, with referral to specialised teams as necessary.

Growth Characteristics

Growth failure in young people with BA is less common compared to in early childhood, with limited number of studies describing growth trajectory and bone health, usually being a part of larger retrospective reviews, often with incomplete data. Ohhama et al. positively correlated early resolution of jaundice (defined as serum bilirubin <1.0 mg/dL within three months post-KPE) with improved ‘growth status’ in adolescent native liver survivors (n = 40), but no further description of growth characteristics were provided [49]. Reassuringly, limited longer-term retrospective reviews, [7, 50] reveal that BA patients that survive to young adulthood with their native liver, reach physical growth parameters comparable to the healthy population. Nio et al. stated that 29 out of 30 BA patients, surviving more than 20 years with their native liver, had physical growth within the normal range, regardless of

their current or previous health status [50]. Although the interpretation of this data should be guarded, it does seem to suggest normal growth in adult native liver survivors, although factors contributing to this favourable outcome have not been established. Chronic liver diseases like BA are also associated with impaired bone mineralisation, where pathogenesis is not entirely clear; malabsorption of vitamin D is likely a key player. Several studies have shown that bone mineral density, and growth, if impaired, can normalise after LT [51–53].

Basic nutritional history and anthropometry should be documented in all young people with BA. In patients where nutrition and/or growth are a concern, a specialist dietician should be involved for more focussed dietary history and possible instigation of dietary interventions, e.g., calorie or vitamin supplementation. If bone health could be contributory to poor growth, additional investigations such as vitamin D levels, bone biochemistry and bone mineral density assessment may be appropriate, with additional endocrinology advice. Although not formally studied, in our clinical experience adolescent male BA patients, in particular, may express concerns regarding body image dissatisfaction, with nutritional supplementation discussed with the hepatologist and dietician on a case-by-case basis.

Puberty

Puberty is a physiological developmental process by which reproductive capability is attained. Disruption of the hypothalamic-pituitary axis, in conjunction with disturbed oestrogen metabolism and other pathophysiological mechanisms in cirrhosis, can lead to pubertal irregularities, such as delayed puberty and amenorrhea. Other generic mechanisms associated with chronic disease, including malnutrition, chronic hypoxia or diarrhoea have well-established links with pubertal delay. Pubertal development is an important aspect of overall growth and development, with delayed puberty having a negative effect on attainment of final adult height. A Japanese study [54] of 11 adolescent BA females, revealed a delayed average age of menarche by 21 months compared to healthy Japanese controls. A multicentre study has shown that even post-transplant, pubertal delay is evident, with 61% of girls and 68% of boys aged 16–18 years reaching Tanner 5, compared to 100% of a peer population [55]. Primary amenorrhoea, secondary amenorrhoea and dysmenorrhoea were revealed in 7/11 patients. Furthermore, a subsequent Japanese study [56] correlated menstrual disorders with liver disease severity parameters at puberty, including higher bilirubin and transaminases, and lower albumin levels. BA patients, however, who reach young adulthood with their native liver, appear to have normal pubertal parameters. In a Japanese study of 30 native liver survivors over 20 years of age [50], 18 out of 20 women and all 10 men had normal secondary sexual characteristics. In a separate Japanese study of long-term survivors with native liver, three of 21 patients experienced amenorrhoea at age 20, but overall 19 of 21 developed menarche between ages of 11 and 16 [9].

Discussions around puberty and menarche in young people with BA are an essential component of adolescent and young adult services. If there are concerns regarding pubertal delay, specialist endocrine advice should be sought. The endocrinologist can help exclude non-BA aetiology for pubertal delay, instigate appropriate investigations (Tanner staging, bone age, hormonal profile), and help with potential management strategies. Hormonal therapy may be beneficial in some scenarios. Menstrual disorders may also benefit from hormonal supplements, with guidance from the gynaecology team.

Pregnancy

As an increasing cohort of female BA patients are surviving with their native liver long-term, information regarding pregnancies within this cohort, is becoming available (see Table 4.1). Successful pregnancies have been reported in cirrhosis, but due to physiological and anatomical changes during pregnancy, morbidity and mortality is significantly higher in this setting, as compared to the general population [60, 61]. Similarly in BA, case reports are documenting successful pregnancies, but deterioration of liver disease during and after pregnancy, remains a real possibility [8, 9, 31, 57–59, 62, 63]. Among specific studies, Sasaki et al. reported uneventful pregnancy in six of nine BA patients [58]. Of the remaining three patients, one

Table 4.1 Summary of studies reporting liver-related complications in pregnancy for BA native liver survivors

Citation	Pregnant patients	Total no. of Pregnancies	Total no. of deliveries	Maternal complications	Neonatal/infant complications
de Vries et al. (2011) [8]	N = 3	3	1 delivery 2 remain pregnant at time of publication	No complications (3)	Not reported
Parolini et al. (2019) [57]	N = 2	2	2 deliveries	Postnatal recurrent cholangitis and subsequent LT (1)	No complications reported
Samyn et al. (2019) [31]	N = 3	3	2 deliveries 1 died during pregnancy	Variceal bleeding in 2nd trimester, subsequently died (1) Variceal bleeding in 2nd trimester and LT (1) Post-partum synthetic failure and LT (1)	Not reported

Table 4.1 (continued)

Citation	Pregnant patients	Total no. of Pregnancies	Total no. of deliveries	Maternal complications	Neonatal/infant complications
Sasaki et al. (2007) [58]	N = 9	14	11 deliveries 2 abortions: personal reasons (1), deterioration of liver function (1) 1 intrauterine foetal death at 35 weeks	Jaundice during pregnancy (1) Liver dysfunction during/after pregnancy (2) ➔ one resulting in abortion; both required LT referral	All 11 infants healthy
Shimaoka et al. (2001) [59]	N = 16	25	23 deliveries 2 abortions; haemorrhagic shock from variceal bleeding (1), atopic dermatitis (1)	LT for fatigue and PHT (1) Variceal bleeding (2) ➔ one resulting in abortion and one requiring endoscopic ligation, Liver dysfunction during pregnancy (1) Post-partum cholangitis (4) Post-partum deterioration of liver function (6) Placental abruption (1)	Mean gestational age 37.5 weeks Mean birth weight 2.898 kg Very low birth weight (1) Respiratory distress syndrome (1) Jaundice requiring phototherapy (1) No congenital abnormalities
Shinkai et al. (2009) [9]	N = 5	9	9 deliveries	Cholangitis during and after pregnancy (2) ➔ one listed for LT	Foetal distress requiring Caesarean section (3) No congenital abnormalities

developed jaundice and two developed liver dysfunction, leading to intra-uterine deaths and terminations, with subsequent LT in both cases. A previous history of cholangitis and PHT were present in both of these patients. Another Japanese study revealed that in 16 patients who underwent 25 pregnancies, complications during pregnancy included deterioration of liver function (n = 5), cholangitis (n = 4) and variceal bleed (n = 2), with one intra-uterine death as a result of variceal bleeding [59]. Authors document that 75% of this pregnant cohort had no evidence of PHT or cholangitis before pregnancy, highlighting that even with mild disease complications can occur.

Pregnancy and delivery do not need to be avoided in BA patients, but preconception counselling regarding complications is essential. Pregnant BA patients should be monitored carefully by adult hepatology and obstetric teams, with regular screening of laboratory parameters and optimal management of PHT. In pregnancy, portal pressure increases due to plasma volume expansion and uterine compression of the inferior vena cava during the second and third trimesters. The American Association for the Study of Liver Diseases guidelines suggest a screening endoscopy during the early second trimester for all pregnant cirrhotic patients with ongoing liver injury or decompensation, and also for all patients who have not had a screening endoscopy in the year before conception [64].

Pre-pregnancy prognostication tools would be helpful in the risk assessment, but available BA reports currently could not provide that. Prognostic markers in a large cohort of cirrhotic patients (including a small cohort of BA patients) at conception have been assessed in one study [65]. Adult liver disease severity scoring systems, based on laboratory parameters, Model for End-stage Liver Disease (MELD), and UK Model for End-Stage Liver Disease (UKELD), at conception, were associated with an increased risk of maternal liver-related adverse events. Furthermore, a platelet cut-off of 110 x 10^9 cells/L had 78% sensitivity and 89% specificity for predicting the presence of varices on screening endoscopy in the second trimester. Further validation of these results, particularly in BA patients, would be valuable.

Regarding the health status of infants born to BA mothers, reports are generally encouraging [58, 59]. In a 2001 Japanese multicentre questionnaire, mean gestational age (37.5 weeks) and mean birth weight (2.9 Kg) in 23 infants born to BA mothers, were within normal range [59]. No infant presented with a congenital abnormality. Furthermore, vaginal delivery was common, with only three infants delivered by Caesarean section.

Education and Employment

Infants and children with any chronic disease are at increased risk for developmental difficulties, including cognitive delay [66, 67]. Delayed neurodevelopmental outcomes are reported in BA infants, and although the exact pathophysiology is unclear, persistent jaundice, delayed growth and ascites are identified risk factors [68]. Hepatic encephalopathy, defined as neuropsychiatric dysfunction associated with liver failure, is linked to cognitive impairment in adults. Although overt hepatic encephalopathy is less common in children, milder subclinical ‘minimal hepatic encephalopathy’ [69] may impact cognitive function, but due to diagnostic challenges, the extent of this association is currently unclear. Longer-term neurodevelopmental BA studies, although few, show reduced cognition in both native liver survival and LT cohorts. A large international multi-centre study (Childhood Liver Disease Research and Education Network) showed a significant difference in school functioning scores between BA native liver survivors (n = 221, mean age 9.75 ± 5.25 years, optimal health 62%) and a healthy age-matched cohort, using

child self and parent proxy questionnaires [26]. In a Dutch study incorporating a mixed BA cohort, neuropsychometric testing revealed lower scores for IQ, attention, visual-motor integration and planning, compared to the Dutch control population, as well as a higher rate of special educational needs (26% vs. 2.4%) [70]. Overall, there were no differences between the transplanted and native liver survival sub-cohorts [70]. This is in keeping with BA studies in younger children, where an improvement in cognition was not demonstrated post-LT and could potentially worsen in the early post-LT period [71, 72].

Despite the evidence regarding cognitive delay in children and adolescents, reports on higher education and employment rates in young BA adults surviving with their native liver are encouraging, albeit limited by incomplete data and a lack of peer controls [9, 57, 63, 73]. In Japanese report of 32 native liver survivors, 21 had graduated from a vocational school, college or university, 6 graduated from high school, 4 were still studying and one attended a special school [9]. In Hong Kong study of 16 native liver survivors, all had completed secondary education, 15 had progressed to tertiary education level or above [73] and subsequently, 14 progressed to employment, with one still studying. Aggressive nutritional therapy and optimal medical management in infancy are essential for the reduction of neurodevelopmental sequelae which when present may not improve after LT. Longitudinal neurodevelopmental assessment from infancy through to adolescence/young adulthood could help to establish early risk factors for poor cognition and provide an objective framework for the instigation and monitoring of neuropsychological interventional programmes. The identification of young people struggling with education or daily functioning is essential within the transitional services in order to ensure that early support is in place. A 2021 systematic review reported that between 2 and 48% of children with BA required additional educational support [63]. Referrals to psychology (or educational psychology, if available) are appropriate for those reporting a high level of concern.

Quality of Life

Quality of life is defined by the World Health Organization (WHO) as an "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [74]. Health-related Quality of Life (HRQoL) questionnaires are standardised scoring metrics encompassing different sub-domains (social, physical, emotional, educational), and are increasingly being applied to young people with BA. A 2019 meta-analysis incorporating 10 studies, of varying methodological quality, comparing HRQoL in young BA native liver survivors to the general population, revealed overall lower scores in the diseased cohort, particularly within social and physical domains [75]. One of the incorporated studies from the Childhood Liver Disease Research and Education Network, (n = 221; mean age 9.75 years) identified black race and elevated total bilirubin (at the time of study) as

risk factors for poorer quality of life [26]. Cholestasis and its association with physical signs, pruritus, nutritional deficiencies and poorer growth, could explain this association. There was no significant difference in quality of life between native liver survivors and age-matched transplanted cohorts, although a larger proportion of the 'well' transplanted patients responded to questionnaires, potentially skewing the data. Quality of life data in young adults with BA are increasingly documented and results are contradictory, likely due to different methodologies. Wong et al. (n = 16, median age 26.8 years) described lower general health and physical scores compared to healthy peers, whereas Lind et al. [76] (n = 25; median age 23.2 years) showed no difference. Similarly, results comparing quality of life measures between native liver survivors and transplanted young adults [73, 77] are varied. Ideally, formal quality of life monitoring should form a part of the standard clinical assessment within the transitional services, identifying patients that could benefit from relevant multi-disciplinary support (social, psychological services, educational). Meeting the young person on their own for at least part of the medical consultation could facilitate open and honest reporting.

Lifestyle Advice

There are some general lifestyle factors, relevant to young people, which should be addressed in transitional clinics, in order to optimise the health of this cohort.

Alcohol/Substance Abuse The prevalence of alcohol, smoking and drug use is relatively high among young people [78]. Alcohol is a well-established risk factor for cirrhosis, hence, abstinence from alcohol consumption is recommended for any patient with liver disease. In one questionnaire-based study of consumption habits at secondary school, 12% (3/25) of BA native liver survivors reported consuming alcohol often or very often, albeit at a lower rate than their healthy age-matched peers (27%, 138/508) [79]. Lykavieris et al. reported three heavy drinkers (5.7%) within their young BA adult cohort [7]. The association between smoking and liver disease is more complex to unpick, but some evidence does suggest smoking to be a risk factor. A self-reporting web-based system in a young adult liver outpatient clinic, revealed 12.4% (n = 178) of young people with liver disease currently smoking [80]. The associated health risks of alcohol and smoking intake should be discussed routinely in clinics and approached in a non-judgmental fashion to encourage disclosure, engagement and possible cessation.

Sexual Education The median age of first sexual intercourse is 16–17 years in high-income countries [81, 82], hence discussions around sex education, particularly the prevention of sexually transmitted infections and the suitability of hormonal contraception, should form a part of the routine discussions in transition clinics. Oestrogen-containing contraceptives are not recommended in patients with liver disease, due to the presence of oestrogen receptors on hepatocytes and the

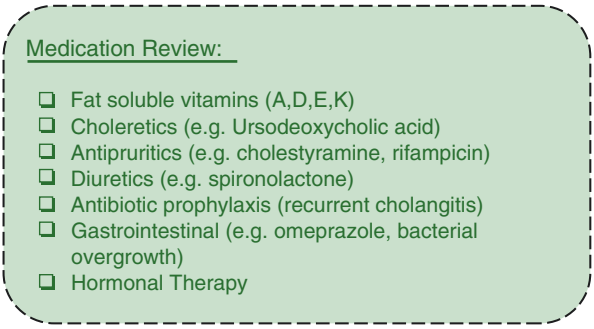

Fig. 4.2 Pharmacotherapy offered to the BA adolescent/young adult patient

potential for liver-related complications, such as cholestasis and adenomatous transformation [83]. If hormonal contraceptives are to be used, progestogen-only preparations are advised, including progestogen-only pill or implant, or the levonorgestrel-releasing Mirena intrauterine device [84].

Adherence Adherence to medications and clinic appointments are key components in developing self-management skills, and are promoted during the transition period [85, 86]. A high prevalence of non-adherence to medications (e.g., immunosuppression) has been described in young people who have undergone LT [87], with increased risk-taking behaviour, varying levels of self-management skills, poorer socio-economic status and disrupted family dynamics, all being contributory factors. Non-adherence in BA native liver survivors is less well studied, but it is important for the transition team to explain the rationale for any medications, especially when the beneficial effects may not be obvious to the patient. Figure 4.2 shows the potential range of pharmacotherapy that may be required by the BA adolescent/young adult, dependent on disease severity and symptomatology. Obstacles to adherence should be sought by the transition team and strategies to potentially improve adherence, such as simplification of treatment regimens and the use of memory-aids (e.g., text messages, alarms for medications) should be considered.

Mental Health

The presence of chronic physical disease in general, exacerbates the prevalence of mental health conditions, such as depression [88]. Furthermore, mental health conditions are increasingly identified in adolescence [89, 90]. The burden of the disease during childhood, together with ongoing medical needs and the daunting prospect of potential liver transplantation, are likely to be contributory factors towards mental health impairment. Poor mental health is associated with non-adherence to medication and disengagement from services. In a study of 187 young people attending a liver transition clinic with mixed liver aetiologies (BA n = 35), 14.5% of the total cohort had probable generalised anxiety disorder, 9.7% had probable major

depressive disorder, and 2.2% reported suicidal ideation [91]. The most common individual distress items were fatigue (42.3%), money (30.8%), feeling worried (30.2%), concerns about work/school (29.1%), and 'not feeling good about themselves' (27.5%). Specifically for BA, Lind et al. assessed anxiety and depression using a self-rating questionnaire in 25 young adults, demonstrating overall relatively mild scores that were not significantly different from healthy peers, however on an individual basis, three and six patients respectively, scored above clinically significant thresholds, warranting referral to a psychologist [76]. Long term retrospective studies in BA have incorporated some mental health data as part of their review, but data is usually incomplete, making it difficult to draw any conclusions [7]. Assessment of mood and emotional wellbeing in young people with BA should be considered routinely within standard clinical care. Simply asking young people about their mood and/or including a brief standardised measure as part of pre-clinic screening, can help identify those most impacted, who could benefit from psychology input. Identification of risk factors for mental health in BA is essential for earlier interventional strategies.

LT Listing/Timing

Official UK LT rates during adolescence are not clearly defined, as UK registry websites do not distinguish adolescence from the general paediatric cohort [92]. Studies have revealed that up to 25% long term native liver survivors subsequently require LT in early adulthood [7, 13]. Indications for LT in young people with BA are illustrated in Fig. 4.3 with cholangitis and PHT-related complications being the most common. Hence, vigilant monitoring throughout transition and adult services is needed to identify patients at risk. In adult liver disease, laboratory

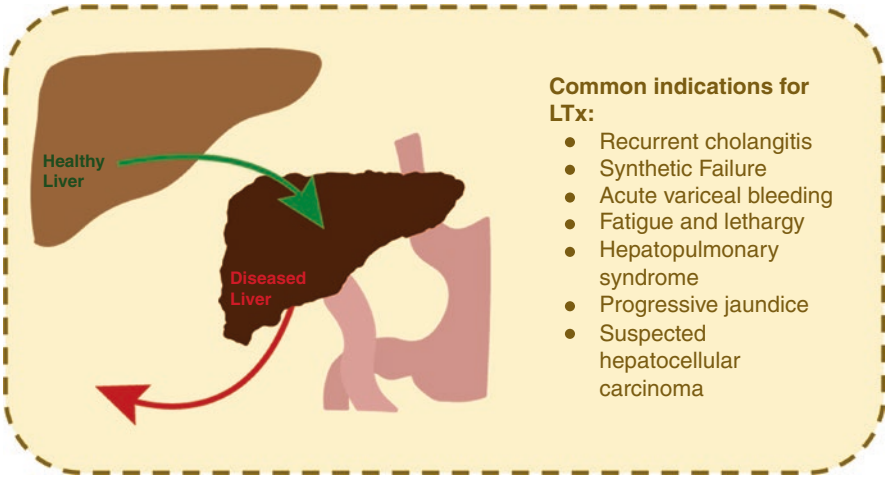

Fig. 4.3 Common indications for liver transplant in BA

parameter-based scoring systems, namely MELD and its modifications, such as UKELD in the UK, are widely accepted tools in assessing the risk of patient mortality and optimising timing and prioritisation of LT. These scores are validated for patients above 12 years of age. Similarly, the Pediatric End-stage Liver Disease score (PELD), incorporating growth failure alongside laboratory parameters, is validated below 12 years of age. However, the utility of scoring systems in children and young people with liver disease is limited, with data suggesting underestimation of the liver disease severity. Samyn et al. showed that only 48% of young people with BA, considered for LT listing, met the threshold criteria from scoring systems [31]. A recent study revealed that PHT and cholangitis (see Fig. 4.4) during adolescence are significant risk factors for subsequent LT in young people with BA, and yet neither parameter is incorporated in current scoring systems [5]. Secondly, low sodium and high creatinine, which are important variables within adult scoring systems, were not identified as risk factors for this cohort. Lastly, as mentioned previously, a bilirubin >21 is an independent risk factor for LT in young people with BA, whereas higher levels would be needed to obtain points in adult scoring systems.

Therefore, current LT allocation scoring systems do not incorporate BA-relevant parameters, likely explaining their questionable utility in this unique cohort [93]. The LT assessment process in the UK is a more subjective process, incorporating health and psychosocial parameters, seeking expert opinions from multidisciplinary

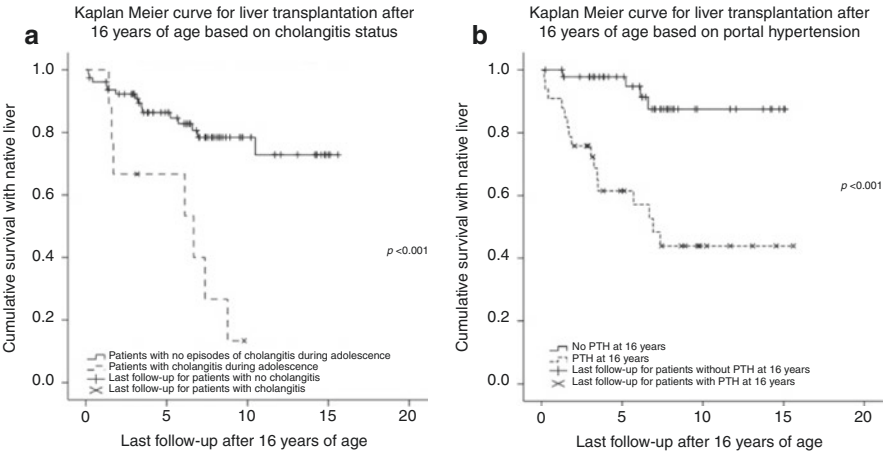

Fig. 4.4 (**a**) Kaplan-Meier curve for NLS in patients >16 years old based on development of cholangitis between 12–16 years. (**b**) Kaplan-Meier curve for NLS in patients >16 years old based on portal hypertension by 16 years of age. For (**a**) and (**b**) Log-rank test was used and a significant difference in survival was found, $p < 0.001$. (**c**) Receiver-operating characteristic curves for bilirubin as a predictor of the need for LT in patients >16 years old. The AUROC was 0.848 with a sensitivity of 85% and a specificity of 74%. Reprinted from Journal of Hepatology 71(1). Jain V, Burford C, Alexander EC et al. Prognostic markers at adolescence in patients requiring liver transplantation for biliary atresia in adulthood. p71–77. Copyright 2019, with permission from Elsevier [5]

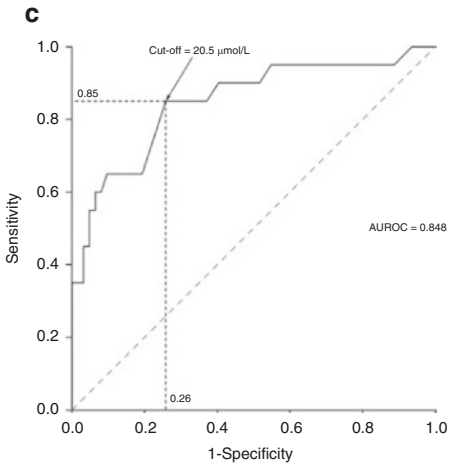

Fig. 4.4 (continued)

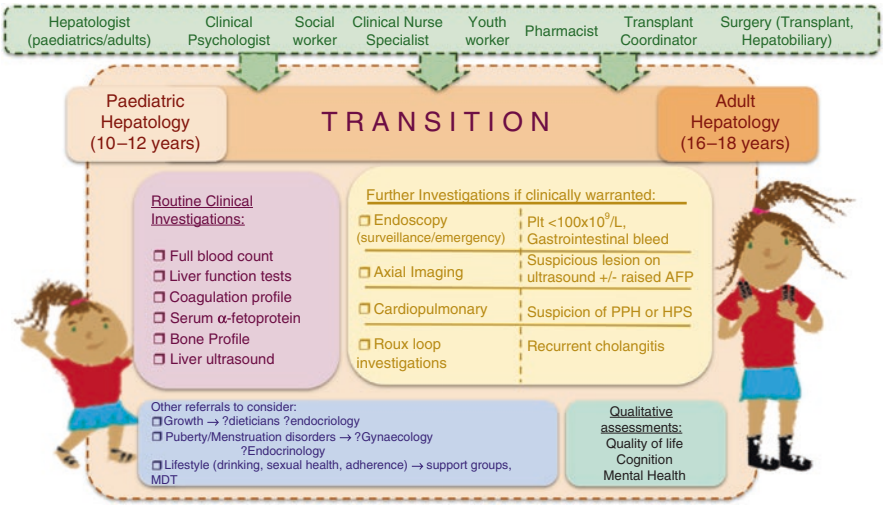

Fig. 4.5 Illustration of the routine and specialist investigations, referrals, and involvement of the multidisciplinary team required at transition to adult services

services (hepatologist, transplant surgeon, anaesthetist, specialist nurse, dietician, psychologist and social worker). Education and counselling to the patient and family, and consideration of their opinions are crucial throughout this process. Figure 4.5 summaries key assessments, multidisciplinary team members and referrals for a young person with BA in the transition services.

Conclusion

There is an increasing number of BA patients surviving through adolescence and young adulthood with their native liver. This unique cohort is at risk of significant medical complications, which should be carefully monitored by paediatric and adult hepatology teams working within the transition services. Growth, puberty/menstruation, pregnancy, cognition, quality of life, lifestyle and mental health should be assessed throughout transition, incorporating appropriate members of the multidisciplinary transition team and with appropriate referral to specialised services. The optimal timing of LT in young people with BA is challenging, and adult LT allocation scoring systems offer a limited utility. Issues surrounding the LT decision-making process require a multi-disciplinary approach while the search for BA-relevant prognostic tools continues.

Key Points for the Adult Hepatologist

- Biliary atresia (BA) is the primary indication for liver transplantation in childhood. Around 21–28% will be surviving with their native liver at 16 and 20 years of age.
- The most commonly recognised BA complications are cholangitis and portal hypertension, with cholestasis, pruritus, and synthetic failure being less prevalent at this age.
- Follow-up should screen for complications including hepatocellular carcinoma, extrahepatic manifestations of liver disease, and impaired bone mineralisation.
- Pubertal delay and liver-related complications associated with pregnancy have been commonly described.
- Identification and early intervention for young people struggling with education or daily functioning is essential.
- Quality of life, mental health monitoring, and lifestyle advice should be part of standard follow-up.
- Risk factors for liver transplantation (LT), in particular jaundice, portal hypertension and cholangitis, should be monitored with a low threshold for LT referral. Standard LT allocation scoring systems have not been modified for this specific cohort.

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Chapter 5
ALGS and Transition: The Prognosis into Adulthood

Alastair Baker and Emily Stenke

Introduction

Alagille Syndrome (ALGS) is a rare genetic autosomal-dominant disease characterized by specific facies, cardiac lesions (mostly right-sided), posterior embryotoxon, butterfly vertebrae and interlobular bile duct paucity [1]. These features form the basis of the clinical diagnosis, with subsequent genetic confirmation obtained in about 95% of patients. The cardiac and hepatic features are accepted as the major determinants of prognosis, at least in childhood. Additional features include renal tubular defects and renal cysts with systemic hypertension and renal artery stenosis [2]; optic nerve head Drüsen and pigmentary retinopathy; bleeding diathesis and intracranial bleeding; vascular and lymphatic defects [3–7]; intracranial hypertension; recurrent otitis media and respiratory infections [8, 9].

A recent systematic review rightly describes ALGS as a severely debilitating, life-threatening disease of childhood, associated with multi-system morbidities each of varying severity and prevalence [10]. However, the current literature on clinical outcomes and natural history in ALGS, particularly in adolescence and into adulthood, includes mainly small, often retrospective, studies with sparse outcome data. Accordingly, it is difficult to gauge the true extent and consequence of ALGS for affected young adults.

The only study to directly estimate the incidence of ALGS was published in 1977 [11]. While this was a large study involving data from over three-quarters of a

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million births over 11.5 years, it was undertaken before a molecular genetic diagnosis was possible. Due to variable expressivity, ALGS is likely to be underdiagnosed in the absence of molecular genetic confirmation.

Given the paucity of suitable studies in this rare disease, it is not possible to assess long term evolution of clinical features, mortality, quality of life, costs, resource utilization or overall economic burden with any great accuracy. The summary of the literature reported information on mortality in patients with ALGS varying from 11% to 35% over a 10- to 40-year follow-up [6, 8, 12–16]. The median age of death ranged from 2.3 to 4 years (2 months to 31 years). Non-cardiac vascular complications, including bleeding, were a leading cause of death [12].

In this chapter we have taken the liberty of extrapolating from cross-sectional data of moderate sized series from various centres, and from case reports and small series of novel features, while acknowledging the inherent biases of this approach.

Hepatic Prognosis

Management of cholestatic liver disease in patients with ALGS currently focuses on controlling pruritus and supporting nutrition and fat-soluble vitamin deficiencies by oral MCT fat supplementation, nasogastric feeding or gastrostomy [17]. Burdensome symptoms such as pruritus and xanthomas affect many patients and can be severe enough to warrant biliary diversion or liver transplantation. Surgery can be associated with increased risk of bleeding [18]. Liver transplantation (LT) and its associated lifelong immunosuppression, carries with it the risk of nephropathy, immune dysregulation and increased risk of infection-related cancers [19] superimposed on the long term risks of ALGS itself.

An early description of an ALGS cohort in 1999 stated that the 20-year survival rate was 75% for all patients, 80% for those not requiring liver transplantation, and falling to 60% for those who required liver transplantation. The major determinant of mortality for those not transplanted was severity of cardiac disease [6, 8]. Since that time, the advent of routine genetic diagnosis has expanded the diagnosis of ALGS, capturing individuals with milder phenotypes, while the anticipation of complications and the outcomes of liver transplantation have all improved since that time [20, 21]. Furthermore, the most severe cardiac lesions are likely to lead to mortality in childhood. Therefore, it is likely that the prognosis of ALGS in adolescents and adults is better than observed in the 1999 cohort, and will be determined more by non-cardiac factors, including liver disease.

Cholestasis and Liver Dysfunction

The presence of bile duct paucity has been reported in 75% to 100% [8, 12, 14, 20, 22, 23] of patients with ALGS and a correlation between degree of bile duct paucity and increased age has been observed [8, 22]. It was reported that the prognosis of

liver disease in patients with ALGS is worse in children who present with neonatal jaundice than those presenting with later onset liver disease, for example cholestasis or complications of PHT [10, 14]. Even so, the rate of progression of hepatic fibrosis towards PHT is less aggressive in ALGS for a similar degree of cholestasis than in other biliary disorders such as biliary atresia or progressive familial intrahepatic cholestasis. Among the largest ALGS follow-up series of 163 patients, followed for median of 10 years, only 25% had evidence of cirrhosis, 18% had evidence of varices and 3.6% had GI bleeding. There is likely a selection bias in these data because patients may have been transplanted for complications of cholestasis (such as itch) before fibrosis had time to develop [14].

A report of a 28-year-old woman with ALGS who underwent urgent LT for liver failure with a good recovery at 24 months points to the possibility of acute-on-chronic liver failure in ALGS as in other biliary conditions [24]. A similar case of acute-on-chronic deterioration is described in an 18-year-old male with ALGS and liver cirrhosis but stable liver function. Severe bleeding developed from gastric varices, an urgent shunt operation was performed, but septicaemia developed on the third postoperative day and he subsequently died from right-heart failure [25]. Thus, although the majority of Alagille patients with liver involvement are transplanted electively for chronic cholestatic disease, these cases illustrate the risk of unpredictable and rapid deterioration in young adults with ALGS.

Prognosis and Spontaneous Remission of Liver Disease

Longitudinal studies show improvement in features of neonatal cholestasis over time, leading to a hypothesis that some ALGS patients ‘mature’ beyond their liver disease, or at least their cholestasis. Seventy-seven percent of children presenting with neonatal cholestasis remained jaundiced at 15 years, compared to only sixteen percent of children who had presented later in life. Pruritus was also more frequent and more difficult to treat in those who presented as infants, and xanthomas were present in 30% of that cohort, while they were not seen among children in the late-onset group [8]. Similarly, a cohort of 163 patients showed poorer outcomes in children who presented with neonatal cholestasis compared to those presenting later in life. Of the 132 patients with neonatal cholestasis, 102 remained jaundiced and 112 had poorly controlled pruritus at median follow up of 10 years, contrasting with only 5 patients with persistent jaundice and 17 patients with well-controlled pruritus in the cohort of 31 patients who had not presented with neonatal jaundice. In addition, children in the neonatal onset group had higher rates of hepatomegaly and splenomegaly, and 44/132 children in the former group progressed to liver transplantation, compared to none in the late-onset group. However, 10-year survival rates were not significantly different between groups, at 65% and 79%, respectively [14]. Although infantile cholestasis is associated with increased probability of persistent cholestasis and pruritus, even in this group these symptoms may remit throughout childhood and adolescence. In 30 of 132 patients, jaundice disappeared

by median 2 years and 10 months (range, 6 months to 18 years), while complete resolution of pruritus occurred by median age of 12.5 years (range, 4–23 years) in 20/132 patients. Thus, within the poorer prognosis group of children with neonatal onset there is a small subgroup of patients in whom a definite improvement in the clinical and biochemical signs of cholestasis occurs with time even until puberty and possibly later.

Pruritus

Pruritus affects 45% to 88% of ALGS patients under the care of hepatologists at some stage during the first 10 years of life [4–8, 14]. Pruritus was reported in at least 80% of patients in 4 of these 6 publications [4, 7, 8, 14] being a prominent symptom in 70% of patients [5]. Forty-five percent of patients were classified as having severe itch. However, there is no universal or consistent tool to assess severity of itch [26, 27]. Pruritus resolves only in less than a quarter of all patients by adolescence [14]. It is severe (although difficult to quantify) in a considerable proportion of patients (15–45%) and is associated with skin lesions, sleep problems, and mood disturbances [14, 26, 28, 29]. Treatment of pruritus appears to be suboptimal, and the condition persists in many patients despite therapy. As such, it is the major influence on quality of life indicating LT. For the majority of untransplanted patients, pruritus persists into young adulthood with varying degrees of severity, depending on the therapy received and adherence to treatment [10, 14, 26, 28, 29].

Partial External Biliary Diversion

Five publications reported use of partial external biliary diversion (PEBD) as a treatment of cholestatic pruritus in ALGS [30–34]. The proportion of patients who underwent PEBD ranged from 4% to 14%. Our own experience, from one study, reported no difference in the itching score between patients who had received PEBD and those who had not, whereas others have reported significant reduction in itch severity. Patients with ALGS who had undergone PEBD continued to experience reduced quality of life (HRQoL on the PedsQL 4.0) compared with healthy peers [35]. Young adults may find PEBD cosmetically and socially unacceptable, but alternatives such as internal diversion (terminal ileal exclusion, or gallbladder-to-colon diversion) have been less well studied, may be less effective and risk diarrhoea [32, 36]. We await clarity on the use of bile acid reuptake inhibitors as alternatives to PEBD [37].

Liver Malignancies

Hepatic involvement is the cause of death in about one-third of patients. Hepatocellular carcinoma complicating the course of liver disease is rare but has been noted in patients both with and without cirrhosis. Reports include a family in which three of four child siblings with ALGS developed hepatocellular carcinoma and died as a result of it [38]. None of the children had a liver disease, other than ALGS. This report recognised 15 other cases complicated by hepatocellular carcinoma [39]. A further case concerns a 31-year old man who died of hepatocellular carcinoma [40], while the series of Lykavieris also had one case presenting with HCC aged 44 years [14]. There are no data to clarify whether the incidence differs from other causes of biliary cirrhosis, but we recommend annual monitoring of adult ALGS patients with liver disease by imaging and AFP.

Liver Transplantation in ALGS

Seven publications include studies of patients who underwent LT [6–8, 13, 14]. In these studies, 15% to 47% of patients had a transplant and the median age at surgery was from 4 to 6.5 years. Frequently reported indications for LT, either alone or in combination, are shown in Table 5.1. Signs of end-stage liver disease were present in a minority of patients, only 11% in one study, at the time of transplantation [8, 14], and quality of life issues exceed end-stage liver disease indications by about 2 to 1.

One year survival rates ranged from 71 to 91.7% in 4 series of patients transplanted since 2001 [10]. In an older study of 163 patients, of whom 44 underwent transplantation, actuarial survival rates with native liver were 51% and 38% at 10 and 20 years, and overall survival rates were 68% and 62%, respectively [14].

Table 5.1 Aggregated indications for liver transplantation in ALGS

Indication for transplantation	Publications	Number of patients
Refractory pruritus	4	53
End-stage liver disease	2	51
Disfiguring xanthomas	3	41
Bone fractures	3	24
Synthetic liver failure	3	9
Failure to thrive	2	9
Bleeding diathesis	1	3
Portal hypertension	1	2
Osteodystrophy	1	2
Encephalopathy	1	1
Cholangitis	1	1

Patients with ALGS differ from patients undergoing LT for other indications due to their high rate of co-morbidities, which must be managed in order to minimize intra-operative and post-transplant risks. A higher surgical risk in paediatric patients with ALGS undergoing OLT has been highlighted in a large multi-centre retrospective review, showing that of the patients who had died, all deaths were due to post-transplant complications and most deaths occurred within the first 30 days. The most common complications following surgery were vascular (20.9%), and biliary (15.4%). Renal complications were also common (9.9%) and children with pre-existing renal insufficiency were less likely to show improved renal function, suggesting that intrinsic renal disease is not reversed in the medium term by LT [13]. Recent data from United Network for Organ Sharing show that one and five year outcomes of LT for adults with ALGS are better than for children, or even adults with biliary atresia (summarised in Table 5.2), although the ALGS patients had higher MELD scores [41].

In the early transplant era, post-transplant mortality plagued LT for ALGS. Tsazis et al. followed a cohort of 23 paediatric patients for up to 9 years post LT, by which time 10/23 patients had died (at a mean of 4.4 years post-LT). Of these ten, three had early cardiac deaths and one suffered primary graft non-function [20]. In response to a similar experience, we have required RV:LV pressure ratios <0.5 in ALGS patients at dobutamine challenge test (DBT) before listing for LT [42] and have managed peripheral pulmonary artery stenosis (PPAS) aggressively in patients likely to need LT. On the other hand, Ovaert et al. reported 10 patients in a cohort of 17 patients undergoing LT for ALGS having evidence of raised RV pressure at prior cardiac catheterization, but DBT was not performed. Mean RV to LV systolic pressure ratio was above 0.5 in 6 patients (median 0.66, range 0.5–0.8). All patients underwent initial successful LT. Five patients died but not of cardiac causes and 2 of these 5 had had catheter studies with RV:LV pressure ratios below 0.5 [43]. Although there is reason to take particular care from the cardiac point of view, there is currently insufficient evidence to mandate a particular line of cardiac management.

Overall, LT in ALGS is most often undertaken for quality-of-life indications and requires consideration and management of specific peri-operative risks compared to LT for other conditions. Of relevance to the young adult population, one study

Table 5.2 UNOS data comparing adult ALGS patient and graft survival with paediatric ALGS and adult BA outcomes. The differences in relative selection criteria are unclear but results are excellent for ALGS patients (Arnon 2012 [41])

	1 year survival (%)	5 year survival (%)	Number of patients
Alagille adult patients	95.5	90.9	44
Alagille adult graft survival	84.1	79. 5	
Alagille paediatric patients	88. 7	86.2	407
Alagille paediatric patient graft survival	80.3	76.1	
BA adult patients	89.3	87.5	56
BA adult graft survival	82.1	78.6	

showed that only approximately 10% of all LTs for ALGS were performed in the adult age group, with the remainder performed in children. Consistent with this, ALGS was the indication for only 0.05% of all adult transplants compared to 3.5% of paediatric transplants [41]. Clinicians caring for patients with ALGS who have not required transplantation by early adulthood can therefore counsel them that significant deterioration requiring future LT is uncommon.

CVS Involvement in ALGS

Death occurred in 21 (26%) patients with syndromic paucity of interlobular bile ducts (PILBD) in the original ALGS description with cardiac defects as the major cause [4]. Cardiac disease still significantly impacts on the life expectancy of patients with ALGS, contributing to the 34% of total cardiovascular (CVS) mortality [12]. The syndromic CVS features of ALGS are summarised in Table 5.3, of which the commonest and most characteristic is peripheral pulmonary artery stenosis (PPAS), occurring alone or complicating other CVS lesions [44].

Patients with *JAG1* mutations and pulmonary atresia had a poor outcome, with 6 of 8 patients not surviving infancy [15]. Congenitally very small pulmonary arteries of severe PPAS tend to fail to grow following systemic-to-pulmonary arterial shunts such as the Glen or Fontan procedures. Lesser degrees of PPAS in ALGS are found to be generally non-progressive in childhood, but it is unclear if pulmonary artery growth in PPAS keeps pace with other physical growth in puberty as right ventricular pressure may deteriorate. More proximal PPAS is often amenable to stenting or occasionally to use of cutting stents, but in all patients very small distal vessel disease, especially in small patients, may be beyond treatment with current devices. Patients with PPAS and pulmonary hypertension (PH) approaching systemic pressures tend ultimately to develop RV dysfunction and conduction arrythmias so that the RV of patients with severe PH seems unable to compensate for its increase in afterload completely [45]. The prognosis for such patients is therefore poor even before reaching adulthood.

Table 5.3 The spectrum of cardiac lesions in ALGS

Murmur only detected	18–22%
All ALGS patients with any CVS findings	94%
Pulmonary stenosis—all types	67–76%
Isolated PPS	35%
Intracardiac lesions associated with worse PPS:	
Tetralogy of Fallot	7–12%
Right sided lesions	37–55%
Left sided lesions only	7–9%
Left and right sided lesions together	6%

The long-term outcome of valvular and pulmonary arterial disease amenable to surgery or stenting is better and may be comparable to repaired pulmonary valve stenosis of other aetiology [46]. In long term repaired cono-truncal congenital heart disease not associated with ALGS, narrowing of the pulmonary artery branches is common and can have serious clinical consequences. Primary intravascular stent implantation is recommended in significant branch pulmonary artery stenosis when the vessel or patient is large enough to accommodate a stent that can be dilated to an adult diameter; an indication that applies equally in ALGS. A variety of specialized stents are now available, improving applicability despite complex vessel size. Thus, while the prognosis of ALGS cardiac disease into adulthood is not clear, it seems likely that aggressive control of RV pressure by decreasing afterload with stents where possible may be better for long term prognosis, as well as suitability for LT if indicated.

Xanthomas and Hyperlipidaemia

Presence of xanthomas in ALGS was considered in 6 reports affecting 30% to 42% of patients [4–9, 14] and appearing at median 20–48 months of age [4, 5]. In 3 reports, LT was indicated for xanthomas [7, 8, 14]. Three reported moderate improvements in xanthomas after the patients reached the age of 10 years [4, 6, 14], with one describing complete disappearance of xanthomas by median age 7 years in those patients who had not presented with neonatal jaundice [14]. They were associated with severe prolonged cholestasis and high serum cholesterol, and have improved with falling serum cholesterol [4]. Xanthomas also improved following PEBD [30]. Notably, the presence of xanthomas was found to be associated with a worse 10–year survival rate than absence of xanthomas in patients who survived without LT [14].

Hypercholesterolaemia correlated with hyperbilirubinaemia and cholestasis is a consistent feature of ALGS which clinically distinguishes it from other aetiologies of progressive intrahepatic cholestasis. Total cholesterol, LDL cholesterol, HDL cholesterol, and lipoprotein X are increased in patients with ALGS [47], whereas in patients with PFICs, increase in triglycerides and decrease in HDL cholesterol are characteristic [48]. Despite this chronic dyslipidaemia, ultrasonographic and biochemical assessments in young ALGS children suggested that they may be less susceptible to atheroma than patients with PFIC [48] or BA [49], although rare examples of atheroma have been described [50].

A possible explanation for this may lie in the protective role of HDL cholesterol. HDL level is a strong inverse predictor of cardiovascular events in the general population. HDL is believed to retard the formation of atherosclerotic lesions by removing excess cholesterol from endothelial cells by the ‘reverse cholesterol transport pathway’ and by preventing endothelial dysfunction. Lecithin cholesterol acyltransferase (LCAT) plays a central role in the formation and maturation of HDL, and in the intravascular stage of reverse cholesterol transport. It has been suggested that LCAT exhibits two activities in normal plasma: a) alpha-LCAT activity, specific for

lipoproteins that migrate with alpha mobility upon gel electrophoresis, when deficiency is associated with low HDL levels and a lesser phenotype called Fish-Eye disease, and b) beta-LCAT activity which is specific for pre-beta- and beta-migrating lipoprotein (very low-density lipoprotein [VLDL] and LDL). When both beta- and alpha-deficiency occur together, the phenotype is the more severe familial LCAT deficiency which is characterised by extremely low or undetectable HDL-cholesterol levels, xanthomas, early adulthood development of corneal opacities, anaemia, and renal disease. One might expect to find more atherosclerosis in these patients with low HDL but in fact current studies suggest that individuals with LCAT mutations have very few cardiovascular events, albeit accurate data are difficult to acquire in this rare disease [51]. As a possible explanation for this, it was suggested that important proteins and enzymes of the reverse cholesterol transport pathway which alter the effect of LCAT on atherosclerosis may moderate the vasculopathic process.

LCAT activity, modified by bilirubin levels or other mechanisms related to cholestasis, may play a role in the dyslipidaemia observed in patients with ALGS. One study of paediatric patients with ALGS observed that patients with bilirubin >100 umol/L had significantly lower LCAT levels associated with low LDL, high unesterified cholesterol and high lipoprotein X, compared to the patients with bilirubin <100 umol/L [47]. It is not found to be a phenotypic feature in first degree relatives of children with ALGS [52]. Like in other cholestatic disorders, dyslipidaemia in ALGS correlates with serum bile acid levels [53], improves with PEBD [32] and resolves after LT.

The incidence of ischaemic vascular disease in adult patients with ALGS is unknown and requires longitudinal studies. The exact mechanism explaining the higher HDL levels in ALGS patients remains elusive, and in the absence of any clinical data it is unclear whether adult patients with ALGS are protected from ischaemic vascular disease, despite their hyperlipidaemia and other vascular anomalies, or whether they would benefit from statin therapy in adulthood.

Renal Disease and Prognosis

Renal anomalies in ALGS are estimated to occur in 30–40% of patients who have end-stage liver disease [54] but the true prevalence is likely to be higher and may change with age. Renal abnormalities occurred in 19% to 74% of patients specifically studied for renal involvement [4, 6–8, 22, 55], including glomerular mesangiolipidosis [4, 29], renal tubular acidosis [6, 7, 55], renal anatomic defects or dysplasia [7, 8] and kidney failure [8, 13, 14]. Nephropathic abnormalities may be categorised according to Table 5.4. Following LT, the effects particularly of tacrolimus with both tubulopathy and glomerulopathy, tend to be particularly pronounced in ALGS such that post-transplant nephropathy may be considered an independent category. Finally, two cases of nephroblastoma associated with ALGS have been described, associated with a new V136G *JAG1* missense mutation and a constitutional deletion of 20p12, respectively [56].

Table 5.4 Categorisation of renal conditions in ALGS

Abnormality	Characteristics
1. Malformations: cystic and structural	Dysplasia, cysts, absent kidney, horseshoe kidney, duplex ureter; may be associated with vesico-ureteric reflux
2. Glomerulopathy and mesangiolipidosis tubulopathy	Fanconi type renal tubular acidosis, defective *JAG1* expression in collecting ducts, mesangiolipidosis, osteopathy
3. Vascular anomalies and their consequences	Renal artery stenosis, mid-aortic syndrome and hypertension
4. Immunosuppression-related	Glomerulopathy, tubulopathy, hyperkalaemia

Structural Defects and Renal Dysplasia

Notch-signalling pathway functions in both primitive and developed nephrons by directing cell fate decisions during embryonic development of pronephros and metanephros. It functions as a cyst-suppressor and maintains fundamental importance during development and homeostasis of the kidney [57]. Notch activity may also regulate mature renal physiological adaptation [58]. In a 3D in-vitro model of kidney development, acute inhibition of Notch-signalling for only two days is sufficient to disrupt tubule formation and affect the ability of renal epithelial cells to form spherical structures with a single lumen, similar to the effect of elevated Akap12 expression. This may explain how diseases associated with defective Notch-signalling, such as Alagille syndrome, may be anatomically and functionally related to ciliopathies [59].

Structural defects described in ALGS include dysplasia, cysts, absent kidney and horseshoe kidney (Fig. 5.1). Dysplasia may be diffuse or focal/cystic, while cystic defects vary from one or few simple cysts to renal cystic dysplasia; vesico-ureteric reflux (VUR) may be present. Renal dysplasia (manifesting as hyperechogenicity on ultrasound) is estimated to be the most common renal anomaly seen in ALGS, affecting approximately half of those patients with renal involvement. Up to 50% of patients with renal dysplasia over the age of 2 years had some degree of renal impairment [6, 55]. Although correlation between deteriorating GFR and increased age has not been formally documented, renal impairment due to dysplasia was more prevalent in patients over the age of 2 years compared to those younger than 2 years [55], thus it is likely that deterioration occurs with age.

Glomerulopathy and Tubulopathy

ALGS glomerulopathy is characteristically associated with mesangiolipidosis with cholesterol deposition disrupting glomerular function. Glomerular and tubular basement membranes in ALGS patients with severe renal disease show a prominent vacuolated appearance and focal subepithelial “spike” formation, which appears

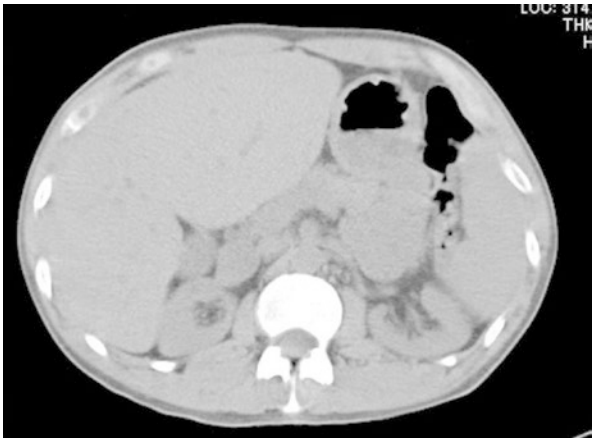

Fig. 5.1 CT scan of a patient with ALGS showing a hypoplastic right kidney and a malrotated left kidney. (Hayashi et al. [60])

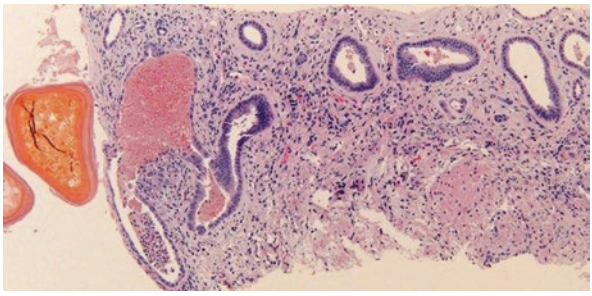

Fig. 5.2 Renal biopsy from a patient with Alagille syndrome. (Bissonnette et al. [61])

identical to membranous nephropathy [61, 62], (Figs. 5.2 and 5.3). As discussed above, the rare familial disease of LCAT deficiency has a strikingly similar dyslipidaemia profile to Alagille syndrome. Although renal disease is not ubiquitous in these patients, it is the leading cause of morbidity and mortality in familial cases, and a subgroup progress to renal failure by a median age of 46 years, with post renal transplant recurrence by a median of 10 years [63, 64]. In a large cohort of LCAT-deficient patients, high plasma unesterified cholesterol level was a predictive factor for rapid deterioration of kidney function [63]. This association has not been confirmed in ALGS, where small studies have instead shown a correlation between renal disease and age [62] or bilirubin [65].

A mouse model of LCAT with accumulation of plasma lipoprotein X (LpX) is strongly associated with a spontaneous glomerulopathy, providing in vivo evidence that LpX contributes to the LCAT deficiency-related nephropathy [66]. Since LCAT and ALGS patients have similar renal manifestations, and since an association between renal disease and bilirubin levels [65], as well as LCAT-like dyslipidaemia and bilirubin levels [47] have been shown in patients with ALGS, it is plausible that progressive renal disease in ALGS is mediated by dyslipidaemia in the same way as in LCAT. As yet, no studies have examined the effect of statins on either lipid

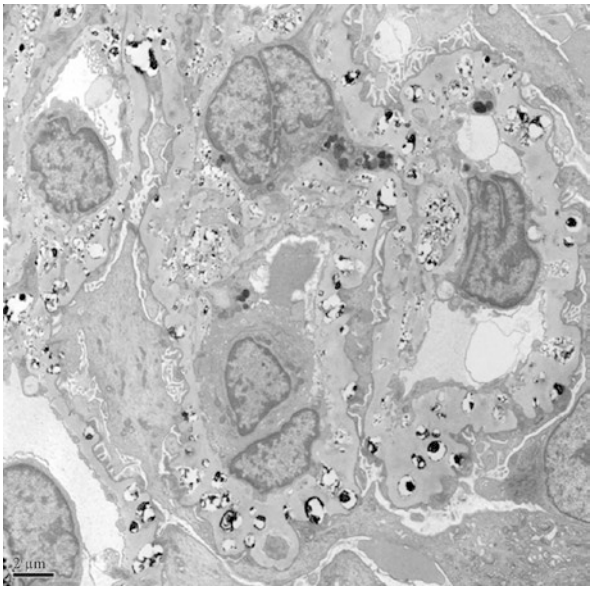

Fig. 5.3 Mesangiolipidosis—Numerous lipid vacuoles with characteristic electron dense and lucent areas are embedded in the glomerular basement membranes and some mesangial cells. Some of the lipid vacuoles are subepithelial, intramembranous, or subendothelial (Bissonette et al. [61])

profiles or renal disease in ALGS, while any potential renal benefits of LT in the resolution of hyperbilirubinaemia/dyslipidaemia may be obscured by the nephrotoxic immunosuppressant regimes. Interactions between cholestasis, dyslipidaemia and renal disease in ALGS provide an area ripe for research and potential therapeutic interventions.

The tubulopathy of ALGS is poorly described. The role of *Notch-2* and *Jagged1* in formation of proximal nephron structures and podocytes that is disrupted in ALGS could explain some of the observed phenotypes of renal dysplasia and proteinuria. ALGS tubulopathies are associated with Fanconi type renal tubular acidosis and osteopathy. Clinical assessment of this component of ALGS renal dysfunction is more complex than for glomerular filtration rate (GFR). Tacrolimus, in particular, seems to worsen the features of both glomerular filtration and tubulopathy. The long-term prognosis of ALGS nephropathy is, however, unclear.

Renal Vascular Disease

Vascular defects such as stenoses or hypoplasia as a consequence of impaired Notch signalling in foetal vascular development may result in renal vascular hypertension and secondary reduced GFR. Among five adult patients with ALGS and renal artery stenosis, all had systolic hypertension and a narrowing of the abdominal aorta, corresponding to a secondary mid-aortic syndrome. Renovascular disease progressed during follow-up, with increases in blood pressure, decreases in GFR and/or kidney atrophy [67]. There are several anecdotal reports of ALGS associated with

hypertension, renal artery stenosis and/or mid-aortic syndrome, while a larger study identified bilateral renal artery stenosis in 2/74 patients [55].

Renal Outcomes After Transition

Renal prognosis is unclear in epidemiological terms and there are no reliable data concerning the natural history of ALGS renal disease. Renal impairment of some degree is common as noted above, and particularly clinically significant in children with ALGS who have end-stage liver disease, and following transplant immunosuppression with tacrolimus. Structural defects may not show progression unless complicated by secondary phenomena such as VUR. Vascular hypoplasia may not progress by itself, but failure of growth in renal arteries may lead to persistent systemic hypertension and secondary progressive loss of renal function.

While few ALGS patients proceed to end stage renal failure in the paediatric age group, case reports including small family series show that renal transplantation in ALGS may be warranted for end-stage renal failure appearing in young adults [60, 68]. It is therefore likely that nephropathy progresses over decades to ultimate renal failure in a subgroup. Increased awareness of ALGS amongst nephrologists may lead to more diagnoses in patients with apparently isolated renal disease [54], with implications for living-related donor transplantation. For some patients, the age of transition from paediatric to adult care may coincide with a development of progressive renal disease just as childhood liver disease may have abated or been treated with LT. Therefore, the transition period represents an opportunity for a complete reassessment of renal function using ultrasound, serum biochemistry with measured GFR, cystatin C and urinalysis, with referral to adult nephrology services where warranted.

Immunology

The complement system has been associated with the modulation of human T cell responses. CD46 is a complement regulator and functions as a cofactor in the factor I-mediated cleavage of C3b, thereby preventing unwanted complement attack of ‘self’ tissues [69, 70]. CD46 has additional immune-related roles. It functions as a pathogen receptor for a number of important human pathogens [71] and is a potent co-stimulator for the induction of interferon (IFN)-γ-secreting Th1 effector T cells and their subsequent switch into interleukin (IL)-10-producing regulatory T cells, thus balancing IFN-γ versus IL-10 production [72]. *Jagged1* has been identified as a new physiological ligand for CD46, the binding site within *Jagged1* being close to its Notch site. This CD46-*Jagged1* interaction on resting T cells limits the *Jagged1*-Notch1 interaction and thereby prevents the unwanted engagement and signalling of these two receptors in the steady-state [70, 73, 74]. However, on T cell receptor

activation, CD46 is activated by T cell-derived C3b, which triggers the CD46-*Jagged1* interaction and allows for the Th1-fostering *Jagged1*-Notch1 interaction. CD46 also regulates Notch receptors and ligand expression during T cell activation. Disturbance of the CD46-Notch signalling crosstalk from defective *Jagged1*-CD46 interactions impedes IFN-γ induction and IL-10 switching [75]. CD46 deficient patients suffer a propensity to recurrent infections, such that 50% of homozygous CD46-deficient patients suffer a variant of common variable immune deficiency (CVID) despite normal cell stimulation responses. CD46, *Jagged1* and Notch1 interact with human CD4+ T cells to form a bridge between the Th1 cell population and the complement system, and also modulate the immune response via IL-10.

Epidemiological data on clinical immune dysfunction in ALGS patients are scarce and they are not usually recognised to be immunodeficient beyond what is seen in chronic liver diseases. However, some data do suggest a higher incidence of respiratory infections and otitis media in ALGS patients [8]. In our mechanistic study of four ALGS patients with *JAG1* mutations, although key lymphocyte populations were normal, we found a series of consistent abnormalities: increased *Jagged1* expression on resting T cells was associated with inability to mount appropriate Th1 responses in vitro and in vivo [74]. In addition, this inability of T cells to produce normal amounts of IFN-γ extended into a failure to subsequently switch into an IL-10-secreting regulatory phenotype, compatible with immune dysregulation in keeping with a defective pro-inflammatory state. Although these findings require further confirmation in other studies, they provide a possible mechanism for the previously unexplained recurrent symptomatic infections in ALGS patients. These findings would also be expected to predispose to symptoms of asthma, eczema, food allergies and airway atopy with otitis media, which are Th2-driven [76–78]. Our brief survey suggests infections remain frequent into adulthood in ALGS although further epidemiological and functional studies are necessary.

Neurological, Vascular and Eye Abnormalities

Bleeding Diathesis and CNS Vascular Malformations

Bleeding events in patients with ALGS were recognized as recently as 2003 [6, 7, 12, 13, 18, 21, 79]. Intracranial bleeding was the most common episode, occurring in 11% to 14% of patients and included subarachnoid haemorrhage, subdural hematoma, epidural haemorrhage, and other cerebrovascular accidents [6, 12]. In a study of 38 patients who had experienced a bleeding event, 49 bleeding episodes had occurred, the majority of which were spontaneous haemorrhages or resulted from surgery [18]. Spontaneous bleeding may be difficult to distinguish from non-accidental injury in the paediatric population [80]. When considered from the

perspective of mortality, in patients with ALGS non-cardiac vascular complications were a leading cause of death [12]. The precise mechanisms that predispose to bleeding are unclear, although an association has been observed with between bleeding risk and hyperbilirubinaemia/hypercholesterolaemia [12]. It is not clear to what degree the problem carries over into adulthood; a case report describes bleeding from an intracranial aneurysm at age 21, however no population data exist [81].

The confluence of bleeding diathesis with intracranial vasculopathy constitutes a risk for a significant minority of patients. The cerebral vasculopathy of ALGS predominantly involves the internal carotid arteries and may be progressive. Emerick et al. examined intracranial MR angiography reports in 22 asymptomatic paediatric patients: of these, 5 were shown to have vascular abnormalities. Two additional patients with normal angiography nevertheless went on to have fatal ischaemic CNS vascular events years later. Thus, intracranial vasculopathies (most commonly internal carotid artery stenoses or arterial aneurysms) are more prevalent than would be suggested by the number of symptomatic individuals, may be progressive, and are associated with a high risk of stroke-like events [82]. In another cohort of 268 patients, intracranial bleeds were seen in 29 patients (14%) and accounted for 25% of all mortality, while intra- and extra-cranial vascular disease together accounted for 34% of mortality; significantly higher than liver disease (10%) or cardiac disease (21%) [12]. Although no consensus guidelines exist, some centres now perform MR angiography screening of intracranial vascular abnormalities in ALGS patients, while we only screen those going for major procedures, particularly LT. Even in the absence of routine screening programs, clinicians and their young adult patients should be aware of the possibility of bleeding diathesis and intracranial vasculopathies in ALGS, which should result in prompt radiographic evaluation of any intracranial symptoms, and consideration of screening in individuals pursuing high risk sports or lifestyles.

Prognosis of Eye Abnormalities

Ten publications report various eye abnormalities [4–8, 22, 83–86], the most frequent of which was posterior embryotoxon, affecting 56% to 95% of patients [5, 84]. The eye abnormalities of ALGS rarely progress or result in significant loss of vision. However, idiopathic intracranial hypertension (IIH) has been described in 3 children (all aged under 6 years) out of a cohort of 41 ALGS patients, with another patient having optic atrophy, and another who suffered unilateral sight loss from optic pit [85, 86]. Although the authors recommend screening for IIH in children with ALGS, no cases of late-onset IIH or visual loss in adults have been reported, thus ophthalmological surveillance is not routinely performed in the adult population.

Cranial Synostosis

Anomalies of fusion of the cranial vault are uncommon but well recognised in ALGS, and a significant cause of increased intracranial hypertension [87]. They are amenable to conventional treatment and by their nature only relevant to young adults if they have left consequences such as raised intracranial pressure before treatment, and for cosmetic reasons.

Hypothyroidism

ALGS patients have an increased risk of non-autoimmune hypothyroidism, manifest in a series of 6/21 (28%) ALGS patients at ages of 3, 6, 10,11, 21 and 25 years, two of them with thyroid hypoplasia. In a comparison group of 100 unrelated congenital hypothyroid subjects (66 thyroid dysgenesis and 34 with gland in situ), the authors identified 2 distinct *JAG1* sequence variants in 4 unrelated patients. One had atrial septal defect, 1 had thyroid ectopy with pulmonary artery atresia and ventricular septal defect. The remaining two had no features of ALGS. Clinical and experimental data including a zebrafish model demonstrate a role for the *Jagged1*-Notch pathway in thyroid morphogenesis and function and indicate that ALGS patients have an increased risk of non-autoimmune hypothyroidism [88, 89]. Emerick et al. series of 92 patients reported only one case of hypothyroidism [6]. Heterozygous variations in the *JAG1* gene represent a novel predisposition to congenital thyroid defects that may present from birth to adulthood.

Growth, Puberty and Fertility

Birth weight was low in 29% of babies who presented with neonatal jaundice but in only 5% of those without neonatal jaundice [14]. Failure to thrive in patients with ALGS is common in earlier years and has been reported with a prevalence of 50% to 87%, but the definition of growth impairment was not defined consistently among the studies, which may account for the wide range [4–6, 8, 13, 14, 22, 34]. Children with ALGS had greater growth impairment than patients with BA, A1AT deficiency or bile acid synthesis disorders, but similar impairment compared to children with intrahepatic cholestasis in terms of height, weight, and BMI [90, 91]. Some children with ALGS may be insensitive to growth hormone [92, 93] which may contribute to the failure to thrive, together with factors including poor nutrition secondary to cholestasis and liver disease, or untreated renal tubular acidosis. Although final height compared with mid-parental height has not been formally studied, it is likely to be somewhat reduced.

Puberty was described as delayed in Alagille's early description [4] of the condition. It is unclear whether that was a primary consequence of the syndrome, or secondary to the liver disease and its complications. A study of familial inheritance undertaken before the advent of mutation analysis identified features of ALG in 6 parents (3 mothers and 3 fathers) out of 14 families. In the era of genetic diagnosis, it is likely that in fact significantly more than 50% of patients have inherited ALGS from a parent, suggesting that neither male nor female fertility are significantly impaired [94]. However, this study was small, and affected parents of probands were identified through screening, suggesting that their phenotype was mild. No studies have assessed fertility in cohorts of patients with ALGS, although it is likely that female fertility may be reduced in ALGS patients with severe liver disease. Case reports highlight the possibility of obstetric and/or anaesthetic complications for affected mothers related to severity of liver and cardiac disease, and 3rd trimester miscarriage of affected foetuses [95]. A series of 10 successful pregnancies in women with ALGS describes pre-conception counselling in 7/10 women and delivery by Caesarean section in 3/10 versus vaginal delivery in 2/10 (mode of delivery unknown in the remainder). Of the 5 babies unaffected by ALGS, 4/5 were healthy newborns (missing data for the remaining child), suggesting that if maternal health can be successfully mantained, neonatal outcomes in unaffected offspring are good [96]. Clinicians should initiate discussions on fertility and contraception with both male and female patients from adolescence on, explaining the 50% recurrence risk (albeit with variable penetrance) in any future children. Female patients should be additionally counselled about the risks of pregnancy superimposed on underlying liver, renal or cardiac disease, and thus the importance of appropriate contraception and formal pre-conception counselling by an obstetrician experienced in the care of high-risk patients.

Bone Health

Skeletal abnormalities are associated with ALGS [4–8, 13, 14, 21, 22, 97] and are considered one of the clinical diagnostic criteria. Vertebral anomalies were the most common, which occurred in 24% to 87% of patients investigated for skeletal abnormalities [4, 14]. A history of bone fractures was reported in 2% to 14% of patients [8, 13]. *Jagged1* expression is important for skeleton growth and osteoblastic activity while Notch2 enhances osteoclastogenesis and bone resorption [98]. Congenital disorders of Notch loss- and gain-of-function present with severe clinical manifestations, often affecting the skeleton. Dysfunction may lead to spine and long bone abnormalities, neoplastic changes and osteoporosis. In addition to the possibility of bone abnormalities directly resulting from *JAG1* or *NOTCH2* mutations, bone disease may occur as a secondary effect of liver and renal disease, related to vitamin D deficiency of cholestasis and/or renal tubular acidosis. In a large study of children

with cholestatic liver disease of different aetiologies, patients with ALGS were more likely to have low densitometry scores, but after correction for lower weight and height, densitometry scores were comparable to other conditions. There was a negative correlation between densitometry scores and serum bilirubin, serum bile acids, and history of fractures [91, 99]. Multiple fractures and osteoporosis can be anticipated with increased frequency in young adults with ALGS in follow-up, indicating need for monitoring with bone densitometry, particularly in individuals with cholestatic disease and/or a history of previous fractures.

Quality of Life, Education and Employment

Children with ALGS have significantly impaired health-related quality of life (HRQoL) compared with healthy controls. However, assessment of HRQoL and disease symptoms is hampered by the absence of disease-specific tools [29, 100, 101].

The HRQoL in children with ALGS has also been compared with that in children with other disorders. One study compared scores on the Pediatric Quality of Life Inventory (PedsQL 4.0) in children with ALGS, A1AT deficiency or PFIC [100], and another compared scores on the Child Health Questionnaire Parent Form 50 (CHQ-PF50) in children with ALGS versus attention-deficit/hyperactivity disorder (ADHD) and juvenile rheumatoid arthritis (JRA) [29]. In children with ALGS, the psychosocial function domain score on the CHQ-PF50 was worse on average than among children with JRA ($P < 0.0005$), but interestingly, it was better than in children with ADHD ($P < 0.0005$). However, the mean physical score by the same tool was worse in children with ALGS than in those with ADHD ($P < 0.0005$) [29]. Those with ALGS also had a worse mean self-reported physical domain score on the PedsQL than children with A1AT deficiency or PFIC, and a worse mean parent-reported physical domain score than children with A1ATD. Of note, subject growth status was positively associated with Peds QL HRQoL scores ($P = 0.008$) [100].

In ALGS HRQoL studies, pruritus was an adverse factor in 59% to 82% of patients [26, 100, 101]. A third of parents confirmed that itching had the most adverse effect on their children with skin damage, sleep problems and mood disturbances [101]. HRQoL was strongly negatively correlated with pruritus severity measured with the Infant Dermatitis Scale and lower psychosocial function, suggesting a greater psychosocial burden of their specific disease [35]. Thus, from a patient perspective, research efforts should focus on effective anti-pruritic treatments in order to improve QoL, educational and professional attainment, and delay/avoid LT. Moreover, lower QoL scores in ALGS were associated with the presence of several other ALGS-related features, namely cardiac disease, mental health disease, and poor sleep.

Early reports of Alagille syndrome describe learning disabilities as a feature of the condition [4]. A study compared paediatric patients receiving LT for ALGS liver disease to those with biliary atresia: a higher proportion of ALGS patients were

currently receiving special education or had received special education in the past (50% versus 30% and 60% versus 36%, respectively; $p < 0.02$) [13]. However, it is difficult to ascertain whether this is a primary feature of ALGS, or rather a secondary effect of severe pruritus, resulting in a cocktail of poor concentration, insufficient sleep, and high rates of use of sedating antihistamines, all of which may have a significant impact on educational attainment and increase the need for special educational supports.

Adult data are scarce, however a cohort of 39 adult patients described 21 in employment/further education, including as university student, secretary, factory worker, farmer, nurse or other healthcare worker, and professional violinist [14]. This suggests that while learning difficulties are more prevalent in children with ALGS, likely for multifactorial reasons, the neurodevelopmental phenotype covers the whole spectrum, similar to the phenotypic variability observed in liver, renal, cardiac and vascular disease of ALGS.

Key Points for Adult Hepatologist

Alagille syndrome is historically conceptualised as a rare inherited childhood disorder typically manifesting as cholestasis, most often in the neonate, and potentially leading to end-stage liver disease and LT, or death. Cardiovascular and liver complications are considered the major prognostic determinants in childhood, and nutritional management is often problematic. In recent years renal abnormalities have been increasingly identified as a major feature of Alagille syndrome, either alone or in conjunction with other features. Renal disease is frequently progressive, and thus may increase in importance or even present *de novo* in the adult population. Additional features such as vascular involvement, bleeding, and immune dysregulation have an unspecified impact on outcome as childhood progresses. HRQoL is typically impaired and particularly poor when itch is present. It is a frequent indication for LT, and should be routinely assessed to ensure optimal engagement in educational, social and employment activities. Genetic confirmation is now mandatory, because clinical presentation and disease severity are phenotypically highly variable with some individuals, who typically have a better prognosis, expressing only few of the characteristic features of ALGS.

With the advent of widespread application of genetic diagnosis, the beginning of understanding Jagged-Notch interactions and the passing of time we are seeing the early phase of the emergence of a different, new and highly complex cohort of young people. Many of these did not begin life with neonatal cholestasis, while others have liver disease that has progressed to LT, and yet others without significant liver disease have had successful cardiac interventions but not to the point of physiologically normal function or a normal cardiac prognosis. Apart from complications of their existing organ pathology, this cohort has risks of developing renal, vascular, bleeding,

thyroid, bone, immunological and malignant complications that challenge the experience of the organ-based specialists who will take over their medical care during transition to adult services. These risks may be overlooked, particularly as the incidences of almost all the complications of this still uncommon condition are unknown in the medium and long term.

ALGS is therefore an exemplar of a particular form of rare disease, in that its care needs are diverse and are changing very considerably during the time of transition from paediatric to adult services. Because the evidence is currently very sparse, multidisciplinary expertise and experience is required to develop services with the skills to manage new, recognised but unpredictable complications and develop new tools to treat existing problems such as liver disease, pruritus and xanthomas. These patients should be cohorted together for expert follow-up in highly specialised centres.

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Chapter 6
Alpha-1 Antitrypsin Deficiency in the Transition Period

Nedim Hadžić

Alpha-1 antitrypsin (A1AT) is a polypeptide, encoded by *SERPINA1* gene and primarily produced by the liver, which constitutes an important part of systemic inflammatory response in humans [1]. It acts as a protease inhibitor (PI), controlling destructive tissue injury by neutrophil elastase, fuelled by the innate immunity acute phase response. Alpha-1 antitrypsin deficiency (A1ATD) is inherited in autosomal co-dominant manner and represents the commonest genetic cause of chronic liver disease (CLD) and chronic obstructive pulmonary disease (COPD) in Caucasians. However, these two organ involvements are caused by completely distinct pathophysiological mechanisms; CLD is associated with the retention of abnormal A1AT polymers in the hepatocytes leading to chronic inflammatory injury ("gain-of-function"), while COPD is secondary to the alveolar wall destruction caused by the uninhibited destructive protease activity in the lungs ("loss-of-function"). In humans, apart from a wild type PiM, there are many different variants of A1AT, but the commonest ones associated with the clinical problems are PiZ (liver, lungs), PiS (lungs) and PiNull (lungs) [2].

The estimated prevalence of aberrant PiZ allele, secondary to a single amino acid change (Glu342Lys), is 1 in 25 persons of European descent (approximately 1 in 2000 persons are homozygotes). A founder mutation originates from Scandinavia and has spread both west to North-Western Europe and east to the Baltic countries and Poland. A milder—PiS A1AT deficiency, stemming from a different amino acid replacement (Glu264Val), does not result in the liver injury [3] and its abnormal allele is found in 1 in 4 persons from Iberian peninsula [1].

However, it has been clear for a long time that only a small proportion of genetically affected individuals have the clinical symptoms [4]. Seminal epidemiological

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study from Sweden, which screened all 200,000 neonates born there between 1972 and 1974 demonstrated than only between 10 and 15% of the affected ones develop liver disease [5]. Of their overall 170 newborns diagnosed with PiZZ and PiSZ A1ATD, eighteen PiZZ children, but none of the PiSZ children, have been affected with liver disease early in life. Five PiZZ children and 1 PiSZ child died before the age of 8 years [6]. After 40 years, in the A1ATD subjects available for follow up there was just a mild difference in the liver stiffness, assessed using acoustic radiation force impulse (ARFI) elastography and serum GGT and bilirubin levels in the PiZZ men cohort, but not between PiZZ women and PiSZ women or controls [6]. When the same group was assessed for the lung involvement, using lung function tests and chest CT densitometry, the significant differences were only found in ever-smokers, but not in the other PiZZ/PiSZ individuals [7].

For the lung disease no comparable prospective study exists, as the disease typically presents later—in early adulthood, but it is clear that there are many symptom-free A1AT deficient individuals, particularly amongst the ones who are never-smokers. The reasons why majority of PIZZ and PiSZ non-smokers, who do not abuse alcohol, remain free from the clinical liver or lung disease, and also why the male subjects appear to have slightly worse liver involvement are not well-understood.

What the Paediatric Hepatologist Needs to Know About the Natural History?

The unsolved clinical mystery of A1ATD-related liver disease is about what determines who will develop end-stage liver disease and who will recover following a typical initial presentation with prolonged neonatal jaundice. About one-quarter of the symptomatic PiZZ A1ATD children will require liver transplantation [8]. It appears that the ones with more severe clinical involvement—assessed on the basis of initial serum bilirubin, AST and GGT levels, and presence of portal inflammation and fibrosis in the liver biopsy—are more likely to be in that category [9]. After early childhood, the liver disease secondary to A1ATD becomes much more predictable. Monitoring of chronic liver disease and treatment of portal hypertension, if required, is the backbone of the management [10]. Of those presenting with prolonged neonatal jaundice in infancy, 43.7% normalise liver function tests during childhood, while around 26% have a clinically significant liver disease, most of them remaining completely asymptomatic [8]. Although rarely, hepatocellular carcinoma can develop even in childhood in the context of chronic liver disease secondary to A1ATD [11]. Annual ultrasound scan and FibroScan elastography follow up with regular blood tests (AST, GGT, alpha-fetoprotein, albumin, platelet count) to monitor AST-to-platelet ratio index (APRI) are recommended for the ones with established liver disease. Transient elastography, however, appears to be less helpful in the milder forms of fibrosis. Minimising alcohol use and avoidance of active and passive smoking is routinely advised.

What the Adult Hepatologist Needs to Know When Taking Over a Young Person with A1ATD?

Most of the long-term A1AT deficient paediatric patients will reach transition period of adolescence in a stable condition. However, in addition to the hepatological follow up they will also need additional intermittent assessment by respiratory specialists in the future. There is no obvious correlation between presence or severity between the lung and the liver disease [12]. Clark et al. [13] performed liver biopsies in 94 adult patients with primarily lung disease and noted that the largest cohort (43%) had mild target organ (lung and liver) involvements—with FEV1 > 50% and liver fibrosis grade < 2. The remainder of their group was divided into three smaller, similarly sized, cohorts with no relation between the functionally impaired lung function and grade of liver fibrosis. They also found a good correlation of transient elastography with more advanced histological stages of liver fibrosis (F2 and above) and noted that the liver injury was more associated with obesity, diabetes, hypercholesterolaemia and metabolic syndrome [13].

Carrier PiMZ state is not linked with the liver disease in childhood, but it is conceivable that it could contribute to adult liver pathology, particularly if associated with comorbidities such as alcohol abuse, NAFLD or autoimmunity. One retrospective liver transplant study noted that 90% of the PiMZ adult recipients had additional pathology in contrast to only 8% of the PiZZ ones [14]. Individuals incidentally transplanted from PiMZ carriers or electively from the parent carriers often have alpha-1 globules detectable in the liver grafts [15] and may require closer clinical surveillance for development of chronic complications such as focal dysplastic lesions. Cirrhotic adults with homozygous PiZ A1ATD have a cumulative rate of hepatocellular carcinoma of 0.88% per year, which is similar to alcoholic liver disease, but two-fold lower than in non-alcoholic steatohepatitis and three-fold lower than in chronic hepatitis C [16].

Therapeutic Approaches

Only effective present treatment for A1ATD with advanced liver disease is liver transplantation [10]. There are several described different approaches to modify its natural history and progression of liver disease, but a lack of clear understanding of pathology makes the candidate selection for therapeutic trials potentially biased and thus difficult. Recent study in homozygous PiZ adults with lung disease noted correlation between the size of misfolded A1AT polymers in the liver and degree of hepatic fibrosis [13], although majority had no clinical liver disease. On the other hand, different rare forms of A1ATD have different rates of polymerisation, which do not necessarily correspond to the degree of liver injury [1, 2]. For example, the described King's variant has a strong polymerogenic features, but no considerable liver injury (Fig. 6.1). Additional epigenetic and environmental factors determining

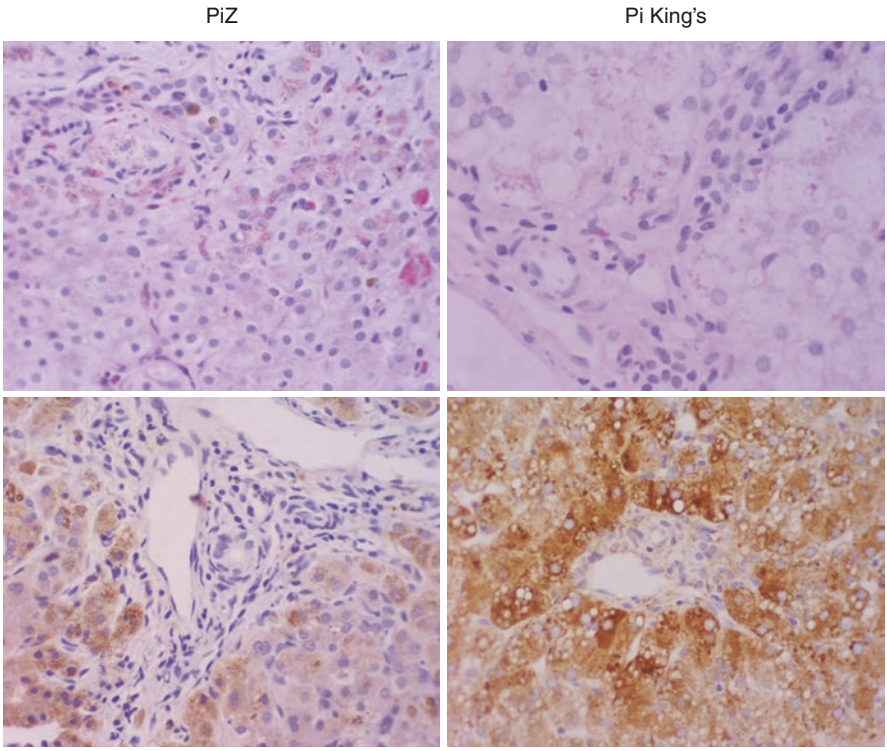

Fig. 6.1 Different polymerisation grades of abnormal Alpha-1 antitrypsin. Top panels: Periodic acid Schiff (PAS) staining demonstrating in pink retained A1AT polymers in homozygous PiZ variant (left) and rare King's variant (right). Bottom panels: Alpha-1-antitrypsin immunostaining demonstrating more significant polymerisation in King's variant (right) than in homozygous PiZ variant (left), but with less significant inflammatory component

individual severity of the liver damage remain to be identified. Presumably lifelong treatments with disease-modifying medications can only be justified in the patients with more severe forms of chronic liver disease.

As the presumed mechanisms for liver and lung disease are different—therapeutic approaches vary considerably [17]. Furthermore, benefits for the lung pathology may not necessarily be assumed for the liver disease and *vice versa*. Augmentation therapy with regular intravenous supplements of A1AT, approved only in the USA, provides a biochemical correction of the serum A1AT levels [18] and some improvements in lung densitometry, but sustained clinical benefits on preserving lung function and quality of life remain unproven [1]. Several different approaches have been described as potentially effective for liver disease in the experimental settings. To complicate the matters, some of the liver-targeting treatments may need to be considered in conjunction with augmentation A1AT therapy.

Blocking Polymerisation

The earliest attempts to modify natural history of liver disease in A1ATD were made by *in silico* searching and eventually constructing chemical compounds able to block aberrant polymerisation in the hepatocytes [19]. Chang et al. reported a monoclonal antibody (4B12) which blocked A1AT polymerization *in vitro*. They produced a single-chain variable fragment (scFv) intrabody, which reduced expression of scFv4B12 within the endoplasmic reticulum and consequently intracellular polymerization of Z alpha-1 antitrypsin by 60% [20]. However, clinical delivery of such elegant conceptual models *in vivo* and maintaining the beneficial effects long term is not realistic at present.

Chemical Chaperoning

Some agents could potentially aid in exporting retained abnormal A1AT from the hepatocytes. The drugs known as chemical chaperons, such as phenyl-butyrate or sodium-benzoate, have been in clinical use in other settings, primarily as ammonia-scavenging drugs. However, their effects could not be achieved in A1ATD, primarily due to considerable side effects noted in small phase 3 trials [21].

Augmentation of Autophagy

Exporting A1AT from the liver cells, even of abnormal type, could increase the serum levels and theoretically positively affect lung disease. Based on the observations that intracellular autophagy is altered in A1ATD, some licensed drugs, such as carbamezapine, sirolimus, glybenclamide and fluphenazine have been identified by computational screening and then in the animal models of A1ATD shown to enhance autophagy and potentially improve liver fibrosis [22–24]. However, to obtain the effects reported dose of carbamazepine had to be suprapharmacological [24]. Further clinical trials to test these hypotheses in older children and adults have been recruiting patients for several years, but have not yet been reported.

iRNA Interference Techniques

Recently, short interfering RNA (siRNA) molecules have been constructed to target hepatocyte mRNA encoding human A1AT. In a double-blind placebo-controlled phase 3 study they have been demonstrated to have the potential to reduce A1ATD polymer formation in the liver with a reduction of A1AT serum levels [25]. This

proof-of-concept endeavour could pave the way to further pharmacological attempts to neutralise the clinical effects of A1ATD on the liver medium to long term [26]. Obviously, development of side effects should be carefully monitored once paediatric patients are considered for such studies.

Transfer of Genetic Material

Specific molecular approaches are attractive due to their potential to treat both liver and lung disease, but their clinical application is in its infancy. Wild type hepatocyte transplantation could potentially be considered in A1ATD due to selective advantage of these cells towards the A1AT globule-containing ones [17]. It has been shown that differentiated mesenchymal stem cells (MSCs) from homozygous PiZ individuals could generate hepatocyte-like cells amenable to genetic alteration followed by their autologous transplantation. Yusa et al. showed that the PiZ mutation could be *in vitro* corrected in induced pluripotent stem cells (IPSCs) isolated from skin fibroblasts of A1ATD patients. These modified cells were then able to produce a wild type A1AT when reinfused in a mouse A1ATD model [27]. Again, there will be several hurdles to overcome before this exciting approach reaches the clinical setting.

Key Points
Despite exciting developments in basic research and potential novel modes of delivery of the disease-modifying treatments, the patients with A1ATD still await clinically relevant and safe therapy. The abnormal cellular proteostasis underlying this condition and huge phenotypic variability are yet to be better understood. It has become clear that both liver and lungs can be affected simultaneously in variable degrees of severity and at different age, but due to distinctive pathogenic mechanisms the effective future treatment will need not to harm the other potential pathologies inflicted by A1ATD. A cohort of carefully monitored paediatric patients with A1ATD-related liver disease approaching adolescence, generally in excellent clinical condition, should be handed over to adult specialists to monitor not only hepatological, but also possible ensuing respiratory aspects. Paediatricians and physicians looking after these patients need to be aware of the continuum, complications and remitting nature of this intriguing multisystem condition.

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Chapter 7
Inherited Metabolic Diseases

Roshni Vara and Yusof Rahman

Introduction

Inherited metabolic diseases (IMD) are caused by an enzyme, cofactor or transport protein deficiency which results in the accumulation of toxic intermediate metabolites or deficiencies of essential end products. IMDs are a heterogeneous group of conditions many of which result in significant morbidity and mortality. IMDs affecting the liver can affect any age group and there are now more than 400 monogenic disorders described involving the liver [1]. Hepatocytes play a key role in several biochemical pathways including protein synthesis, bile production and metabolism of proteins, fats and carbohydrates. Disorders of mitochondrial, lysosomal and peroxisomal function can also present with liver manifestations. Historically, IMDs were considered rare diseases and presenting in infancy or early childhood. However, over the past few years studies have shown a higher incidence rates and older ages at presentation than previously thought [2]. With the introduction of extended newborn screening programmes, improved diagnostic techniques and novel therapies, children with IMDs are surviving into adolescence and adulthood. Transition of adolescents with IMDs to adult services can present several challenges as often the families have been in the care of the paediatric metabolic service since infancy. Adolescents with IMDs can often have multi-organ involvement, complex needs and intensive dietary and medical treatments hence presenting challenges specific to the IMD population.

IMDs can be classified in various ways and for the purposes of this chapter we will summarise some relevant disorders of carbohydrate, protein and lipid

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metabolism, lysosomal storage and mitochondrial and disorders. This chapter aims to give a brief medical overview of common liver-based IMDs in adolescents and aspects of care involved in these individuals long-term. Table 7.1 demonstrates some specific features of individual IMDs for the paediatrician and hepatologist.

Overview of IMDs

Disorders of Carbohydrate Metabolism

Galactosaemia

Classical galactosaemia is an autosomal recessive disorder due to deficiency of galactose-1-phosphate uridyl transferase (GAL-1-PUT) and typically presents in the first week of life when milk feeds are introduced. The introduction of galactose in the form of lactose leads to the accumulation of toxic metabolites including galactose-1-phosphate and galactitol, and the metabolites subsequently cause the classical clinical presentations with jaundice, liver dysfunction and frequently acute liver failure in the neonatal period. A more insidious presentation with symptoms beyond the first few weeks of life can occur with failure to thrive, cataracts, renal tubulopathy and rarely developmental delay. Diagnosis is made by measurement of GAL-1-PUT activity in erythrocytes with a clear distinction between affected (absent or barely detectable), heterozygote carriers and unaffected cases, and follows by confirmatory genetic testing of the *GALT* gene. The treatment is a strict lactose restricted diet with prompt resolution of clinical manifestations and long term monitoring of adequate vitamin D and calcium intake. Despite treatment, long term complications of classical galactosaemia are not abolished and include speech and language delay, learning difficulties, neurocognitive issues, movement disorders, osteoporosis and primary ovarian insufficiency (POI) in females [3, 4]. The development of liver disease in the long-term in patients' adherent to treatment has not been reported.

Glycogen Storage Disorders (GSDs)

Glycogen is a branched polysaccharide structure consisting of glucose units and is the main storage form of glucose primarily in liver and muscle tissue. Hepatic glycogen is broken down to release free glucose into the bloodstream and is crucial for maintaining blood glucose concentration to support the needs of other tissues. Glycogen synthesis and degradation are highly regulated multi-step processes involving distinct set of enzymatic steps. GSDs are caused by a deficiency of

Table 7.1 Specific features for Paediatricians and Hepatologists in IMD

IMD	Specific features for Paediatricians	Specific features for Hepatologists
Disorders of carbohydrate metabolism		
Galactosaemia	Conjugated jaundice Coagulopathy	Often no liver disease Primary ovarian insufficiency
Glycogen storage disorders	Hepatomegaly Short fasting tolerance Short stature Hypoglycaemia + / − ketosis Hyperlipidaemia Elevated CK (GSD III) Lactic acidosis (GSD I) Hyperuricaemia (GSD I)	Liver dysfunction Risk of hepatic adenoma Progressive liver disease (GSD IV, IX)
Hereditary fructose intolerance	Aversion to specific sugars Good dentition	Often no liver disease
Transaldolase deficiency	Dysmorphic features Organomegaly Cardiac involvement	Chronic liver disease / cirrhosis
Disorders of protein metabolism		
Urea cycle defects	Hyperammonaemia Metabolic decompensation	Liver dysfunction / coagulopathy Acute liver failure Chronic liver disease (ASL deficiency)
Tyrosinaemia Type 1	Elevated tyrosine / succinyl-acetone / AFP Acute liver failure Renal tubulopathy / rickets	Chronic liver disease Risk of HCC
Organic acidaemias	Metabolic acidosis Renal dysfunction Cardiomyopathy Basal ganglia injury	Risk of pancreatitis / liver disease / liver tumours
Disorders of fatty acid oxidation	Hypoketotic hypoglycaemia Hepatomegaly and liver dysfunction Cardiomyopathy and myopathy	Liver dysfunction Acute liver failure Rhabdomyolysis
Mitochondrial disorders	Lactic acidosis Multi-organ involvement	Acute liver failure Chronic liver disease
Lysosomal storage disorders		
Gaucher disease	Hepatomegaly / splenomegaly Neurological involvement Pancytopenia Bone lesions	Risk of liver disease and HCC

(continued)

Table 7.1 (continued)

IMD	Specific features for Paediatricians	Specific features for Hepatologists
Cholesterol ester storage disorder	Hepatomegaly Failure to thrive Adrenal calcification Elevated cholesterol and low HDL cholesterol	Elevated transaminases Hepatic steatosis/NAFLD Progressive liver disease/ cirrhosis
Niemann Pick disease	Hepatosplenomegaly Cholestasis Pulmonary involvement Neurological involvement	Dyslipidaemia Chronic liver disease
Peroxisomal disorders	Cholestasis Hepatomegaly Liver dysfunction Abnormal very long chain fatty acids	Mainly neurological phenotype

enzymes and are characterized by accumulation of glycogen in the liver and / or muscle. Subtypes are defined by the specific enzyme deficiency and those involving the liver are GSD type I, III, IV, VI and IX. The major clinical manifestations are hepatomegaly and shortened fasting tolerance with symptomatic hypoglycaemia. Diagnosis of a GSD can be initially established with biochemical profiling and / or liver biopsy findings of glycogenated hepatocytes. Subsequent molecular confirmation is gold standard and will aim to confirm the subtype. The improvement in molecular techniques has more recently obviated the need for invasive liver biopsy in cases where clinical and biochemical suspicion is strong.

GSD I is the most severe subtype and most patients present in infancy in significant hypogylcaemia and hepatomegaly, nephromegaly can also be a feature. There is often lactic acidosis, hyperuricaemia and hyperlipidaemia. GSD 1 is further classified into 1a and 1b. GSD 1a is the most common and caused by deficiency of glucose-6-phosphatase (G6Pase). G6Pase catalyzes the conversion of glucose-6-phosphate (G6P) to glucose and inorganic phosphate. G6Pase is anchored onto the endoplasmic reticulum and requires the G6P transporter (G6PT) to bring G6P into the endoplasmic reticulum lumen before it is hydrolyzed. A defect in this translocase activity is known as GSD 1b. Neutropenia, recurrent infection due to abnormal neutrophil function and inflammatory bowel disease are unique features of GSD 1b.

Dietary intervention is the cornerstone of management with regular carbohydrate intake to maintain good metabolic control and avoid long term complications of disease. Traditional approaches in infants utilise continuous overnight feeding regimens to maintain normoglycaemia and reduction of lactate. In addition, the use of uncooked cornstarch aims to maintain normoglycaemia during the day and night as required. Guidelines for the dietary management of GSD 1 are well published [5, 6].

Allopurinol is prescribed when serum urate concentrations are elevated, and fish oil supplementation or a prescription of a fibrate may be used to lower serum triglycerides and reduce the risk of pancreatitis. Treatment with an

angiotensin-converting enzyme (ACE) inhibitor is used in patients with proteinuria to reduce intra-glomerular capillary pressure and provide renoprotection. Preventive calcium and vitamin D3 supplementation is also recommended to prevent osteoporosis. Granulocyte-colony stimulating factor (GCSF) is used when neutropenia and infections are severe and vitamin E supplementation has been shown to be of benefit [7, 8]. More recently, empagliflozin, a SGLT2-inhibitor has been shown to improve neutropenia and neutrophil dysfunction in GSD 1b patients [9]. Long term complications include hepatic adenoma and osteoporosis, but with improvements in medical therapy outcomes into adulthood are good. Many successful pregnancies have occurred [10]. Surgery should be undertaken with caution due to a bleeding tendency and risk of intraoperative lactic acidosis. Orthotopic liver transplantation has been performed for some individuals with unresectable adenomas or hepatocellular carcinoma. Liver transplantation has been otherwise deemed a treatment of last resort since renal failure has been a common complication due to the impact of immunosuppression on abnormal kidneys [11].

GSD III is caused by a deficiency of the glycogen debrancher enzyme that results in the accumulation of abnormal glycogen. It is divided into two types: type IIIa, with both hepatic and muscle involvement, and type IIIb, which primarily presents with liver disease. Clinically GSD III may be indistinguishable from type I but fasting tolerance and hypoglycemia are not typically as severe and nephromegaly is not a feature. Lactate characteristically increases postprandially and creatine kinase is commonly raised. Complications aside from the myopathy are rare. A minority of patients (4–10%) develop hepatic adenomas [10]. Cirrhosis can also develop in patients with GSD III and rare cases of hepatocellular carcinoma have been reported [12, 13]. Unlike in GSD Ia, hepatocellular carcinoma can develop anywhere in the liver, and it is not the result of malignant transformation of a hepatic adenoma [14]. Although all individuals with GSD type III show liver involvement, in rare instances the hepatic symptoms are mild and the diagnosis is not made until adulthood when individuals show signs of neuromuscular disease. Other clinical findings include abnormal nerve conduction studies and osteoporosis. Successful pregnancies have been reported. Dietary treatment includes maintaining normoglycaemia with frequent feeds and uncooked cornstarch. Glycogenolysis is impaired in GSD III whilst gluconeogenesis is intact allowing lactate, amino acids, and glycerol (from fatty acid oxidation) to be used to maintain blood glucose concentrations. Protein supplementation is also used as a primary source of energy in GSD type III since it also can be used directly by the muscles and has been associated with improvement in the myopathy [15].

GSD IV is due to deficiency of the branching enzyme and results in abnormal glycogen structure known as amylopectin or polyglucosan. Histologic examination of liver tissue reveals periodic acid-Schiff (PAS)-positive, diastase-resistant intracytoplasmic inclusions consistent with abnormal glycogen. Clinical manifestations range from a severe neonatal neuromuscular form (often fatal), a progressive hepatic form and non-progressive hepatic form. Cardiomyopathy can be present. Children tend to present with hepatomegaly, evidence of chronic liver disease and classical findings on liver biopsy. The majority have absence of fasting hypoglycaemia.

Recently the clinical spectrum of this disorder has widened considerably [16]. Liver transplantation is the only treatment option for those with the progressive hepatic form who can go on to develop decompensated liver disease. Regular liver and cardiac surveillance is recommended [17]. Treatment otherwise is supportive.

Phosphorylase (GSD type VI) and its activator phosphorylase b kinase (GSD type IX) are required for the removal of glycosyl molecules from the straight chains of glycogen. GSD VI presents with hepatomegaly and a tendency to ketotic hypoglycemia in early childhood. Growth failure may be marked but catch-up growth occurs with treatment and normal adult height is achieved. The disorder may be so mild that it remains undiagnosed. Long-term outlook is generally excellent, although hepatic adenomas have rarely been described. GSD type IX has a number of subtypes including three that have a hepatic component. Type IXa is by far the most common and has a relatively mild isolated hepatic phenotype similar to type VI. Type IXb is very rare and has a mild mixed liver/muscle phenotype. Type IXc has more severe phenotype often associated with significant hypoglycemia and progression to cirrhosis [18–21]. Treatment for both subtypes is aimed at maintaining normoglycaemia and eliminating ketosis.

Hereditary Fructose Intolerance

HFI is an autosomal recessive disorder due to deficiency of aldolase B with the inability to metabolise fructose, sorbitol and sucrose. Fructose is a monosaccharide that is found in many food sources, notably sucrose (glucose–fructose disaccharide), fruits, vegetables and honey. Sorbitol is an artificial sweetener that is metabolised to fructose. The classical presentation is that of a healthy milk-fed infant that develops symptoms when it is first exposed to fructose upon weaning. Gastrointestinal upset progresses to persistent vomiting, sweating, lethargy and coma if intake continues. These symptoms are accompanied by liver failure and evidence of renal proximal tubulopathy. Hypoglycemia and hyperlactatemia is common but can be masked by glucose administration. There is a considerable spectrum of disease severity; infants can present with a chronic course of failure to thrive, hepatomegaly and liver impairment. School-age children may present with avoidance of sweet foods and hepatomegaly, with dentition that is unusually free of caries. Patients may develop self-selected food aversion to avoid sources of fructose that allow them to remain quite well.

Biochemical associations include lactic acidosis, hyperuricemia, marked liver dysfunction, often without jaundice and renal tubulopathy. The enzyme deficiency results in accumulation of fructose-1-phosphate, an inhibitor of both glycogenolysis and gluconeogenesis that depletes inorganic phosphate, thus restricting adenosine triphosphate (ATP) production. Cellular depletion of ATP is postulated to be a significant mechanism of hepatocellular toxicity [15].

There is no rapid test that can exclude HFI. If it is suspected clinically, then fructose should be excluded immediately. A rapid correction of biochemistry and liver function can be expected over a number of days to weeks. Transferrin glycoforms

can show a type 1 pattern of glycosylation in the untreated state. Hepatomegaly and raised serum or plasma liver transaminases may take several months to resolve. Direct enzyme assay is restricted to liver tissue, and liver biopsy may be contraindicated in the acute phase due to coagulopathy. Genotyping of the *ALDOB* gene can often provide a definitive diagnosis however if pathogenic variants are not detected, enzymology may need to be performed if clinical suspicion remains high. Treatment requires specialist dietetic input with a lifelong restriction of fructose, sucrose and sorbitol from the diet and can be a challenge due to its restrictive nature. In addition, medicines and formulas in which fructose/sucrose may not be listed as a primary component, need to be avoided. During hospitalisations special caution is advised to avoid the use of fructose-containing intravenous fluids. Given that reduced fruit and vegetable intake is a dietary requirement, daily supplementation with a "sugar-free" multivitamin is recommended to prevent micronutrient deficiencies, specifically water-soluble vitamins in particular vitamin C and folate. No formal guidelines for surveillance exist. Once the diagnosis of HFI has been made, annual assessment of liver function, renal function, and growth is recommended, particularly if compliance with the fructose/sucrose/sorbitol-restricted diet is not absolute. Long term outcomes are good if treatment is adhered to [22].

Transaldolase Deficiency

Transaldolase (TALDO) deficiency is a rare disorder of the pentose phosphate pathway, first described in 2001 [23]. Patients can present either prenatally, with intrauterine growth restriction (IUGR) and/or oligohydramnios; in the neonatal period, with dysmorphic facial features, cardiovascular defects, and hepato(spleno)megaly; or later in life, with a milder phenotype or even no symptoms. A large cohort review showed that the liver is the most frequently affected organ, seen in >85% of patients, and is where TALDO enzyme activity is highest and thus where the greatest impact can be expected. This results in liver dysfunction and damage, leading to cirrhosis, liver failure and the development of malignancy [24].

Disorders of Protein Metabolism

Urea Cycle Disorders (UCD)

The urea cycle is the main pathway for detoxification of nitrogen waste products i.e. ammonia to non-toxic urea and is predominantly expressed in the liver. There are 6 main enzymatic steps and 2 transport protein: N-acetyl-glutamate synthetase (NAGS), carbamyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (Arg1), citrin and mitochondrial ornithine transporter (ORTN1) [25]. Complete

or partial deficiency can result in the clinical manifestations at any age from the neonatal period to adulthood. Clinical presentation in the proximal defects (NAGS, CPS1, OTC and ASS) is predominantly with hyperammonaemia, encephalopathy, liver dysfunction, seizures and coma. Distal defects tend to present with a more chronic neurological presentation with mild to moderate hyperammonaemia. Partial urea cycle enzyme deficiencies, individuals may go decades before encountering an environmental stress that overwhelms their marginal ureagenesis capacity, resulting in an hyperammonemic episode. Clinical presentation tends to be preceded by a trigger such as a dietary protein load, fasting, surgery, pregnancy or any other catabolic stress. All UCDs are inherited in an autosomal recessive manner except for OTC deficiency which is X-linked, and is the most common UCD. Females can present with symptoms due to the effects of lyonisation if sufficient wildtype OTC genes are inactivated in the liver. Diagnosis is based on biochemical analysis of plasma amino acids and urinary orotate and is confirmed with molecular analysis of the relevant genes. Genetic confirmation is important for providing counselling for future pregnancies and cascade screening in OTC deficiency.

Acute management aims to lower hyperammonaemia urgently with omission of protein, promotion of anabolism and the use of ammonia scavenging agents (sodium benzoate, sodium phenylbutyrate) and supplementation of arginine and / or citrulline dependent on the site of the defect. The use of extra-corporeal clearance is often required when hyperammonaemia is severe, particularly in the neonatal period. Duration of coma, raised intracranial pressure and peak ammonia level are predictors of neurological outcome [26]. Long-term management involves specialist dietetic supervision of a protein restricted diet, ammonia lowering medications, emergency regimens for sick days and regular monitoring by a metabolic specialist [27]. Liver transplantation has been widely reported for UCD patients, particularly those with frequent decompensations and poor quality of life and is associated with successful outcomes. It is the mainstay of treatment for males with neonatal onset OTC deficiency [28]. ASL deficiency demonstrate a high incidence of chronic progressive cirrhosis with eventual fibrosis of the liver. This finding is not commonly seen in the other UCDs and studies are underway to better determine the exact pathophysiology.

Citrin Deficiency

Citrin deficiency results from a deficiency of the glutamate–aspartate transporter which has a role in gluconeogenesis from lactate and transporting cytosolic nicotinamide adenine dinucleotide (NADH)-reducing equivalents into mitochondria as part of the malate aspartate shuttle. Citrin deficiency causes three age specific phenotypes: neonatal intrahepatic cholestasis associated with citrin deficiency (NICCD), in older children as failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD), and in adults as recurrent hyperammonemia with neuropsychiatric symptoms in citrullinemia type II (CTLN2). Diagnosis is confirmed by SLC25A13 genotyping. Management includes the

supplementation of fat soluble vitamins and the use of lactose-free or formulas containing medium-chain triglyceride (MCT) during the period of liver dysfunction. Many children subsequently develop aversion to carbohydrate-rich food and prefer protein-rich or fat-rich foods developing hyperlipidemia and the risk of fatty liver and pancreatitis. CTLN2 is characterised by acute onset recurrent hyperammonemia with neuropsychiatric symptoms. Precipitants include alcohol, sugar intake, medicines such as anti-inflammatories or analgesics, or surgery. Not all patients have a preceding history of NICCD. Liver transplantation is the most effective treatment, preventing hyperammonemic crises and reversing the biochemistry. Careful dietary supervision is required to provide appropriate carbohydrate (low) and protein (high) intake as the standard hyperammonemic treatment. Intercurrent illness and low protein with high carbohydrate can precipitate crises in these patients. This is because carbohydrate suppresses ureagenesis in citrin deficiency. Emergency regimens consist of high protein and low carbohydrate [29].

Lysinuric Protein Intolerance (LPI)

LPI is a rare disorder resulting from recessive inherited mutations involving the *SLC7A7* gene. Defects occur in the y^+LAT1 sub-unit of the cationic amino-acids transporter localized at the basolateral membrane of the tubular kidney and small bowel cells, leading to the classical hallmarks of the disease: leakage of cationic amino-acids in the urine (arginine, ornithine, lysine) with associated normal to low plasma levels. y^+LAT1 is also expressed in the lung and spleen and in circulating monocytes and macrophages, which would explain the wide spectrum of symptoms that have been described, such as failure to thrive, protein intolerance, hepatosplenomegaly, osteoporosis, lung involvement, kidney failure, immunological disorders with autoimmunity and haemophagocytic lymphohistiocytosis. Plasma lysine, ornithine, citrulline and arginine are low with corresponding increases in urinary excretion. Plasma glutamine, alanine and glycine can be elevated. Ammonia can be elevated, particularly post-prandially due to arginine depletion and secondary urea cycle dysfunction. Lactate dehydrogenase, ferritin and hyperlipidaemia are common. In the acute situation treatment with arginine and ammonia scavenging agents may be required for hyperammonaemia. Long-term treatment requires protein restriction, citrulline and lysine supplementation and ammonia scavengers. Periodic evaluation of renal function; evaluation of lung involvement; periodic serum LDH and ferritin and plasma amino acids is recommended [30].

Hereditary Tyrosinaemia Type 1 (HT1)

HT1 is an inborn error of tyrosine metabolism, caused by a deficiency of the enzyme fumaryl-acetoacetate hydrolase. Toxic products such as maleyl-acetoacetate (MAA), fumaryl-acetoacetate (FAA) and succinyl-acetone (SA) are accumulated and cause severe liver dysfunction, renal tubulopathy, porphyria-like syndrome, cardiomyopathy in early life and subsequent risk of hepatocellular carcinoma. Prior to 1992 life expectancy was rather low and many patients needed a liver transplantation until a new treatment option became available, c2-(2-nitro-4-trifluoromethylbenoyl)-1, 3-cyclohexanedione (NTBC). NTBC is an herbicide that blocks the catabolism of tyrosine upstream of the initial enzymatic defect, preventing the formation of the toxic products. With this treatment, liver failure, renal tubulopathy, cardiomyopathy and porphyria-like syndrome resolved and the life expectancy strongly increased, while the risk of liver cancer largely decreased [31]. The mainstay of management is NTBC with a phenylalanine- and tyrosine-restricted diet with dried blood spot monitoring of tyrosine and phenylalanine levels. The risk of hepatocellular carcinoma is markedly reduced in patients treated early (< 6 months). α-fetoprotein monitoring in clinic should therefore continue with 6 monthly to annual imaging of the liver [32]. Non-adherence to NTBC can result in acute porphyric-like crisis with intermittent abdominal pain, muscle weakness and even respiratory failure that could mimic the progressive weakness of Guillain–Barre syndrome. Interruption of treatment leads inhibition of porphobilinogen synthase by excess succinyl-acetone. Long-term outcomes of HT1 are associated with neurocognitive and IQ deficits despite treatment, the exact pathophysiology remains unclear [33].

Organic Acidaemias

Classical organic acidaemias; methylmalonic acidaemia (MMA), propionic acidaemia (PA) and maple syrup urine disease (MSUD) are due to enzyme deficiencies in the catabolism of branched chain amino acid. In MMA and PA, toxic metabolites accumulate and cause a multi-system disease; whereas in MSUD, accumulation of toxic keto-acids manifest as neurotoxicity without other organ involvement. Although the metabolic pathways for organic acidaemias are not predominantly expressed in the liver, liver transplantation has been shown to result in a milder phenotype of disease in PA and MMA with variable outcomes - mostly excellent in MSUD patients [34]. The mainstay of medical therapy is a supervised protein-restricted diet, amino acid supplementation, ammonia-lowering agents as required and regular surveillance of other organ involvement; renal dysfunction, cardiomyopathy, pancreatitis, optic atrophy in PA and MMA [35]. Liver disease is not a characteristic feature of organic acidaemias but there have been reports of liver disease and tumours in some patients [36, 37]. Following liver transplantation in

this group of patients, it is vital to continue surveillance for long-term complications of the disease, particularly in PA and MMA as transplantation provides only a partial enzyme replacement and extra-hepatic expression remains significant [38, 39]. The emergency regimen should be continued in all patients following transplantation.

Disorders of Fatty Acid Oxidation

The major pathway for the degradation of long-chain fatty acids is mitochondrial fatty acid β-oxidation (FAO). FAO not only fuels the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, but also stimulates hepatic synthesis of the ketone bodies 3-hydroxybutyrate and acetoacetate. Mitochondrial fatty acid oxidation (FAO) is an essential pathway for energy production particularly during fasting and exercise. Long-chain fatty acids are the most abundant fatty acids in the human diet and in body stores, and approximately 20 different proteins are involved in FAO including the carnitine shuttle which enables long chain fats to enter mitochondria. Individual FAO disorders will not be considered in this chapter and the reader is directed to previously published reviews [40]. Symptoms tend to occur during catabolic situations, such as fasting, illness and exercise. The clinical spectrum is heterogeneous, ranging from hypoketotic hypoglycemia, hepatomegaly, liver dysfunction, rhabdomyolysis, cardiomyopathy and early death. Hepatic symptoms are common with associated elevated lactate, hyperammonaemia and hepatomegaly in the acute situation due to fatty acid mobilisation. Liver failure can also occur. Hepatic symptoms may also occur in carrier mothers carrying an affected fetus. Cardiac involvement, either cardiomyopathy and/or arrhythmias may be seen in all FAO disorders except carnitine palmitoyl transferase 1 (CPT 1). Episodic muscle pain, rhabdomyolyis and myoglobinuria may be precipitated by metabolic stress such as exercise or intercurrent infections. Creatine kinase is elevated during muscle crises. Proximal muscle weakness may have a more chronic progressive course. Neuropathy and pigmentary retinopathy are long-term complications of long chain hydroxyl acyl CoA dehydrogenase (LCHAD) deficiency. Diagnosis is based on the detection of specific acylcarnitine profiles in blood and urinary organic acids with subsequent genetic confirmation. Full characterisation may require fat oxidation studies on cultured fibroblasts. Management focuses on maintaining safe fasting times with the use of nocturnal feeding in severe defects, use of carbohydrate emergency regimens during intercurrent illness and long chain fat restricted diets with medium chain fat supplementation. Carnitine replacement is essential in the carnitine transport defects. Low levels of carnitine are seen in many FAO defects due to accumulation of acylcarnitines, however the use of carnitine in long-chain FAO defects remains controversial with the theoretical risk of compounding mitochondrial toxicity with the accumulation of long-chain acylcarnitines [41].

Mitochondrial Disorders

Mitochondria are ubiquitous intracellular organelles with complex roles in intermediary metabolism and cell signalling. Functions of mitochondria include ATP generation via the oxidative phosphorylation system consisting of five respiratory chain enzyme complexes, homeostasis of intracellular calcium levels, reactive oxygen species (ROS)- mediated cell signalling and regulation of programmed cell death (apoptosis). Clinical manifestations of mitochondrial disorders are highly variable and can present at any age, affecting any organ and with any symptom. Hepatic symptoms are a frequent manifestation of primary mitochondrial disease and may be the presenting feature. However, they are rarely isolated symptoms, occurring more usually in the context of multisystem disease. Mitochondrial hepatopathy can be classified broadly into 3 groups:

(i) disorders of mtDNA maintenance (the hepatocerebral mtDNA depletion syndromes, MDDS);
(ii) disorders of mitochondrial protein synthesis; and
(iii) defects of OXPHOS complex assembly (particularly complexes III and IV).

MDDS tends to present in early infancy with acute liver failure and often neurological involvement; the disease tends to be fatal early in life. The hepatocerebral form of MDDS has been linked to 5 genes; *POLG*, *PEO1*, *DGUOK*, *MPV17* and *SUCLG1*. Establishing a diagnosis is often fraught with difficulties and more recently relies on genetic analysis. A multi-disciplinary approach is required and investigation for extra-hepatic involvement is vital. Muscle tissue analysis for respiratory chain complex deficiencies can often direct specific genetic testing. Treatment is mainly supportive as liver transplantation has been reported in some cases with a poor outcome in the majority. However, there are some reports of longer term outcomes in some patients with *DGUOK* and *MPV17* mutations and isolated liver disease. MPV17 mutations have been associated with chronic liver disease and risk of hepatocellular carcinoma. Liver transplantation remains controversial in mitochondrial diseases and a multidisciplinary approach in decision making is vital [42].

Lysosomal Storage Disorders (LSDs)

LSDs are a group of inherited metabolic disorders that are caused for the most part by enzyme deficiencies within the lysosome, resulting in accumulation of undegraded substrate. Clinical manifestations are variable and depend on the specific substrate and site of accumulation. The majority are progressive disorders although the rate of progression is variable, and the advent of novel therapies has changed the natural history of the disease in some cases. Diagnosis is made from specific enzyme assays and subsequent genetic confirmation.

Gaucher disease is the most common and results from mutations in the β-glucocerebrosidase gene leading to reduced enzyme activity and accumulation of *glucocerebroside* in cells of the monocyte-macrophage system ("Gaucher cells") throughout the body, but mainly in specific target end-organs including spleen, bone marrow and liver. There are 3 subtypes; type 1 is primarily visceral without neurological involvement while types 2 and 3 have a rapidly progressive and a more chronic neurological course, respectively. Liver involvement includes hepatomegaly, non-HCC focal liver lesions and fibrosis; severely affected patients may develop cirrhosis, portal hypertension and potentially hepatocellular carcinoma [43]. Specific enzyme replacement therapy and substrate reduction therapy are successful in patients with Type 1 disease and have been shown to reduce liver and spleen volume significantly [44].

Niemann Pick A and B disease are due to deficiency of lysosomal acid sphingomyelinase. The disease spectrum ranges from a rapidly progressive neurovisceral neonatal form (NPA), a chronic neurovisceral form (intermediate) and a chronic visceral form without neurological involvement, usually presenting with hepatosplenomegaly. Pulmonary function may worsen over time, and interstitial lung disease and pulmonary infections are common. A mixed dyslipidemia is seen early in the disease course and some patients develop coronary artery disease later on in life. Development of hepatic fibrosis ranging from minimal to cirrhosis is common, and progression of liver disease contributes to early mortality in some patients. Progressive splenomegaly may result from deposition of sphingomyelin and progressive portal hypertension [45].

Niemann Pick C (NPC) disease is caused predominantly by mutations in *NPC1* (95% of cases) or *NPC2* genes that decrease intracellular cholesterol trafficking resulting in accumulation of unesterified cholesterol. The clinical spectrum of NPC disease ranges from a rapidly progressive fatal disorder in the neonate (often with jaundice and acute liver failure) to an adult-onset chronic neurodegenerative disease. The age at onset of the first (beyond 3 months of life) neurological symptoms may predict the severity of the disease and determines life expectancy. Diagnosis is based on genetic testing; filipin staining of cultured fibroblasts and biomarkers such as oxysterols and lysosphingolipids can also be indicative of NPC. Treatment is currently supportive with the use of substrate reduction therapy in selected patients. Clinical trials for novel therapies are ongoing [46].

Cholesterol ester storage disorder is a result of lysosomal acid lipase deficiency (LAL-D) with progressive accumulation of cholesteryl esters and triglycerides in the lysosomes of hepatocytes and macrophages, thereby inducing organ damage over time. The disease spectrum ranges from a severe infantile form with rapidly progressive disease to a milder later onset form, which can remain undiagnosed. The infantile form presents with marked hepatosplenomegaly, failure to thrive and without intervention progressive liver disease and death by 6 months of age. Later onset disease is characterised by a fatty liver with mildly elevated aminotransferases, with the development of fibrosis and cirrhosis, a gradual decline in liver function and an atherogenic dyslipidemia profile with low high-density lipoprotein (HDL) cholesterol, high low-density lipoprotein (LDL) cholesterol and

triglycerides, triggering premature atherosclerotic vascular disease [47]. Diagnosis is based on measurement of enzyme activity and genetic confirmation. Exclusion is essential in patients presenting with atypical non-alcoholic fatty liver disease. The childhood/adult-onset form is likely underdiagnosed due to its often non-specific clinical presentation and variability in progression of liver disease. Liver transplantation has been reported in several individuals with childhood/adult-onset LALD with variable success and sometimes recurrence of disease. Haemopoetic stem cell transplantation has been attempted in several individuals with infantile-onset LALD, and while this is a potentially curative approach, outcomes have generally been poor, with significant comorbidities and a mortality rate of >50% [48]. In 2015, regulatory agencies approved the use of a human recombinant LAL for the treatment of LALD. This long-term enzyme replacement therapy has been associated with significant improvements in the hepatic and lipid profiles of patients with LALD, increasing survival rates markedly in infants with an otherwise rapidly progressive disease [49]. Clinical trials have also shown significant improvement of disease parameters such as liver transaminases, hepatomegaly, and dyslipidemia in childhood/adult-onset LALD patients. However, longer-term follow up is needed to establish the full extent to which patients benefit from treatment and whether complications such as liver cirrhosis and cardiovascular events can truly be prevented over time in patients with childhood/adult-onset disease [50].

Peroxisomal Disorders

Peroxisomes are subcellular organelles present in all cells except mature erythrocytes, and are especially abundant within the liver. Key functions include β-oxidation of very long chain fatty acids and fatty acid derivatives, pipecolic acid and glyoxylate degradation, phytanate α-oxidation, plasmalogen, cholesterol, and bile acid biosynthesis. Biochemically, peroxisomal disorders are characterised by the extent of peroxisomal dysfunction from complete absence of peroxisomes (biogenesis disorders), to multiple enzyme defects and single enzyme defects. The clinical picture ranges from very severe developmental disorders that are lethal within the first year of life to mild degenerative disease with symptoms such as blindness, hearing loss and ataxia. The clinical phenotype is most often dominated by pathologies in the central and peripheral nervous system but other organs are also affected, including liver, kidney, eyes, ears, adrenals and bone [51]. Liver involvement tends to occur in the form of cholestasis, liver dysfunction and occasionally liver failure in severe disease. Treatment remains supportive.

Acute Management and Novel Therapies

The liver is a critical metabolic organ and responsible for many of the biochemical perturbations seen during metabolic decompensation. Ongoing care for patients with liver-related IMD requires judicious monitoring of growth and developmental parameters, as well as nutritional and biochemical status, in particular during early childhood. Despite strict adherence to practice standards, certain sub-groups of IMD patients may still experience periodic episodes of metabolic decompensation in particular those with organic acidaemias, fatty acid oxidation defects, amino acid disorders, urea cycle defects and mitochondrial disorders. During infection, systemic cytokines and the hepatic innate immune system may play a role in precipitating metabolic decompensation [52]. Metabolic decompensation is potentially life threatening, with high rates of morbidity. Prompt intervention is essential to avoid long-term sequelae.

Metabolic decompensation occurs following functional deterioration due to inherent defect(s) in the intermediary metabolism pathway and leads to disease-specific biochemical perturbations such as metabolic acidosis in organic acidemias; hyperammonemia in the urea cycle disorders; hypoglycemia in FAOD or some glycogen storage disorders, and bioenergetic failure and end-organ dysfunction in mitochondrial disorders. Disease specific management has been briefly touched in the paragraphs above, and it is beyond the scope of this chapter to discuss acute management of each condition in detail. Management of an acute metabolic decompensation usually involves correcting small molecule toxicity either via scavengers, chelating agents or dialysis; to replenish energy insufficiency by providing an alternative metabolic fuel and at the same time to treat the potential cause which may lead to catabolic state such as infection, inflammation or others.

Traditionally the management of inherited metabolic disorders consists of diet therapy and supportive management, however in recent years other treatment options have become available. Dietary therapy has been the mainstay of treatment for many liver-related IMD, especially in small molecule disorders and energy metabolism defects. The main approaches of dietary management include restricting the offending substrates or metabolites and providing deficient products or alternative energy sources to bypass the defective pathway. In order to maintain normal growth and development, synthetic product which is devoid of offending substrate(s) and fortified with vitamins and essential minerals as per recommended daily allowances, are supplemented to the daily diet. Uncooked corn starch has also been useful to help regulate the glycaemic control in patients with glycogen storage disorders.

Certain disorders may also require some supplementation such as carnitine to help eliminate the organic acid via the kidneys, or vitamins such as biotin, pyridoxine, folic acid and others to help boosting the residual enzyme activities. However, despite massive development of medical food products over the last three decades, often these supplements are not particularly palatable, and are difficult to incorporate into a normal diet. This poses a massive challenge in maintaining a good dietary compliance especially in adolescent age.

In some other disorders, patients may require regular scavengers such as sodium benzoate or phenylbutyrate to help divert nitrogen products from the urea cycle. Substrate reduction therapy (SRT) also plays a role in certain liver-related metabolic disorders. The general principle of SRT is to use a small molecule drug to decrease biosynthesis of any toxic substrates that accumulate due to the primary defects in substrate degradation. Some of the SRT target an enzymatic pathway upstream of the defect, and could restore the balance between production and degradation of specific substrates; and minimizing the toxic by-product(s). Good examples of SRT include NTBC for HT-1, and Miglustat and Eliglutat for Gaucher disease [53, 54].

Other treatment modalities include enzyme replacement therapy or enzyme substitution therapy, organ transplantation, bone marrow transplants and gene therapy. Enzyme replacement therapy directly replaces the deficient enzyme to improve the body physiological metabolic processes, via intravenous infusion at regular intervals and predominantly is used in LSDs. Due to the molecular size of the recombinant enzyme, there has been some issue with crossing the blood-brain barrier (BBB) that limits the usage to disorders with non-neurological involvement [55]. Enzyme substitution therapy on the other hand introduces an enzyme to bypass the physiological defect and convert accumulated substrate to a harmless product using an alternative metabolic process. However, recent developments on these have hampered by immune reaction to the foreign proteins [56].

While an understanding of the pathophysiology of inherited metabolic disorders leads to the development of various treatments with a different focus on substrate, product or enzyme, the goal of most current treatments is to ameliorate disease symptoms, not offer a cure. IMDs are single gene disorders and, in principle, the replacement of the mutated gene would provide a definitive cure. However, gene therapy has its hurdles—the blood brain barrier, the immune response, cellular toxicity, and potential oncogenesis. Several inherited metabolic diseases have been the targets of gene therapy trials. While gene replacement strategies are moving into a variety of phases of clinical development, the much-celebrated CRISPR/Cas9 system for gene editing also adds an exciting prospect for potential gene therapy in the near future [57].

Outcomes for Adolescents with IMD

Long Term Outcomes in IMDs

Much has happened since Garrod's seminal lecture in 1908, and several factors have led to an increasing number of children with IMD surviving into adolescent and young adults. No comprehensive data on overall long term outcome of IMD are available, however limited publications on the outcome of some groups of disorders are available such as PKU, glycogen storage diseases,

galactosaemia and MCADD. Improved diagnosis has shown that the incidence of these diseases is much higher than was previously thought, and with improved treatment these patients are now frequently surviving into adulthood. This is likely to increase further with the expanded newborn screening for fatty acid oxidation defects, organic acidaemias and aminoacidopathies, introduced in the late 90's [58].

As patients grow older, acute metabolic decompensations generally became less of a problem and instead we started to see the development of long-term complications. IMDs are generally multi-organ and multi-system disorders and certain aspects of non-liver involvement have been touched briefly above. Metabolic decompensation during early childhood such as recurrent hyperammonaemia, metabolic acidosis and hypoglycaemia may lead to lasting neurological and neurocognitive deficit. These patients may require ongoing support either from the community paediatricians, learning disability services and neuro-rehabilitation including physiotherapists, occupational therapists and others supporting care depending on the extent of the disabilities. Some of them also suffer from chronic seizures which requires input from epileptologists or general neurologists.

In some disorders, other organs are also directly affected, for example chronic renal deterioration in organic acidaemia related to non-B12-responsive methylmalonic acidaemia which may lead to the need for dialysis or transplantation. Haematological abnormalities with gut problems are the common features for GSD 1B, while non-specific gut symptoms have been reported commonly in propionic acidaemia (PA), OTCD cases and lysosomal storage disorders. Limited intake of dairy products and compounded by primary ovarian insufficiency (POI), galactosaemia patients are at risk of developing severe osteoporosis; and needing particular input of their bone health. In certain amino acid disorders, organic acidaemia and urea cycle disorders; patients are usually managed with natural protein restriction, and supplemented with "safe protein" which are fortified with essential minerals and vitamins to meet their daily recommended daily allowance (RDA). Adolescents seem to have issues to comply with their diet, and social and peer pressure may contribute heavily to this. Hence it is vital to check their vitamins and mineral status at regular intervals as they are at risk of developing deficiency in vitamin B12, iron and folate.

Pregnancy, Fertility and Labour Management

As patients become older, issues of fertility, future family, sexual relationship and the risk of transmitting the gene to their offspring might come up in the clinic discussions. In general, fertility is not a major issue in the majority of IMD affecting the liver. However, galactosaemia is one exception—secondary to POI. The majority of liver-related metabolic disorders are autosomal recessive in inheritance, with a few rare exceptions of X-linked disorder such as OTCD—in which the risk of having an affected child is relatively low in a non-consanguineous

relationship. However, some parents and the patient are often anxious about the risk and in these scenarios genetic counselling is recommended. It is beyond the scope of this chapter to discuss pre-implantation genetic diagnosis (PGD), antenatal and pregnancy care, and management during labour and post-partum period. Ideally, pregnancy in most of the liver-related metabolic disorders should be planned with adequate counselling on the potential impact of pregnancy on the condition, the potential challenges of their condition to the pregnancy and the outcomes in general. The goal is to optimise metabolic control and nutritional status prior to conception [59].

Conclusions

With increasing numbers of children surviving into adolescents and young adults with illnesses they developed in early childhood, the need for transitional care appropriate to their age and development is becoming more obvious and acute. Adolescence is also a time when adult behaviours become established and therefore represents a window of opportunity to promote healthy behaviour and influence the public health burden of tomorrow's adults. The key challenges for health services in transition relate primarily to bridging the differing cultures of paediatric, adolescent, and adult health care [60]. Multi-system and multi-organ involvement of liver-related metabolic disorders requires a more structured multi-disciplinary team approach. Psychosocial aspect of having a chronic disease needs to be addressed. The transition care to adult service has to be done in a structured manner and in stages. Much can be learnt from other services such as diabetes, renal services and other conditions which span both early childhood and young adulthood [61].

Top Tips for Professionals Looking After Young People with IMD

- Acute emergency management regimens (often individualised)
- Long term supervised intensive dietary regimens and specialist medications
- Long term surveillance of extra-hepatic involvement (renal, cardiac, gastrointestinal, neurological sequelae)
- Contraception, genetic counselling, fertility and pregnancy management
- Multi-disciplinary transition processes

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Chapter 8
Autoimmune Liver Disease

Nedim Hadžić and Marianne Samyn

Autoimmunity represents one of the main treatable causes of chronic liver disease in childhood. Autoimmune hepatopathies tend to present in the second decade of life, often preceding all important transition into adolescence and adulthood. Inconsistent and interrupted management can contribute to a poor control of chronic inflammatory injury of the liver and clinical complications including liver decompensation. In addition, a multitude of non-medical issues, unique to adolescent age group and elaborated in other Chaps. (2, 3, 18), further complicate the stability and effective management of these conditions.

Autoimmune liver disease (AILD) includes autoimmune hepatitis (AIH), autoimmune sclerosing cholangitis (ASC) and post-transplant *de novo* AIH [1]. Primary sclerosing cholangitis (PSC) is much more common in adults, but can occur in childhood. Defining these conditions is not always straightforward as there is a degree of overlapping clinical, radiological and histological features and possible evolution from one into another [2, 3]. In addition, the medical treatment could be different, particularly with respect to the use of medium-to-long term immune suppression. Typically, children with AIH have positive liver-specific and/or organ non-specific autoantibodies, hypergammaglobulinaemia, suggestive portal inflammatory changes and plasmacytic interface hepatitis in the liver biopsy with positive family history of autoimmune disorders [1]. ASC has a more biliary pattern of histopathological changes and radiological findings of cholangiopathy, while PSC has advanced cholangiopathy on imaging and biliary features, but no active inflammation in the liver biopsy with variable degrees of hypergammaglobulinaemia and detectable autoantibodies [4]. Considerable cholangiographic changes, occasionally complicated by dominant biliary strictures, itching and cholestasis are exceptional in paediatric ASC and PSC patients [5]. Lam et al. have recently

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suggested that serum levels of MMP7 could serve as a useful biomarker to distinguish the cholangiopathies from other forms of AILD, possibly secondary to underlying cellular mechanisms of biliary injury and fibrosis [6].

There was only one epidemiological study estimating prevalence of AILD in childhood—from USA [7]; it identified 3 cases of AIH, 0.6 of ASC and 1.5 case of PSC per 100,000 children. Nowadays, these numbers could be possibly increasing [8] in relation to increased awareness among health professionals and better radiological techniques, but also possibly due to yet unrecognised environmental or behavioural reasons. A considerable number of AILDs can be associated with inflammatory bowel disease (IBD), such as ulcerative colitis (UC), Crohn disease or nonspecific colitis [8]. The link between ASC and UC appears to be particularly strong [3].

Pathogenesis

Pathogenesis of AILD is complex and incompletely understood. Uncontrolled disease involves activation and interaction between several arms of innate and adoptive immunity. Following an antigenic trigger, the pathogenic chain involves sequential interaction of antigen-presenting cells, usually dendritic cells (DC) or Kupffer cells, with non-committed T-cells via MHC class II-restricted antigen presentation, leading to differentiation of CD4+ T-cells into predominantly Th1 phenotype [9]. This proinflammatory immune state drives further proliferation of NK lymphocytes and B-cells, evolving into plasma cells that produce immune globulins, activate complement and inflict the final inflammatory injury on the hepatocytes.

What triggers the disruption of tolerance and autoimmune attack is unclear; proposed mechanisms include impaired mechanisms of self-deletion for autoreactive T-cells in the thymus (“negative selection”), molecular mimicry between amino acid sequence homology between certain viruses and antigenic targets on the hepatocyte membrane (e.g. hepatitis C virus and cytohrome P4502D6 in anti-LKM-1 positive AIH), and/or aberrant T-cell suppressor function [1]. These coexistent and complementary mechanisms lead to inflammatory injury which clinically results in elevated transaminases or even deranged clotting and jaundice, if the liver injury is more severe. Recently, it has been noted that defective numbers and function of T-regulatory cells are frequently detected at presentation of autoimmune conditions, including AIH, and that their recovery is often associated with the clinical improvement, which led to consideration of various strategies for their manipulation in order to facilitate a sustained clinical response [10].

In some families there is undoubted increased non-Mendelian prevalence of AILD and often other autoimmune conditions. Susceptibility for AIH type 1 in children is conferred by possession of human leukocyte antigen (HLA) *DRB1*03* and by HLA *DRB1*0701* for AIH type 2, according to the British studies [1]. In South America the primary susceptibility allele in children with AIH type 1 is *DRB1*1301* [11]. This allele and also *DRB1*0701* appear to be associated with more severe disease in both

British and Brazilian children [1, 11]. The HLA variations are not consistent in paediatric and adult studies and could have a regional variability. A recent Dutch genome-wide study in adults identified a positive association between AIH and locus *SH2B3*; encoding a gene involved in negative regulation of T-cell activation, interferon-γ, tumour necrosis factor-alpha, and JAK2 and JAK3 signalling [12].

Histological injury in AILD is typical and often pathognomonic, representing one of the main diagnostic criteria. It includes a dense plasma cell and mononuclear infiltration of the portal areas with disruption of the limiting plate ("interface hepatitis") and necrotic changes, leading to different degree of collagen deposition, fibrosis and cirrhosis, resulting in bridging collapse spreading into the lobular parts of the liver. Hepatocyte giant cell change and emperipolesis could be seen within the parenchyma with variable degrees of the biliary changes, possibly reflecting involvement of the biliary system, severity of the liver damage or attempted regeneration of the hepatocytes (Fig. 8.1**).** Biochemical and immune response are presumed clinically to correlate with the histological control and improvement and therefore repeating liver biopsies is usually not required. This, however, is not always the case, as biochemical and histological signs of the controlled disease may differ.

Types of AIH

The conventional distinction of AIH is into type 1, characterised by anti-nuclear (ANA) and/or smooth-muscle (SMA) antibody positivity, and type 2, where liver-kidney microsomal-1 (LKM1) antibody and/or anti-liver cytosol-1 (LC1) antibodies are identified. Occasionally, direct anti-globulin test (Coombs) and additional autoantibodies, such as p-antiperinuclear cytoplasmic (p-ANCA), anti-single or

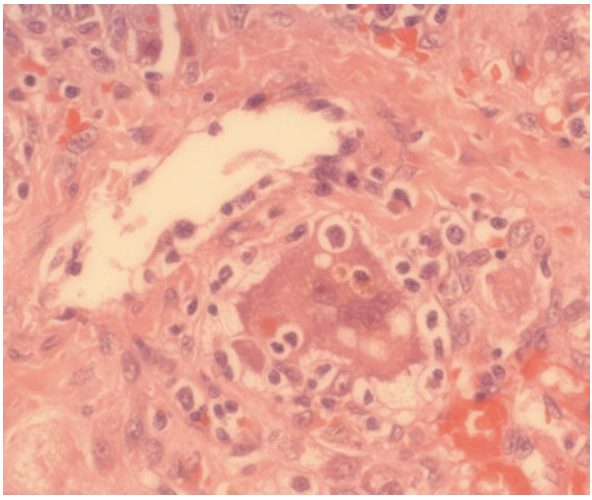

Fig. 8.1 Multinucleated hepatocyte from the explanted liver of a child with type 2 autoimmune hepatitis demonstrating cholestasis, lymphoid emperipolesis and small droplet steatosis (H&E x400 magnification). (Courtesy of Dr. Maesha Deheragoda, King's College Hospital, London)

double stranded DNA or anti-soluble liver antigen (SLA) antibody could be detected in AILD [1]. The latter have been suggested to indicate a more serious clinical disease, irrespective of the AIH type [13]. Type 2 AIH is only very exceptionally associated with abnormal cholangiograms.

Diagnosis

AILD should be excluded in all children and young people presenting with deranged liver function tests considering its presentation could be variable. Clinical presentation can be classified as (1) Acute (nonspecific symptoms of malaise, nausea/vomiting, anorexia, abdominal pain, jaundice, dark urine, pale stools); (2) Insidious (fatigue, headache, amenorrhoea, joint pain); (3) Asymptomatic (incidental finding of abnormal liver function tests during investigation of non-hepatic conditions, including IBD). Acute liver failure although relatively rare, is more common in AIH-2.

Table 8.1 illustrates the criteria for diagnosis of juvenile AILD.

Diagnostic scoring systems used in adults (IAIHG) are not reliable in juvenile AILD particularly when the disease presents as acute liver failure [15]. When assessed in a cohort of 83 patients with AILD, application of the IAIHG scoring system failed to diagnose 26% of patients and was unable to differentiate AIH from ASC [8, 16]. The recently published ESPGHAN diagnostic scoring system suggesting a lower cut-off for antibody titres and inclusion of cholangiography was more reliable [1].

Considering that up to 80% of the patients with ASC have or will develop inflammatory bowel disease, gastrointestinal symptoms should be proactively explored

Table 8.1 Criteria for the diagnosis of juvenile AILD

Blood tests:
Elevated transaminase levels
Positive autoantibodies:
ANA and/or SMA (titre ≥1:20) = AIH-1 or ASC
anti-LKM-1 (titre ≥1:10) and/or anti-LC-1 = AIH-2
Elevated immunoglobulin G (IgG) levels[a]
Exclusion of other liver diseases (hepatitis A, B, C and E; Wilson disease; non-alcoholic fatty liver disease; alpha-1-antitrypsin deficiency)
Histology:
Portal tract lymphocytic/lymphoplasmacytic infiltrates
Interface hepatitis
Rosette formation
Cholangiography:
Normal = AIH or small duct disease
Abnormal = ASC

[a]Elevated IgG levels are not necessarily required for the diagnosis of juvenile AILD, as they can be within the normal range at presentation in up to 20% of cases [14]

during the history taking and there should be a very low threshold to check faecal calprotectin levels and consequently proceed to a formal endoscopic assessment.

Treatment

Standard treatment of AILD is non-specific immune suppression, which includes prednisolone, given initially at induction dose of 2 mg/kg/d (not exceeding 60 mg/d) and weaned down to a maintenance of around 5 mg/d over 6–8 weeks [1]. To fully control the biochemical abnormalities about 70% of children require gradual addition of steroid-sparing agents, azathioprine (up to 2 mg/kg/d) or mycophenolate mofetil (up to 40 mg/kg/d) [17, 18]. Ursodeoxycholic acid (20 mg/kg/d) is used when cholangiopathic changes are evident radiologically, histologically or biochemically. Regular blood tests are required to monitor transaminases, but also effects of the treatment on peripheral blood counts and immunoglobulin levels. The described regimen with careful tapering of steroids, closely linked to the biochemical response, usually does not induce well-known and feared steroid side-effects such as excessive weight gain, bone changes due to osteoclast hyperactivity, behavioural changes or susceptibility to infection [1]. We recently investigated the long-term effect of daily low dose maintenance steroid treatment in 74 patients with juvenile AILD (AIH n-48). Median age at start of treatment was 12.85 (IQR 9.44, 14.14) years and follow up 12.07 (IQR 8.68, 13.97) years. Mean z-scores for weight, height and BMI at diagnosis, 1 and 5 years post diagnosis and at age 18 years were within the normal range as per WHO classification, indicating normal anthropometry. There was no statistically significant difference at any time point when comparing gender (male vs. female), ethnicity (Caucasian vs. non-Caucasian), diagnosis (AIH vs. ASC), age at diagnosis (<12 years vs. >12 years), and presence of IBD [19].

Budesonide is an alternative steroid which has a presumed better side-effect profile due to different pharmacokinetics (significant “first pass” hepatic effect) and relatively smaller dose required. However, it is not effective when the portal flow is impaired secondary to more advanced histological liver injury. The only prospective paediatric study noted fewer side-effects, but reduced effectiveness compared to prednisolone, particularly in more severe forms of AILD [20].

Biochemical remission is defined as normal transaminase levels; immunological remission as normal transaminase and IgG levels with negative/low titre (ANA/SMA <1:20) autoantibodies, whereas histologic remission includes absence of inflammation on liver histology.

Relapse is common affecting one third of patients and sometimes associated with worse outcome including need for liver transplantation [8]. Management includes temporary increase of steroid dose and/or consideration of alternative second or third line immunosuppression. Exploration of adherence to treatment is recommended in particular in adolescents and young adults where suboptimal adherence to treatment is more prevalent.

We will address this further later in this chapter.

Difficult-to-Treat Patients

Between 10 and 20% of patients do not respond to the standard mono- or dual therapy and require further augmentation of immune suppression [21]. Initially, calcineurin inhibitors—cyclosporine A or tacrolimus are recommended, but ideally only for a limited period, e.g. 6–12 months, due to nephrotoxicity and diabetogenic effects [22–24].

Sirolimus and everolimus belong to mTOR inhibitors, regulatory proteins involved in T-cell proliferation by blocking IL-2 signalling, and therefore inhibiting effector T-cell activation and proliferation. Recent small, uncontrolled studies both in children and adults have reported beneficial effects on elevated transaminases in some, but not all difficult-to-treat patients with sirolimus and everolimus [25, 26]. Obviously, long term side effects remain a major concern while using these omnipotent medications in younger patients.

Potential next-line treatments include targeted approaches with monoclonal antibodies such as anti-B cell (rituximab) [27–29] or anti-tumour necrosis factor (TNF)-alpha (infliximab) antibodies [30], that have been anecdotally tried, but with the mixed results. Further therapeutic options in the future could include low dose interleukin-2 [31] with manipulation of T-reg inflammatory response [32], and blockade of B-lymphocyte activating factor using belimumab [33]. It is obvious that paediatric hepatologists will have to await outcome and potential side-effects of these considerable immune manipulations in the adults before safely considering them for children with AILD.

Adoptive transfer of autologous *ex vivo* manipulated regulatory T-cells has been shown to restore peripheral tolerance and induce biochemical remission in a mouse AIH model [34] and that could represent an attractive option for selected patients in the future.

It is also conceivable that some of these "difficult-to-treat" children could have an underlying aberrant immune reactivity due to minor primary immune deficiency or some other genetic reason. Recently, we have noted a 2.5 year old girl with LKM-1 positive AIH, who was diagnosed with signal transducer and activator of transcription (STAT)-1 gain-of-function (GOF) disease after requiring massive doses of immune suppression to bring her AIH type 2 in control (unpublished observation). This is an area where future collaboration between hepatologists and immunologists is indicated in order to identify whether some of these challenging patients harbour subtler primary immune defects or genetic variations and to optimise their long-term immune suppression.

Liver transplantation (LT) is required in 5–10% of patients presenting with acute liver failure or with very resistant clinical phenotypes. In our recent study the transplantation requirements were higher in ASC than AIH cohorts (28% vs 9%) [8]. One-year LT success rates are between 90% and 95%, but the recurrence risks are not insignificant and are quoted between 33% to 39% [35, 36]. The likely explanation for that is a prompt recurrent reaction of recipient T-memory cells, pre-sensitised to autoantigens presented by recipient antigen-presenting cells invading the graft

and possibly accelerated by HLA susceptibility alleles from the donor. The biochemical and histological changes in the graft are very similar to the original features of autoimmune disease and could develop insidiously. In paediatric LT recipients frequent biliary complications need to be ruled out first. The management options include increase in the steroid dose, addition of sirolimus or retransplantation. In paediatric ASC the recurrence risks appear to be relatively higher and were reported in about two thirds of LT recipients, particularly the ones who had concomitant uncontrolled IBD [37].

Chances of immune suppression withdrawal after prolonged biochemical remission in AILD have been described to range between 20% and 40% [1, 38]. Histological assessment before attempting gradual reduction is recommended as ongoing inflammatory changes in the liver do not always correlate with biochemical or immunological abnormalities. Failure to stop immune suppression is more likely to occur in more advanced histological injury and with associated autoimmune comorbidities. In our centre we prefer to attempt immune suppression withdrawals after puberty, following normal transaminases for 2 years and ideally after liver biopsy with no inflammatory changes. Discontinuation of treatment is not recommended in those with AIH-2.

Links with IBD

Co-occurrence of AILD with IBD is well described with a prevalence of up to 78% of patients with ASC and PSC [39, 40]. The most common IBD phenotype is ulcerative colitis followed by unclassified IBD and Crohn's disease, the latter more likely associated with small duct liver disease [16]. The literature is ambivalent about the impact of IBD on severity of liver disease. In adults, presence of IBD, particularly UC, has been associated with an increased risk for adverse liver-related outcomes, whilst in paediatric age group a milder liver disease course was noted in those with PSC-IBD compared to isolated PSC [39] Currently, there is no consensus on the benefit of colectomy at the time of liver transplantation for those patients with ASC/PSC and IBD [40]. The combined liver gut phenotype has lead however to increasing interest in studying "gut-liver axis" and possible shared pathogenetic mechanisms. The immune-mediated liver injury could result from a myriad of intestinal factors, including increased gut permeability due to chronic inflammation leading to microbial translocation and more extensive exposure to gut-derived antigens, altered intestinal microbiome ("intestinal dysbiosis") producing possibly antigenic by-products, and shared network of activated lymphocytes, which could potentially elicit the proinflammatory immune cascade in both organs. Some groups have reported the beneficial effects of prolonged antibiotic courses on inflammatory markers of AILD [41].

On the other hand, abnormal liver function could derange the biliary enterohepatic circulation with abnormal profile of intestinal bile acids leading to chronic inflammation. Portal hypertension could also potentially *per se* induce a chronic

enteropathy. Recurrence of these autoimmune conditions after liver transplantation have also suggested influence of extrahepatic pathogenetic factors.

De Novo AIH

De novo autoimmune hepatitis is a separate entity sharing biochemical, immune and histological features with classical AIH, but developing after LT for non-immune indications [42]. About two thirds of children have detectable *de novo* autoantibodies >1 year after LT, but only around 5% develop *de novo* AIH. Recently, histological description of post-LT "plasma cell-rich" hepatitis was suggested to minimise the use of other descriptive terms but its aetiology is still debated [43]. Opinions are still divided whether this is an atypical form of organ rejection or phenomenon related to prolonged use of calcineurin inhibitors, affecting physiological processes of elimination of autoreactive T cells in the thymus and peripheral circulation of susceptible individuals.

Medical treatment of *de novo* AIH is similar to AIH, except that CNI levels should be kept relatively lower and the steroid dose should be maintained at 2.5–7.5 mg/day longer term. With that regimen the prognosis is usually good, although retransplants and deaths have been described.

Medication Adherence

As highlighted earlier, relapses are prevalent in AILD and their relation with adherence to treatment is always worth exploring in young people, prior to making new immediate changes to the treatment. Medication adherence should be routinely checked in all patients with AILD including adults, but this has not yet become a routine practice. In adolescents, sub-optimal adherence to treatment is considered to be "developmentally appropriate" and will be discussed in more detail in other Chap. (17) (Michaud).

One of the challenges is how to monitor adherence in AILD in absence of reliable serum markers available in other settings like diabetes mellitus or organ transplantation, where biochemical markers such as HbA1c and tacrolimus level standard deviation scores have been respectively demonstrated to be useful tools. For those on azathioprine, reference ranges for thioguanine nucleotide levels (TGN) are derived from IBD experience and large, multicentre data is unavailable in the paediatric population to assess their validity. A study including 70 adult patients with AIH concluded that TGN concentrations of >220 pmol/8 x 10^8 red blood cells was associated with remission and suggested that the serum measurements may help identify inadequate immunosuppression [44].

By default, healthcare professionals typically rely on patient self-report, which has high specificity, but low sensitivity for detection of non-adherence [45]. In a

recent study involving 68 patients with AILD followed up in our young adult multidisciplinary clinic, 73% self-reported their medication adherence as >80%, whereas only 51% were clinically considered to be in biochemical remission at the time. Older patients were less adherent, but more worried and emotionally affected by their chronic condition. With regard to adherence patterns, 63% reported forgetting to take medications at times, 44% were taking medications more frequently prior to attending appointments and 31% did not have a routine for taking medications [46].

What Adult Hepatologist Needs to Know

When taking over a care of adolescent patient with AILD, adult physician needs to be aware of the consequences related both to the chronic illness and treatment. Many patients would be keen to reduce or to stop immune suppression due to fear of perceived side-effects. Some young patients would take medications intermittently while not necessary sharing that with their carers. Contraception, subfertility and conception issues are discussed elsewhere (Chap. 20). Portal hypertension often needs to be re-evaluated using adult protocols and criteria with upper gastrointestinal endoscopy, which usually does not require general anaesthetic anymore, in contrast to paediatric guidelines.

If pregnancy is planned potentially teratogenic medication mycophenolate mofetil should be replaced by azathioprine, which is regarded to have acceptable early pregnancy risks, similar to the steroids.

For young adults with severe liver disease leaving the secure paediatric environment may be more challenging as the medical and social responsibilities become much more personal and organ competition more fierce, with longer transplant waiting times. Therefore, individual risk assessment should be an essential part of transition process.

On a more positive note, the innovative treatments tend to become available for adult patients with resistant disease much sooner. Additional complicating element of concomitant pathologies such as IBD or endocrine problems, including obesity and insulin resistance may add to the complexity of management of young adult patients.

Future

Present standard anti-inflammatory treatment with steroids is fairly broad and non-specific. It is possible that better insight in AILD pathogenesis could lead to more tailored treatments in the future. Innovative strategies could include more specific control of proinflammatory response and enhancing a key role of T-regulatory cells by improving their relative numbers and/or function. Improved understanding of underlying

mechanisms driving interrupted tolerance status between regulatory and effector mechanisms in other autoimmune conditions may also help understand complex pathogenesis of AILD in children. In addition, some more refined immune reactivity issues may also need to be more specifically targeted. For example, using JAK inhibitors such as ruxolitinib in STAT1 GOF disease associated with AILD was shown to reduce observed cellular hyperphosphorylation [47, 48], which may have been implicated in the mechanisms of steroid "resistance". Advent of next generation genetic sequencing methods to interrogate specific subtler immune defects and variation is potentially an important impetus for better classification and management of AILD.

Key Points for Adult Hepatologists

- AILD is a chronic condition, where only a minority of patients may be successfully weaned of long term immune suppression
- Presence of cholangiopathy usually indicates more severe form of the disease, with limited therapeutic options
- Some of the difficult-to-treat patients could have undiagnosed underlying gastrointestinal or immunological disorders
- Affected young people are particularly vulnerable during period of transition due to combination of behavioural and social factors

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Chapter 9
Wilson Disease

Atchariya Chanpong and Anil Dhawan

Introduction

Wilson disease (WD) is an inherited disorder of copper metabolism with a reported prevalence of 1:30,000–50,000 [1–5]. This disease is caused by mutations in the *ATP7B* gene, encoding enzyme (transmembrane copper-transporting ATPase) which is critical for copper excretion into the bile and for copper incorporation into caeruloplasmin (Fig. 9.1). Impaired copper excretion results in a progressive accumulation of copper in the liver and other organs such as the nervous system, corneas, kidneys, and heart. Clinical presentation in childhood can vary from asymptomatic liver disease to cirrhosis or acute liver failure (ALF), with or without neurological and psychiatric symptoms [1]. Approximately 20–30% of WD patients present with ALF, while most of others develop chronic progressive liver disease or cirrhosis if unrecognised or untreated [6].

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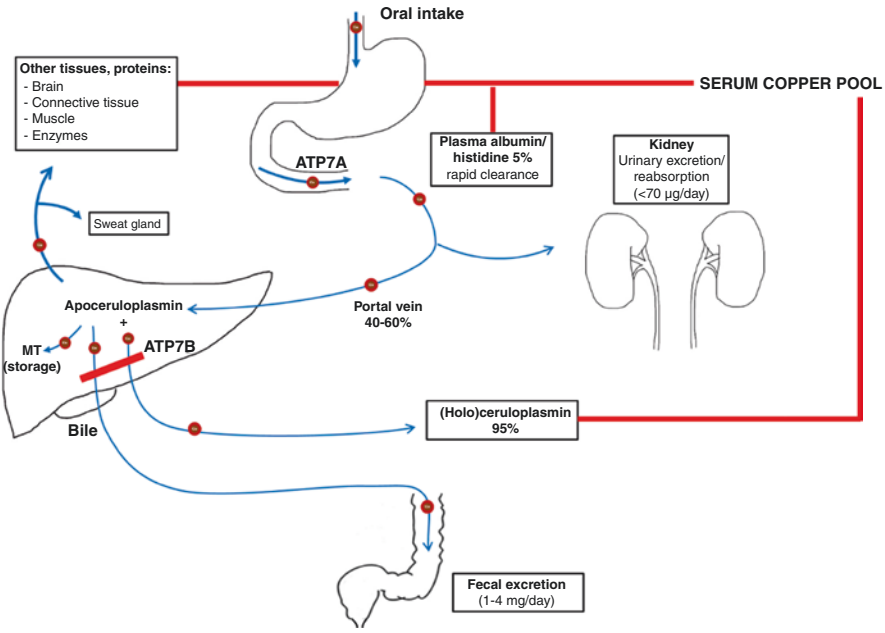

Fig. 9.1 Human copper metabolism

Pathophysiology

Genetics

WD is an autosomal recessive disorder caused by mutations of *ATP7B* gene, located on chromosome 13. The common mutations are missense and nonsense and patients can be either homozygous for one mutation or two different disease-causing mutations (compound heterozygous). Although more than 700 mutations have been found to cause WD, missense mutation H1069Q is the most prevalent one (50–80%) in European and American population [7, 8], while mutation R778L is more common (14–49%) in Far East Asian countries [9, 10].

Several studies [11–16] also found that different ATP7B variants could lead to different disease phenotypes; for example, patients with homozygous H1069Q mutation frequently present with neurological symptoms but at a later onset than compound heterozygous [12, 13]. Additionally, patients with truncating mutations often present with ALF [15]. Lack of definite genotype/phenotype correlation suggests a potential role of epigenetics from environmental and nutritional factors on WD presentation [17].

Copper Metabolism and Homeostasis in Hepatocytes

Copper is an essential trace element vital for human physiology, especially for mitochondrial activities. Dietary copper is absorbed into the body through intestinal mucosa using ATP7A transporter and transported via portal blood to the liver. A minority is excreted via the urine and sweat (Fig. 9.1).

Copper enters hepatocytes through copper transporter 1 (CTR1) before being transported into the trans-Golgi network via ATP7B. Following that, copper incorporates into apocaeruloplasmin (half-life 5 hours) to form holocaeruloplasmin (half-life 5 days) [18], the major copper-containing protein with six copper atoms per molecule, and excretes into circulation. Moreover, ATP7B also promotes copper excretion into the bile by forming vesicles that traffic to the canalicular membrane (Fig. 9.2).

Mutations of the *ATP7B* gene not only reduce the levels of *ATP7B* encoding protein but also increase the protein degradation. These abnormalities in ATP7B gene product lead to toxic accumulation of copper in the liver and subsequently to an excess of non-caeruloplasmin-bound copper in the bloodstream (Fig. 9.2). The excess copper is taken up by other tissues (e.g. brain, eyes, heart) via CTR1 and divalent metal transporter (DMT) even when in excess intracellularly. Cellular copper overload leads to oxidative stress and subsequent oxidative damage to cellular proteins, lipids, DNA, RNA and mitochondria [17].

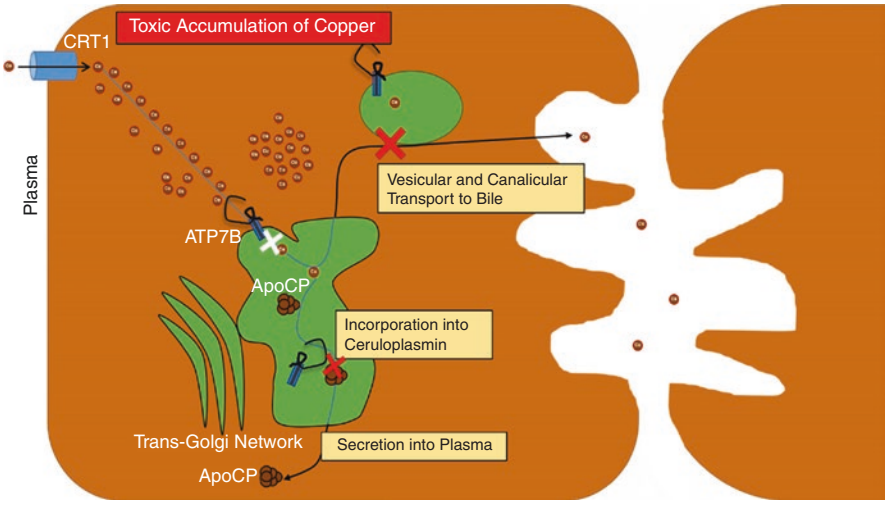

Fig. 9.2 Copper homeostasis in the hepatocytes and biliary canaliculi.

Liver injury is the earliest and most frequent manifestation in children with WD as liver is the major organ responsible for copper balance and metabolism [17]. Initially, copper binds with metallothioneins (MT), intracellular proteins capable to store and detoxify metal ions. This can be detected with special staining (rhodanine and orcein) on liver histology [19]. With time, copper accumulates in lysosomes and causes mitochondrial damage leading to hepatic steatosis, hepatitis, fibrosis and subsequently macronodular cirrhosis.

Non-ceruloplasmin bound (toxic) copper leaks into the blood and accumulates in other tissues. In the brain, chronic toxicity of copper leads to damaged astrocytes, demyelination and tissue disintegration, often in the basal ganglia, thalamus, cerebellum and upper brainstem [17, 20].

A rapid increase of free copper in the blood leads to Coombs-negative hemolysis by oxidative damage of haemoglobin and cell membrane [21]. This may also be associated with rhabdomyolysis due to copper-induced inhibition of Na^+/K^+-ATPase activity in the muscle [22]. Likewise, excess copper in renal medulla can cause renal tubulopathy [20].

Clinical Presentations

Although WD in children may present at any age the median age is about 13 years [20, 23]. Symptomatic disease is uncommon before 3 years [20, 24]. Hepatic disease as presentation is more common in children, although some (4–6%) also initially experience subtle neurological symptoms. It is more common for older children and young adults (aged 20–30 years) to present with neurological or psychiatric disease with or without liver involvement [1, 17].

Hepatic Manifestations

Hepatic manifestations range from asymptomatic or incidental findings of abnormal liver tests, complications of chronic liver disease to ALF [1]. At early stage, patients may be asymptomatic, but present with elevated liver enzymes or findings of hyperechogenic liver on ultrasound. During the disease progression, the patients may present with signs/symptoms of chronic liver disease (e.g. hepatosplenomegaly) or complications from liver cirrhosis (e.g. ascites, gastrointestinal bleeding). Diagnosis of WD should always be entertained in any child or young adult presenting with abnormal liver tests as clinical or immunological features of non-alcoholic fatty liver disease and autoimmune liver disease may mimic WD [25, 26].

ALF is a severe form of WD characterized by jaundice, hepatitis, hepatomegaly, coagulopathy with or without encephalopathy in previously well children. Paediatric Acute Liver Failure (PALF) study group suggests the definition of ALF: an INR of $\geq$1.5 in the presence of encephalopathy, or an INR of $\geq$2.0 regardless of the

encephalopathy [27]. Some children may have past history of acute self-limited hepatitis-like illness, recurrent jaundice, haemolytic anemia or elevated transaminases [17].

The differentiating features from other causes of ALF are relatively milder elevation of the liver enzymes (AST/ALT), high total bilirubin and low alkaline phosphatase [17, 20, 28]. Some clinicians consider this presentation as acute-on-chronic liver failure as invariably there is evidence of pre-existing chronic liver damage on liver histology. Associated hemolysis due to free copper could lead to a high total bilirubin.

Neurological Manifestation

Neuropsychiatric symptoms are only occasionally seen in children, especially in younger than 10 years, while 5–15% of children presenting with liver disease could also have neurological symptoms [17, 29]. Patients may present with incoordination (e.g. handwriting deterioration—dysgraphia), declining performance at school, mild cognitive impairment such as working memory, language difficulties (dyslalia) or movement disorders (e.g. tremor). Psychiatric symptoms can vary from behavioural and personality problems (aggressive and impulsive), mood disorders (depression, anxiety, bipolar), to psychosis.

Brain MRI has become an important examination for the patients presenting with neurological signs/symptoms, but diagnostic yields are variable. However, it could be used for treatment monitoring as some findings may reverse during copper-chelating therapy. Typical abnormalities in WD brain MRI include hyperactive intensity lesions visualised on T2-weighted images located in the basal ganglia (mainly putamen and caudate nuclei), thalamus, midbrain, and pontine white matter [30, 31]. These findings suggest cerebral involvement in WD, whilst high-signal intensity lesions in the basal ganglia on T1-weighted images can be secondary to chronic liver disease therefore reflecting the hepatic involvement in WD [17, 20].

Other extrahepatic manifestations are shown in Table 9.1**.**

Diagnosis

Clinical manifestations of WD are varied. Although hepatic manifestation is the most common presentation in children, there are other possible causes of liver disease which could mimic WD. In 2001, a WD diagnostic score (Table 9.2) has been developed by the Working Party on Wilson's disease [34]. The score has been widely used and included into the diagnostic algorithm in the European Association for the Study of the Liver (EASL) guidelines, as it provides good accuracy for the diagnosis of WD [35]. This score was further validated in children and young adults by Koppikar and Dhawan, who demonstrated high diagnostic value of the score [36].

Table 9.1 Clinical presentations of childhood Wilson disease

Clinical manifestations	Signs/symptoms	Prevalence	Age at onset (years)
Hepatic	• Increased serum transaminases • Acute hepatitis • Hepatomegaly • Fatty liver • Acute liver failure with hemolysis • Portal hypertension: Esophageal varices, splenomegaly, thrombocytopenia • Decompensated cirrhosis with ascites	60–70% [17, 20]	>2
Neuropsychiatric	• Dysarthria • Dysphagia, excessive salivation • Mood/behavioural changes including depression, irritability • Incoordination (e.g., handwriting deterioration) • Declining performance at school • Resting and intention tremors • Gait disturbance, dystonia, rigidity • Mask-like face, risus sardonicus, • Stroke-like symptoms	20% [29]	>10–15
Ophthalmologic	• Kayser-Fleischer rings: gold or grey-brown opacity in the peripheral cornea (copper deposition on Descemet membrane), seen by slit-lamp examination or with naked eye * Always present in neurological involvement [32]	< 5%	>6–8 [7, 33]
Haematological	Coombs negative acute intermittent/chronic haemolytic anaemia	7% [21]	>7 (earliest age of 3 years)
Other: • Renal	Renal tubular dysfunction Nephrolithiasis Nephrocalcinosis	–	–
• Cardiac	Cardiomyopathy, heart failure Arrhythmia		
• Musculoskeletal	Rickets/osteopenia/osteoporosis Arthropathy		
• Endocrine	Hypoparathyroidism Infertility and miscarriages		
• Skin	Lipomas, hyperpigmentation		
• Pancreas	Pancreatitis		
Asymptomatic	Detected on family screening Incidental finding of abnormal liver enzymes	–	–

Table 9.2 Wilson diagnostic score [34]

Score	−1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms suggestive of WD (or typical brain MRI)		Absent		Present	
Coombs-negative haemolytic anemia + high serum copper		Absent	Present		
Urinary copper (in the absence of acute hepatitis)		Normal	1–2 × ULN	>2 × ULN or normal, but >5x ULN 1 day after challenge with 2 × 0.5 g D-penicillamine	
Liver copper quantitative	Normal		<5 × ULN (<250 μg/g).	>5 × ULN (>250 μg/g).	
Rhodanine positive hepatocytes (only if quantitative Cu measurement is not available)		Absent	Present		
Serum caeruloplasmin (nephelometric assay)		>0.2 g/L	0.1–0.2 g/L	<0.1 g/L	
Disease-causing mutations detected		None	1		2

Assessment of the WD diagnostic score: 0–1: unlikely; 2–3: probable; 4 or more: highly likely
Abbreviations: *ULN* upper limit of normal, *WD* Wilson disease

Serum Copper and Exchangeable Copper (CuEXC) Determination

In WD patients, total serum copper, including one incorporated in caeruloplasmin, generally decreases in accordance to the level of caeruloplasmin. However, the level can be normal or increased irrespective of the level of caeruloplasmin which indicates a sudden release of free copper from the liver tissue to bloodstream (non-caeruloplasmin-bound copper; NCC), which is suggestive of WD. The amount of NCC is calculated from total serum copper and caeruloplasmin concentrations with the following equation [37]:

$$NCC\left(\mu g/L\right) = \text{Serum copper}\left(\mu g/L\right) - \left[3.15\,\mu g/\text{mg ceruloplasmin} \times \text{ceruloplasmin}\left(\text{mg}/L\right)\right]$$

In normal individuals, NCC is approximately 50–100 mg/L. In Wilson disease, the concentration is more than 200 mg/L, or even 10 times higher in the presence of acute liver failure and haemolysis. However, one drawback of this calculation is that its determination is highly dependent on the correct measurement of serum copper and caeruloplasmin.

Alternatively, a new promising test, exchangeable copper (CuEXC), has been developed to accurately measure plasma unbound copper in the plasma compartment and it does not rely on the level of caeruloplasmin. Reference values for CuEXC are between 0.62–1.15 μmol/L; the values above this range represent blood and tissue copper overload. Moreover, a cut-off of 2.08 μmol/L may predict presence of extrahepatic manifestations [38]. However, the availability of this test is limited, mainly to research facilities, and its analytic cost is quite high.

Relative exchangeable copper (REC) is a ratio between CuEXC and total serum copper, representing toxic blood copper fraction. A value of >18.5% could be used as a cut-off for the diagnosis of WD with 100% sensitivity and specificity [38–40].

Urinary Copper and Penicillamine Challenge Test

Since patients with WD excrete excess copper in urine, urinary copper has been accepted as one of the diagnostic tests for WD diagnosis. Of note, the accuracy of urinary copper measurement is technically dependent on the careful collection timing, type of container, and laboratory expertise.

For baseline 24-h urinary copper, a cut-off of 0.64 to 1.60 μmol/24 h has been used providing a sensitivity of 50% to 80%, and a specificity of 76% to 98% [41], as this value can be <1.6 μmol/24 h at presentation in 16–23% of WD patients, particularly in asymptomatic or mild liver disease patients [42]. Moreover, the interpretation of 24-h urinary copper excretion can be difficult due to the overlap with findings in other types of liver disease, particularly during acute hepatic failure of any origin [42].

Penicillamine challenge test (with 2 doses of 500 mg penicillamine given at 0 and 12 h during 24-h urine collection) has been proposed to be used for diagnosis of WD in children since 1992 [43]. A cut-off value of 25 μmol/24 h has provided sensitivity and specificity of 76% and 93%, respectively [44]. The sensitivity can be high up to 92% in symptomatic patients, but only 46% in asymptomatic patients. Nicastro et al. reported that by lowering the cut-off to 5 times the upper normal limit of baseline, 24-hr urinary copper excretion (3.2 μmol/24 h), the sensitivity increased to 88%. Conversely, its specificity is reduced to 24% [35]. The penicillamine challenge test may not be required if the lower threshold for basal urinary copper excretion of 0.64 μmol/24 h is applied as this increases the sensitivity of the test.

Spot urinary copper or urinary copper/creatinine ratio have not been recommended for the diagnosis of WD. Few studies reported a significant correlation between 24-h urinary copper excretion and urinary copper/creatinine ratio; and proposed the cut-off values of 0.5 mmol/L and 0.1 mmol/mmol Cr for spot urine copper and the ratio with creatinine, respectively [45, 46].

Liver Copper

A liver biopsy is essential if there is suspicion of other or additional liver pathology, or the clinical signs and other non-invasive biochemical tests do not provide a definite diagnosis [42]. The measurement of hepatic parenchymal copper concentration is recommended, while there is limited diagnostic value on liver histology alone or copper deposition identified by rhodanine, orcein, or rubeanic acid staining. Liver histology changes are nonspecific including fatty deposition, irregular shaped cytoplasmic inclusions, copper deposition, glycogen-containing vacuoles in the nuclei, lipofuscin and iron deposition (in those with haemolysis), portal fibrosis and inflammation similar to autoimmune hepatitis [1, 20]. The positive staining can be seen in many cholestatic liver diseases, whilst negative staining does not rule out WD [47]. Hepatic copper content of >4 μmol (250 μg)/g dry weight liver is considered as the best cut-off value, given that its sensitivity was 66% to 94%, with a variable specificity of 52% to 99% [41]. Of note, hepatic copper concentration can be underestimated due to sampling errors or increased in other liver diseases with impaired bile secretion. Preferably, two biopsy specimens with an adequate size of >1 cm long (minimum 0.5 cm), placed on a small piece of paper for drying and in a dry plastic copper-free container, is recommended for an accurate interpretation [1].

Serum Caeruloplasmin

Caeruloplasmin is a 132 kDa protein; its function are to transport copper (95% of total circulating copper), to act as an antioxidant, and to be involved in the oxidation of ferrous ion (ferroxidase activity) and aromatic amines. The concentration of serum ceruloplasmin varies with patients' age—very low in neonates (<6 months) with peaks in mid-childhood [48, 49]. Therefore, serum ceruloplasmin can be tested for the diagnosis of WD in children older than 1 year. As this protein is mainly produced by the liver and it is also considered acute-phase protein, the level of ceruloplasmin can be affected by other liver diseases, malnutrition and inflammatory conditions. For example, it can be elevated to normal range in WD patients with active infection, or it can be low in protein-losing enteropathy.

Serum ceruloplasmin can be detected by different methods including enzymatic assays and immunologic or antibody-dependent assays. Enzymatic assays are the preferred method as it measures copper-dependent oxidase activity, whilst immunologic assays measure both apoceruloplasmin and holoceruloplasmin, therefore, could misleadingly over-estimate serum ceruloplasmin [1, 50]. Despite that, current guidelines [1, 24, 42] have recommended that a serum ceruloplasmin level of <0.2 g/L, measured by immunologic methods, supports a diagnosis of WD. Several studies [49] proposed different thresholds for a better WD diagnosis; a level of <0.14 g/L has been reported with a sensitivity of 93% and specificity of 100% in patients presented with liver dysfunction and/or neurological manifestations [51].

In asymptomatic children with elevated liver enzymes, it has been reported that a level of <0.2 g/L provided sensitivity and specificity of 95% and 85%, respectively [35]. Of note, normal serum ceruloplasmin levels could be identified in approximately 20% of children and adults with WD.

Mutational Analysis

Mutational analysis has become a more important diagnostic tool for WD, as it can distinguish healthy heterozygote carriers from affected presymptomatic WD patients [7]. Although, mutant alleles can be identified with next-generation sequencing in 95% of affected subjects, the genetic tests may be less accessible in some countries, and results may take time. Additionally, some patients may require further molecular analysis including Multiplex Ligation-dependent Probe Amplification (MLPA) to search for large gene defects such as whole exome deletions or duplications which are not easily identified by direct DNA sequencing [7].

As mentioned earlier, more than 700 mutations within the ATP7B gene have been identified [20] and most affected individuals are compound heterozygotes. Although it is rare that some children do not have any identifiable mutation, the diagnosis in this group can be established by long-term follow-up and evaluation of treatment responses. Alternatively, if only one known mutation is identified, the child is either a heterozygote carrier or a WD patient in whom the second mutation is not yet identified. WD is highly likely if the laboratory tests are suggestive [7] and the diagnosis can be reached according to WD diagnostic score (Table 9.2).

Genetic counselling is essential for families of the WD patients and screening first-degree relatives is recommended by both European and North American guidelines.

Treatment

The aims of treatment are to reduce copper absorption, remove excess copper and prevent its accumulation in the liver and other organs especially central nervous system.

Dietary copper restriction does not prevent copper accumulation; however, it is advisable to avoid excessive consumption of copper-rich food (shellfish, nuts, chocolate, mushrooms, and liver) until remission of symptoms and improvement of biochemical abnormalities [1].

Pharmacological Treatment

The goal is to increase urinary or fecal copper excretion and to block intestinal absorption of copper. It is recommended to start treatment promptly once the diagnosis is established [1].

Although there is a lack of high-quality evidence to recommend the optimal first-line treatment choice in WD, penicillamine (used since 1956) is still a standard first-line therapy. Penicillamine contains a free sulfhydryl group to bind copper and is excreted via the urine. It has been reported that penicillamine not only increases urinary copper excretion but also induces the endogenous hepatic metallothionein leading to copper detoxification [52]. The initial dose for children is 150–300 mg/day, with gradual weekly increases up to 20 mg/kg/day divided into 2 or 3 doses, or total up to 1000 mg (max 1500 mg) in young adults given in 2 or 4 divided doses [20]. A slow introduction with dose titration is necessary, as paradoxical worsening of neurological symptoms of WD during the initial phase of penicillamine therapy has been reported in 10–50% of patients (particularly in those presenting with neurological signs and symptoms). Although this unexpected neurological deterioration could be found in approximately 10%, regardless of drug types [17], it tends to be reported mainly in patients treated with penicillamine [53]. Moreover, penicillamine is associated with several adverse effects including hypersensitivity reactions, fever, neutropenia, thrombocytopenia, lymphadenopathy or proteinuria, which improve after discontinuation of the drug. Penicillamine may interfere with pyridoxine action, hence, pyridoxine should be supplemented at a daily dosage of 25–50 mg by mouth [24].

Trientine was introduced in 1969 to be a second-line chelating therapy in WD patients who could not tolerate penicillamine. The use of trientine as a first-line therapy has been increasing, even though it was reported that the drug could worsen neurological symptoms. Trientine chelates copper by forming a stable complex with the four constituents nitrogen in a planar ring and promotes copper excretion by the kidney [24]. The starting dose is 20 mg/kg/day or 1000 mg (max 1500 mg) in young adults given in 2 or 3 divided doses; it can be up to 900–1500 mg/day in 2 or 3 divided doses during maintenance as the weight-based dose has not been established yet [20]. Trientine also chelates iron, thus iron deficiency anemia or sideroblastic anemia is one of its adverse effects. However, coadministration with iron should be avoided because trientine-iron complex is nephrotoxic.

While the mechanism of action for penicillamine and trientine is to increase copper excretion via urine, zinc acts differently—by interfering the uptake of copper from gastrointestinal tract. Zinc induces enterocyte metallothionein to form a complex with copper, inhibits the entry of this complex into portal circulation and ultimately increases copper excretion in the stool [54]. Furthermore, zinc may also induce the level of hepatic metallothionein, which could prevent hepatocellular injury and improve hepatic resistance to copper toxicity [55]. Generally, zinc is reserved for maintenance treatment. Due to its good tolerability, zinc is also used as first-line therapy for asymptomatic or presymptomatic patients and could be used, as first-line monotherapy in patients with neurological WD. Caution should be taken when used in hepatic WD patients due to the risk of hepatic deterioration. Gastric irritation or actual gastritis is the most common adverse effect on zinc therapy, dependent on the type of zinc salt used [17, 20, 24, 42].

Ammonium tetrathiomolybdate is a very strong decoppering agent but still an experimental therapy without standard availability. Its actions are to bind copper in the intestinal tract to prevent absorption and to make copper in the circulation unavailable for cellular uptake [42, 56]. In a randomized control trial,

tetrathiomolybdate was found to be better than trientine in preservation of neurologic function in patients presented with neurological involvement [57]. There is limited data regarding the drug administration and its outcome in children.

The dosage, administration and adverse effects of the drugs are summarized in Table 9.3.

Liver Transplantation

Indications for liver transplantation [59] in patients with WD are: 1) ALF defined by the rapid development of severe hepatic insufficiency with coagulopathy and with hepatic encephalopathy, 2) progression of liver dysfunction to liver failure despite drug therapy, 3) acute on chronic liver failure due to WD [1, 17, 42]. Consideration of LT in patients with neurologic WD is still controversial.

Children presenting with ALF but no hepatic encephalopathy can be initially treated with chelation agents, however, the response to medication may take time with improvement of prothrombin time after a minimum of 1 month and normalization within 3 to 12 months [60]. It is quite challenging to determine when patients with WD will require LT. The revised King's prognostic Wilson Index has been proposed to evaluate those who most likely would fail medical therapy and die without LT (Table 9.4). The index score of $\geq$11 was a strong predictor of mortality without LT [61] with sensitivity and specificity of 93% and 97%, respectively. The score also provided high positive and negative predictive values of 92% and 97%, respectively [62].

Future Therapeutic Strategies: Liver Cell Transplantation and Gene Therapy

Human hepatocyte transplantation has shown promising results in various animal models, although there are some concerns regarding the shortage of donor organs, low cell engraftment, and a lack of long-lasting effects [63, 64].

Another alternative therapy option is the genetic correction of the ATP7B gene or gene therapy. Currently, its practical application still requires further investigation, although good outcomes have been reported in experimental animal models by using infusion of recombinant adeno-associated virus bearing *ATP7B* cDNA [65–67]. A recent study reported the use of CRISPR/Cas9 technology to correct *ATP7B* point mutation frequently detected in WD patients [59]. However, clinical studies for WD gene modification are required, so these could become alternative curative strategies in the future.

Table 9.3 Drug administration and monitoring [1]

	Penicillamine	Trientine	Zinc acetate/ sulphate	Ammonium tetrathiomolybdate
Initial dosage	150–300 mg/day, gradually increasing once a week up to 20 mg/kg/day given in 2 or 3 divided doses or 1000 mg (max 1500 mg) in young adults given in 2 or 4 divided doses	20 mg/kg/day or 1000 mg (max 1500 mg) in young adults given in 2 or 3 divided doses	Age > 16 years and body weight > 50 kg: 150 mg/day in 3 divided doses. Age 6–16 years and body weight < 50 kg: 75 mg/day in 3 divided doses Younger than 6 years: 50 mg/day in 2 divided doses	20 mg 3 times daily with meals and 20 mg 3 times daily between meals (doses in adult trials) [57]
Maintenance dosage	10–20 mg/kg/day up to 750 mg–1000 mg/day in 2 divided doses	900–1500 mg/day in 2 or 3 divided doses	Same	200–260 mg/day (in adults) [58]
Administration	1 h before meal or 2 h after meal	1 h before meal or 3 h after meal	1 h before meal or 2 h after meal	
Supplements	Pyridoxine	Iron	Nil	Nil
Parameters for adequate treatment	Urinary copper excretion: 3–8 μmol/L/24 h on maintenance treatment	Urinary copper excretion: 3–8 μmol/L/24 h on maintenance treatment	Urinary copper excretion: 0.5–1.2 μmol/L/24 h on maintenance treatment; Serum zinc >125 mg/dL; Urinary zinc >2 mg/24 h on maintenance treatment	N/A
Time to improvement	2–6 months	2–6 months	2–6 months	Not known
Adverse effects	Hypersensitivity reactions, fever, neutropenia, thrombocytopenia, lymphadenopathy or proteinuria	Allergic reactions, arthralgia, sideroblastic anemia	Gastric irritation (e.g. nausea, abdominal pain, gastric ulcerations), immunosuppressive effects, reduced leukocyte chemotaxis, hyperlipasemia and/or hyperamylasemia	Bone marrow depression, hepatotoxicity, overly aggressive copper removal causes neurological dysfunction

Table 9.4 The revised King's prognostic Wilson Index [62]

Score	Bilirubin (μmol/L)	INR	AST (IU/L)	WCC (x 10^9/L)	Albumin (g/L)
0	0–100	0–1.29	0–100	0–6.7	>45
1	101–150	1.3–1.6	101–150	6.8–8.3	34–44
2	151–200	1.7–1.9	151–300	8.4–10.3	25–33
3	201–300	2.0–2.4	301–400	10.4–15.3	21–24
4	>301	>2.5	>401	>15.4	<20

Follow-Up and Prognosis

In patients without advanced liver or brain injury, liver function can improve in >90% of patients, usually over 2–6 months, while neurological improvement is observed in 50–60% of patients over a longer time course of 1–3 years, if early and correct pharmacological treatment has been introduced [42].

Most importantly, adherence to the therapy is essential for long-term success. A recent study has proposed the use of 24-h urinary copper excretion to monitor adherence in children with WD [68]. This study suggested that the level of 24-h urinary copper should drop to ≤8 μmol/day and <6 μmol/day after one and five years of treatment, respectively.

Prevention and Screening

Being an inherited disease, WD may be difficult to prevent. However, early detection and treatment play a key role. Not only that genetic counselling is essential for families of patients with WD, but screening first-degree relatives is also strongly recommended [24, 42]. The assessment should include physical examination, biochemical tests (serum caeruloplasmin, urine copper and liver function tests) and molecular testing for *ATP7B* mutations. This should be considered in both parents of a child newly diagnosed with WD, as well as all available siblings [1].

Specific Issues in Young Adults Compared to Children

As mentioned earlier, it is more common for older children and young adults (aged 20–30 years) to present with neurological or psychiatric disease [1, 17], which could be misdiagnosed [69, 70]. Additionally, NAFLD is quite prevalent in early adolescence (age 12–15 years) [25] and thus may interfere with the diagnosis of WD. WD should be considered in young adults presenting with neurologic or psychiatric symptoms and/or NAFLD. This is because the prognosis is dependent on the prompt initiation of therapy.

One of the challenging issues in young teenagers is adherence to treatment, especially in chronic disease like WD where non-adherence could have an important negative effect on clinical outcome [71]. Other factors such as alcohol consumption, smoking and illicit drug use could also worsen the liver disease. Thus, it is essential to emphasize that WD patients must avoid alcohol consumption and other potential hepatotoxic drugs [1].

Another important issue is liver cancer surveillance, as it has been reported that approximately 4% of WD patients developed abdominal malignancy, including hepatocellular carcinoma (HCC), after 10–19 years of follow-up [72]. This incidence is higher as the duration of follow-up increases. Therefore, surveillance for HCC is recommended for WD patients with cirrhosis.

Fertility and Pregnancy

Counselling young adults regarding fertility and management during pregnancy and lactation is essential. Untreated or uncontrolled female WD patients can have menstrual and ovulatory dysfunction due to the liver disease and copper intoxication of specific enzymes involved in the normal ovulatory mechanisms and menstrual cycle, which could reduce their fertility or lead to early pregnancy complications (e.g. spontaneous abortion). These ovulatory disturbances can be reversed by commencing chelating agents to achieve adequate copper control and recover liver function; therefore, pre-pregnancy copper chelation therapy is necessary [73, 74].

To avoid exacerbation of symptoms, treatment should be continued during pregnancy with the same medication that the patients have already been on [74, 75]. A hepatologist with experience in WD should ideally supervise the treatment during pregnancy. Dosage reduction to the minimum necessary to maintain clinical and biochemical stability is recommended for penicillamine and trientine [42], especially during the first trimester as the risk of teratogenicity is the highest. During the last trimester it is important to avoid insufficient copper supply to the fetus, and/or insufficient wound healing after Caesarean section or episiotomy [24]. After delivery, recommencing the same dose of chelating agents used before pregnancy is advisable. Regular clinical evaluation and assessments of liver function tests and copper monitoring in blood and urine are essential both during and after pregnancy [74]. Since all chelating agents are excreted into the breast milk, breast feeding is not recommended [42].

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Chapter 10
Nonalcoholic Fatty Liver Disease

Emer Fitzpatrick

Top Tips for the Clinician

Investigation
• NAFLD is a diagnosis of exclusion (Table 10.1)
• Remember coexisting conditions; check HbA1C, lipid profile and blood pressure
• In those without other features of metabolic syndrome or in those with evidence of chronic liver disease e.g. splenomegaly, biopsy should be considered
Monitoring
• Abdominal circumference is a useful measure of progress in addition to BMI centile or Z score
• Ultrasound is useful for monitoring degree of steatosis and spleen size
• Transaminases may fluctuate and are not a good marker of fibrosis
• Non-invasive markers in blood may not be as useful in growing adolescents as in adult.
• Transient elastography/MR elastography and PDFF allow non invasive longitudinal monitoring of both steatosis and fibrosis
Management
• Healthy lifestyle is key, no medication currently is useful for all
• Mental health often central to achieving control and anxiety and depression are prevalent in this cohort
• The dietician and psychologist are central to the management team
• Individualised plan for teenagers focusing on what is practical and achievable is useful, in younger children the whole family may need to be involved
• Regular telephone or clinic contact to motivate and educate

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Introduction

Nonalcoholic fatty liver disease (NAFLD) was first described in 1980 in obese adults who had a pattern of injury similar to alcoholic hepatitis but who denied alcohol consumption [1]. The disease was described shortly afterwards in children in 1983 [2]. In paediatric practice, NAFLD most often presents from just before the onset of puberty and throughout adolescence, though children as young as 6 years may be affected by the condition. The disease is characterized by fatty droplet accumulation in the hepatocyte with or without inflammation and fibrosis, most often in the setting of other features of the metabolic syndrome. The presence of inflammation implies the diagnosis of nonalcoholic steatohepatitis (NASH), which previously was felt to be a more progressive condition than steatosis alone. It is now understood that inflammation is not a good predictor of disease progression, and the term steatofibrosis may be more applicable to more progressive disease [3]. Though typical features are seen on liver biopsy, diagnosis requires the exclusion of all other causes of liver disease including alcohol, other toxins and liver-based metabolic disease [4].

It is well recognised that non-alcoholic fatty liver disease (NAFLD) in adults is fast becoming the most common indication for liver transplantation [5]. The number of admissions to hospital with NAFLD as the primary indication is rising dramatically and accompanies exponential increase in the healthcare burden of the disease [6].

The rise in prevalence of NAFLD is closely associated with the worldwide rise in obesity [7]. The reliance on body mass index to predict those at risk does not measure the entire problem however, with reports of patient with lean NAFLD, though there is still often an association with visceral adiposity, insulin resistance and poor metabolic health [8].

The paediatric population has also seen this rise in prevalence of NAFLD, again likely related to the rise in obesity [6]**.** Arguably as this disease is of relatively early onset, it may be a more severe phenotype, often presenting with significant fibrosis at time of diagnosis, following only a relatively short time of exposure to overnutrition and usually without exposure to alcohol and other cofactors [9]. Thankfully, children and young people (CYP) often present with a potentially modifiable condition. Clinical experience confirms that fibrosis up to and including the point of cirrhosis is often reversible once the precipitating factor is removed [10] and thus, changing habits during this time of life can lead to a lifetime of decreased risk.

Both genetic predisposition and lifestyle factors influence the development and progression of NAFLD, the pathophysiology of which has not yet been fully elucidated. In view of the high prevalence of NAFLD and the potential to progress to serious liver disease, the ability to recognize and manage the condition in young people is of great importance.

CYP with NAFLD are often asymptomatic or may present with vague nonspecific symptoms such as abdominal pain and/or fatigue. The majority are overweight (gender and age specific BMI > 85th centile) or obese (> 95th centile) [11]. Hepatomegaly may be present and acanthosis nigricans (a black pigmentation of the skin folds, axillae and neck), is seen in those with insulin resistance (IR) and found in 30–50% of young people with NAFLD [12, 13].

In the diagnostic work-up of NAFLD, alternative causes of chronic liver disease should be excluded including chronic hepatitis B and C infection, Wilson disease, α1-antitrypsin deficiency, autoimmune hepatitis and drug effects. Conditions such as cystic fibrosis, coeliac disease, malnutrition and parenteral nutrition-associated liver disease may also present with a fatty liver on ultrasound and can be excluded on clinical or biochemical grounds. In addition, mitochondrial/metabolic disease and cholesterol ester storage disease may also look very similar on liver biopsy and need to be considered (Table 10.1) [4].

Table 10.1 Conditions which need to be excluded before a diagnosis of NAFLD is made

Clinical condition	Clinical features
Other liver specific diagnoses	
Wilson disease	Acute or chronic liver disease, haemolytic anaemia, neurological disease, Kaiser-Fleischer rings Low serum caeruloplasmin, high urinary copper pre and post penicillamine, high liver copper, genetic confirmation
Alpha 1 antitrypsin deficiency	Alpha 1 anti-trypsin phenotype ZZ (or ZS)
Hepatitis C	Positive serology
Congenital portosystemic shunts	Presence of focal nodular hyperplasia, high ammonia levels Imaging compatible
Drugs/Medication exposure	
Drugs—steroids, amiodarone, alcohol, methotrexate, ecstasy, l-asparaginase, vitamin E, valproate, tamoxifen, antiretrovirals	History of drug ingestion
Systemic conditions	
Malnutrition	Clinical examination
Coeliac disease	May have failure to thrive, diarrhea, constipation Tissue transglutaminase positive/compatible jejunal histology
Intestinal failure-associated liver disease	Compatible history
Cystic Fibrosis-associated liver disease	History/examination Positive sweat test/genetics positive
Mauriac syndrome	History type 1 diabetes with high HBA1c Glycogen on liver biopsy
Myopathic disorders	Myopathy, elevated CPK Genetics
Hypothyroidism	Other features of hypothyroidism TFTs
Shwachman syndrome	FTT, pancreatic insufficiency, bony changes, cyclical neutropenia Genetics

(continued)

Table 10.1 (continued)

Clinical condition	Clinical features
Lipodystrophies	Examination Genetics
Inborn errors of metabolism	
Mitochondrial disease/fatty acid oxydation defects	May be history of neuro-developmental problems or other system involvement Abnormal respiratory chain enzymes liver/muscle, abnormal acyl-carnitines,/skin fibroblast studies, genetics for mitochondrial disease
Lysosomal LAL-D, NPC	Positive enzymology or genetics
Galactosaemia	Presents in neonatal period on exposure to lactose Abnormal Gal-1-PUT result
Fructosaemia	May be history of avoiding sweets Enzymology on liver biopsy, HFI genetics
Glycogen storage disease	Hepatomegaly, short stature, history of fasting hypoglycaemia Positive enzymology/genetics, glycogen on biopsy
Peroxisomal disorders	May be hypotonic/have wide AF, developmental delay Abnormal Very Long Chain Fatty Acids, genetics
Hypobetalipoproteinaemia/abetalipoproteinaemia	Low serum triglycerides, may be history of fat malabsorption, FTT Low or absent Apo1B levels, genetics
Inborn errors bile acid synthesis	Cholestasis in infancy, spasticity later on Urine bile acids, genetics
Organic aciduria	Neonatal encephalopathy, later developmental delay, mild elevation in transaminases, hyperammonaemia Enzymology, genetics
Congenital disorders of glycosylation	100 subtypes, can be variable presentation, may have hepatocerebral phenotype Transferrin isoelectric focusing, Genetics
Endoplasmic reticulum function disorders e.g. Wolcott Rallison, NBAS	Recurrent Acute Liver Failure Genetics
Tyrosinaemia	Jaundice, progressive liver disease, coagulopathy Urinary succinyl-acetone, genetics

Prevalence and Risk Factors

In order to determine prevalence of NAFLD, an appropriate standard criterion for diagnosis needs to be defined. At present this standard criterion is liver biopsy, though this is not practical in population studies. Schwimmer at al. reported an

autopsy study of CYP who died of accidental injury [14]. This study found a prevalence of NAFLD of 9% with NASH (steatohepatitis) present in 3% [14]. Other population studies in children vary in prevalence from 1.7% to 42.5% [15] likely due to variability in the definition of NAFLD, but also a difference in population studied. In a study of morbidly obese children undergoing bariatric surgery, NAFLD was identified in biopsy in 83% [16]. A UK longitudinal population study found fatty liver in 20% of otherwise completely healthy young adults with fibrosis (evaluated using FibroScan) present in 2.5% [17].

The prevalence of NAFLD appears to increase with age and in general, boys are more at risk [14, 18, 19]. Ethnic variations are also important; Hispanic children and adolescents have a greater risk of NAFLD compared to Caucasians. Black, non-Hispanic CYP are less susceptible despite a higher incidence of insulin resistance [13, 14, 19]. Both genetic and environmental factors are likely to be involved in ethnic distribution. Familial clustering is also seen [20, 21].

Rapid advances in the field of genetics including the ability to perform Genome wide association studies (GWAS) have greatly contributed to our understanding of NAFLD susceptibility. Single nucleotide polymorphisms (SNPs) in DNA (resulting in the altered expression of a gene or altered protein function) and other epigenetic modification influence the phenotype of this polygenic disease [22]. In both GWAS and candidate gene studies, variants in Patatin-like phospholipase domain-containing protein (PNPLA3; adiponutrin) variant I148M, the Transmembrane Superfamily 2 (TM6SF2) variant E167K, and in GCKR (Glucokinase regulatory protein) and MBOA7 (membrane bound O-acyltransferase domain containing 7), amongst others most consistently convey a susceptibility to NAFLD in both adults and children [23–26].

The presence of obesity amplifies the effect of the variants [27]. Cumulative risk of several variants is also relevant. In a study of 450 children the combination of variants in *PNPLA3* rs738409, *TM6SF2* rs58542926, *GCKR* rs1260326 and *MBOAT7* rs626283 explained 19% of Hepatic fat fraction (HFF%) variance as quantified by MRI with amplification in the presence of obesity and overweight [28].

Antenatal programming of a child's liver to injury due to lipid accumulation, oxidative stress and innate immune dysfunction may play also a role in the susceptibility to NAFLD [29].

In an animal model, the effect of a high fat diet (HFD) in dams can be seen in the predisposition to developing fatty liver in offspring. A cumulative effect can be seen when the pup offspring of HFD dams are fed with a methionine choline deficient (MCD) diet [30]. An alteration of DNA methylation and a decrease of microbiome diversity in the gut was found possibly to mediate the effect. In mice, maternal obesity and a post weaning high fat diet were independent risk factors for steatosis and steatohepatitis and fibrosis at 12 months with a significant increase in liver injury when both risk factors were present [29]. A macaque model of HFD prior to breeding and during pregnancy showed similar findings with increased steatosis in the offspring of treated mothers [31].

The equivalent antenatal priming of the liver in humans may result in a more severe phenotype. Antenatal effects of maternal health have been explored in a

study of stillborn infants of mothers with gestational diabetes (GDM) who were found to have steatotic livers in 78.8% of cases versus 17% of those born to nondiabetic mothers [32]. Live born infants to mothers with GDM in another study demonstrated a higher liver fat content on MRI in those born to mothers with GDM than in controls [33]. Adipose tissue deposition occurs in the 3rd trimester, thus excess fetal substrate can accumulate in the liver prior to this in addition to the *de novo* lipogenesis due to a high transplacental glucose supply in infants of diabetic mothers [34]. Sixty percent of mothers are now obese at the time of conception and thus at high risk of GDM [35].

Further evidence of the importance of a healthy pregnancy is that birth weight is associated with the development of NAFLD in childhood in a large cohort [36].

Early nutrition is likely also important in modification of the risk of later NAFLD with observational studies of breast fed infants suggesting that breast feeding likely protective against progression of the disease from simple steatosis to steatohepatitis and fibrosis [37].

The role of maternal obesity, the method of delivery and of early infant feeding may all be mediated in part via the microbiome and a decrease in diversity conveyed to the infant microbiome which is associated with later obesity [38].

Nutrition and physical activity are particularly important environmental factors determining risk of NAFLD, with lifestyle modification as the primary recommendation in the prevention and management of the disease [39, 40]. Excess food intake and lack of exercise contribute to weight gain and contribute to the progression of liver fibrosis and inflammation in patients with NAFLD [41, 42].

Body growth is unique to paediatric population, with higher body weight to calorie requirements, compared to adults. Liver in childhood has lower probability of exposure to toxins like alcohol and other environmental toxins. The complex interaction between nutritional toxins (saturated fats and sugar) with the liver cells of the maturing liver is however less well studied.

Specific dietary factors either protect against or worsen the progression of NAFLD. Food based analyses have suggested that higher meat and fructose intake [43–45] and higher consumption of low-nutrient, high calorie, high salt food [46] are associated with NAFLD. Fructose has been identified as a particular culprit in increasing fat, inflammation and fibrosis. Children and teenagers are the highest consumers of fructose [47, 48], with emerging evidence that this may be implicated in the development and severity of NAFLD possibly through increasing intestinal permeability and translocation of endotoxin [49, 50]. In a population study a Western diet is significantly associated with the development of steatosis at 17 years [51].

Dietary chemical composition of fatty acids may be important factors in lipotoxicity observed in insulin resistance. A study of fish intake and omega 3 fatty acid intake in children with NAFLD revealed a dietary deficiency of both and association with increased portal and lobular inflammation [52].

The association of NAFLD and insulin resistance is clearly established. Periods of maximum insulin resistance during the lifetime include pregnancy and the

preadolescence, particularly in boys. It may be the case that during these periods of maximal insulin resistance, fatty liver develops in susceptible individuals [53].

Differences Between Adult and Paediatric NAFLD

Liver biopsy is still the standard criterion in diagnosis though not commonly undertaken as part of the work up of NAFLD. Histology reveals variation between the pattern of disease found in adults and in CYP. The typical pattern of macrovesicular steatosis, mixed or polymorphonuclear lobular inflammation, ballooning degeneration with Mallory hyaline and a perivenular distribution of fibrosis is classified as Type 1 NASH and seen predominantly in adults [54]. CYP often have a different pattern of disease with greater degree of steatosis, less prominent ballooning and portal rather than pericentral accentuation of inflammation and fibrosis (type 2 NASH) (Table 10.2) [55]. In fact, fifty to seventy percent of CYP with NAFLD may have either a type 2 pattern or a crossover between type 1 and type 2 [56–58]. Type 2 disease when present across paediatric and adult cohorts, is likely to be accompanied by more fibrosis than type 1 NASH [59, 60]. It is not clear if this pattern is due to a separate pathophysiological mechanism, though it certainly seems to be a marker of more advanced NASH.

One possible mechanism of the preferential distribution of disease in younger patients is the result of zonation. Along the liver lobe, the hepatocytes have different functions depending on their location in the lobule. Periportal hepatocytes are more specific for the Krebs cycle and those in the area of the central vein are enriched for cytochrome P450 enzyme activity. The exposure of the liver to dietary components is more marked in zone 1 than in zone 3 (pericentral) [61]. Africa et al. found that in the liver biopsies of 813 children with NAFLD, the presence of periportal (zone 1) steatosis was associated with a younger age and more severe fibrosis. Those with zone 3 fibrosis (the more classical adult Type 1 pattern) were more likely to have significant inflammation or NASH [60].

Portal inflammation was reviewed as a relevant and distinct entity in NASH by the NASH Clinical Research Network (CRN) [59]. A study of biopsies from 728 adults and 205 children found that the presence of portal inflammation in adults was associated with older, female patients with a higher BMI and insulin resistance. In the paediatric group, portal inflammation was associated with younger age, azonal

Table 10.2 Differences in the typical paediatric versus adult histological patterns of NAFLD

	Type 1 pattern	Type 2 pattern
Steatosis	+	+
Perisinusoidal fibrosis	+	−
Lobular inflammation	+	−
Ballooning	+	−
Periportal inflammation	−	+
Periportal fibrosis	−	+

location of steatosis and more advanced fibrosis. There was no association with lobular inflammation in either group. It is not clear if this pattern is due to a separate pathophysiological mechanism, though it certainly seems to be a marker of more advanced NASH. The periportal pattern mirrors that of the ductular reaction which has been reported in NAFLD. The possible epithelial-mesenchymal transition of biliary cells in this process may relate to the pattern of fibrosis seen [62].

It is important to consider the more paediatric pattern of disease as a separate entity, particularly when investigating the pathophysiological mechanisms or putative biomarkers of the disease.

The influence of pubertal changes on the histology of NAFLD has not yet been elucidated, but the prevalence of type 1 NASH versus type 2 NASH rises from those in early to late adolescence.

Noninvasive Biomarkers in NAFLD

The decision 'if or when' to perform a liver biopsy in CYP with suspected NAFLD remains controversial. Liver biopsy in children and adolescents requires admission to hospital and sedation. Risks include bleeding and very rarely death [63]. Repeated biopsy is not a suitable tool for regularly monitoring progression of disease or response to treatment. In addition, the biopsy samples only 1/50,000 of the liver, raising the possibility of sampling error [64].

There has been much focus on the development and validation of noninvasive biomarkers of NAFLD in recent years. There is an urgent need for a less invasive method than biopsy of screening the population, stratifying disease severity and following disease progression.

The pathophysiology and evolution of the condition under scrutiny is an important consideration in the development and evaluation of biomarkers. Most longitudinal cohort studies in NAFLD have shown that prognosis is determined by stage and rate of progression of fibrosis rather than the presence of necro-inflammation [42, 65, 66]. Clinical importance lies with being able to differentiate between no/minimal fibrosis (F0/F1), significant fibrosis (F2), severe fibrosis (F3) and cirrhosis (F4). The presece or absence of inflammation is more controversial, particularly in CYP with type 2 NASH.

Serum Biomarkers

Simple markers such as AST/ALT and GGT are used to determine the presence of disease and guide investigation. We know that in 40% of those with normal liver numbers fibrosis can be present so these simple markers are no sufficient in isolation [67, 68]. A growing understanding of the pathophysiology of the disease has allowed the investigation of more specific, mechanism-based biomarkers [69–71].

Markers of apoptosis/cell death have been shown to be very useful in differentiating simple steatosis from more progressive disease [72]. CK18-M30 fragments have been shown by a number of studies including children and adolescents to correlate well with severity of NASH [73–76].

Numerous other biomarkers of inflammation, oxidative stress and apoptosis are currently under investigation, but few have become routine in the clinical work-ups.

Combinations of simple tests derived from regression analysis of large series of patients include the AST to platelet ratio index [77], the AST to ALT ratio [78], which have been validated in adult NAFLD population with AUROC between 0.67–0.86 for differentiation of severity of fibrosis [79–81]. Algorithms derived from NAFLD cohorts include the BAAT score (consisting of BMI, ALT, age and triglyceride levels) [82], the BARD score (BMI, AST/ALT ratio, diabetes) [83, 84] and the NAFLD fibrosis score (incorporating age, glucose, AST, ALT, BMI, platelets and albumin) [79, 80, 85–87]. These markers do not perform particularly well in children and young people particularly given that age is a part of the algorithm reflecting increased severity of disease in older adults. The same principle cannot be applied to adolescents as early onset of disease and perhaps more rapid progression in childhood onset disease would not be accurately represented.

The European Liver Fibrosis test (ELF) combining hyaluronic acid, procollagen III N-terminal peptide (P3NP) and TIMP1 [88] and has been validated in NAFLD with the addition of several simple markers to improve accuracy [89]. Importantly this test has been shown to correlate well with outcome [90]. Simple markers such as waist circumference and triglycerides were added to a study of ELF in Italian adolescents [91] yielding an AUROC for any fibrosis (0.92), significant fibrosis (0.98) and advanced fibrosis (0.99). There were only 6.5% in the more advanced fibrosis group. The same group developed the paediatric NAFLD fibrosis index (PNFI) in children and young people with NAFLD using logistic regressional analysis with gender, age, BMI, waist circumference, ALT, AST, γGT, albumin, prothrombin time, glucose, insulin, cholesterol and triglycerides [92]. AUROC for fibrosis was 0.85.

Alkhouri et al. validated both the PNFI and ELF in a cohort of 111 children with NAFLD (69% with fibrosis) [93]. The area under the curve for presence of fibrosis was 0.76 for PNFI, 0.92 for ELF and when the two indices were combined: 0.94. It should be noted however that P3PN is a marker of muscle growth and has a different normal range in adolescents than it does in adults. This may lead to a signficant bias in using ELF in the adolescent population.

Non-invasive Biomarkers and Imaging

Ultrasound (US) is a reliable and relatively cost-effective tool to diagnose steatosis >30%, but is not good at detecting fibrosis. Because of the low cost, the absence of radiation exposure and the wide availability, US is often used in screening for NAFLD. The accumulation of fat causes the liver to appear hyperechoic compared with the kidney. This finding is nonspecific and does not differentiate fat from

other substances such as glycogen or indeed in certain cases from inflammation. The sensitivity of US to detect fat infiltration below 30% of the liver is also low [94].

Computed tomography (CT) is rarely used for the assessment of NAFLD in children and young people because of its ionizing radiation exposure. Magnetic resonance imaging (MRI) and spectroscopy are the imaging techniques with the greatest accuracy to determine hepatic fat content in studies of both adults and children [95–98]. MRI Proton Dense Fat Fraction (PDFF) has been compared to liver biopsy. PDFF in those with grade 1 steatosis on biopsy was 9.2% (mean), 15.1% for grade 2 and 26.8% for grade 3 with an ability to distinguish between stages. Other methods include MR elastography which visualises and measures propagating shear waves and has a high sensitivity (>85%) and specificity (>90%) for fibrosis [99]. A combination of both techniques using MRI is in progress and of use in clinical trial as an alternative outcome measure to liver biopsy findings. Cost of this technique may be preclusive however.

There is an emerging literature examining the use of acoustic radiation force-based shear stiffness in NAFLD, an ultrasound based investigation which uses short bursts of high-intensity acoustic pulses that produce shear waves through the liver tissue, the velocity of which correlates with liver stiffness and correlates well with the stage of fibrosis in the condition [100, 101].

Transient elastography (Fibroscan®) has been shown to be a useful method for detection of liver fibrosis. In NAFLD, studies have demonstrated the efficacy of TE in distinguishing severity of fibrosis [102, 103]. A report of 52 CYP with NAFLD has shown an AUROC of 0.977, 0.992 and 1 for distinguishing any, significant and severe fibrosis [104]. Feasibility and reproducibility of transient elastography is an issue when patients have a BMI >30 [105]. An XL probe is available for better accuracy with a high BMI [106].

Non-hypothesis Driven Search for Novel Biomarkers Using New Technologies

The use of relatively new techniques such as proteomics [107–110], glycomics [111, 112], lipidomics and metabolomics in the derivation of panels of biomarkers associated with a disease may also give an insight into pathophysiology of the condition.

So how should adolescents with NAFLD be followed up and what longitudinal monitoring do they need? Clearly those with significant fibrosis need to be transitioned to and followed by adult services to perform surveillance for complications of liver disease. Currently this surveillance is usually with USS, simple blood markers and transient elastography where available. The multidisciplinary team is a key tool in providing the appropriate support to enable long term lifestyle change and the disease reversal. Differentiating those with more severe disease from those who may be followed in the community is not always easy and the potential to progress needs to be recognised in all those with steatosis.

Natural History and Treatment

There are few longitudinal studies of natural history in paediatric NAFLD though case series describe occasional need for liver transplantation as treatment in young adulthood [113, 114]. The rate of progression is not known [115], but a study reviewing paired liver biopsies in 122 children all who had enrolled in the placebo arm of two randomised clinical trials in NAFLD showed that fibrosis progressed in 23% and improved in 34% [116]. In children who present in childhood or adolescence with stage 2–3 fibrosis, the rate of progression may be more rapid than seen in adults [117]. The heterogeneity within the population is not yet well understood but variability in phenotype may be due to underlying genetic susceptibility rather than environmental exposure.

NASH cirrhosis has been reported in children as young as 10 years [12, 114]. Feldstein et al. describe the long term outcome of 66 children with NAFLD over 20 years [118]. Five children who underwent follow-up biopsy, of which 4 showed progression of fibrosis. During the study period two patients required liver transplantation and in both there was recurrence of disease necessitating retransplantation in one.

Management of NAFLD encompasses lifestyle modification, medication or both. Primary prevention is the ideal. In adults, weight reduction of 5–10% body weight consistently leads to normalisation or improvement of serum transaminases and reduced hepatic steatosis, inflammation and fibrosis [119–121]. In CYP weight maintenance can be all that is required as the child or adolescent crosses the height centiles achieving the same effect.

In a meta-analysis of adults with NAFLD, weight loss of 5% or more resulted in improvement in steatosis, whereas ≥7% weight loss resulted in improvement in steatohepatitis and in those with ≥10% weight loss all features of NAFLD were reversed or stabilised [122]. In a prospective study again in adults these outcomes were confirmed [123]. Only 50% of the cohort were able to achieve 7% of weight loss or more, though of note in 94% of those who achieved ≥5% weight loss, the fibrosis stabilised or reversed.

A small number of trials in CYP have verified these outcomes. Weight loss (average 4 kg) in 84 CYP over a 12 months period achieved an improvement in ALT and steatosis on ultrasound [57] - seventy percent of CYP completed the 12-month intervention. A further study of intensive lifestyle intervention in CYP achieved improvement in BMI Z-score with a decrease of 0.1 U ($p < 0.05$) from baseline to one year and decrease in ALT in 69% of the follow up cohort. There was a 53% drop out rate [124]. In a study of 53 CYP comparing lifestyle intervention plus antioxidant, or lifestyle intervention plus placebo, similar improvements have been demonstrated in both groups in terms of steatosis, inflammation, ballooning and NAS score [125].

Control of both quality and quantity of dietary components may be important. A high intake of simple carbohydrates such as fructose with a low intake of polyunsaturated fatty acids correlate with pathogenesis and progression of disease [49, 126].

The type of fat consumed is possibly more relevant than quantity with higher saturated fat and lower PUFA intake associated with IR and NAFLD in some studies [46, 126]. Several small studies of PUFAs in adults and one in children have demonstrated improved liver enzymes and histology in the treatment group [127–130].

Insulin resistance is well recognised as an accompanying feature in 70% of those with NAFLD. Insulin sensitizers have been studied frequently in clinical trials, but without clear benefit in CYP to date. The TONIC trial compared metformin, vitamin E and placebo in 173 CYP with biopsy proven NAFLD [131]. There was no statistically significant difference in the outcome measure (improvement in ALT) in those treated with metformin compared to those with placebo. Other studies of metformin in CYP showed significant improvement in serum ALT and hepatic steatosis as assessed with MR spectroscopy [132] and another lower severity scores of fatty liver on US and a decrease in prevalence of fatty liver disease in the metformin group [133]. Other insulin sensitisers such as thiazolidinediones (TZDs) have the side-effect of weight gain. There have also been concerns about cardiovascular events and diminished bone mass with their use [134]. There are no available data on the safe use of TZDs in CYP though the class of drug has been used in adults with NAFLD with varying results.

Oxidative stress, most likely mediated by accumulation of fat droplets and the low grade inflammatory response accompanying visceral adiposity in the setting of genetic predisposition, is known to occur and perpetuate injury in NAFLD. Antioxidants, most commonly vitamin E have been studied and shown in the adult PIVENS trial to reduce steatohepatitis [135] and in TONIC to reduce ballooning. A significant difference in the main outcome measure (ALT) in the paediatric study TONIC was not found [131].

Current recommendation in adult practice is to use Vitamin E in non-diabetic patients with biopsy proven NASH [136]. The PIVENS study has not yet been adequately validated and thus caution is advised generally. There is no consensus on vitamin E use in CYP with NAFLD.

Ursodeoxycholic acid is another antioxidant which has been used in trials though without consistent effects. Cysteamine bitartrate works by increasing glutathione synthesis. This was used in the CyNCh trial CYP with NAFLD in comparison to placebo over 52 weeks. Though there was an improvement in alanine aminotransferase, the primary outcome of histological improvement was not achieved with statistical significance [137].

The gut microbiome and its relationship to bile acid metabolism is an emerging area for therapeutic targets. Obesity-associated dysbiosis lead to an increased permeability of the intestinal epithelium [138]. In addition, the production of short chain fatty acids mediates the *de novo* triglyceride synthesis, modulation of choline metabolism, lipopolysaccharide production and bile acid metabolism [139]. Manipulation of gut microbiota with probiotics may be an effective way of treating NAFLD [140–143].

Weight loss, whether dietary induced or following bariatric surgery has been found to have a similar effect on the microbiome. Other potential ways in which bile

acid metabolism and its effect on steatosis may be modulated is by using FXR agonists which have been trialled in adults but not yet in CYP with NAFLD [144].

Bariatric surgery (both Roux-en-Y bypass and gastric band) in management of NAFLD can have beneficial effects in the management of NAFLD in adults with improvement in AST, ALT, NAFLD fibrosis score and NAFLD activity score [145, 146]. In children and young people, Manco et al. described a comparison of sleeve gastrectomy to intragastric balloon and lifestyle advice only and found reversal of NASH at 1-year post surgery in 100% of those who underwent sleeve gastrectomy [130].

There are many novel and repurposed therapies currently under investigation in the context of NAFLD. The peroxisome proliferator activated receptor alpha and gamma agonist elafibranor acts as an insulin sensitizer; obeticholic acid is a synthetic agonist for FXR and losartan may have antifibrogenic potentials.

Though there is a major interest in the search for a single effective agent for NAFLD, in reality the heterogeneity of the condition means that individualised treatment is required and everything considered, the most effective treatment for NAFLD is lifestyle modification and weight loss. Adherence to lifestyle change is a major logjam to success of treatment. This is especially the case in adolescence where the young person is almost entirely dependent on their family being involved in treatment. In addition, the need for long term diet and activity changes, the consequences of peer pressure and competing priorities make lifestyle change an even more difficult task.

Social deprivation, a lack of education about healthy lifestyles and cost of fresh, unprocessed foods are all important considerations and not all which can be successfully managed in the context of a clinical lifestyle intervention programme.

Psychosocial Aspects

An important yet underexplored area in the effectiveness of lifestyle change in adolescents is the importance of mental health. The prevalence of depression and anxiety in children and young people and adults with obesity is high [147, 148]. Depression is common in adults with NAFLD with 53% exhibiting subclinical depression and 14% clinical depression, 45% with subclinical anxiety with 25% clinical anxiety [149]. Studies of the quality of life in adults and CYP with NAFLD show that QoL in those with NAFLD is consistently inferior to normal controls. In a survey of 239 children apart of the NASH CRN, children with NAFLD had worse total physical and psychological quality of life scores as determined by the PedsQL questionnaire with fatigue, trouble sleeping and sadness accounted for almost a half of the variance [150]. Obstructive sleep apnoea (OSA) may contribute to daytime somnolence in obesity; non-OSA sleep problems and the pathogenesis of this fatigue have not yet been systematically studied in NAFLD.

Response to lifestyle intervention in NAFLD is significantly less effective in the presence of depression particularly in the context of acute major depressive disorder

[151]. Some studies in adults and even fewer in children have used a psychological approach to lifestyle change in obesity-related disorders [152–154]. This approach included counselling sessions and cognitive behavioural therapy.

Both adult and paediatric studies have drawn a link between depression, inflammation and the coexistence of complications of obesity, most frequently visceral adiposity-associated conditions [155–157]. Immune challenges in these settings can lead to prolonged inflammatory responses [155]. The resulting sickness behaviours, depressive symptoms, and poor lifestyle choices may lead to further inflammation. In a time of such tremendous change as adolescence, the vicious cycle that is perpetuated is compounded by a lack of autonomy with dependence on family and peers, poor self-esteem and risk-taking behaviours. Tackling this cycle with effective psychological treatments may halt both the amplified inflammation and depressive symptoms.

Conclusions

Recognising the presence of NAFLD in adolescence and investigating and managing these young people in an age-appropriate manner is a real opportunity to prevent progressive disease through adulthood. Though closely associated with overweight and obesity, genetic and epigenetic factors clearly lead to susceptibility to the disease in the setting of an unhealthy lifestyle. At presentation 15% of children and young people with NAFLD will have bridging fibrosis at presentation. Liver injury is reversible, however, and lifestyle change is fundamental but achievable in less than 50% of those undergoing an intensive programme with dietary advice and support. In part this poor outcome is mediated by the high prevalence of depression and anxiety in adolescents with the disease and in part due to a failure to engage these young people with an effective programme. There is a growing industry in treatments which target one of more pathophysiological process involved. Stratifying patients with NAFLD according to their susceptibilities and stage of life and recognising comorbid mental health problems will facilitate individualised therapy and hopefully more successful outcomes.

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Chapter 11
Portal Hypertension

Tassos Grammatikopoulos

Abbreviations

BA	biliary atresia
CEC	circulating endothelial cells
CLD	chronic liver disease
CPR	clinical prediction rule
CSPH	clinically significant portal hypertension
CSV	clinically significant varices
CYP	children and young people
ECM	extracellular matrix
EHPVO	extra hepatic portal vein obstruction
eNO	endothelial nitric oxide
EST	endoscopic sclerotherapy
EV	oesophageal varices
EVL	endoscopic variceal ligation
GAVE	gastric antral vascular ectasia
GI	gastrointestinal
HO-1	haeme-oxygenase-1
HOMA-IR	homeostatic model assessment for insulin resistance
HVPG	hepatic venous pressure gradient
IFALD	intestinal failure associated liver disease
KVaPS	King's variceal prediction score
LSM	liver stiffness measurements

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LSPS	liver stiffness prediction score
LT	liver transplantation
MELD	model for end stage liver disease
MR	magnetic resonance
MRB	meso-Rex bypass
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
NO	nitric oxide
NSBB	nonselective beta blockers
OGD	oesophagogastroduodenoscopy
PCMRI	phase contrast magnetic resonance imaging
PHT	portal hypertension
PVT	portal vein thrombosis
SSM	spleen stiffness measurements
SVT	splenic vein thrombosis
TIPSS	transjugular intrahepatic portosystemic shunt
US	ultrasound
VITRO	von-Willebrand factor antigen thrombocyte ratio
VPR	varices prediction rule
VPS	variceal prediction score
vWF-Ag	von Willebrand factor antigen

Key Points for Adult Hepatologist

- Children and young people (CYP) with severe portal hypertension (PHT) are at risk of gastrointestinal (GI) bleeding from gastro-oesophageal varices and portal enteropathy.
- Monitoring of hypersplenism is essential and early referral for surveillance endoscopy may prevent future decompensating GI bleeding.
- Increasingly many paediatric liver centres use surveillance endoscopies to monitor PHT and will also prophylactically treat high-risk varices.
- Non-invasive markers of PHT can be used to identify patients at risk of developing GI bleeding. A combination of imaging techniques and serum biomarkers may offer the greatest predictive ability for PHT in the future.
- Surgical bypass options in CYP with PVT should be considered early in the management of PHT to avoid future complications.

Introduction

Portal hypertension (PHT) is the term used for increased pressure within the portal venous system. The increase in pressure results from altered blood flow either at a pre-hepatic (e.g. portal vein or superior mesenteric vein thrombosis) [1],

intrahepatic—subcategorised into pre-sinusoidal (e.g. congenital hepatic fibrosis, schistosomiasis), sinusoidal (cirrhosis), post-sinusoidal or at post-hepatic level (e.g. Budd-Chiari Syndrome, hepatic vein occlusion, right heart failure) (Fig. 11.1). An important clinical distinction is the presence or absence of cirrhosis. The rate of PHT secondary to EHPVO in children has been shown to vary greatly, with ranges from 7% to >50% [2]. Some geographical variations in aetiology of PHT have been described, but EHPVO and portal cavernoma is consistently more prevalent in children than in adults (Fig. 11.3d).

Normal pressure within the portal system ranges normally between 5–10 mmHg [3]. Portal hypertension is defined as portal venous pressure of >10 mmHg. Varices are abnormal venous communications between portal and systemic circulation that develop to decompress the portal venous system. The varices commonly develop in the lower oesophagus, stomach and rectum. Gastro-oesophageal varices are more prone to bleeding due to their position and exposure to food and acid, while varices in other sites like splenorenal or in the retroperitoneal region are less likely to bleed. The hepatic venous pressure gradient (HVPG), normally 1–4 mmHg, is the current widely acceptable surrogate marker of PHT in adults with pressures >5 mm Hg indicating sinusoidal hypertension. HVPG, measured via interventional venography, can also differentiate the origin of PHT as HVPG is normal in pre-sinusoidal PHT and raised >5 mmHg in sinusoidal and post-sinusoidal PHT. A pressure

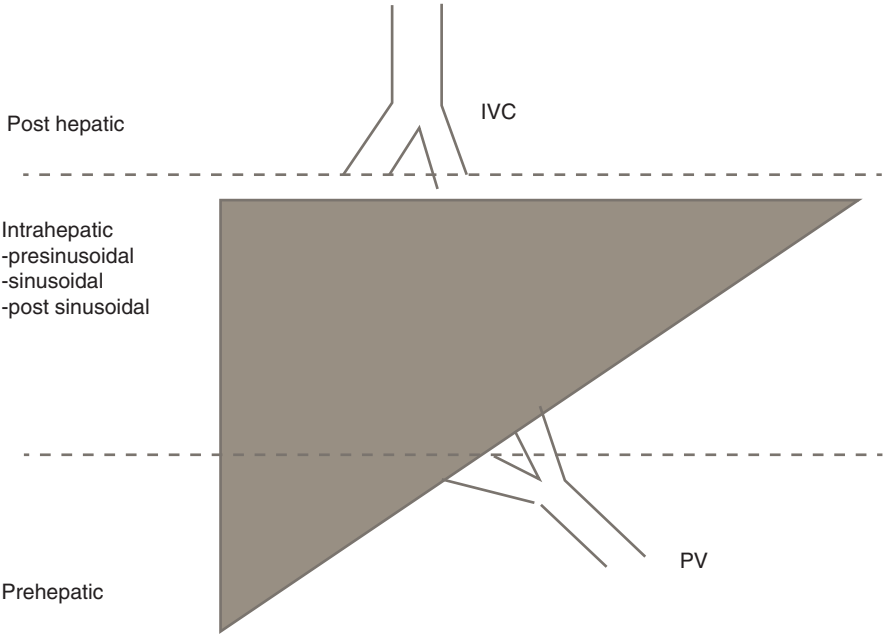

Fig. 11.1 Portal hypertension classification: (i) prehepatic (Portal vein thrombosis), (ii) intrahepatic (chronic liver disease) and (iii) posthepatic (Budd-Chiari syndrome)

gradient >10 mmHg is associated with clinically significant varices and > 12 mmHg with high risk of GI bleeding in adults, but there is no linear correlation with the risk of bleeding [4]. In children the invasive nature of procedure has limited the utilisation of such tools in the objective measurement of portal venous pressure plus there is no large data on HVPG in healthy children and in those with PHT. In paediatrics, PHT diagnosis is commonly based on clinical/biochemical findings of PHT complications such as splenomegaly and thrombocytopenia, or radiological evidence (Fig. 11.3). Criteria of clinically and/or radiologically confirmed splenomegaly and persistent thrombocytopenia (platelet count below $150x10^9$) are commonly used for patients to be offered surveillance endoscopy.

Although there is a degree of inter-observer variation amongst endoscopists in the grading of varices [5] the overall accepted classification is: grade 0: no oesophageal varices; grade 1: small and non-tortuous oesophageal varices; grade 2: tortuous oesophageal varices, but occupying less than 1/3 of the distal oesophageal radius; and grade 3: large and tortuous oesophageal varices covering more than 1/3 of the distal oesophageal radius [6]. The presence of red spots and wales markings along with gastric varices either at the fundal or the lesser/great curve are associated with the higher risk of GI bleeding (Fig. 11.2). Other endoscopic signs of PHT include presence of gastropathy manifesting with vascular congestion, oedema and gastric antral vascular ectasia (GAVE) [7]. There is a consensus amongst paediatric endoscopists in the endoscopic grading of medium and large size varices but there is ongoing work on variceal classification (personal communication) [6].

Gastrointestinal (GI) bleeding from a ruptured varix is the most common symptom of PHT. GI bleed may present as haematemesis or melaena; this is commonly the first symptom of previously undiagnosed PHT. Varices that are ≥ grade II or grade I with red wales, as per UK national guidelines, are clinically significant varices (CSV) and are at a greater risk of bleeding [8, 9]. The risk of GI bleeds in children with PHT is significant, with one study showing a risk as high as 75% over 12 years without treatment [10]. In children with biliary atresia (BA) and their native liver oesophageal varices are found in between 30–50% by 10 years of age.

There is a lack of prospective data on the mortality associated with first variceal bleed, which has recently been reported as between 1–3% [11]. A recent study highlighted, however, that life-threatening complications from a GI bleed were reported in up to 20% of those who had cirrhosis [11, 12]. The overall mortality of children following a GI bleed with an underlying chronic liver condition, such as BA, is higher due to ensuing decompensation of their liver disease, while children with PVT, if adequately managed, have a much better outcome [13]. Variceal bleeding in children with chronic parenchymal liver disease usually becomes an indication for liver transplantation. There is no current consensus about indication for performing diagnostic endoscopy in children with chronic liver disease [14], although many centres will perform surveillance endoscopies to directly visualize and often prophylactically treat varices [15]. Due to the risks and expense of surveillance endoscopies in children, non-invasive screening tests, markers and/or scores are essential to optimise specificity to its maximum potential, in order to balance the risk of PHT and the procedure itself.

The variceal size and its association with the risk of bleeding have been mainly studied in children with BA [8, 9]. The timing of GI bleeding varies between 1 [8] and 5 years of age [16]. Endoscopic band ligation is a safe and highly effective

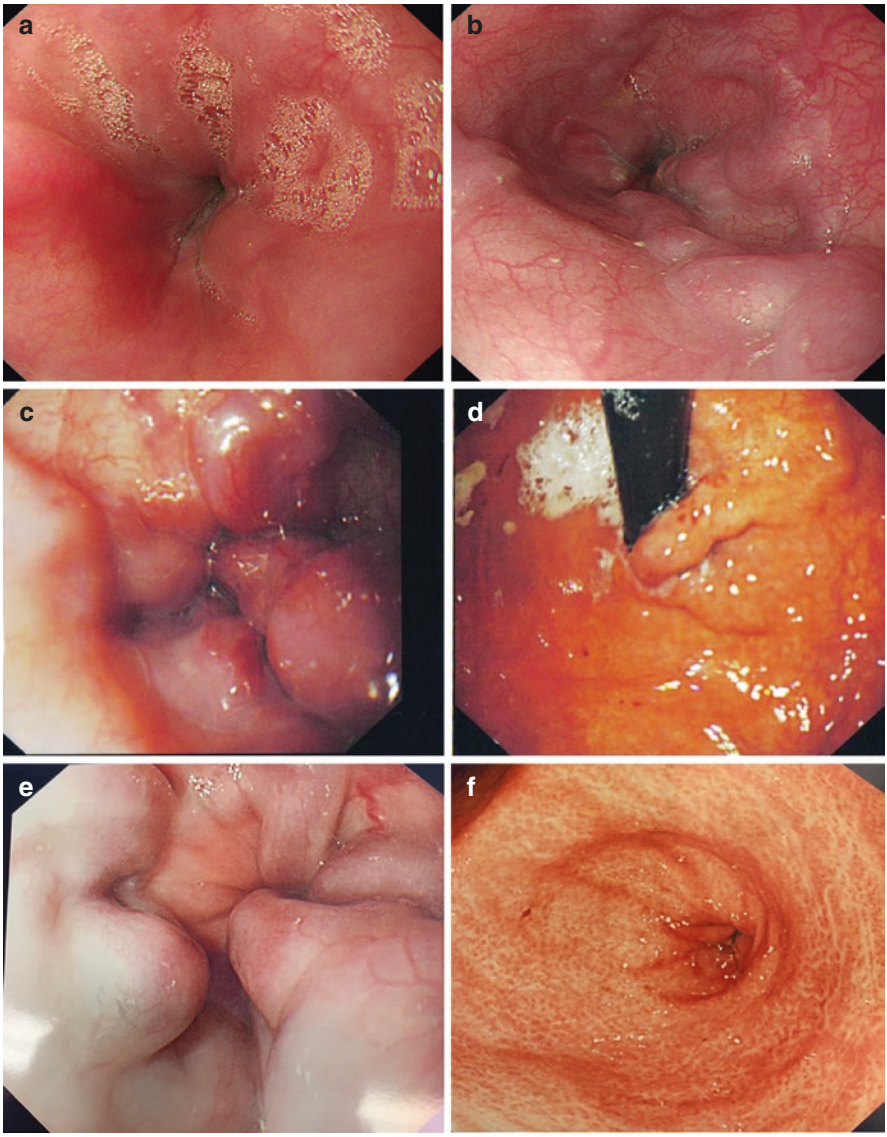

Fig. 11.2 Endoscopic appearances of gastroesophageal varices in adolescents with PHT. (**a**) grade I oesophageal varices flattening on insufflation, (**b**) grade II oesophageal varices non flattening on insufflation, (**c**) grade III oesophageal varices occupying >2/3 oesophageal diameter and touching in the middle, (**d**) gastric varix with red stigmata, (**e**) well covered oesophageal varices grade II and (**f**) gastric antral vascular ectasia and severe gastropathy

procedure shown in a prospective study of 39 children who underwent primary prophylaxis [17]. In a study from King's College Hospital, there was a further bleeding episode in 6% of patients despite the endoscopic surveillance and treatment. Six of these 7 patients presented with bleeding at the time of the first endoscopy. There are no adequately powered, randomized or even prospective studies in children with

CLD to guide the best treatment modality [18]. There is also a lack of prospective data on the mortality and morbidity associated with first variceal bleed, which is currently estimated around 1% [11].

PHT Complications

The major life-threatening complication of PHT is GI bleeding with most PVT children having a GI bleed in the 1st decade of life [1, 19]. Other complications include splenomegaly and thrombocytopaenia, ascites, increased intestinal permeability [20], hepatic encephalopathy [21], hepato-pulmonary syndrome and porto-pulmonary hypertension [22], growth failure [23], vascular coagulation [24], biliopathy [25], endocrine abnormalities/delayed puberty and overall poorer quality of life [26, 27].

The control of PHT may be achieved with pharmacological agents, therapeutic endoscopy, interventional radiology or surgery [28].

Quality of Life

In a study by Krishna et al. children with PVT had a poorer Quality of Life (QoL) scores in physical, emotional, social, and school-functioning health domains. The main variables affecting QoL were splenomegaly and growth retardation. Although variceal eradication did not have a favourable effect, shunt surgery did show a trend towards significance in improvement of physical, psychosocial, and total QoL scores [27]. Wong et al. reported a comparison study on QoL of young adults with BA utilising the Short Form-36 Health Survey version 2.0. The authors identified 2 subgroups (native liver or post LT) and a healthy control group and found no statistical significance between the LT patients and those with native liver in the norm-based scale scores of the various sections. Furthermore, the BA patients who were documented to have active complications (PHT incidence in 47–66%) had a significantly lower vitality score (50.7 vs 57.5, P 0.015, CI 1.5–12) [29]. In contrast, a larger study of BA patients with their native livers reported to have no statistically significant differences in Health Related QoL questionnaires as BA patients who had undergone LT. The authors acknowledged that a significant proportion of children with evidence of more advanced liver disease and worse PHT did not complete the questionnaires, which may have skewed their results towards better QoL [30].

Endoscopic Therapy

Recent recommendations in PHT based on the Baveno VI consensus are that children ‘would be considered’ for surveillance OGD based on splenomegaly (Fig. 11.3a, c) and thrombocytopaenia with intention to treat depending on the

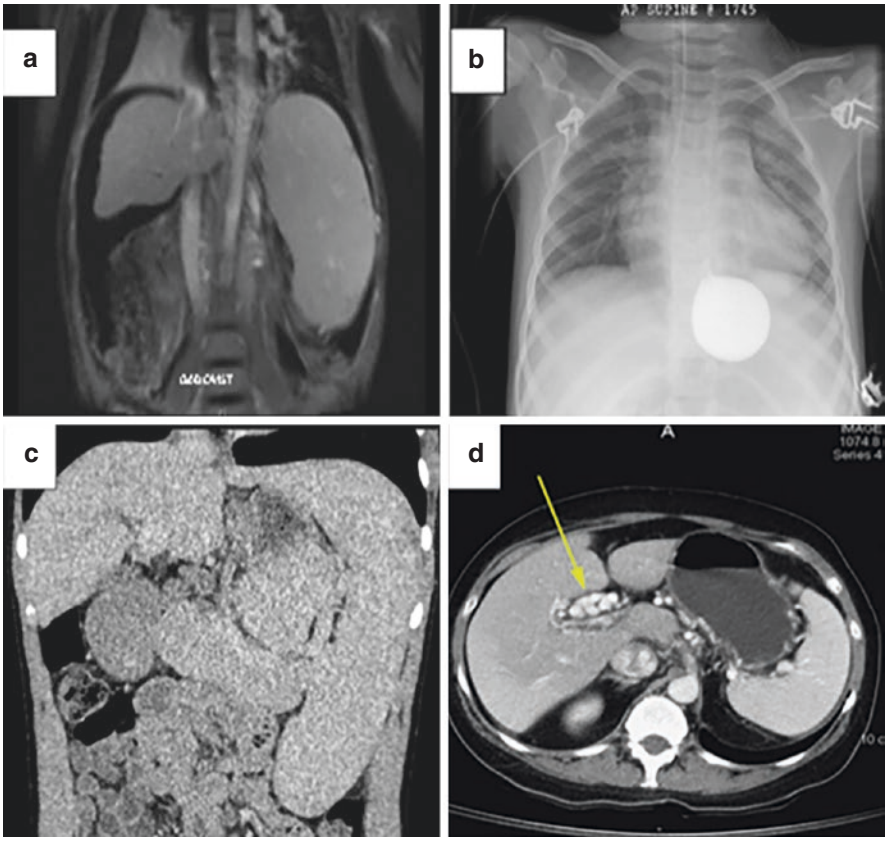

Fig. 11.3 MRI appearances of an adolescent with liver cirrhosis, ascites and splenomegaly (**a**). Chest X-ray image of a patient with inflated Sengstaken-Blakemore gastric balloon for management of variceal bleeding (**b**). MRI imaging of a young person with Joubert's syndrome with fibrotic liver and significant splenomegaly (**c**). MRV imaging of a child with PVT and formation of portal cavernoma (arrow) with ascites following a GI bleed (**d**)

grade of varices [14]. There are 2 options for endoscopic treatment: endoscopic sclerotherapy (EST) or endoscopic variceal ligation (EVL). EST involves variceal injection with a sclerosant agent causing it to stop haemorrhaging and shrink over time. EVL involves cutting off the blood flow to the varix by applying a rubber band tightly around it with subsequent thrombosis of the varix. Both EST and EVL have been shown to eradicate varices with a 90% success rate [31, 32]. EVL is now used more commonly, as it is an easier and safer modality. A randomized trial comparing the two procedures showed significantly lower mortality and less complications, while providing similar efficacy for active bleeding and recurrent GI haemorrhage [33]. More recently data on endoscopic ultrasound variceal management in adults are emerging, but there are obvious size limitations in small children [34–36].

Both options are associated with some risk and a small procedural mortality. EVL appears to have a higher risk in young children because of the risk of entrapping the full oesophageal wall thickness in the band, causing ischaemia. On the other hand EST has been reported to potentially cause major complications such as ulceration and stricture formation [37] with also a risk of bacteraemia [38].

Primary Prophylaxis

Primary prophylaxis before the first GI bleed using endoscopy or NSBB is an accepted modality of management in adults with PHT [4]. However, there is little consensus amongst paediatric liver centres on the role of surveillance endoscopy and different approaches are adopted in their management. While 30% of paediatric hepatologists would not perform a surveillance OGD in children with PHT and splenomegaly, about 50% would not consider providing endoscopic primary prophylaxis [39]. However, recent international survey of specialised paediatric liver units showed that 70% of paediatric centres would perform surveillance OGDs and instigate primary prophylaxis [40]. According to current recommendations for children with PHT, based on the Baveno VI consensus, children 'would be considered' for surveillance OGD on the basis of hypersplenism with intention to treat depending on endoscopy findings [14]. The decision for a surveillance OGD in children is based on either evidence of splenomegaly on the background of chronic liver disease (CLD) or radiological evidence of PHT with limited data on predictor models for bleeding risk or presence of varices [41].

Due to the limited data available on children with PHT concerning the efficacy and safety of primary prophylaxis either by non-selective beta-blockers (NSBB) and/or endoscopic therapy, there is currently a need to determine if prophylactic endoscopic treatment can result in a reduction of GI bleeds and improve overall outcome [18].

Pharmacological Therapy

A well-established pharmacological treatment in adults involves NSBB (often propranolol and more recently carvedilol), in order to decrease the pressure within the portal system [42]. These medications work by reducing cardiac output through β1 receptor blockage and increasing splanchnic vasoconstriction via β2 blockage. NSBB are well established in adults with confirmation of potential therapeutic effect following HVPG measurements [4] aiming to reduce it below 12 mmHg or by 20% from initial pre-treatment measurement. Newer agents such as carvedilol appear to be more potent [4]. In children though, there is a lack of prospective randomised controlled trials investigating the potential safety and efficacy of NSBB [18]. The combination of NSBB and secondary endoscopic prophylaxis did not show any significant benefit to a small number of children [43]. In studies from

adults with medium/large varices of NSBB plus EVL the results have been inconclusive and, given the risk-benefit ratio with the combined therapy, American and European Associations for the Study of Liver Disease consensus was that combination EVL and NSBB was not recommended in this group [44].

Other possible pharmacological therapies reducing portal pressure in cirrhotic adult patients under consideration include statins, which have shown to increase endothelial nitric oxide (eNO) synthase affecting sinusoidal endothelial and stellate cells and subsequently liver fibrosis and PHT [45]. Angiotensin II receptor antagonists (losartan) have also been studied in the past, but when compared with NSBB in a randomised controlled trial did not show a beneficial effect in HVPG reduction [46].

Shunt Surgery

The management of PHT via surgical procedures has not been well standardised and fully adopted by paediatric liver centres worldwide. Possible surgical options are different between children with PVT and those with CLD. Children with extrahepatic PVT may be considered for Meso-Rex Bypass (MRB) procedure involving the surgical connection via interpositional autologous vascular graft (usually IJV) between the superior mesenteric vein and the Rex recessus, a remnant of the ductus venosus once they achieve body weight > 8 kg [47, 48]. The patients must fulfil specific criteria including absence of an underlying liver disease, patency of the intrahepatic porto-venous system demonstrated on axial imaging and/or portal venography and absence of inherited prothrombotic conditions.

Recent consensus guidelines suggest that MRB should be used prophylactically where there is favourable anatomy and suitable surgical expertise. Where anatomically possible this is the favoured surgical option for the early management of PHT [49]. There is limited data on the long term prognosis, medical and psychosocial outcome of these children to critically appraise its full efficacy and potential [50]. Once the patients reach adolescence or early adulthood their liver changes may become irreversible, and the surgical outcome could be further complicated.

In children, with refractory PHT due to CLD, TIPSS has been rarely considered with direct transhepatic portal vein puncture via the transjugular route and insertion of a shunt to establish porto-systemic communication with reduction in PV pressure. Current studies in children remain limited in patient numbers and with only short term follow up available, most often utilising TIPSS as a bridge to LT [51].

Acute Variceal Bleeding

Portal hypertension is the commonest cause of severe gastrointestinal bleeding in children, which may be the first presenting feature of liver disease [14]. Families of children with varices (or suspected varices) should be provided with a written plan for this

scenario and all paediatric gastrointestinal units should have an established local pathway for its management. The bleeding is usually acute with haematemesis or melaena, but also may present insidiously with anaemia. There is often a preceding history of an intercurrent illness and occasionally fatigue and non-specific abdominal pain.

Children with suspected variceal bleeding should be urgently admitted to hospital, permanent intravenous access established, and samples taken for haemoglobin, coagulation profile, electrolytes, blood culture and blood cross matched (20 ml/kg).

Blood and fluids should be transfused to achieve normal heart rate and blood pressure while maintaining a haemoglobin in the range of 70–90 g/l. Over-transfusion should be avoided as it may increase intravascular pressure, but severe coagulation disturbance (INR > 1.5) and thrombocytopenia (<100 x 10^9/l) should be proactively corrected [52].

Antibiotic prophylaxis with gram-negative cover has been shown to decrease mortality and rebleeding in adults with cirrhosis, hence antibiotic therapy compatible with local antibiotic stewardship policies is also recommended in children [53], but the evidence is not so clear in cases with PVT.

The acute management of variceal bleeding is similar in children with intestinal failure associated liver disease (IFALD) and/or PVT, who may be bleeding from intestinal stoma varices [54].

Pharmacotherapy for Acute Variceal Bleeding

Pharmacotherapy should be started on admission, prior to endoscopy and continued for 2–5 days [53]. Somatostatin analogues such as octreotide have been shown to be effective and safe with early control of active bleeding in most cases. The most common dosage regimen is 1 mcg/kg as slow bolus followed by 1–3 mcg/kg/hour. An alternative treatment used as standard practice in adult patients is Terlipressin**.** This is a synthetic analogue of Vasopressin with an intrinsic vasoconstrictive effect followed by a sustained portal haemodynamic effect as it is converted to vasopressin. There are no large studies on the use of Terlipressin in children and it has been used *pro rata* to the adult regimen of 2 mg IV followed by 1–2 mg every 4–6 hours for 48–72 hours maximum by some specialist liver units including ours [52]. Saxena et al. reported on its safe use in the management of hepato-renal syndrome in patients admitted to our Intensive Care Unit with favourable impact on kidney function but not on its effect on PHT [55].

Endoscopic Treatment Pathway

Endoscopy should be carried out as soon as possible, and ideally within 24–36 hours after bleeding episode, provided the patient is haemodynamically stable and in a unit with experience in the management of PHT. This should be undertaken under general anaesthesia by a team capable of undertaking therapeutic endoscopy.

Management pathways should reflect the availability of local expertise and in individual centres this may require collaboration with local adult gastroenterologists in extreme circumstances or for planned transfer of patients, after stabilisation, to paediatric hepatology units with therapeutic endoscopy facilities.

EVL [56] is the preferred technique in children with oesophageal varices. However, it may not be possible to pass the loaded banding apparatus in some small children usually under 10 kg of body weight. As a result, EST with ethanolamine should continue to be available in the acute management of bleeding with the awareness of the potential risk of oesophageal ulcerations, strictures and perforations. Gastric varices should be managed by endoscopic injection of tissue adhesive (such as cyanoacrylate) - with the similar possible complications, or thrombin [57].

Following the endoscopic therapy patients should fast for at least 2 hours and solid feeding withheld until liquids are tolerated. Sucralfate or antacid drugs should be given for 5–7 days.

Initial failures with combined pharmacological and endoscopic therapy are probably best managed by a second attempt at endoscopic therapy, while the use of TIPSS may also be considered, depending on local expertise and facilities.

Balloon tamponade is highly effective and has been shown to control bleeding in up to 90% of patients, but re-bleeding is common when the balloon is deflated. Balloon tamponade should only be used in an intubated and sedated patient, following a failure to conventionally control active bleeding, as a bridge to definitive treatment, or to facilitate transfer to a specialist centre [52]. Sengstaken-Blakemore tube could be used for tamponade under guidance from specialist liver units (Fig. 11.3).

Haemostatic spray is a simple technique where powder is sprayed under direct vision through the endoscope onto actively bleeding lesions, where it subsequently forms a mechanical haemostatic barrier in cases of oozing portal gastropathy. There is limited experience with the technique in childhood, but it appears safe and is easy to use, particularly if experienced interventional endoscopists are not immediately available [58]. Haemostatic spray cannot substitute the need for EVL or EST but can be useful in gastric erosions or oozing portal gastropathy.

Recombinant factor VIIa may be considered in intractable bleeding cases resistant to conventional treatment to optimise coagulation factors [56].

Secondary Prophylaxis

Following a variceal bleed, recurrence is likely with subsequent bleeding rates as high as 80%. Hence all children should receive secondary prophylaxis [52]. Several techniques are available including endoscopy, pharmacotherapy, TIPSS and surgery. Determining factors in individual cases should include local facilities and expertise, the nature of the underlying disease and whether it remains compensated. For children with compensated chronic liver disease, EVL is the treatment of choice.

It is recommended to carry out EVL every two to four weeks following the first variceal bleed to ablate gastro-oesophageal varices. Subsequent follow up endoscopies are recommended at 6–12 monthly intervals with recurrent varices being ablated where possible [57].

Sports and Travelling with Portal Hypertension

There is minimal data on this specific clinical dilemma and the most common advice from paediatric hepatologists is to discourage CYP with PHT from contact sports with physical impact such as football, hockey, skiing, rugby, martial arts and boxing. In a recent questionnaire splenic rupture in CYP with PHT and splenomegaly was rare as reported by paediatric hepatologists from 30 tertiary academic centres in the United States, Canada, and the United Kingdom [59]. The reported splenic rupture cases were mostly related to falling (and not to participation in sports). In respect to the use of a spleen guard during sports there is variation in the recommendations and most patients find it uncomfortable and restrictive. Physicians should also consider the risk of undiagnosed splenic aneurysms which can predispose to bleeding and as such axial imaging would be recommended to delineate the intra-abdominal vascular anatomy.

Unfortunately, there are only isolated case reports on the issue of air travel for CYP with PHT and varices and these include only those who have bled. The general consensus is that CYP should avoid flying very close to an endoscopic treatment session for the risk of early rebleeding, but overall, there are no clear guidelines on the issue. Patient support groups are sharing individualised experience on social media and web platforms, but the evidence is simply not there to provide consistent advice for or against flying. Advice on travelling should also be based on the availability of medical facilities in the travelling destination and information should be sought well in advance to minimise unnecessary risk [60].

Fertility and Pregnancy

Pregnancy in women with cirrhotic portal hypertension is not common due to hypothalamic pituitary dysfunction leading to anovulation and hypogonadotropic hypogonadism [61]. When pregnancy does occur though it is considered high risk, mainly due to the possibility of variceal haemorrhage (15–34% in NCPHT and up to 42% in those with cirrhosis), reduced blood counts due to hypersplenism, development of splenic artery aneurysm (SAA), porto pulmonary hypertension or hepatopulmonary syndrome [62]. Variceal bleeding in these young women is also associated with maternal mortality of 18–50%. There are reports on the impact of PHT in pregnancy in women with liver cirrhosis [63–65], non-cirrhotic PHT [66] and those with PVT [67]. Hemodynamic changes such as increased blood volume and pulse pressure, along with compression in the inferior vena cava by the enlarged uterus, may divert blood to the azygous system and subsequently formation of

GOV. Cirrhotic portal hypertension can be complicated further by hepatic decompensation and encephalopathy (10%), hepatorenal syndrome, ascites and bacterial peritonitis. Maternal death has been reported in 1.6% and foetal mortality is reported in 10–66% of patients with cirrhosis with a 20% risk of miscarriage [68] and around 20% risk of premature birth.

If the young woman is already on NSBBs these may be continued but close monitoring is recommended as there is risk of intrauterine growth retardation (IUGR), neonatal bradycardia and hypoglycaemia. Carvedilol may be the preferable option as it has not been associated with IUGR and it has been shown to be more effective at reducing the hepatic venous pressure gradient than other NSBBs [69].

Portal hypertension peaks in the 2nd trimester and regular monitoring of blood indices, liver function tests and liver USS is recommended. The risk of variceal haemorrhage is higher during the 2nd and 3rd trimesters, and during the 2nd stage of labour, and may be complicated further due to hypersplenism and/or coagulopathy. The current recommendations are that all pregnant women with portal hypertension should have a routine surveillance endoscopy in the 2nd trimester. If variceal bleeding occurs endoscopic variceal band ligation is deemed safe and somatostatin analogues (Octreotide) have been used throughout pregnancy although there is possible effect on foetal growth and its use is advised only if potential benefit outweighs risk to the foetus [70].

There are no recommendations regarding mode of delivery, which should be based upon obstetric indications and severity of PHT. Elective Caesarean section is recommended in young women with large GOV and regional anaesthesia may also be preferable. Caesarean section may though be complicated by the presence of dilated varices on the anterior abdominal wall and an early discussion between professionals is advisable on mode of delivery, timing of endoscopy and the role of splenic artery ligation to improve platelet count [71]. Postpartum haemorrhage has been reported in 7–26% of women with portal hypertension.

In young women with compensated cirrhosis, there is no restriction on the use of any hormonal contraceptive method [61], but in those with decompensated cirrhosis and PHT and Budd-Chiari syndrome such contraception is not recommended. In women with severe decompensated cirrhosis the risks of hormonal oral contraception outweigh the benefits with progesterone only contraceptives, such as Depot medroxyprogesterone acetate, being the preferred choice [72]. There are also reports of high risk of spontaneous bacterial peritonitis with the use of intrauterine contraceptive devices and these should be used with caution (See more in Chap. 20).

Non-invasive Prediction Tools of Portal Hypertension

Serum Biomarkers

To reduce the number of unnecessary endoscopies performed on CYP a non-invasive method that can predict the presence of PHT and/or varices is needed. A variety of methods have been proposed as potential non-invasive markers of PHT. Serum

biomarkers have been investigated as a potential area to identify a non-invasive marker that could be used to predict the presence and grade of gastroesophageal varices. The pathophysiology of PHT involves a complex relationship between the liver, the spleen and the vascular system that connects them. Biochemical changes associated with each aspect of the pathophysiology may provide useful information for the diagnosis and monitoring of PHT. Changes in serum biomarkers associated with liver fibrosis, immune activation, vascular epithelium, and haemostasis have been looked at as potential markers of PHT.

In liver cirrhosis activated Kupffer cells release soluble CD163, a scavenger receptor, which is involved in clearing haemoglobin-haptoglobin complexes. The process involves the enzyme haeme-oxygenase-1 (HO-1), which is specific to Kupffer cells [73]. It has been reported that soluble CD163 was independently correlated to HVPG measurements in cirrhotic adults [74], but also associated with an increase in variceal bleeding [75]. Other markers of inflammation such as IL-1β, IL-1Rα, VCAM-1, Fas-R, TNF- β and HSP-70 studied by Buck et al. were significantly correlated with increased HVPG pressures in adults with cirrhosis [76].

Nitric oxide (NO), a molecule with vasodilation properties, and circulating endothelial cells (CEC), a marker of vascular injury, have both been studied as potential markers of PHT. NO levels were found to be elevated in both intra- and extrahepatic causes of PHT [77] and more specifically in CYP with biliary atresia (BA) and choledochal cysts [78, 79]**.** These studies have been able to demonstrate that NO levels are closely correlated with the portal pressure, but did not assess NO's predictive power for the consequences of PHT. Improvement in the NO pathway has been demonstrated via pharmacological inhibition of leptin and subsequent reduction in portal pressure in a murine model emphasizing the role of nutrition in PHT [80, 81]. Age- and size-appropriate nutritional intake and reasonable levels of physical activity can improve the outcome of patients with cirrhosis and/or PHT when studied in the context of conditions such as sarcopenia or malnutrition [82, 83].

Circulating endothelial cells (CEC) are sloughed off from the vascular wall under mechanical stress and are considered a marker of endothelial dysfunction. Their numbers have been shown to be higher in patients with cirrhosis (diagnosed on histological, radiological, laboratory and clinical criteria) compared to controls (73.7 vs. 28.7 cells/4 ml) [84]. Additionally, Sethi et al. identified a combination of CECs with aspartate aminotransferase-to-platelet ratio (termed CAPRI), which distinguished cirrhotic patients from controls with 98% sensitivity, 85% specificity and AUROC = 0.98 [85].

Obesity and metabolic disorders have increasingly been associated with decompensation of liver disease [86]. Pathophysiological mechanisms driving this include insulin resistance that is known to develop with hepatic fibrosis, as well as insulin ability to induce endothelial dysfunction by stimulating the synthesis of NO [87, 88]. A significant correlation between EV and raised homeostatic model assessment for insulin resistance (HOMA-IR) index (measure of insulin resistance) and adiponectin levels has been reported [89]. Furthermore, HOMA-IR was associated with an increased risk of GI bleeding.

In adults, various markers of fibrosis have been proposed and studied as potential predictors of PHT. Although these would not be applicable for PHT secondary to EHPVO, they may be useful in CYP with known chronic liver disease to test for developing PHT. During the process of fibrosis there is an increase in the production and destruction of the extracellular membrane (ECM). Various components of the ECM such as hyaluronic acid, a glycosaminoglycan found in connective tissue produced by hepatic stellate cells, and laminin, a basement membrane glycoprotein have been studied as potential markers of PHT [90–94].

One of the sequelae of PHT is the development of splenomegaly, and thrombocytopenia as a result of platelet sequestration. Although in adult patients platelet count has been shown to be an unreliable predictor of EV, in several paediatric studies isolated reduced platelet count has been able to successfully predict the presence of EV with various optimal cut-off values [95]. Also in CYP, since there is variation in normal spleen size based on age and height, the spleen size Z-score may be considered for a more reliable assessment of splenomegaly [96].

Von Willebrand factor antigen (vWF-Ag) is released from dysfunctional vascular endothelial cells, as a result of mechanical stress from increased intraportal pressure. It was initially shown to be elevated in patients with cirrhosis and was used to predict clinical outcome [97], including as a potential marker of PHT and found to be significantly elevated in patients with EV [98]. The vWF-Ag was also combined with platelet count to develop a novel prediction score, the Von Willebrand factor antigen/thrombocyte ratio (the VITRO score) [99].

Variceal Prediction Scores

A number of novel prediction scores have been developed. In adults the most commonly used EV predictors in cirrhosis include aspartate aminotransferase-to-platelet ratio, aspartate aminotransferase-to-alanine aminotransferase ratio, FIB-4 (age x AST/platelet x $(ALT)^{1/2}$), Lok index ($-5.56–0.0089 \times$ platelet $+ 1.26 \times$ AST/ALT $+ 5.27 \times$ INR) and Forns index [7.811–3.131 × (platelet count) + 0.781 × (GGT) + 3.467 × [100] – 0.014 × (cholesterol)] and "Risk Score" [101, 102].

A number of EV prediction scores for CYP have also been proposed. Through multivariate logistic regression Gana et al. developed a clinical prediction rule (CPR) using platelet count, spleen length Z-score and albumin [(0.75 x platelets/SAZ + 5) + 2.5 x albumin] [103]. CPR was able to predict the presence of EV better than any individual marker.

Another recent EV prediction score for CYP was the King's Variceal Prediction Score (KVaPS), which utilizes albumin and equivalent adult spleen size [(3 x albumin)- (2 x equivalent adult spleen size)]. KVaPS was modeled using CYP with chronic liver disease only, but was shown to perform better than CPR with a sensitivity and specificity of 72% and 73%, respectively [104]. Despite this study including 124 CYP, only 89 were actually endoscoped for varices.

The application of CPR in CYP with intra and extra-hepatic PHT, as well as its high AUROC (0.93 and 0.80) make it a promising area of future research. Its use in differentiating presence of any EV and high-risk EV still requires further study as CSV significantly affect management.

Imaging Techniques

In addition to the laboratory biomarkers a number of imaging techniques have been used to assess PHT both in CYP and adults. These methods include ultrasound (US) to measure spleen size, portal vein dilatation and vascular resistance with Doppler, FibroScan measuring liver and spleen stiffness and some others. The majority of the studies have been conducted in adult patients.

It has been shown that spleen enlargement (defined as >1 cm/year) had a higher probability of EV formation in adults with cirrhotic liver disease [105]. In addition to determining the spleen size/diameter, US can be used to monitor vascular and haemodynamic changes within the portal system. One of these changes is the development of porto-system shunting through collateral formation as a diversion route of a high-pressure system. The presence of porto-systemic shunts was shown to be associated with EV, and in a longitudinal study the development of porto-systemic shunts during follow-up was associated with EV formation [106, 107]. Other haemodynamic changes can be measured with Doppler USS, including portal blood flow reversal, congestion index, and portal blood flow velocity [108–111]. Although some of these observations have shown a significant correlation with HVGP, they have not been investigated in CYP to determine applicable cut-offs that could predict PHT [112]. Additionally, inter-observer and inter-equipment variability has been shown to impact the reliability of such measurements [113, 114].

In addition to US, magnetic resonance (MR) technology has been studied in the adult population for its applicability in prediction of PHT. Magnetic resonance elastography (MRE) has been used to determine LSM and SSM in both animal and human models [115, 116]. Raised LSM and SSM, measured by MRE, have been shown to be associated with an increased risk of any varices, while raised SSM has been closely associated with a risk of CSV [117]. A study of only 38 adults with CLD found 100% of those with EV had a SSM ≥ 10.5 kPa [118]. Shin et al. found that both SSM and LSM measured by MRE were associated with EV and high risk EV [119].

FibroScan

The use of FibroScan to measure liver and spleen stiffness (elastography) as a means of predicting PHT has recently become an area of intensive research. In the Baveno consensus meeting in 2015 the working group focused on the stratification of adult

patients developing significant PHT. Amongst other key points, the group recommended the combination of liver stiffness reflected by transient elastography (TE) measurements <20 kPa on 2 occasions and platelet count >150 x 10^9/L to accurately identify adults at a very low risk of having clinically significant varices and therefore avoiding screening endoscopy [4]. Most data where the recommendations were stemming from, were extracted from studies on adult patients with virus-induced (Hepatitis B or C) advanced but compensated liver disease, somewhat different to the paediatric population. This non-invasive method of predicting PHT has attracted a particular interest in paediatrics and prompted several studies looking exclusively at CYP. Although there are several types of elastography techniques, the most commonly studied in CYP utilises TE.

Chongsrisawat et al. found that in CYP with BA liver stiffness measurements (LSM) was significantly correlated to the presence of EV or gastric varices, and that a cut-off value of 12.7 kPa was able to predict the presence of varices (AUROC = 0.89) [120]. Unfortunately, this was a cross-sectional study and unable to comment on how changes in LSM could relate to variceal growth and possibility of bleeding. A study looking at CYP with cystic fibrosis found that a similar cut-off (12.5 kPa) for LSM would have reduced the number of unnecessary endoscopies by two thirds (6 vs. 2) [100]. Another study by Colecchia et al. on CYP with BA found that LSM cut-off of 10.6 kPa was able to predict the presence of EV (AUROC = 0.92) [121]. A major limitation of TE FibroScan is that it is contraindicated in patients with ascites, a common complication of PHT. As a result, studies using TE FibroScan risk selection bias by excluding many with severe PHT.

Spleen stiffness measurements are of particular interest in the paediatric population as they can be used for both intra- and extra-hepatic PHT. A systematic review and meta-analysis identified that SSM was able to detect the presence of EV with 78% sensitivity and 76% specificity [122]. Furthermore, it has found that SSM was able to detect clinically significant EV (defined as ≥ grade 2) with 81% sensitivity and 66% specificity. Of note, the studies reviewed were again in the adult population and included a variety of FibroScan modalities. In adult patients a high SSM was able to detect variceal bleeding [123, 124]. As this study was conducted as a part of clinical practice, where endoscopy was only offered to those with a high suspicion of varices, selection bias meant only those with severe PHT were included. In a paediatric study conducted in our institution CYP SSM was the best predictor of CSV presence, with an optimal cut-off value of 38.0 kPa [125].

Summary

Portal hypertension remains a common and serious complication of CLD and portal or hepatic vein occlusion. There is an ongoing need to better understand the multidimensional pathophysiology of PHT and for novel therapeutic options relevant for young people as so far therapeutic preclinical models targeting intrahepatic vascular resistance have not been very successful in clinical application. The role of

surveillance endoscopy and primary prophylaxis in CYP remains open and non-invasive prediction markers are deemed essential for the management [126]. An ideal prediction marker/scoring system would be one that is applicable for both intra- and extra-hepatic causes of PHT and probably focusing on the markers associated with endothelial dysfunction, as both intra- and extra-hepatic PHT demonstrate endothelial dysfunction as a key part of its pathophysiology.

Although there is significant literature on prediction and management of PHT in adult population it is difficult to directly apply conclusions to CYP and adolescents. The aetiologies of both PHT and chronic liver disease are different between adults and CYP which is reflected across the published studies, as they have often been targeting specific patient groups such as hepatotropic virus-induced cirrhosis of adulthood. There are no adequately powered, randomized or even prospective studies in CYP with CLD to suggest the best screening and management modalities.

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Chapter 12
Cystic Fibrosis and Liver Disease

Dominique Debray

Abbreviations

ALT	alanine aminotransferase
APRI	AST-to-platelet ratio index
AST	aspartate aminotransferase
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
FIB-4	Fibrosis-4 index
GGT	gamma-glutamyl transferase
HVPG	hepatic vein pressure gradient
LT	liver transplantation
MRCP	magnetic resonance cholangiopancreatography
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
PH	portal hypertension
SWE	shear wave elastography
TE	transient elastography
US	ultrasonography

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Key Points

- Liver disease develops progressively in the lifetime of patients with CF with a cumulative incidence of cirrhosis and PH of 10% by age 30.
- Several non-invasive tools to measure liver stiffness as an indirect measure of fibrosis show promising results for the assessment of early stages of liver fibrosis and progression overtime.
- PH is the most significant complication that impacts clinical outcomes.
- Management is directed towards the prevention and treatment of complications of PH.
- As longevity increases in CF, an increasingly complex cohort of patients with multiple comorbidities over time are entering adulthood. This highlights the need for the timely pre-emptive forward planning, resource allocation and training of future multidisciplinary adult CF teams.
- The effects of CFTR modulators on hepatobiliary outcomes remain unknown.

Cystic fibrosis (CF; OMIM 219700) is the most common autosomal recessive disease of the Caucasian population, caused by pathogenic variants in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel expressed in epithelial cells. CF is a multiorgan disease and typical manifestations are chronic and progressive obstructive lung disease, pancreatic insufficiency, diabetes mellitus, malabsorption and malnutrition, liver disease, and infertility in males. Medical advances have dramatically improved the long-term prognosis of patients with CF. Nowadays, the median age of survival is above 40 years and is expected to improve beyond 50 years with the availability of CFTR modulator therapies [1]. Consequently, an increasing number of CF adolescents with liver disease are now entering adult services. Moreover, recent studies suggest the occurence of liver disease in adulthood, highlighting the need for lifelong screening for liver disease [2, 3]. Based on a large cohort of 3328 CF patients with pancreatic insufficiency recruited into the French CF Modifier Gene Study since 2004, the cumulative incidence of liver involvement, defined according to the Debray et al. criteria [4], was found to increase by approximately 1% every year, reaching 32.2% by age 25 years [2]. In this study, the incidence of advanced liver disease i.e. cirrhosis and/or portal hypertension (PH) increased after the age of 5 years reaching 10% by age 30 years [2]. Most of the complex morbidity and specific management such as liver transplantation (LT) occur in adolescents and young adults [5].

In the liver, CFTR expression is restricted to the apical membrane of cholangiocytes lining the intra- and extrahepatic bile ducts. There is increasing evidence

supporting the view that cholangiopathy arising in CF is the result of an ill-adapted innate immune response to endotoxins coming from the intestine that trigger a pro-inflammatory response leading to peribiliary inflammation and fibrosis [6]. Male gender, CFTR *F508del* homozygosity and history of meconium ileus, have been recognized as independent risk factors for developing liver disease in a large cohort of patients recruited into the French CF Modifier Gene Study [2]. It remains, however, to be explained why only one-third of CF patients develop liver disease and why the liver disease shows a great degree of variability in terms of its severity [6]. To date, *SERPINA-1* is the only reported modifier gene, whereby the heterozygous Z-allele mutation of alpha-1-antitrypsin is over-represented in the CF children with liver disease and PH in comparison with the others [7, 8].

Spectrum of Liver Involvement in Adolescents and Young Adults

The prevalence of liver disease in CF remains uncertain since diagnostic criteria do not differentiate CFTR-related hepatobiliary disease from other forms of liver involvement not related to the CFTR defect (Table 12.1).

Table 12.1 Main forms of liver involvement in cystic fibrosis

Spectrum of liver involvement in CF	Frequency (%)
Hepatobiliary involvement	
Focal biliary cirrhosis	20–70 (at autopsy)
Multilobular biliary cirrhosis	7–10
Portal hypertension Sclerosing cholangitis	2–5 Frequent in adults, often silent
Large duct biliary stricture Microgallbladder	Rare 10–40
Cholelithiasis Cholangiocarcinoma Hepatic/biliary abscesses	1–20 (increases with age) Rare Unknown
Vascular	
Obliterative portal venopathy (OPV)	Unknown
Hepatic congestion	Rare
Hepatic steatosis	20–70
Other causes related to: Drug hepatotoxicity Parenteral nutrition Infections Concomitant liver diseases	

Hepatobiliary Involvement

- *Focal biliary cirrhosis* is the most frequent histological lesion ascribed to the CFTR defect in cholangiocytes, resulting from biliary obstruction by inspissated secretions and progressive periportal fibrosis. Most patients are asymptomatic and remain so for life. Liver enzymes are often normal, but ultrasonography (US) of the liver may show a heterogenous appearance of the liver. In minority of the cases, extension of the initially focal fibrogenic process may lead to multilobular biliary cirrhosis.
- *Multilobular cirrhosis* most often manifests with signs of PH such as splenomegaly and hypersplenism. In the largest series of 561 CF patients with cirrhosis and PH, 90% presented by 18 years of age at a mean of 10 years [9].
- *Other biliary manifestations* in CF include biliary dyskinesia, cholelithiasis, large duct biliary strictures, and intrahepatic sclerosing cholangitis [10]. These manifestations are not well described with a consequent unknown prevalence. Symptomatic gallbladder disease requiring consideration for cholecystectomy may occur in up to 4% of patients, the majority of whom are adults. Intrahepatic biliary strictures, similar to those found in patients with primary sclerosing cholangitis (PSC), have been reported mostly in adults, sometimes in association with inflammatory bowel disease [11, 12]. Notably, there is a frequent lack of association between the biochemical liver test abnormalities and presence of the biliary strictures.

Obliterative Portal Venopathy (OPV)

Obliterative portal venopathy (OPV) has been recognized in a subset of CF patients, mostly adolescents and young adults, with non-cirrhotic PH (NCPH) [13–15]. The prevalence of OPV remains unknown and the cause of this portal branch venopathy remains obscure. It could be due to spillover of inflammatory infiltrate of the bile ducts, to microthrombosis from platelet activation, or to endothelial injury related to the CFTR defect. Extreme care should therefore be taken not to underestimate the risk of PH, even if there is little evidence of liver disease clinically or on imaging.

Steatosis

Steatosis is usually mild and detected in CF patients of all ages with a wide range of reported frequencies (20 to 70%), but does not seem to be directly related to the CFTR defect in the biliary epithelium [16]. It has been associated with selective nutritional deficiencies including essential fatty acids, and with altered phospholipid metabolism, diabetes or long-term antibiotic therapy. Although steatosis is considered benign in CF, a possible relationship to developing cirrhosis remains conceivable.

Outcome Related to Liver Disease

Portal hypertension develops in about 2 to 5% of CF patients most often during adolescence, resulting either from progression of biliary fibrosis towards cirrhosis or OPV, whereas hepatic function remains usually well preserved for a long time [9, 17–20]. Variceal bleeding is, however, relatively rare in terms of bleeds per patient years, but could be associated with significant morbidity (ascites and infections) [17–21]. In a recent large study including 943 participants with reported cirrhosis (41% females, mean age 18.1 years) in the CF Foundation Patient Registry from 2003 to 2012, ten-year cumulative variceal bleeding, LT and liver death rates were 6.6%, 9.9% and 6.9%, respectively [20]. More recently, in a longitudinal birth cohort study of 577 CF patients, 51 of whom developed PH, combined mortality-liver transplant rate was significantly increased in patients with PH versus those without PH (23.5% vs 4.8%, $p < 0.001$) [21]. Other complications included ascites, hepatopulmonary syndrome and portopulmonary hypertension [4, 17, 22].

Malignancy is a worrying problem. Hepatocellular carcinoma has been reported in young patients with or without cirrhosis [23, 24]. There are also multiple case reports of adult patients with CF and biliary disease who developed gallbladder cancer or cholangiocarcinoma, both pre- and post-lung transplantation, suggesting that absence of CFTR throughout the biliary epithelia contributes to a chronic inflammatory state that increases the risk of epithelial dysplasia and neoplasms [25–27].

Influence of liver disease on lung function remains a matter of debate [2, 19, 28–31]. It has been reported that cirrhosis is independently associated with mortality and lung transplantation risks in adults [19]. In a more recent study, while both the 6-year survival rate (77 vs. 93%; $P < 0.01$) and the median age at death (27 vs. 37 years; $P = 0.02$) were significantly lower in cirrhotic ($n = 95$) compared to non-cirrhotic CF controls, the primary cause of death was pulmonary in 68% of cirrhotic cases, and liver failure-related in only 18% of cases [29]. Conversely, a recent cross-sectional large cohort study indicates that advanced liver disease is not associated with worsened CF lung disease when compared to a large CF reference population [30].

Specific Features for Paediatricians Looking After Adolescents with CF

Assessment of Liver Disease

Evidence of liver disease in CF patients is usually subclinical, with normal or mild abnormalities of liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT)], and therefore it is often underdiagnosed unless annual screening is implemented [4]. An algorithm for the

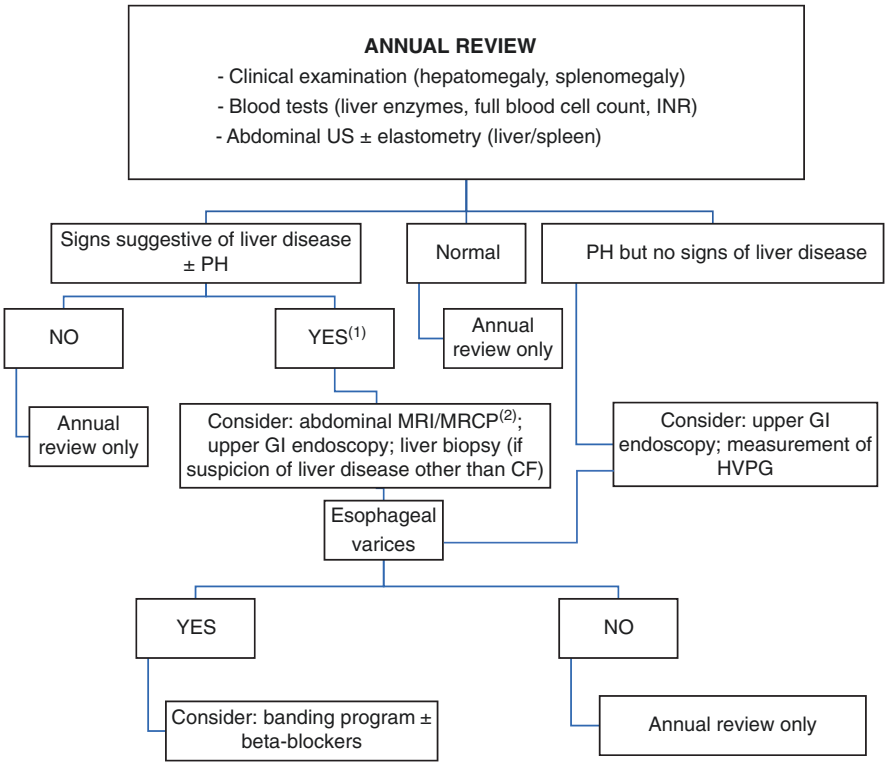

Fig. 12.1 The algorithm for assessment of liver disease in cystic fibrosis (1). Once signs of liver cirrhosis, portal hypertension or any biliary complication develop, referral to a specialized gastroenterologist or hepatologist for management and follow-up is recommended (2). If concern exists about biliary tract involvement an MRCP is indicated. Abbreviations: *CF* cystic fibrosis, *US* ultrasonography, *MRI* magnetic resonance imaging, *MRCP* magnetic resonance cholangio-pancreatography, *PH* portal hypertension, *GI* gastrointestinal, *HVPG* hepatic vein pressure gradient

annual assessment of liver disease is proposed (Fig. 12.1). The main objective is to detect signs of hepatobiliary disease or PH prior to the development of complications, and refer the patient to a hepatologist for management and follow-up. Attention should be paid to the signs of PH (splenomegaly, thrombocytopenia, distension of abdominal wall veins) even in the absence of other evidence—clinically or at US, and signs of chronic liver disease such as jaundice, spider naevi or palmar erythema. Abdominal pain, a frequent symptom reported by patients with CF, is most often not specifically related to the liver involvement, as massive splenic enlargement or chronic gastrointestinal problems may result in abdominal discomfort. Also uncommon, the right upper quadrant abdominal pain with or without jaundice may indicate a biliary complication and warrants an abdominal US [10]. Abnormalities of liver enzymes are common in CF, but lack specificity and sensitivity [32, 33] and could be secondary to an underlying acute or chronic liver disease that should always be excluded. The examples include acute or chronic hepatitis B

or C, alpha-1 antitrypsin deficiency, autoimmune hepatitis, Wilson disease or non-alcoholic steatohepatitis [4]. US is the most suitable initial method of investigation for assessment of abnormalities of the liver parenchyma and of the biliary tract in patients with CF, as abnormal echogenicity may precede clinical manifestations and identify patients at risk of progressive liver disease [34–36]. Nevertheless, US is associated with substantial inter-observer variability, and the positive predictive value of a normal ultrasound can be as low as 33% with 57% sensitivity [37]. MRCP has become the best modality for the assessment of the biliary tree. It is also a valuable method to quantify and assess the severity of steatosis [38]. Histological assessment remains controversial in CF patients because of the patchy distribution of lesions, the potential risk of sampling error and under-representation of the extent of the disease. Using a dual-pass needle core liver biopsy may increase the sensitivity of the detection of hepatic fibrosis compared with a single-pass liver biopsy [39]. Particular attention should be paid to portal vein branches (obliteration, absence of portal veins) suggesting obliterative portal venopathy [14]. Although liver biopsy is not a routine investigation in many centers, it may be helpful for CF patients suspected of having a concomitant liver disease.

Clinically relevant biomarkers to identify patients at risk of bile duct injury, fibrosis development, or PH are still lacking, but continue to be under investigation [40]:

Serum biomarkers. A persistent increase in serum levels of GGT only appears to be an early predictor of advanced liver disease (i.e cirrhosis) [32, 41]. The AST-to-Platelet Ratio Index (APRI) and FIB-4 (Fibrosis-4) that incorporate standard laboratory data (i.e. AST, ALT, platelet count, age) show a good correlation with severe fibrosis, but could not differentiate fibrosis at earlier stages [42].

Non-invasive assessment of hepatic fibrosis by several methods, such as transient elastography (TE), acoustic radiation force impulse (ARFI), point shear-wave elastography, supersonic shear wave elastography (SSWE), and magnetic resonance elastography (MRE), have shown promise for the detection of clinically silent fibrosis among the CF population, but better quality studies and further validation are still needed particularly for the diagnosis of mild to moderate fibrosis [43–47]. Indeed, in a recent prospective study evaluating 55 adult CF patients, both TE and ARFI did not significantly discriminate between non-cirrhotic liver disease and CF without liver disease. SSWE may be more accurate for assessing early stages of fibrosis, but further investigations in the CF population is warranted [44]. MRE is a new mode to detect earlier stages of liver fibrosis under investigation in the CF population [47].

Management of CF Adolescents with Liver Disease

No therapy, including ursodeoxycholic acid (UDCA) and CFTR modulators, has yet proven effective to prevent or halt the progression of liver disease towards cirrhosis and PH. UDCA is the only medical therapy currently used for liver disease in

CF, aimed at reducing bile viscosity, modifying bile acid composition and improving biliary excretion. The recommended dosage for CF patients is 15–20 mg/kg/day [4], but a recent Cochrane review, which analyzed its reported use for all variants of CF liver disease, concluded that there is insufficient evidence to justify its routine use in CF [48].

Key management issues for paediatricians taking care of CF adolescents are detailed in Table 12.2. Importantly, in addition to pancreatic insufficiency, the development of liver disease may further exacerbate malnutrition by increasing fat malabsorption, abnormal metabolism of nutrients and protein wasting with an increase in resting energy expenditure. Nutritional support is essential and is summarized in Table 12.3. In the patients in whom anorexia is a problem, enteral tube feeding may be required to ensure adequate caloric intake. Gastrostomy feeding is not recommended in those with advanced liver disease, varices, or portal gastropathy because of the risk of gastric haemorrhage. During adolescence a particular

Table 12.2 Key management issues for paediatricians looking after CF adolescents with liver disease

- Annual screening for liver disease and signs of portal hypertension, based on clinical examination and a combination of biochemical tests and imaging techniques.
- Referral to a hepatologist for management and follow-up once signs of liver cirrhosis, portal hypertension or any biliary complication develop.
- Vaccination against hepatitis A and B.
- Contraindication for aspirin and non-steroidal anti-inflammatory drugs in patients with liver involvement at risk of developing portal hypertension to prevent bleeding from portal hypertensive gastropathy and varices.
- Nutritional support to increase the energy intake to about 150% the estimated average daily requirement and fat-soluble vitamin supplementation
- Annual assessment of impaired glucose tolerance
- Education regarding smoking, the use of illicit drugs and alcohol.
- Education regarding fertility and use of contraceptives for women, knowing that CFTR modulators might reduce their effectiveness.
- Referral to a hepatologist in the event of pregnancy.

Table 12.3 Nutritional support in adolescents with CF and liver disease

- Supplement regular food with vegetable oils or add high-energy carbohydrate and protein drinks.
  - To ensure a fat proportion around 40–50% of the energy content with special attention to increase supplementation of polyunsaturated fatty acids.
  - To ensure a protein intake of 3 g/kg/day.
- To ensure adequate caloric intake, consider enteral tube feeding for the patients in whom anorexia is a problem.
- Ensure that sufficient pancreatic enzymes are prescribed to allow optimal absorption of long-chain triglycerides and essential fatty acids.
- Supplement fat-soluble vitamins, including high oral doses of vitamin A (5000–15,000 IU daily), vitamin E (α-tocopherol 100–500 mg daily), vitamin D (α-calcidiol 50 ng/kg to a maximum of 1 μg/day), and vitamin K (1–10 mg daily).
- Monitor serum levels of vitamins A, E, D and prothrombin time.
- Consider regular bone density scans.

attention is required towards the increased risk of developing CF-related diabetes (CFRD), with an estimated prevalence of 20% in adolescents and up to 40–50% in adults with CF [31, 49, 50]. In addition, CF adolescents and young adults are at risk of CF-related bone disease (osteopaenia and osteoporosis) resulting from a variety of factors, including pancreatic insufficiency, calcium, vitamin D and K deficiency, low peak bone mass, hypogonadism, CFRD, recurrent pulmonary exacerbations and increased osteoclastic bone resorption [5]. Education is required regarding smoking, the use of illicit drugs, alcohol, fertility and pregnancies. These issues need to be regularly addressed during adolescence.

Once signs of liver cirrhosis or PH or any biliary complications develop, referral to a hepatologist for management and follow-up is recommended. Serum α-fetoprotein levels should be measured annually to monitor for possible development of hepatocellular carcinoma [23, 24].

Specific Features for Hepatologists Looking After Adolescents with CF

Specific management issues of advanced liver disease in CF should take into account CF comorbidities such as progressive bronchiectasis, recurrent infective pulmonary exacerbations, pancreatic insufficiency and CFRD [5]. These include the management of esophageal varices, requiring repeated general anaesthesia—notwithstanding the lung disease, the decisions about timing for liver or liver-lung transplantation,

Table 12.4 Key management issues for hepatologists looking after CF adolescents with advanced liver disease

- Management of advanced liver disease is directed towards the treatment of complications of portal hypertension.
- Band ligation of large esophageal varices with red wale signs (grade 2 and more) is the main method of primary prophylaxis, generally preferred over non-selective beta-blockers.
- Transjugular intrahepatic portosystemic and surgical shunting procedures may be considered in patients with recurrent bleeding.
- Attention should be paid to the occurrence of acute jaundice, bile duct strictures, and gallbladder polyps due to increased risk of biliary tract cancer.
- Liver transplantation is considered when hepatic decompensation or complications of portal hypertension such as refractory bleeding, hepatopulmonary syndrome and portopulmonary hypertension occur.
- Education is required regarding smoking, use of illicit drugs and alcohol.
- For sexually active female adolescents basic education is required regarding fertility, risks of unplanned pregnancy and need for the contraception use.
- In the event of pregnancy, an upper gastrointestinal endoscopy is indicated between the 20–24th week of gestation to screen for and to treat varices.
- The keys to success are to start transition preparation in early adolescence and to actively engage all main stakeholders, especially adult hepatologists, throughout the process.

but also genetic counseling, the risks during pregnancy, contraindications to medications, and unknowns about new therapies.

Key management issues for hepatologists looking after CF adolescents with advanced liver disease or portal hypertension are shown in Table 12.4.

Management of PH

Portal hypertension with the development of varices is the most significant complication that impacts clinical outcome. There is no available evidence of the benefit of primary prophylaxis (before the first variceal bleed) in terms of safety, efficacy and survival outcomes in the CF population [40]. CF patients with severe PH may remain stable for years and long-term survival has been reported even after variceal bleeding [20]. However, most centres offer upper gastrointestinal endoscopy to selected patients who develop splenomegaly or hypersplenism for detection and treatment of large varices with red wale signs (grade 2 and more) to prevent bleeding [4, 40]. Oesophageal band ligation is the preferred method for primary prophylaxis. It is generally preferred over non-selective beta-blockers due to concerns of their poor tolerance and potential respiratory effects. An important consideration is the safety of repeated general anesthesia. Generally safe and well tolerated, oesophageal capsule endoscopy for the evaluation of oesophageal or small bowel varices could be useful, particularly in the CF population to avoid deleterious repeated general anesthesia, but requires further evaluation [51, 52]. Elastography of the liver or the spleen may contribute to the bleeding prediction [53, 54]. Additional therapeutic interventions may be required in patients with intractable esophageal bleeding, recurrent bleeding from gastric or rectal varices and portal hypertensive gastropathy. Transjugular intrahepatic portosystemic and surgical shunting procedures have both been successfully employed for portal decompression in CF patients with recurrent bleeding, both as a long-term therapy for PH or as a bridge to LT [18, 55].

Distinction of NCPH from cirrhosis is quite important while considering a decision to shunt or transplant, especially when assessing the patient for lung transplantation. For diagnostic purposes, measurement of the hepatic vein pressure gradient (HVPG) and histological assessment may therefore be indicated: a normal ($\leq$5 mmHg) or only slightly increased (5–10 mmHg) HVPG indicates intrahepatic presinusoidal (non-cirrhotic) PH [13–15]. In view of the good hepatic synthetic function, patients with CF who have NCPH should likely benefit from alleviation of their PH by shunting procedures rather than being considered for LT.

Screening for hepatopulmonary syndrome and portopulmonary syndrome is mandatory, especially when considering a portosystemic shunting procedure to prevent variceal bleeding [4, 17].

Timing for LT

LT is an effective therapeutic option for CF patients with end-stage liver disease, but selection criteria and timing have not been clearly established. This is even more complex because the liver failure is a late event and biochemical parameters and classification systems used to monitor severe liver disease—such as Child-Pugh score, model for end-stage liver disease (MELD), and pediatric end-stage liver disease (PELD) model—are less suitable for CF, where the serious complications of PH may occur with isolated hepatic fibrosis and good hepatic synthetic function. Median 1 year and 10-year survival after LT is approximately 90% and 80%, respectively [22, 56, 57], but long-term outcome is dependent on other CF manifestations. In particular, late mortality is generally related to progression of the pulmonary disease.

Recommendations for LT evaluation have been recently proposed [22]. In absence of severe respiratory failure, those who develop hepatic decompensation (hypoalbuminemia <3 g/dL and declining, hypoglycemia, and/or worsening coagulopathy [INR > 1.5] that is not corrected by administration of intravenous vitamin K, ascites, and jaundice), or complications of PH such as refractory ascites, recurrent variceal bleeding not controlled by endoscopic management, or hepatopulmonary syndrome/portopulmonary hypertension, may benefit from LT. Adequate consideration should be given to the nutritional status and severity of other organ involvement (pulmonary, cardiac, renal and pancreatic functions). LT is neither beneficial nor detrimental to pulmonary function in CF [58]. Combined lung and LT should be considered for young adults with severe lung disease (<50% FEV1) and liver failure [59]. Notably, renal impairment is a frequent complication [60].

The increased risk of insulin-dependent diabetes mellitus in this population, particularly after LT, urges consideration of combined liver-pancreas or islet cell transplantation [50, 61]. An analysis of United Network Organ Sharing data from 1987 to 2014 reveals low rates (<1%) of pancreas transplants (with or without liver, lung and kidney transplants) in the CF population, despite generally encouraging outcomes [62]. Post-transplant diabetes mellitus developed in only 7% of CF pancreas transplant recipients versus 24% of CF liver and 29% of CF lung recipients. In a recent poll of 50 paediatric transplantation centres, 94% reported that they would consider combined liver/pancreas transplantation for CFLD and diabetes, 50% for CFLD and glucose intolerance, and 24% for CFLD and pancreatic insufficiency [63]. Overall, according to the French CF registry, 968 organ transplantations were performed between 1992 and 2017 in France at a mean age of 35 ± 9.9 yrs. (range 3.5–68.3 yrs), including 812 (93.4%) lung, 28 isolated liver (3.2%), 52 kidney (6%), 2 isolated islet cell (0.2%) transplantations, and 74 (8.3%) multiorgan transplantations (8 lung/islet cell, 30 lung/heart, 27 liver/lung ± heart, 4 lung-kidney, 1 liver/pancreas, 3 kidney/pancreas, and 1 liver-kidney) [64].

Novel Therapies

To date, information on the effects of CFTR modulators on hepatobiliary outcomes remain limited. A large observational analysis of data from the USA and UK CF registries indicated that patients treated with Ivacaftor had a lower incidence of hepatobiliary complications (defined by gallstones, liver disease, cirrhosis, cirrhotic complications, hepatic steatosis, and abnormal liver enzymes) compared with their untreated counterparts, but a direct treatment effect could not be clearly established [65]. Furthermore, there is one case report of a 17-year-old female (*F508del-CFTR/G551D)* with findings of hepatic steatosis on liver biopsy who experienced its complete resolution after Ivacaftor therapy over a 2-year span [66]. Although these studies would support the hope that CF hepatobiliary disease might be prevented or improved by CFTR modulator therapy, larger and more detailed studies are awaited.

Fertility and Risks of Pregnancy

Nearly all (98%) of men with CF have azoospermia secondary to bilateral congenital absence of the vas deferens. But, despite thicker cervical mucus and possible ovulation issues, women with CF are fertile. However, pregnancy is uncommon in women with advanced liver disease, though infertility is not always present. The use of CFTR modulators that correct the underlying defect might improve fertility. For this reason, regardless of how severe CF disease may be, sexually active female adolescents should use contraception to prevent possibility of unplanned pregnancies. The United States Medical Eligibility Criteria for Contraceptive Use (USMEC) recommends that estrogen-containing methods should be avoided and that progestin-only contraceptives, levonorgestrel or intrauterine devices are used in women with cirrhosis [67]. CFTR modulator therapies might, however, reduce effectiveness of hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives.

Women with cirrhosis who do become pregnant are at increased risk for early pregnancy loss, fetal growth restriction, preterm delivery, low birth weight and perinatal death. They are also at risk of experiencing liver-related complications during pregnancy including bleeding varices [68]. In pregnancy, an elective oesophagogastroscopy (with or without variceal band ligation) is recommended between the 20–24th week of gestation [69]. Close follow up by specialist teams is recommended. Non-teratogenic medications such as ursodeoxycholic acid (UDCA) can be continued in pregnancy and whilst breast feeding. At present, there is a paucity of human safety data on the use of CFTR modulators during pregnancy and lactation [70, 71].

Transition to Adult Care

The improved survival in people with CF has led to an increasing number of patients reaching adulthood resulting in the need to increase the number of centres with expertise in the management of adult patients with CF. These centres should be capable of delivering multidisciplinary care addressing the complexity of the disease, including psychological burden on the patients and their families. Although declining lung function during adolescence drives most of the clinical care requirements, the transition phase, that could last from approximately 12 to 24 years of age, constitutes the period in life when major life-threatening complications related to cirrhosis or PH may occur, leading to repeated hospitalisations and possibly LT. Medical management of CF requires one of the highest treatment time investments of all chronic diseases, which makes the treatment adherence critical, but often not addressed. Adolescents with CF report a sense of vulnerability, loss of independence and opportunities, isolation, and disempowerment [72]. Importantly, prevalence of depression ranges from 8%–29% in children and from 13%–33% in adults with CF [73, 74]. Additionally, rates of depression of 20–35% have also been reported among caregivers of people with CF.

There is no available evidence that transfer to adult care is associated with worse clinical health outcomes in CF [75]. Existing programs for CF adolescents and young adults highlight the importance of a multidisciplinary patient-centered care that promotes shared decision-making, supervision and good communication in management [76]. Ideally, adult hepatologists should have a close working relationship with the paediatric hepatologists who refer patients. The lack of experienced adult hepatologists and difficulties in identifying them could impede the transition process. Starting transition preparation in early adolescence, active engagement of all key stakeholders, especially adult hepatologists throughout the process, are keys to success. Recommendations for the transition process of young people with paediatric onset hepatobiliary diseases from pediatric to adult healthcare services were recently published [77, 78].

Conflicts of Interest None.

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Chapter 13
Sickle Cell Disease

Sue Height

Introduction

The estimated global incidence of Sickle Cell Disease (SCD) is 300,000 births annually, 80% occurring in Sub-Saharan Africa, representing the commonest inherited disorder in the UK and USA. Mutation of the β-globin gene (*HBB*) causes synthesis of abnormal β-globin (β6Glu- >Val) forming Sickle haemoglobin (HbS) instead of normal adult haemoglobin (HbA) in erythrocytes [1]. Sickle haemoglobin (HbS) polymerises in hypoxic, acidotic conditions causing irreversible red cell distortion—'sickling', with shortened red cell survival. The diverse systemic effects of this single molecular change and red cell sickling are due to vascular obstruction (vaso-occlusion) and red cell breakdown (haemolytic anaemia with reticulocytosis). Intravascular haemolysis releases free haemoglobin (a nitric oxide scavenger), affecting vascular tone and endothelial function, and sickled red cells are phagocytosed by macrophages including Kupffer cells. Haem metabolism increases bilirubin, and as vascular occlusion resolves there is reperfusion and inflammation.

HbSS (Sickle Cell Anaemia) is the commonest genotype, while compound heterozygosity of HbS with other β-globin variants including HbC (HbSC) and β thalassaemia HbSβ thalassaemia causes sickling disorders with variable phenotypes; HbSS and HbSβ0 thalassaemia are the most severe. Other genetic and environmental factors also influence severity. Fetal haemoglobin (HbF) levels normally fall from birth to <5% by 1 year, but some genetic variants including *BCL11A* polymorphisms are associated with higher levels of HbF which impedes HbS polymerisation in the sickle cells. Coinheritance of alpha-thalassaemia with HbSS also

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confers a milder phenotype. Environmental factors including infection, air pollution and poverty also contribute to disease severity [2].

Acute vaso-occlusion causes severe pain due to bone marrow infarction, and in infants involvement of the hands or feet (dactylitis) can be the earliest event. Vaso-occlusive episodes can also involve any organ causing acute ischaemia and organ failure, e.g. acute chest syndrome and stroke, whilst chronic vaso-occlusion affecting the cerebrovascular, renal, pulmonary and hepatic vessels leads to more insidious functional impairment, often becoming apparent in teenagers in the absence of disease modifying treatment.

Splenic infarction occurs by 6 months of age causing a hyposplenic state with increased risk of overwhelming sepsis from capsulated organisms, particularly Streptococcus pneumoniae, largely accounting for the mortality of up to 90% under 5 years of age in Sub-Saharan Africa. Early diagnosis of affected infants by newborn screening programmes, introduction of Penicillin V prophylaxis by 3 months of age, and vaccination including Pneumovax from age 2 years reduces the risks [4]. The spleen can enlarge acutely with a rapid fall in haemoglobin and shock (splenic sequestration) which tends to occur in infants. The spleen remains enlarged in 10% of the patients and can contribute to more severe anaemia and hypersplenism [3]; acute hepatic sequestration occurs less commonly. Acute severe anaemia is typically caused by Parvovirus B19 infection (‘aplastic crisis’).

Acute chest syndrome (ACS), with vaso-occlusion and inflammation in the pulmonary vessels, is a major cause of death in young adult patients. It occurs with infection, but 50% of episodes evolve during vaso-occlusive episodes or inflammatory states. The risk factors include opioid-induced sedation, fluid overload, abdominal pain and immobility and they can be reduced by incentive spirometry [5]. Treatment includes antibiotics, blood transfusion (top up or exchange), occasional steroids, and supplemental oxygen with non-invasive or invasive ventilatory support in a critical care unit. Recurrent severe episodes may be associated with restrictive lung disease; chronic vaso-occlusion is associated with pulmonary hypertension and risk of sudden death in young adulthood.

Cerebrovascular effects of SCD include acute stroke, silent infarcts and increased risk of intracranial haemorrhage, acute stroke occurring in 11% by the age of 20 years without intervention [6]. Progressive stenosis of vessels in the anterior circle of Willis causes watershed cerebral ischaemia; risk factors include acute severe anaemia, obstructive sleep apnoea and recent ACS. Annual screening by Transcranial Doppler velocity measurement until age of 16 years enables identification of those at high risk, and intervention with regular blood transfusion to maintain HbS <30%. ‘Silent’ cerebral infarcts identified on MRI imaging with a prevalence of 37% by 14 years are associated with cognitive impairment that may affect future employment prospects. Haemorrhagic stroke from aneurysms or neovascularisation is a cause of sudden death in young adults. Onset of sickle nephropathy with hyposthenuria and progressive renal impairment may be detected in older teenagers; end stage renal failure accounts for up to 18% of adult mortality.

The wider range of organ complications in SCD is shown in Table 13.1.

Table 13.1 Complications in sickle cell disease

Neurological and ophthalmological	Acute ischaemic stroke/Transient ischaemic attack Intracerebral haemorrhage Silent cerebral infarcts Cognitive impairment Headaches Retinal artery occlusion and retinopathy
Skeletal	Avascular necrosis Septic arthritis Osteomyelitis—Salmonella, Staphylococcus
Renal	Hyposthenuria and microalbuminuria Nocturnal enuresis Renal papillary necrosis and haematuria Progressive renal impairment
Spleen	Hyposplenism—risk of overwhelming infection Acute and chronic splenic sequestration
Skin	Leg ulcers
Endocrine and reproductive	Delayed puberty Priapism Pregnancy—preterm delivery, growth restriction, Pre-eclampsia, HELLP syndrome
Pulmonary and cardiac	Acute chest syndrome Pulmonary hypertension and risk of sudden death Chronic restrictive lung abnormalities
Hepatic	Gallstones, cholecystitis and cholangiopathy Acute hepatic sickling (hepatopathy) Transfusion-related iron overload Transfusion-transmitted infections including hepatitis
Haematological	Acute severe anaemia: Parvovirus B19 ‘aplastic crisis’, acute splenic or hepatic sequestration Transfusion related—red cell alloantibodies Delayed haemolytic transfusion reactions (DHTR), Hyperhaemolysis, Venous thromboembolism—prothrombotic risk

Treatment

In addition to prophylaxis for overwhelming infection, treatments to modify the course of SCD are increasingly offered to reduce chronic organ damage and improve long-term outcomes; these include hydroxy-urea, blood transfusions and haemopoietic stem cell transplantation (HSCT).

Hydroxy-urea

Hydroxy-urea is approved to treat SCD in the USA and Europe, with evidence for reduced risk of recurrent painful episodes and ACS, reduced need for blood transfusion, possible prevention of damage to the spleen, kidneys and other organs and

improved survival if taken from an early age [7]. Hydroxy-urea increases HbF% expression, reduces HbS polymerisation and causes mild bone marrow suppression. Hydroxy-urea is well tolerated, but has to be monitored and increase in ALT to 2x ULN could limit its use in active liver disease. However, lack of progression of liver disease in adult patients taking hydroxy-urea has been reported, thus a cautious use with close monitoring is recommended.

Blood Transfusion

Red cell transfusion reduces circulating sickle cells (HbS%) and vaso-occlusive complications and corrects anaemia. Top up transfusion to maximum Hb 100 g/L avoids increased viscosity and vaso-occlusive risks, but after 10 transfusions iron accumulation occurs and chelation therapy is required. Regular red cell exchange (RCE) replaces sickle cells with donor red cells (HbA), reducing HbS to <30%, maintaining neutral iron balance and avoiding the need for chelation. Indications for transfusion include acute anaemia and vaso-occlusive episodes with organ involvement, perioperative management and prevention of recurrent or chronic organ failure (Table 13.2).

Complications of transfusion include red cell allo-immunisation, transfusion-transmitted infection (TTI) and iron overload. Red cell alloantibodies occur in 15% of SCD patients, causing delayed haemolytic transfusion reactions and risk of further alloantibody formation. Routine blood group ABO, RhD and C, E or C/c E/e and Kell antigen typing, and extended typing of Jk^a/Jk^b, Fy^a/Fy^b, M/N, and S/s antigens is recommended for patients with alloantibodies [8]. Patients undergoing transplant require irradiated cellular blood products. Autoimmune haemolysis may also occur in SCD, and Passenger lymphocyte syndrome with acute immune-mediated haemolysis due to passive transfer of donor B-cells is recognised post-liver transplant [9].

Cellular oxidative damage from excess iron develops when transport and storage capacity are exceeded, particularly affecting the liver and is exacerbated by inflammation. Non-transferrin bound iron (NTBI) and labile plasma iron (LPI) increase when transferrin saturation is >60%. Ferritin values >1000 mcg/L cease to accurately reflect iron stores, with a non-linear response at higher levels [10]. Ferritin is also an acute phase protein, reflecting inflammation and liver disease. Annual accurate liver iron quantitation with MRI R2 (Ferriscan) is necessary for patients on regular transfusions (Fig. 13.1). Chelation to remove both toxic NTBI/LPI and excess storage iron is started when the ferritin >1000mcg/L or liver iron concentration exceeds 3 mg Fe/g dry weight [11]. The choice of chelation is determined by severity of iron loading, the ability of the patient to adhere to treatment and the presence of liver disease. Deferasirox (Exjade, DFX), an oral iron chelator with once

Table 13.2 Use of blood transfusion in SCD

Indications for emergency transfusion in SCD	
Acute severe anaemia with fall in Hb by >20 g/L	
• Acute splenic sequestration • Acute hepatic sequestration • Parvovirus B19 infection • Acute hepatic crisis with mild hepatic changes (bilirubin <80υmol/L, <50% conjugated or bilirubin 2x steady state, normal INR) • Acute chest syndrome with fall in Hb > 20 g/L	Top up transfusion to baseline or maximum Hb 100 g/L
Deteriorating or severe hepatic crisis	
• Bilirubin >150 υmol/L (or > 5x steady state), >50% conjugated, raised transaminases, normal INR OR	Top up transfusion if Hb <90 g/L or exchange if Hb >90 g/L and deteriorating
• Raised conjugated bilirubin >50 υmol/L with raised INR (liver failure)	Exchange transfusion
Acute vaso-occlusion causing organ failure	
• Acute stroke/Transient Ischaemic Attack • Acute chest syndrome • Multi-organ failure	Exchange transfusion
Indications for long-term transfusion in SCD	
Chronic organ failure including severe chronic liver disease, cholangitis, AILD or recurrent acute hepatic crisis	Exchange transfusions or serial top up transfusions to maintain HbS <30%
Primary & secondary stroke prevention	
Pre-operative transfusion in SCD	
Intermediate risk	
Surgery—splenectomy and cholecystectomy Patient—previous ACS not requiring critical care	Top up transfusion if no additional patient risk if Hb <90 g/L to target Hb 100 g/L and consideration of RCE for those with Hb >90 g/L or with HbSC
High risk	
Surgery—major abdominal surgery, organ transplantation Patient–life-threatening ACS, stroke, previous admission to critical care or other co-morbidity	RCE aiming for HbS <30% or HbS + C % <30% and pre-op Hb 100 g/L
General anaesthesia for radiological procedures (MRCP/ERCP)	
Patient risk factors—severe anaemia, stroke or previous severe ACS	Transfusion generally not required unless patient has risk factors

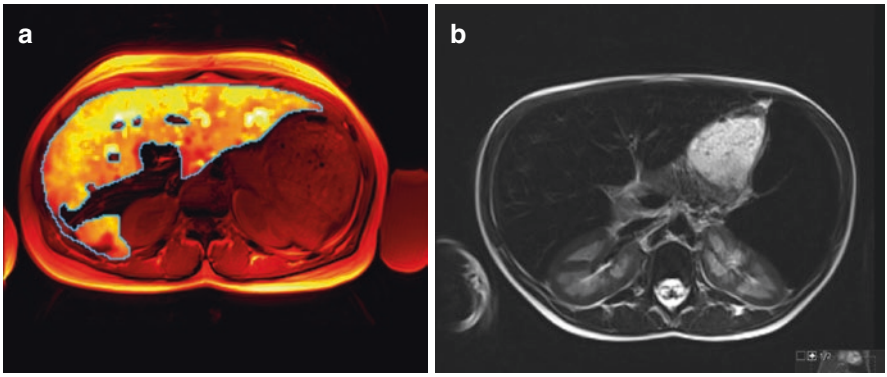

Fig. 13.1 Iron loading in the liver. (**a**) Ferriscan© image—R2/sec axial MR showing severe iron loading 38.6 (normal range 0.17–1.8 mg/g dry weight). Iron 'lights up'—the measurement is extrapolated to mg or iron/g dry weight of liver to allow accurate quantitation (**b**) Comparison with T2* weighted image where signal intensity iron loading appears dark in comparison to surrounding structures

daily dosing can cause reversible increased transaminases, renal toxicity and gastrointestinal symptoms, and should be interrupted for persistent LFT abnormalities. DFX is contra-indicated in severe liver disease, with case reports of acute hepatic failure in SCD. Desferrioxamine (DFO) is used in patients with liver disease, but adherence is a challenge due to the parental route of administration [12, 32]. Deferiprone (DFP) is an oral chelator administered 3 times/day, requiring weekly monitoring for increases in transaminases and agranulocytosis. Severe iron overload and chelation treatment are risk factors for *Yersinia enterocolitica* infection, which may present with abdominal pain and fever; chelation is then stopped and microbiology advice sought [13]. Patient adherence is essential for effective chelation in adolescence, requiring engagement and collaboration with the multidisciplinary team, and minimising iron loading with RCE rather than top up transfusions is helpful.

Transfusion-transmitted infections including viral hepatitis are a risk particularly where donor selection and testing is suboptimal. Hepatitis B immunisation is advised for all patients receiving transfusions or travelling to places with inadequate haemovigilance. Transfusion may be impractical for patients with complex red cell alloantibodies, history of severe transfusion reactions or with familial objections on religious or other grounds, and for these patients hydroxy-urea at maximum tolerated dose would be considered.

Preparation for hepatobiliary surgery entails individual risk assessment of the patient and procedure, and recommendations for transfusion to reduce perioperative complications are evidence-based [14] (Table 13.2). Patients should be prioritised early on the list, avoiding dehydration and cooling, with maintenance of oxygen saturations and postoperative incentive spirometry encouraged to reduce the risk of ACS. Patients considered high risk should have postoperative care in a critical care setting. Intraoperative cell salvage is not appropriate. SCD is a prothrombotic state and thromboprophylaxis, considered in those with additional risk factors unless

contraindicated, should include patients who are post-pubertal, with high BMI, prolonged immobility or previous VTE.

Haemopoietic Stem Cell Transplantation (HSCT)

HSCT is the only curative option for SCD. The best outcomes are achieved with a fully HLA-matched sibling donor, with overall survival 96% and event-free survival 89%, minimising the risk of graft rejection and graft-versus-host disease (GvHD). Conditioning regimes have been refined from myeloablative to reduced intensity conditioning (RIC), minimising toxicity, but inducing profound immunosuppression, thus allowing persistent recipient haemopoiesis and donor chimaerism sufficient to prevent SCD-related complications [15]. Immunosuppression can eventually be withdrawn, unlike in solid organ transplantation. Hepatic complications of HSCT include veno-occlusive disease and acute and chronic liver GvHD, and risks are increased with pre-existing liver disease. Additional risks in SCD patients include sepsis, thrombosis and acute neurological, cerebrovascular and hypertensive episodes related to calcineurin inhibitors and pre-existing organ dysfunction. Pre-transplant cryopreservation of sperm or testis and ovarian tissue may help preserve fertility. However, only 20% of eligible patients have suitable donors, and HSCT using alternative donors including haploidentical parental, or unrelated matched volunteer donors and intensive conditioning regimes involve higher risks of rejection, acute and chronic GvHD, severe viral reactivation syndromes with overall survival 87% and a 20% reduction in event-free survival at 3 years compared with the sibling matched transplants. Age at transplantation is also key to outcomes, with a three-fold increase in mortality in those undergoing HSCT aged 13 years and above, compared with those <13 years, regardless of conditioning regimen, likely reflecting disease burden [16]. Nevertheless, HSCT is increasingly undertaken in older teenagers and young adults. Eligibility criteria for HSCT include severe complications of SCD, including chronic organ damage, failure of response to hydroxy-urea and requirement for long-term transfusions, with comprehensive assessment pre-transplant of organ function. It is paradoxical that those with the most severe disease who would benefit from HSCT may have such severe functional compromise that they are considered ineligible, and this is especially pertinent to liver disease. Identifying patients at an earlier stage before end organ damage could permit HSCT and prevent further progression.

Liver Function Tests in Sickle Cell Disease

Steady state unconjugated bilirubin levels, typically 20–150 υmol/L, are influenced by variables including rate of haemolysis, coexistent G6PD (glucose-6-phosphate dehydrogenase) deficiency, and Gilbert syndrome (*UGT1A1* gene promotor

polymorphism). Increase in bilirubin above baseline should prompt measurement of conjugated bilirubin, which if raised, could indicate a hepatic cause. The AST and LDH are derived from hepatocytes and erythrocytes, and raised unconjugated bilirubin, LDH and AST in isolation usually reflect increased haemolysis due to vaso-occlusion or delayed haemolytic transfusion reaction, rather than liver disease. ALT and γGT are more specific for detecting liver or biliary disease and are unaffected by haemolysis; ALT and/or γGT levels 2x ULN should be repeated in 3 months and if persistent, investigation for chronic liver disease should be undertaken. Alkaline phosphatase increases during growth and is not specific for liver disease. Regular monitoring allows detection of a change from steady state and early identification of evolving liver disorders. Patients should routinely have an 'Annual review' as a minimum, with clinical assessment including LFTs, ALT, LDH, ferritin and CRP, and liver ultrasound from age 5 years as surveillance [17]. Patients having transfusions are monitored at each visit with LFTs, ALT and ferritin, while MRI Ferriscan quantitation of liver iron should be done annually, but more frequently for those with iron overload and liver disease.

Liver Disease in SCD

Liver disease affects approximately 10% of adults with SCD and is associated with poor outcomes; it may become apparent in teenagers, causing severe morbidity [18, 19]. 'Sickle hepatopathy' is an imprecise term that does not address the range of pathology that can occur in SCD [20]. SCD can adversely affect the liver by three main mechanisms, which may occur in any combination [21], and may occur with unrelated liver pathology:

1. Gallstones and cholelithiasis due to haemolysis
2. Vaso-occlusion of hepatic and biliary vessels, causing ischaemia of hepatocytes and/or biliary tree
3. Complications of blood transfusion including iron overload and viral hepatitis

Gallstones (Cholelithiasis)

Pigmented gallstones and biliary sludge are prevalent due to haemolysis and the risk increases in SCD with coexistent G6PD deficiency and Gilbert syndrome [22]. Surveillance ultrasound detects asymptomatic gallstones and/or biliary sludge in up to 43% of older teenagers. Symptoms can include recurrent non-specific abdominal pain, while migration of stones can cause biliary obstruction, cholangitis and acute pancreatitis, which may then be complicated by pancreatic pseudocyst formation (Fig. 13.2). Acute increase in conjugated bilirubin and GGT is usually associated with obstruction; the stones may pass spontaneously, however, recurrent attacks of cholecystitis are likely to be recurrent and cholecystectomy is undertaken when the

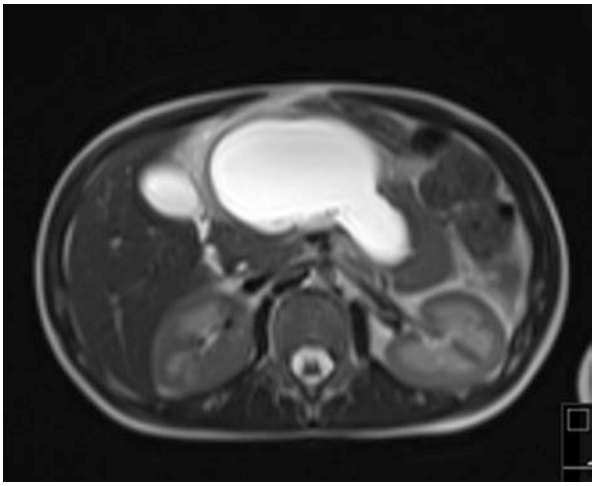

Fig. 13.2 Pancreatic pseudocyst complicating pancreatitis secondary to gallstones

patient is well. Elective cholecystectomy is considered routinely for asymptomatic stones in some countries.

Cholangiopathy

The biliary tree is at particular risk of ischaemia from vaso-occlusion due lack of collateral blood supply leading to cholangiopathy (Fig. 13.3); it can also occur with coexistent autoimmune disease (primary sclerosing cholangitis-PSC), autoimmune hepatitis and inflammatory bowel disease. Presence of MDR3 mutation heterozygosity may also predispose to cholangiopathy.

The symptoms including fatigue, itching and weight loss may be attributed to severe SCD. However, investigations may identify raised gGT and alkaline phosphatase, while liver ultrasound may detect gallstones, biliary calculi and dilatation. MRCP could demonstrate bile duct dilatation without obstruction, stenosis and strictures and biliary stones (Fig. 13.3). Endoscopic retrograde cholangio-pancreatography (ERCP) for direct intervention with strictures or obstructive gallstones may be indicated. This complication is infrequent, but potentially severe, leading to progressive hepatic impairment. Ursodeoxycholic acid supplementation may be helpful.

Acute Hepatic Sequestration and Intrahepatic Sickling (Acute Hepatic Crisis)

Hepatic sequestration presents acutely with painful liver enlargement, falling haemoglobin ≥20 g/l from steady state with reticulocytosis, and can occur with minimal LFT disturbance; precipitants may include infection or steroids. Severe episodes

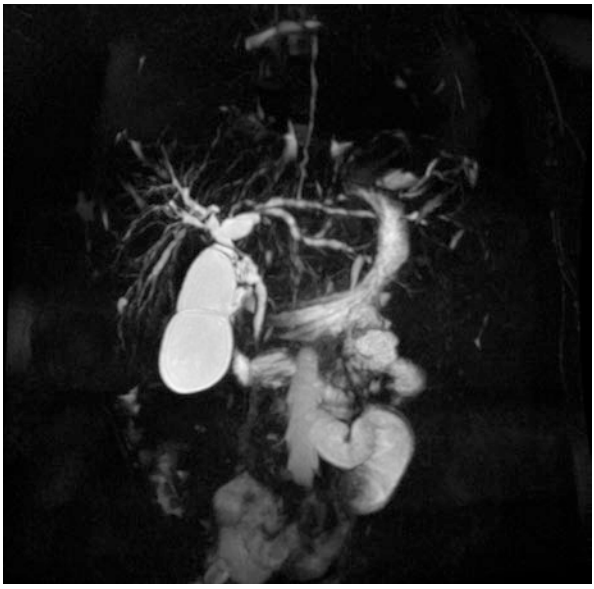

Fig. 13.3 MRCP showing cholangiopathy with attenuation of the biliary tree and focal strictures

can be associated with shock. Increasing jaundice with cholestasis termed 'acute sickle hepatopathy' may develop and management is guided by assessment of severity. For uncomplicated episodes intravenous fluid resuscitation and top up transfusion to baseline or Hb $\underline{\leq}$100 g/L may be sufficient, however, deterioration with conjugated hyperbilirubinaemia, transaminitis and impaired synthetic function and raised International Normalised Ratio (INR) > 1.5, can occur with progression to acute liver failure and requires close monitoring.

Intrahepatic vaso-occlusion causes ischaemia, sinusoid obstruction with Kupffer cell erythrophagocytosis and swelling, and further hepatocyte ischaemia and ballooning with canalicular obstruction and cholestasis. Inflammation and endothelial dysfunction contribute to progression to fibrosis, nodular regeneration and ultimately cirrhosis.

Severity is classified as:

- Mild—bilirubin <80 υmol/L, <50% conjugated or bilirubin 2x steady state, normal INR
- Moderate—bilirubin 80–150 υmol/L or 3-5x steady state, raised transaminases with normal INR
- Severe—bilirubin >150 υmol/L or > 5x steady state, >50% conjugated, raised transaminases, normal INR, OR raised conjugated bilirubin >50 υmol/L with raised INR (liver failure)

Supportive care includes intravenous fluids, broad spectrum antibiotics including pneumococcal cover, 12-hourly monitoring and incentive spirometry to reduce risk of ACS. The patients with severe or deteriorating liver function should be managed in a critical care setting, where RCE can be performed and additional organ support

provided. Long-term RCE transfusions are considered for recurrent episodes and evaluation for liver transplantation should be undertaken for those with progressive disease [23].

Autoimmune Liver Disease (AILD) in Sickle Cell Disease

AILD comprises Autoimmune hepatitis (AIH) and Autoimmune hepatitis-associated sclerosing cholangitis, with exclusion of other causes of liver disease. Although described as rare, AILD was diagnosed in 17% in a series of 77 SCD children with liver disease [24]. Susceptibility to autoimmune disease has a strong genetic component, with higher incidence and prevalence reported in black populations, and the chronic inflammatory state of SCD may also be implicated. Annual monitoring of inflammatory markers including hypergammaglobulinaemia may allow early identification of incipient autoimmune disease [25]. Presentation may be insidious with fluctuating jaundice, fatigue and weight loss, or with acute hepatitis, abdominal pain, increased jaundice, dark urine and pale stools. There may be delay in diagnosis with attribution of the clinical features and raised transaminases and hypergammaglobulinaemia to 'sickling'. Rarely, patients present with acute liver failure (ALF), prolonged prothrombin time (PT > 15 seconds) and hepatic encephalopathy or symptoms relating to portal hypertension and varices. AILD is confirmed by positive autoimmune serology [raised IgG, anti-nuclear antibodies (ANA) and anti-smooth muscle antibodies (SMA), anti-liver kidney microsomal antibody type 1 (LKM-1)], while liver histology demonstrates portal plasma cell infiltration and interface hepatitis. The coexistence of cholangiopathy 'overlap syndrome' is identified on imaging and/or histology in approximately 50% of AILD patients, and subclassification into AIH-1 and AIH-2 types is based on the ANA and/or SMA titre >1/20 or anti-LKM-1 titre >1:10, respectively. Occasional patients have coexistent inflammatory bowel disease requiring investigation if gastrointestinal symptoms are suggestive, and there may be associated ANCA seropositivity [26]. MRCP or ERCP can identify bile duct irregularities with strictures, focal intra- or extrahepatic dilatation, while ultrasonography could detect gallstones, lymphadenopathy at porta hepatis, splenomegaly and hepatic parenchymal abnormalities. Liver biopsy to confirm the diagnosis and exclude alternative pathology is generally avoided in acute liver decompensation.

AILD requires close monitoring of transaminases to assess response to treatment since it can progress to liver failure; Prednisolone 2 mg/kg/day is followed by gradual reduction to 0.1–0.2 mg/kg/day over 6–8 weeks. Rebound painful vaso-occlusion can occur if steroids are withdrawn too quickly [17]. Azathioprine or mycophenylate mofetil (MMF) could be added for resistant disease, but the risk of myelosuppression is increased in patients on hydroxyl-urea. Mesalazine or sulphasalazine may be used for those with coexistent IBD, but are contraindicated in G6PD deficient patients. Complete response to treatment is seen with return to baseline LFTs, normal IgG and negative antibodies, or partial with transaminases to 2x ULN. Patients

Table 13.3 Investigations for increased jaundice with or without signs of chronic liver disease

Haematology	FBC & reticulocytes Haemoglobin electrophoresis including HbF percentage Blood group and antibody screen Extended red cell phenotype Direct anti-globulin test G6PD activity level and Gilbert's polymorphisms Coagulation screen including Clauss fibrinogen
Immunology	Immunoglobulins ANA, SMA and LKM-1 ANCA and faecal calprotectin if IBD symptoms
Virology	Viral serology (Hepatitis B, C, E) EBV, CMV, Hepatitis A if acute presentation
Other	Caeruloplasmin, 24-hour urine copper, ophthalmology review for Kayser-Fleischer rings Alpha-1 antitrypsin phenotype, cholestasis gene panel and sweat test

Adapted with permission from Kyrana E, Rees D, Lacaille F, et al. Clinical management of sickle cell liver disease in children and young adults. Arch Dis Child. 2021;106 (4):315–320.

who subsequently relapse can be reinduced with prednisolone, and those with refractory or progressive disease should be considered for liver transplantation (Table 13.3).

Liver biopsy is undertaken when there is diagnostic uncertainty and the results will influence management decisions, ideally when the patient is stable [21]. Percutaneous liver biopsy in adults with deteriorating LFTs has been described with increased risk of bleeding and mortality, with evidence of hepatic venous congestion and acute sickle hepatic crisis [27]. The transjugular route offers an alternative approach when the perceived operative risks are higher and the biopsy is essential.

Liver Transplantation in SCD

Timely multidisciplinary discussion of liver transplantation and assessment of SCD-associated co-morbidities should be undertaken for patients with progressive liver disease. Identifying those at risk of end stage liver disease and predicting the rate of progression is challenging; there is scant published data on outcomes, with only 6 paediatric transplants reported in a series of 19 [28, 29]. Two groups of patients have been suggested as most likely to benefit from liver transplantation; those with end stage liver disease and no other major SCD organ involvement, and those with severe autoimmune liver disease and relatively mild SCD [23]. Urgent liver transplants performed in adult patients with liver failure and acute severe intrahepatic cholestasis or cirrhosis had poor outcomes, with 5- and 10-year survival rates of 55% and 44%, respectively [30]. Refinements in perioperative management include urgent RCE to reduce and maintain the HbS % at the minimum possible,

even <10% [23]. Modification of the SCD phenotype to prevent recurrent disease in the graft from ongoing vaso-occlusion is achieved with long-term RCE; hydroxyurea can be added to optimize disease modification, and immediate post-transplant chelation would entail desferrioxamine due to lack of hepatotoxicity.

A more radical approach of undertaking sequential liver transplant and HSCT would prevent ongoing vaso-occlusion responsible for liver damage, avoid the need for long-term transfusion and prevent other sickle-related complications [31]. Restoration of normal liver function would be necessary to withstand HSCT conditioning and complications. In children, the requirement for an unaffected HLA-matched sibling donor for HSCT makes it highly improbable that a sibling could be both HSCT and liver donor, although this would be the simplest dual transplant to undertake, the donor liver and bone marrow being HLA-identical, permitting eventual consideration for withdrawal of immunosuppression. Dual transplants involving different donors for the liver and HSCT would require long-term immunosuppression to prevent liver rejection.

New and Emerging Treatments

Recent developments of disease-modifying treatments include gene editing and novel agents

- Voxelotor (Oxybryta) is an oral agent that interferes with HbS polymerisation, indicated for reducing painful vaso-occlusive episodes (with or without hydroxyurea) in children over 12 years of age [32]. Dose reduction for severe liver disease (Child- Pugh C) is advised, and approval is awaited in the UK.
- Crizanlizumab (Adakveo), a monoclonal P-selectin-specific humanised IgGk2 antibody administered by initial 2- then 4-weekly intravenous infusion, reduces the risk of recurrent painful episodes and ACS, but may increase the risk of bacterial infections [33]. There are no recommendations for use or dose adjustment in hepatic disease. It is approved for patients 16 years and above in the USA, and approval is awaited in the UK.
- L-Glutamine (Endari) is an oral agent that decreases painful vaso-occlusive episodes, approved for age 5 and above in the USA, but not approved by the European Medicines Agency due to lack of efficacy, whilst acknowledging its safety profile [34]. It is not recommended in uncontrolled liver disease.

Development of CRISPR-Cas9 gene editing to delete the β-globin gene *BLC11A* locus and enhance HbF production in harvested autologous stem cells provides an alternative approach to disease modification in SCD. Following myeloablative chemotherapy and reinfusion of the genetically modified stem cells, erythropoiesis is re-established with a non-sickle phenotype, durable abolition of vaso-occlusive episodes and normalisation of haemoglobin [35]. This avoids the requirement for an HLA-matched donor and risk of GVHD, and increases the availability of a curative

transplant to patients who would benefit. However, toxicity of the myeloablative regime would limit its utility in patients with severe liver disease but could possibly be considered following liver transplantation.

Fertility and Pregnancy in SCD

Puberty is delayed by up to 2 years and may be longer with coexistent liver disease; absence of pubertal changes by 14 and 15 years in girls and boys, respectively, should prompt further evaluation. Sperm production in post-pubertal boys may be impaired, and priapism may occur at any age. Recommendations for contraception include progesterone-only pills, depot preparations, the intrauterine infused device (Mirena coil) or barrier methods, and avoidance of oestrogen-containing pills due to increased venous thromboembolism (VTE) risk. Pre-conceptual partner testing to establish the risk of an affected fetus, and prenatal diagnosis (chorionic villus sampling) to enable informed decision-making is offered. Pre-implantation Genetic Diagnosis is available for those with an affected child who wish to avoid an affected pregnancy. Folic acid supplementation and stopping hydroxy-urea for 3 months before planned conception is advised due to effects on sperm quality and theoretical risk of teratogenicity; however, the benefits of continuing hydroxy-urea during pregnancy outweigh other considerations for some women. SCD pregnancies are high risk with increased maternal and fetal complications including pre-eclampsia, HELLP syndrome, preterm delivery and growth restriction; pregnancies are managed by multidisciplinary teams. Red cell alloantibodies occur in up to 36% of women, and can cause haemolytic disease of the new-born. Increased VTE risk is mitigated with low-dose aspirin from 12 weeks of pregnancy and prophylactic low molecular weight heparin during immobility. Women with SCD and liver disease, portal hypertension with thrombocytopenia or coagulopathy need careful assessment since they also have a prothrombotic state. Many women continue regular top up or exchange transfusions and severe anaemia (Hb <60 g/L or fall of >20 g/L from baseline), complications such as ACS and stroke would require urgent transfusion. Delivery is planned for 38–40 weeks in a centre equipped to manage SCD and liver complications [36].

What Adult Hepatologist Needs to Know?

Teenage patients with SCD have significantly impaired quality of life, reporting frequent pain, hospitalizations with disruptions to education and social isolation, and appearance of jaundice and pubertal delay can be associated with stigma. The evolution of chronic organ damage (particularly hepatic, renal, respiratory and cerebrovascular) and onset of symptoms may coincide with reduced engagement,

failure to attend appointments and loss of adherence with transfusions, chelation and hydroxy-urea, which are crucial for disease modification. There may be anxiety about moving to adult services with unfamiliar staff. Acknowledgment of the difficulties is important; psychological and peer support, education about SCD and planned transition are essential for this vulnerable group [37]. Whilst over 95% of patients reach adulthood in high resource countries [38], it is salutary that mortality increases in the young adult group in the 2 years following transfer to the adult service [39] highlighting the fragility of the underling condition and risk of severe complications. Adult life expectancy in SCD is at least 2 decades lower than the general population, and more severely affected patients have shortened survival due to the legacy of renal impairment, pulmonary hypertension, cerebrovascular disease and liver disease compounded by episodes of acute life-threatening complications.

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Chapter 14
Vascular Anomalies in the Liver

Arun Kelay and Mark Davenport

Introduction

The vascular set-up in the liver is unique within the body. There is a double, essentially independent, inflow (portal venous, hepatic arterial) into a sinusoidal network designed to present a low-pressure blood flow to stacks of metabolically-active hepatocytes; all draining via a common outflow (hepatic venous) direct to the right side of the heart.

Figure 14.1 illustrates a schematic appreciation of the contents of this chapter. Some anomalies can be considered best as abnormal connectivity, such as congenital porto-systemic shunts (CPSS) and arteriovenous fistulas. Others are more simple structural anomalies of the vascular components such as hepatic aneurysms; portal vein occlusion and thrombosis; and finally congenital hepatic venous outflow problems causing the Budd-Chiari syndrome and veno-occlusive disease. While others are more obviously neoplastic in origin—such as haemangiomas—even here there is a major overlap in their clinical behaviour with congenital arterio-venous fistulas.

Congenital Porto-Systemic Shunts

Although these have been known about for over 200 years since the first description by John Abernethy in 1793 [1], it is only in recent years with rapid advances in liver imaging and increasing awareness that enough cases have been reported to amass reasonable clinical experience. Indeed, up until the 1990s only 15 cases had ever been reported.

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Epidemiology

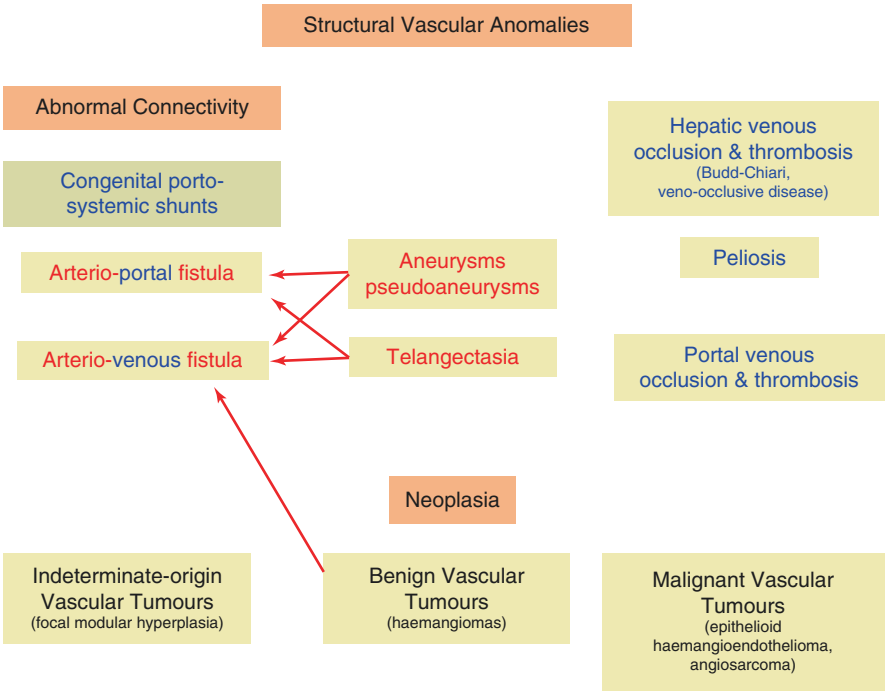

Fig. 14.1 Summary of vascular pathology of the liver

The true incidence of CPSS remains unknown and our data are primarily derived from neonatal screening programmes undertaken to detect hypergalactosemia [2] with one estimate being 1 in 29,000. Still, this is almost certainly an underestimate of the true incidence, as only a minority of children with CPSS are identified through this type of screening programme.

Anatomy

CPSS can be divided into intra- and extra-hepatic shunts [3]. Intra-hepatic shunts are always partial and divert blood from the portal vein (PV) or its branches through to the inferior vena cava (IVC), or a hepatic vein. These may involve the left or right side and can be multiple. A patent ductus venosus (PDV) is a special case of intra-hepatic shunt as it is a persistence of a normal anatomical venous channel between left portal vein and the hepatic venous confluence.

Extra-hepatic shunts can be further subdivided by the degree of portal venous inflow to the liver. The commonest and simplest classification is that of Morgan and Superina from Chicago [4] (Table 14.1). Thus, all portal venous blood empties into

Table 14.1 Simplified classification of CPSS

		Description
Type 1 "h"		End-to-side portal vein to IVC
Type 2 "H"	**A**	R or L portal vein
	B	Trunk of portal vein
	C	Superior mesenteric or splenic vein

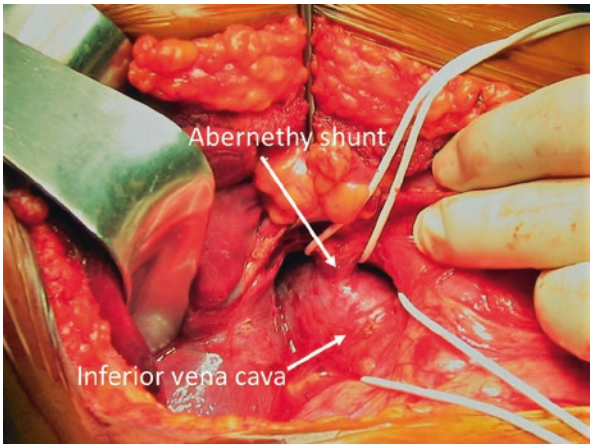

Fig. 14.2 Congenital portosystemic (Abernethy) shunt. The white, vascular slings are around the shunt and the inferior cava. [Photograph kindly contributed by Prof. Gautier, Hopital Bicetre, Paris, France]

the cava as an "end-to-side" Type 1 shunt (*congenital absence of the portal vein*), whereas the connection in a Type 2 shunt is more "side-to-side" with some preservation of the intrahepatic portal venous flow (Fig. 14.2). More complex and esoteric classifications have appeared but offered not much more of a true understanding [5].

A large review of the literature review published in 2013 identified a total of 316 CPSS cases, of which 131 (41%) had an intra-hepatic shunt whilst 181 (59%) were extra-hepatic shunts [6]. The latter was further broken down into 103 (56%) type 1 shunts and 82 (44%) type 2 shunts.

Over the past 15 years though it has been appreciated that the intra-hepatic portal venous system may be somewhat more plastic than formerly realized and what appeared to be inoperable type 1 shunts could actually be closed in a staged fashion without catastrophic portal hypertension [7]. Thus, there should now be a degree of caution in rigidly assigning some CPSS as type 1, without an occlusion test.

Consequences

Attenuated portal venous inflow invariably results in a liver that is smaller than normal and perhaps 45 to 65% of the estimated volume for age. Actual histology is also abnormal and our review of 21 cases [8] defined a number of characteristic changes in peripheral biopsies including (i) presence of prominent thin-walled channels; (ii) arterial-biliary dyads; (iii) increased arterial profiles in the portal

tracts and lobules; and (iv) paucity of the physiological periportal vacuolated hepatocytes.

The consequences of a CPSS may be divided into those that have a detrimental effect on the liver itself and those where the effect is systemic due to flooding of the systemic venous system with unfiltered, unmetabolized blood direct from the mesenteric vascular bed.

Normally 75% of sinusoidal blood arrives in a relatively unsaturated, but nutrient-rich form *via* the portal vein, the remainder of course being fully-oxygenated arterial blood. Sinusoidal saturations may reach 95% compared to normal fasting portal venous saturation of ~85% [9]. As stated, in CPSS there is a gradation of the size of the leak but in some Type 1 shunts all of the sinusoidal blood in the liver is nutrient-poor but fully oxygenated arterial blood and clearly can alter the oxidative sinusoidal microenvironment and may trigger neoplastic change in the hepatocytes (see later).

Tumour formation is increasingly common the older the patient and the degree of portal deprivation is probably the key factor in tumorigenesis. In a study looking at the radiological features of CPSS, we ascribed Type 1 status to 12/45 (27%) [10]. Tumour development occurred in 11 (92%) of these compared to 10/33 (30%) in those with some preservation of intrahepatic venous in-flow. The relative risk was 3.1 where an intrahepatic portal venous system could not be demonstrated. The tumours ranged from benign focal nodular hyperplasia (FNH), nodular regenerative hyperplasia and adenoma to overt hepatocellular carcinoma with an intermediate group currently labelled as "well differentiated neoplasms of uncertain malignant potential". There is some evidence that somatic mutations in beta-catenin gene expression are associated with this malignant transformation [11].

Portal venous diversion may also be felt in a number of other areas. Mesenteric blood bypassing the liver next comes into contact with the vascular bed of the lungs and subsequent vasoconstriction and pulmonary hypertension can be seen as one consequence. Alternatively, unknown unprocessed metabolites open up pulmonary arterio-venous shunts and cause the hepato-pulmonary syndrome (HPS). Such patients present with exertional dyspnoea and can be shown to have hypoxia unresponsive to increasing ambient oxygen levels. The actual mechanism is obscure but presumably involves transient vasoactive mediators that remain unmetabolised. Porto-pulmonary hypertension (PoPH) may also occur with the histological hallmark being plexogenic pulmonary arteriopathy, reflecting the progressive remodeling of the wall of the small pulmonary arteries with mural thickening and vasoconstriction.

The mechanisms of the neurodevelopmental consequences of CPSS are not clear but become increasingly evident with age. In early life this may manifest as global developmental delay and cognitive impairment with possible autistic features. Intermittent encephalopathy is a feature seen in the adolescent or adult with CPSS. MR scan changes have been reported such as an abnormal hyperintense signal in the globus pallidus on T1-weighted scans. Almost invariably there is a mild rise in plasma ammonia levels though this seems to correlate poorly with the symptoms and it is doubtful that this compound is in itself causative.

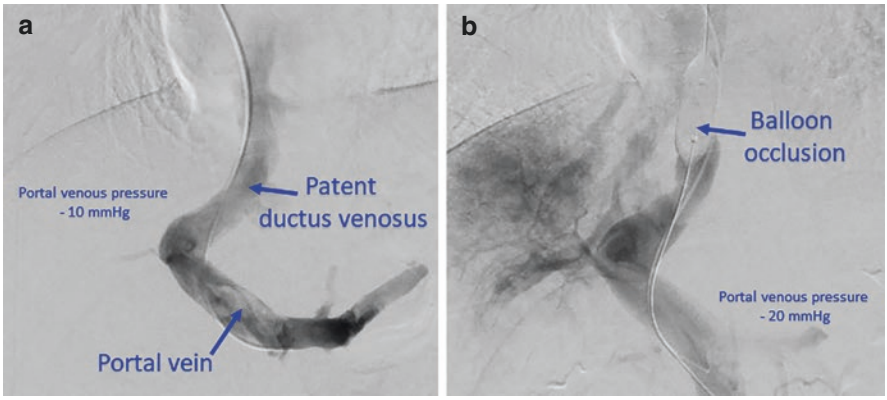

Fig. 14.3 Patent ductus venosus. 13 year old boy with incidental finding of large patent ductus venosus. Retrograde hepatic venogram showing (**a**) communication via left portal vein, and (**b**) balloon occlusion in PDV showing restoration of predominantly right-sided portal venous flow

Clinical Features

Adolescent Demography

Admittedly, most CPSS present during childhood but a significant proportion do not, and either appear with symptoms during adolescence (Fig. 14.3) or even as adults. Most by this stage have overt complications such as pulmonary hypertension, hepatopulmonary syndrome, hepatic encephalopathy and the formation of liver tumours. A literature review (n = 316) published in 2013 [7] showed that 10% of CPSS were diagnosed in adolescence, and 24% were detected in adulthood.

The Hôpital Bicêtre group in Paris have had a major interest in this condition for a number of years and one study illustrates the impact during adolescence [7]. Of 22 patients who presented with symptoms over a 22 year-period, 9 (41%) became symptomatic during adolescence. These included a 10-year-old boy with a history of oesophageal atresia and congenital heart disease who re-presented with jaundice and anaemia and was shown to have an adenoma occupying the entire right lobe and an end-to-side PV to IVC shunt. Two patients presented at 11 and 12 years of age with exertional dyspnoea secondary to pulmonary hypertension and were found to have multinodular livers. Another patient presented at 13 years with exertional dyspnoea and cyanosis secondary to hypoxaemia with an SpO2 of 90% in air as a result of HPS.

Associations

Cardiac anomalies represent the most common association, present in 68 (22%) of 316 patients from the 2013 Toronto review [6]. These were mostly simple defects including ventricular septal defect (VSD) in 18, atrial septal defect (ASD) in 17 and coarctation of the aorta in 4.

Some defined syndromic associations exist with CPSS, with 28 (9%) identified in the aforementioned review [6]. Trisomy 21 (n = 11) appears to be most common but Turner syndrome (n = 3), Leopard syndrome (n = 2) and Noonan syndrome (n = 2) have also been described. Our own review highlighted the association of CPSS (and other vascular abnormalities) with trisomy 21 in 3 children [10]. A further 7 patients were identified from the literature, two of whom developed neonatal cardiac failure.

Abdominal anomalies may also be seen in <10% of cases and most of these appear to be related to splenic malformation, such as polysplenia and situs inversus.

Liver Tumours

This is probably the most important complication and source of most concern. Indeed, liver tumours may be the main presenting feature in adolescents and young adults or may occur during follow-up of a patient with a known CPSS managed conservatively.

The importance of close follow up in anyone diagnosed as having a CPSS is illustrated by the outcome of a girl diagnosed with a side-to-side PV to IVC shunt at the age of 5, which came to light after investigations for hepatomegaly [7]. At diagnosis she had a multinodular liver, was later lost to follow up for several years and did not receive any treatment for her CPSS. She was reviewed at the age of 19 with abdominal pain and was noted to have hepatomegaly with a raised serum alpha-fetoprotein (AFP) level. A post-mortem examination undertaken after her death one month later revealed multifocal HCC together with multiple adenomas, the former being responsible for her demise.

A high index of suspicion for the development of malignancy must be maintained. This should prompt liver biopsy in children displaying large tumours >5 cm, serial tumour enlargement, atypical appearances for FNH or nodular regenerative hyperplasia and elevated serum AFP levels.

Pulmonary Hypertension

Pulmonary hypertension (PH) may manifest as exertional dyspnoea, syncope or with features of right heart failure. The histological hallmark in the lungs is a plexogenic arteriopathy, reflecting progressive remodeling of the wall of the small pulmonary arteries with thickening and vasoconstriction [3]. A review of PH in liver disease [11] showed the onset of PH in children with CPSS throughout childhood and into adulthood, with 7 of 22 cases arising between the ages of 10 and 20 years and a further 3 identified from 22 to 32 years of age.

Outcomes from the Hôpital Bicêtre 22-year cohort showed that CPSS closure could prevent further deterioration of PH. There was no progression of PH in three children aged 5, 11 and 12 years at initial PH diagnosis when right heart

catheterisation was undertaken at 2 to 10 years post-shunt closure. They are now maintained with the pulmonary vasodilators, bosentan and sildenafil.

Thus, it is imperative to identify the emergence of pulmonary hypertension at any early stage in children with CPSS through regular echocardiography to initiate definitive treatment and attempt to prevent the development of irreversible pulmonary vascular changes.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) presents with dyspnoea, hypoxaemia and arteriovenous shunting on pulmonary scintigraphy and may precede the onset of PH. The interval between diagnoses of HPS and PH can range from 4 months to 19 years [12]. Both pulmonary complications have also been reported synchronously in a further three children. Of course, the actual CPSS may remain undetected in cases of HPS [3]. A further intriguing relationship exists with polysplenia and this combination with CPSS seems to be particularly complicated by the development of HPS.

Shunt closure can be expected to resolve HPS in the majority—as observed in 18 of 19 children who underwent shunt closure—or at least improve pulmonary status [9].

Hepatic Encephalopathy

The constellation of symptoms attributable to portosystemic encephalopathy represent the most insidious complication of CPSS. Children with a hitherto undetected CPSS can manifest global or more specific developmental delays over a number of years with associated difficulties in school. There can be additional behavioral problems, a formally diagnosed attention deficit hyperactivity disorder [13] and even seizures. A proportion will present with clear features of portosystemic encephalopathy through exhibiting drowsiness or confusion after meals. On examination, abnormal extrapyramidal neurological signs may be detected but are rare. Biochemically, hyperammonaemia is extremely common. An electroencephalogram (EEG) may show slow waves and an MRI scan may show high signal intensity in the region of the globus pallidus.

A total of 111 (35%) patients from the 316 included in the 2013 Toronto literature review had developed encephalopathy [6]. Fifteen were diagnosed during adolescence, whilst 34 were only recognised in adulthood.

Such neurological changes are reversible following shunt closure. Ammonia levels should normalize and even established MRI changes can resolve. Complete normalisation of neurological sequelae, however, is not common though improvement is to be expected.

Endocrine Abnormalities

Hyperandrogenism has been described in two teenage girls—at 14 and 15 years of age—together with hyperinsulinaemia [14]. The CPSS in the former patient was diagnosed after liver dysfunction was identified on preoperative blood tests prior to tonsillectomy. She was found to have primary amenorrhoea and virilisation, with hyperandrogenism and insulin resistant hyperinsulinaemia. Reduced hepatic degradation of insulin is presumed to lead to the hyperinsulinaemia. The putative mechanism of hyperandrogenism is stimulation of androgen production in the ovary and adrenal gland by insulin, as suggested in patients with polycystic ovarian syndrome.

Management

Although small CPSS between portal branches and hepatic veins may spontaneously resolve by the age of 1 to 2 years—as observed in 12 children from the 2012 review [3]—the majority persist throughout childhood into adolescence and engender the risk of complications.

Benign tumours respond well to shunt closure alone—whether surgical or radiological—with significant regression or complete resolution of the tumour in most. These results suggest that benign tumours can be managed with shunt closure only, while simultaneous resection and shunt closure are reserved for malignant tumours.

Symptomatic CPSS mandate intervention to achieve stabilisation or potential resolution of the aforementioned complications. In cases with associated cardiac anomalies it is essential to determine which symptoms are truly attributable to the CPSS. Controversy exists with regard to the indications for intervention in asymptomatic patients. However, compelling arguments for early intervention include prevention of the development of complications, protection of the developing brain from raised ammonia and manganese levels and exploitation of the presumed enhanced plasticity of the intrahepatic portal venous system at a younger age.

Endovascular techniques have gained progressive prominence though the specific shunt anatomy dictates whether radiological and/or surgical techniques should be employed. Endovascular occlusion can be attempted in situations where the anatomy implies that the Amplatzer device or coils will remain within the shunt, with low risk of migration into the systemic circulation. The position of the occlusive device must also permit subsequent development of the portal venous system and not impede flow in the IVC or HVs.

Certain anatomical configurations demand surgical closure, such as side-to-side PV to IVC shunts. In some cases—including an “end-to-side” main PV to IVC shunt—a two-stage surgical procedure is necessary to minimise the risk of inducing acute portal hypertension. This decision will be guided at the point of shunt occlusion by an assessment of portal venous pressure and bowel perfusion. A 15-minute clamping test is recommended to gain an adequate understanding of the haemodynamic effect of shunt closure.

When a two-stage procedure is selected the shunt is banded at the first stage which prompts hepatopetal portal venous flow and the subsequent development of the intrahepatic portal network. At the second stage several months later, the shunt is completely closed, ensuring that this is achieved immediately adjacent to the systemic circulation to maximise portal venous flow.

Arterioportal Fistulae

Arterio-portal fistulae (APF) are abnormal connections between the high-pressure hepatic arterial network and the low-pressure portal venous system. They, therefore, cause non-cirrhotic pulsatile portal hypertension with its consequences of splenomegaly, gastrointestinal varices and occasionally ascites and oedema. If congenital it may also cause failure to thrive. Cases can be divided into congenital and acquired with a long list of secondary causes such as penetrating and blunt liver trauma, percutaneous biopsy and post-surgical (e.g. Kasai portoenterostomy). Congenital arterioportal fistulae (CAPF) can be multiple or diffuse fistulae [15], whilst an isolated fistula may point to a prior precipitating event.

A team from British Columbia proposed an angiographic classification based on afferent arterial supply as these vessels are both the target of intervention and their anatomy is the key determinant of outcome [15]. Type 1 intrahepatic APF (IAPF) refers to afferent supply from either right or left hepatic artery (RHA or LHA) or the main HA exclusively. Bilateral supply from both RHA and LHA is classified as Type 2 IAPF. A combination of RHA and/or LHA with further afferent arterial supply not arising from the hepatic artery (e.g. gastric artery) constitutes complex supply, classified as Type 3 IAPF. A literature review in 2006 identified 30 paediatric cases with a mean age at presentation of 3 years and a range of 1 week to 16 years [15]. Unilateral IAPF accounted for 17 (53%) of cases and tended to present later than bilateral or complex IAPF at a mean age of 5 years, but again with a wide range of 3 weeks to 16 years.

Doppler ultrasound is the initial imaging modality of choice and in addition to the shunt, typically shows: (i) dilatation of both the artery and vein; (ii) pulsatile hepatofugal flow in the portal vein; and (iii) aneurysmal dilatation of the portal vein and turbulent flow within it [16]. Angiography with digital subtraction permits precise assessment of shunt anatomy for operative planning.

As an example, a type I IAPF was fortuitously identified in an initially asymptomatic 13 year-old who presented to his general practitioner with an asthma attack [21]. An epigastric murmur was detected on examination, subsequently shown to be from a solitary IAPF from the LHA to the left portal vein (LPV). During the period prior to planned angiography he developed haematemesis and melaena. Endoscopy showed grade III oesophageal varices and portal hypertensive gastropathy. Successful occlusion of the IAPF was achieved with an Amplatzer occlusion device restoring normal hepatopetal portal venous flow and resolution of his varices [22].

Transarterial embolisation (TAE) is the mainstay of treatment for the majority of IAPF with simple anatomy and has proven definitive in 10 patients with unilateral (Type 1) IAPF [15]. The presence of bilateral arterial inflow (Type 2) may necessitate multiple endovascular procedures, or indeed surgical ligation. Complex IAPF often require a combination of radiological and open surgical techniques due to their propensity for collateralisation or simply recurrence after initial embolisation. Partial hepatectomy and even liver transplantation have been undertaken after unsuccessful prior endovascular procedures.

Arterio-Venous Malformation

Congenital AV malformations typically present during infancy with failure to thrive or cardiac failure and are dependent on the size of the shunt. Rarely do significant ones remain silent until adolescence. There is also a degree of overlap with haemangiomatous lesions as described later. Acquired AV fistulae are a possible complication of penetrating and blunt liver trauma sharing the same mechanism as pseudoaneurysms and these are much more likely to be the aetiology of a presentation during adolescence. They of course can remain clinically silent, though perhaps a bruit may be discernable if sought. Doppler ultrasound is the usual first investigation followed by CT angiography to define anatomy. Angiography and embolisation is the principal method of treatment.

Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), formerly known as Osler-Weber-Rendu syndrome, is a rare autosomal dominant condition involving multiple arteriovenous malformations scattered throughout the lungs, gastrointestinal tract, brain and liver etc. The commonest presenting features are recurrent epistaxis and gastrointestinal bleeding from telangiectatic lesions. There are two clinical types, 1 and 2 which correspond to different mutations in *ENG* (Ch9) and *ALK1/AcVRL1* (Ch12). Most clinical data is from adult series where liver involvement is suggested in up to 80% of affected individuals, albeit with a much lower proportion—about 5%, that might be considered symptomatic. An Italian group screened a group of 30 children with HHT using multi-slice CT scans and identified specific lesions in 35%, all clinically silent [17]. Hepatic arterial dilatation was only seen in those with HHT Type 2.

Liver lesions may cause arterio-venous shunting and even high-output cardiac failure and pulmonary hypertension, though arterio-portal fistulae can be clinically relevant. Currently, in addition to the routine treatment options for hepatic AVM, the

anti-vascular endothelial growth factor (VEGF) humanized monoclonal antibody, Bevacizumab, may have a specific role in controlling the hepatic telangiectasia lesions [18].

Hepatic Arterial Aneurysms, Pseudoaneurysms & Telangectasia

Aneurysm & Pseudoaneurysm

True hepatic artery aneurysms are rare and occur in the setting of a generalized arteriopathy such as polyarteritis nodosa, Ehlers-Danlos syndrome [19]—both more typical of adult population, and maybe Kawasaki disease, occuring in a younger age group. Most intrahepatic aneurysms when part of a systemic disorder are clinically silent, at least during childhood [19].

Pseudoaneurysms are, however, a relatively common sequel to blunt or penetrating liver injury in children and adolescents (Fig. 14.4). The affected individuals reflect the usual predisposing characteristics for the underlying liver trauma in being predominantly male and related to road traffic accident, horse riding or cycle handlebar trauma. Penetrating injury due to knife attack is almost exclusively seen in adolescent boys as well. The overall incidence of pseudoaneurysms is disputed and was formerly held to be only a rare event. More detailed post-injury follow up using CT scanning and especially contrast-enhanced ultrasound (CEUS) has shown this view to be erroneous. Durkin et al. from our institution identified 14 patients with PA formation, 25% of all those children and adolescents (median age 14 years) admitted with liver trauma [20]. There was no association with grade of liver injury or the overall injury severity score. About 40% of the lesions developed symptoms (e.g. drop in haemoglobin, abdominal pain etc.) and were treated by urgent interventional embolisation.

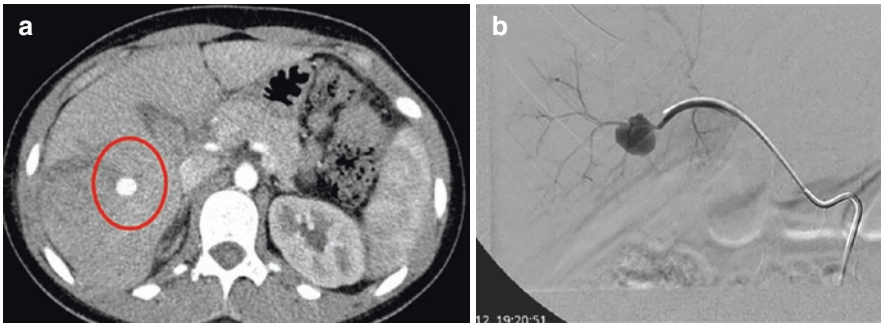

Fig. 14.4 Hepatic arterial pseudoaneurysm. 13-year-old girl with blunt liver trauma due to a horse-riding accident. CT scan (**a**) and hepatic angiogram (**b**) showing right lobe arterial pseudoaneurysm. Treated by embolisation (not shown). [Images kindly contributed by Ms. Erica Makin, Kings College Hospital, London, UK)

Mycotic aneurysms follow septic emboli (bacterial or fungal) which lodge in the hepatic arterial network and in adult practice are typically found in intravenous drug users. Liver transplant recipients may also be susceptible and Camagni et al. describe 4 paediatric cases in their series [21].

Hepatic Venous Anomalies

Budd-Chiari Syndrome

This syndrome implies venous occlusion of the major hepatic venous outflow and has a multiplicity of causes, most not particularly relevant to the adolescent. However, congenital venous webs have been described which can present with the typical features of hepatomegaly, caudate lobe sparing, ascites and portal hypertension.

Most experience with BCS in children and adolescents has been reported from South Asia. For instance, Shukla et al. from Mumbai, India reported the largest experience of BCS in 43 adolescents [22]. By comparison with younger children and adults, this group experienced less episodes of ascites, and tended to present with hepatomegaly alone. Thrombogenic disorders were identified in 37% and the *JAK-2 V617F* mutation was found in 3 patients. Response to therapy was also better than in younger children.

Our own recent experience with BCS in children is smaller [23] with all 7 children having an associated thrombogenic predisposition. Transjugular intrahepatic portosystemic shunt (TIPS) was the predominant therapy although liver transplant and a mesocaval shunt were also performed. There was a single late death.

Veno-Occlusive Disease (Sinusoidal Obstruction Syndrome)

This term implies occlusion to the smaller intrahepatic central venules and is almost always secondary to some acquired toxic event. An alternative name is sinusoidal obstruction syndrome (SOS). It can be divided into acute, sub-acute and chronic depending on the timing of presenting features. The latter is more insidious in onset with hepatomegaly, splenomegaly and established portal hypertension [24].

Currently the commonest cause is chemotherapy or bone marrow ablation regimens involving the agents busulfan and melphalan. Typically these agents may be used for myeloablation in stem cell and bone marrow transplants or the initial chemotherapy of acute lymphoblastic leukaemia (especially thioguanine). In some parts of the world chronic SOS has also been linked with consumption of bush or herbal teas containing pyrrolizidine alkaloids (e.g. Senecio or Crotalarias).

Management is typically supportive but specific agents such as defibrotide [25] seem to have consistent benefit while N-acetyl cysteine and ursodeoxycholic acid may also have a role in acute VOD [24].

Peliosis Hepatis

The first description of this rare and potentially lethal disease of unknown aetiology was in German as a '*Blutcyst'* by Wagner in 1861 [26]. The term *peliosis* derives from the Greek word for purple and refers to its appearance secondary to the extravasation of blood within an organ, usually the liver but others such as the spleen can also be involved. A multiplicity of blood-filled cysts throughout the liver parenchyma is probably due to dilatation and destruction of the limiting walls of the sinusoidal lumen or space of Disse [27] (Fig. 14.5).

Two peliotic patterns have been described—parenchymal and phlebectatic [28]. The former is evidenced by blood-filled cysts lacking an endothelial lining, dispersed throughout the lobule with potentially concomitant hepatocellular necrosis. The latter describes cysts lined by endothelium, with a centrilobular distribution incorporating communications with the hepatic sinusoids. These cysts have also been noted within other organs of the reticuloendothelial system including the spleen, lymph nodes and lung.

As in adults, it predominantly manifests on a background of a chronic systemic illness including cystic fibrosis and Fanconi anaemia. A link with infectious agents has been suggested including urinary tract infection due to *Escherichia coli* in children [29] and *Bartonella henselae* in adults. Multiple drugs have also been implicated in its pathogenesis in adults, including anabolic steroids, immunosuppressants such as azathioprine and 6-mercaptopurine as well as the oral contraceptives.

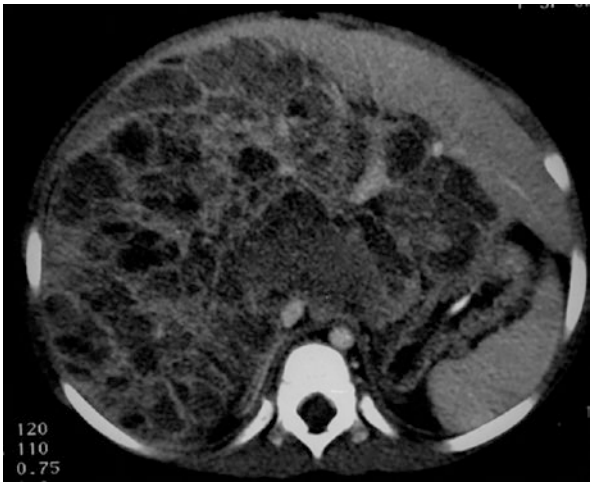

Fig. 14.5 Peliosis. Three-year-old girl with acute onset hepatomegaly and haemoperitoneum. MR images show disruption of liver architecture and multiple vascular spaces. Full recovery after supportive care. [Reproduced with permission from Quaglia A, Davenport M. Benign Liver Tumors. In: Surgery of the Liver, Bile Ducts and Pancreas. Davenport M, Heaton ND, Superina R. (3rd ed) CRC Press; 2017]

Presentation ranges from an incidental imaging finding, through non-specific abdominal pain to acute liver failure and life-threatening hypovolaemic shock secondary to intraperitoneal haemorrhage. It is often initially mistaken on imaging for primary or secondary liver tumours, abscesses or focal nodular hyperplasia. Imaging features are variable and definitive diagnosis rests on histology, which may only be available *post-mortem*.

An adolescent example of peliotic hepatic lesions was identified 18 months after the introduction of oxymethalone therapy for a new diagnosis of Fanconi anaemia in a 10 year-old boy [30]. He subsequently developed hepatomegaly and abnormal liver function tests prompting imaging with US. This showed multiple hypoechoic areas containing small cysts, which were hyperintense on both T1- and T2-weighted MRI. The diagnosis was reached through combining the imaging features with the context of anabolic steroid therapy. One warning of note is that percutaneous biopsy can be extremely hazardous, due to the attendant risk of bleeding [31].

As similar case was reported by Choi et al. in a 20-year-old man who had been taking oxymethalone for Fanconi anaemia [32]. He presented with profound shock, marked anaemia and increasing abdominal distension. A CT scan of the abdomen showed right lobe liver pathology and presumptively spontaneous liver rupture. Angiography showed multiple small contrast-filled round lesions throughout the right lobe suggestive of peliosis hepatis. He survived though a hemi-hepatectomy was required.

Peliosis hepatitis can also arise in the absence of an underlying systemic disease though these tend to be younger. Samyn et al. [27] described four such children with multi-organ failure being the mode of presentation in all. *Escherichia coli* could be also often isolated, suggesting some kind of causal relationship.

No specific treatment exists, though consideration should be given to the immediate discontinuation of potentially-related pharmacological therapies. In the setting of intraperitoneal haemorrhage, laparotomy appears to represent the best approach for achieving haemostasis.

Portal Vein Occlusion and Thrombosis

As portal hypertension is the main clinical sequel to portal vein anomalies then this is largely covered elsewhere in more detail (see Chap. 11). However, it is worth considering some issues as separate examples from the perspective of “vascular anomaly”.

Extrahepatic Portal vein occlusion (EHPVO), is the principle manifestation of portal venous pathology and can have a multiplicity of causes. Some are probably congenital and structural and usually seen in association with other vascular or skeletal anomalies as part of a syndrome. About 20% of our historical series of EHPVO had one or more of these features (unpublished observation). Other cases appear to arise as acquired thrombosis during the neonatal period with secondary

collateralization forming a "cavernoma" [33]. Prematurity, umbilical vein catheterization and abdominal sepsis are common features which seem to predispose leading to later presentation some years later with established varices or splenomegaly [34]. Initial presentation during adolescence with a congenital or a neonatal acquired cause is, however, rarely observed but possible. Typically, adolescents with portal vein thrombosis have a different set of causes such as a history of portal pyaemia and pylephlebitis. The frequent predisposing cause could be complicated appendicitis or inflammatory bowel disease. Another possible underappreciated cause in this age group is portal vein thrombosis post-splenectomy [35]. Very large spleens seem to be particularly at risk for this scenario and with these, surveillance Doppler ultrasound scans may prompt early anticoagulation.

Benign Vascular Tumours

The terminology of hepatic vascular tumours can be confusing and may at times include congenital haemangioma, infantile haemangioma (IHE), cavernous haemangioma (CH), and arteriovenous malformations (AVM) (Table 14.2). Cavernous haemangioma is the usual nomenclature for those presenting in adolescents or young adults, merging into the common adult liver haemangiomas, though even these may be congenital in origin. Most of these are asymptomatic, and therefore treated conservatively.

Infantile hepatic haemangiomas (IHH) are better characterised using a 2007 classification, developed by a multidisciplinary team from Boston Children's Hospital [36, 37]. They defined three forms of IHH—focal, multifocal and diffuse—each with fairly distinct pathophysiology and radiological appearances. Focal IHH are often detected antenatally, are typically asymptomatic and almost

Table 14.2 Hepatic tumours with vascular elements

		Glut-1	Growth potential	Age group & gender
Benign				
Infantile & congenital	**Focal**	-ve	↑↓	M = F
	Multifocal	+ve	↑↓	F > M
	Diffuse	+ve	↑	F > M
Cavernous haemangiomas		-ve[a]	Indolent (usually) ↑ (possible)	M = F 10 y onwards
Focal nodular hyperplasia		-ve	↑	F > M 6 y onwards
Malignant				
Epithelioid haemangioendothelioma		+ve (~30%)[a]	↑↑	M = F
Angiosarcoma		+ve (~50%)[a]	↑↑	M = F

[a] Gill et al. [55]

invariably without associated cutaneous haemangiomas. Their behaviour mimics that of cutaneous Rapidly Involuting Congenital Haemangiomas (RICH). They accordingly do not stain positively for the erythrocyte-type glucose transport protein GLUT-1. On MRI they appear as a well-circumscribed, spherical tumours, with T1-weighted sequences showing hypointensity and T2-weighted sequences hyperintensity relative to the liver. As with their cutaneous counterpart, they exhibit three phases of development: (i) rapid proliferation and growth commencing in early postnatal life and continuing for 9 to 12 months; (ii) subsequent involution occurring over 5 to 7 years with progressive replacement of the previously proliferating endothelial and myeloid cells with stromal tissue; and (iii) a quiescent state with fibrofatty tissue persisting in place of the original vascular lesion.

It is likely that the majority of IHH remain entirely asymptomatic. However, an increasing proportion are identified on antenatal imaging with some becoming symptomatic during infancy, most often with features of high-output cardiac failure secondary to high-flow arteriovenous shunting [38]. The mass effect of the abnormally enlarged liver can produce abdominal compartment syndrome, and liver function itself can be disrupted culminating in liver failure.

Multifocal IHH are frequently identified on imaging obtained after detection of multiple cutaneous haemangiomas. As for cutaneous IHs they demonstrate positive GLUT-1 immunostaining. Arteriovenous or portovenous shunting can prompt high-output cardiac failure. This is reflected by dilated hepatic arteries or veins or tapering of the aortic calibre beyond the coeliac axis on CT [38]. The lesions themselves are hypodense on CT, with uniform or centripetal enhancement.

The liver parenchyma can be almost completely occupied by myriad haemangiomas in the diffuse form of IHH, heralding greater morbidity compared with the other two patterns of hepatic involvement. Massive hepatomegaly may prompt respiratory distress and even abdominal compartment syndrome. Somewhat counterintuitively, high-output cardiac failure was not noted in this group in the Boston review [36].

Thyroid dysfunction may also be seen in IH, both hypo- and hyperthyroidism [39–41]. Overproduction of type III iodothyronine deiodinase, produsedby the tumour tissue, seems to be a mechanism for hypothyroidism in diffuse or multifocal IHH.

Management is guided by the type of IHH encountered and the presence of symptoms. Children with asymptomatic focal or, less commonly, multifocal disease may simply be observed with serial ultrasound scans. Symptomatic cases with significant shunts can initially be managed with medical therapy—previously corticosteroids, but now primarily propranolol to induce lesion regression—which may also include diuretics and digoxin or ACE-inhibitors, to manage the high-output cardiac failure. Failure of medical management may prompt liver resection if single, or embolisation/ligation of the hepatic artery, even transplantation, if multifocal or diffuse [38].

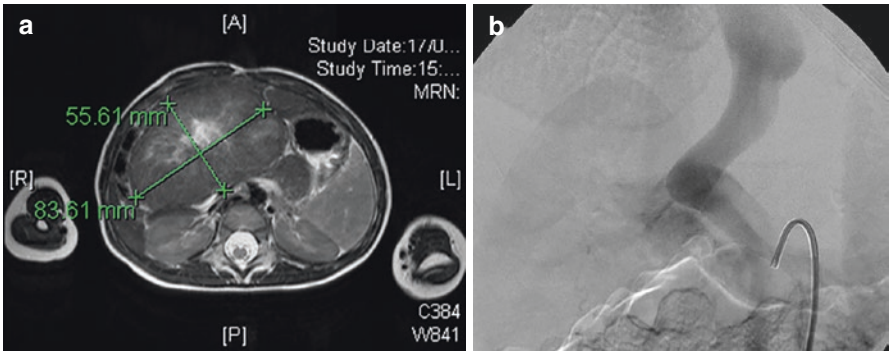

Fig. 14.6 (**a & b**) Focal nodular hyperplasia and porto-caval shunt. Five-year-old girl presenting with exophytic abdominal tumour (**a**), resected as left hepatectomy. Only later during follow-up was a congenital portal caval shunt (Type 1) detected (**b**—angiography shown). [Reproduced with permission from Quaglia A, Davenport M. Benign Liver Tumors. In: Surgery of the Liver, Bile Ducts and Pancreas. Davenport M, Heaton ND, Superina R. (3rd ed) CRC Press; 2017]

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is a rare lesion that may be an isolated finding typically in adolescent girls, or in association with certain conditions such as hereditary hemorrhagic telangiectasia, following hematopoietic stem cell transplantation or congenital porto-systemic (Abernethy) shunts [10] (Fig. 14.6).

The aetiology of the disease is still unknown, although there is undoubtedly a disturbance in the normal vascular supply to the liver. Most present later in childhood and adolescence either discovered incidentally or following investigation for relatively non-specific symptoms [42, 43]. Some larger lesions can compress adjacent organs and present with abdominal pain. The US appearance of FNH is of a mass with different degrees of echogenicity, but with a characteristic hyperechogenic central scar. Doppler studies show that about half are hypervascularised, with an arterial-type flow that radiates from the centre towards the periphery. CT scan shows FNH to be hypodense or isodense compared with liver parenchyma with a characteristic central scar enhancement in the arterial phase followed by a slight enhancement on the portal venous phase.

There is no evidence that that FNH undergoes malignant transformation, and only a few cases have been complicated by rupture and haemoperitoneum. A non-operative approach may be appropriate if the lesion is asymptomatic and remains non-progressive, after malignancy has been categorically ruled out.

Malignant Vascular Tumours

Hepatic Epithelioid Haemangioendothelioma

This represents the visceral form of the rare intermediate-grade vascular sarcoma first described as epithelioid haemangioendothelioma (HEH) by Weiss and Einzinger in 1982 [44] with reference to soft tissue vascular tumours of endothelial origin. Visceral involvement can also include the lungs and spleen often manifesting multifocal lesions. Clinical course spans the spectrum from spontaneous regression, through benign behaviour similar to IHH, to a malignant phenotype as encountered with angiosarcoma [44–46]. HEH is the third most common unresectable paediatric liver tumour requiring liver transplantation.

The macroscopic appearance is white, usually multinodular with a firm consistency. Microscopically, the tumour is composed of epithelioid and dendritic cells with intracellular vacuoles. Immunohistochemical staining is positive for at least one endothelial marker—factor VIII-related antigen, CD31 and/or CD34 [47]. A disease-defining t(1;3)(p36;q25) chromosomal translocation has since been identified [48].

A recent 2017 literature review identified 25 children with liver and/or lung EH [49]. The median age at diagnosis was 12 years (range, 4.4–18 years), with 21 (84%) diagnosed at or beyond 10 years of age. Multifocal disease was present in 23 (96%), with multiorgan involvement in 18 (72%). Abdominal pain was the presenting feature in 5 cases, whilst 6 were asymptomatic. Features of Budd-Chiari syndrome or portal hypertension such as ascites prompted investigation and diagnosis in 3 patients.

Conventional chemotherapy alone was administered to 4 patients with liver and lung involvement. Two—aged 12 and 15 years—died of progressive disease within one year of diagnosis. The other two patients had stable disease at up to 2 years following diagnosis. Chemotherapy was combined with liver transplantation in three adolescents, two of which also had lung EH. Complete remission was achieved in terms of the liver involvement together with stable lung disease [49]. One further 13 year-old girl with Budd-Chiari syndrome and ascites was treated primarily with liver transplantation, but died of transplant-related complications within a year.

Complete surgical resection is essential to achieve remission, usually achieved through transplantation in the setting of unresectable disease. A nationwide American series of paediatric liver transplantation from 1987–2001 showed five-year survival for HEH at 60%, lower than for HB (72%), but more favourable than HCC (53%) [50].

Hepatic Angiosarcoma (HAS)

In contrast to HEH, HAS is a uniformly malignant neoplasm with poor prognosis, though it may also arise from the vascular endothelium. Histologically, these appear as hypercellular whorls of spindle shaped cells interspersed with biliary ductules,

blood vessels and collagen. The cells usually contain Periodic acid Schiff-positive eosinophilic granules and stain focally for Factor VIII antigen and α-1-antitrypsin. Immunohistochemistry for the endothelial cell markers CD31 and CD34 is positive and the lymphatic marker podoplanin may also be seen. The incidence of angiosarcoma overall is 2 in 1,000,000 and it represents 1–2% of all paediatric liver tumours, with less than 50 cases described in the literature [51]. There is a female preponderance and mean age at diagnosis of 3 years [52].

Worryingly, malignant transformation from IHH and benign haemangioendothelioma has also been reported [53, 54]. A combined series of HAS from America, Australia and Poland described 8 patients all of whom were initially diagnosed with IHH or haemangioendothelioma [52]. Mean length of time from initial symptoms—abdominal pain and/or distension in 5—to confirmation of HAS was 1 year. Metastatic disease (lungs, brain, bone, skin) was present at diagnosis of HAS in 5 out of 8 children. The characteristic IH marker GLUT-1 can also be immunoreactive in HAS, which contributes to initial diagnostic uncertainty. It is plausible that previous reported cases of malignant transformation originally reflected low-grade HAS.

All children in our 1997 series died [53]. The 2017 multicentre series [52] was similarly bleak though there were 2 survivors in their 8 children but both required liver transplant and were disease-free at 3 and 5 years post-transplant.

Key Point for Adult Hepatologists

- **Congenital porto-systemic shunts**, typically the portal-caval or Abernethy shunt, my present later in childhood, adolescence or even as an adult with encephalopathy, liver tumours (including focal nodular hyperplasia) and less commonly pulmonary hypertension or hepatopulmonary syndrome.
- Investigate with colour Doppler ultrasonography, MR venography or contrast CT scan, and a cardiac echocardiogram. Measure plasma ammonia levels.

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Part III
Liver Transplantation in Adolescence

Chapter 15
Patient and Graft Outcome in Paediatric Liver Transplantation

Naire Sansotta, Paola Stroppa, and Lorenzo D'Antiga

Worldwide Practises and Long Term Outcome

Pediatric liver transplantation (LT) has dramatically changed the prognosis of many infants and children with different types of end-stage liver disease [1]. According to recent US Studies in Pediatric Liver Transplantation (SPLIT), patient survival rates at 1 and 5 years after LT reach 91.4% and 86.5%, respectively [2–9]. The European Association for Study of the Liver reported significantly improved survival rates in the last 25 years, achieving 96% and 71% at 1 and 10 years after LT, respectively as well [10]. In agreement with these results, the Japanese liver transplantation society (JLTS) found that 1–5–10 and 20 year survival rates in their patients were 91.6%, 91.5%, 87.1% and 79.9%, respectively [11]. The documented 5 year survival rates for transplantation are >90% for chronic liver disease and 89% for metabolic liver disease [12, 13].

In our Center, in a cohort of 620 LT pediatric recipients followed in the last 20 years, patient survival rates at 5, 10 and 20 years after LT are 86.4%, 84.1% and 78.9%, respectively (Fig. 15.1), whereas graft survival reaches 63.7% at 20 years from LT.

In a cohort of 806 post-liver transplant children, the predictors of patient survival were found to be renal function, mechanical ventilation at time of transplantation and aetiology of liver disease [14]. In other studies, donor BMI, ABO incompatibility, graft type, recipient age, center experience and transplant era were found to be significant predictors of overall graft survival [11]. The main causes of graft loss in the first weeks include primary nonfunction, hepatic artery thrombosis or portal

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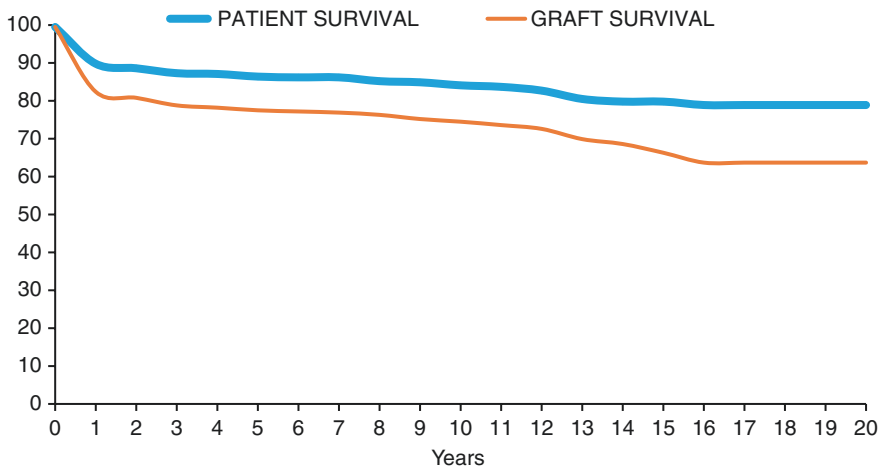

Fig. 15.1 Kaplan-Meyer curve of patient and graft survival in paediatric liver transplant recipients followed at Hospital Papa Giovanni XXIII of Bergamo (620 patients)

vein thrombosis, systemic sepsis and multiorgan failure (<10%) [1]. Rejection, either acute or chronic, was the most common cause of late graft loss in 48.5% of cases, followed by hepatic artery thrombosis and biliary strictures in 20%. Independent factors associated with late graft loss were malignancy as indication for LT, occurrence of steroid resistant rejection, surgery within 30 days from LT and more than 5 hospital admissions during the first post-transplant year [2]. Late mortality for patients in the SPLIT database was caused by malignancy, infections, multisystem organ failure and post-transplant lymphoproliferative disorder (PTLD). In the first years following LT, recurrence of the underlying disease is a common problem. Disease recurrence can be viral (most commonly hepatitis B, C), immunological (autoimmune hepatitis, primary sclerosing cholangitis), metabolic (non-alcoholic fatty liver disease), malignant (hepatocellular carcinoma, hepatoblastoma) or idiopathic [15]. Multiple factors impacting the liver graft survival are described in Fig. 15.2.

As survival rates increase, the resources are allocated mainly to long-term care. Moving away from immediate survival and the prevention and management of early post-operative complications, the attention has been focusing on long term outcomes and quality of life. Most LT recipients are seen by the transplant center once a year, while general practitioners take care of the patients in shared care. The long term issues include adverse effects of immunosuppression (such as chronic kidney disease, hypertension, hyperlipidaemia), the development of malignancies (post-transplant lymphoproliferative disease, skin tumors) and the management of adolescents' transition to adult care [15].

Fig. 15.2 Factors affecting long-term allograft survival after paediatric liver transplantation. *DSA* donor-specific antibodies, *AutoAb* Non organ specific autoantibodies

Graft Outcome Including Protocol Liver Biopsies at 5 and 10 Years Post LT

Long term allograft health is currently the primary aim in liver transplantation. However, the only reliable tool reflecting graft status is liver histology.

The majority of post-transplant liver biopsies are performed in response to changes in liver enzyme levels and/or abnormal imaging findings (*per cause* biopsies). However, as patient and graft survival continues to improve, the importance of doing liver biopsies in patients with normal biochemical liver function tests (*per protocol* biopsies) has become more and more evident. Protocol biopsies allow to reveal the natural history of the graft, diagnose rejection or CMV/EBV infection, identify graft hepatitis or fibrosis, guide the withdrawal of immunosuppression and detect subclinical biliary strictures or recurrent disease [16–18] (Figs. 15.3 and 15.4). The complications are relatively rare, although 2% to 5% of children may have mild bleeding after the biopsy [19, 20]. In adult centers, protocol biopsies have been performed at 7 to 21 days, at 1, 2, 5 and 10 years, or annually to detect recurrent hepatitis B or C or other diseases [21–23]. Few pediatric centers have evaluated serial protocol liver biopsy samples after LT to assess histological features. Most of them found that histology at 1 year in children with normal liver enzymes was mostly normal (68% in one report) without providing additional detailed information on graft histology [24, 25]. However, more than two thirds of 10 year post transplant biopsies (69–73%) were reported as abnormal [15, 25–28]. In a series of

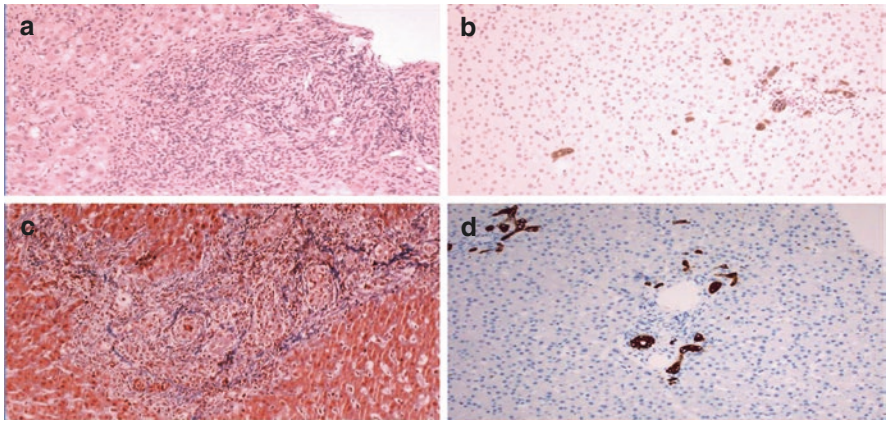

Fig. 15.3 Histological signs of graft dysfunction in protocol liver biopsies (40× magnification). (**a**) T-cell mediated rejection: prominent portal infiltrate, endothelitis and bile duct aggression (H&E); (**b**) chronic rejection: vanishing bile ducts (Cytokeratin 7); (**c**) chronic rejection: portal fibrosis (Trichrome); (**d**) biliary stricture: cholangiolar proliferation (Cytokeratin 7)

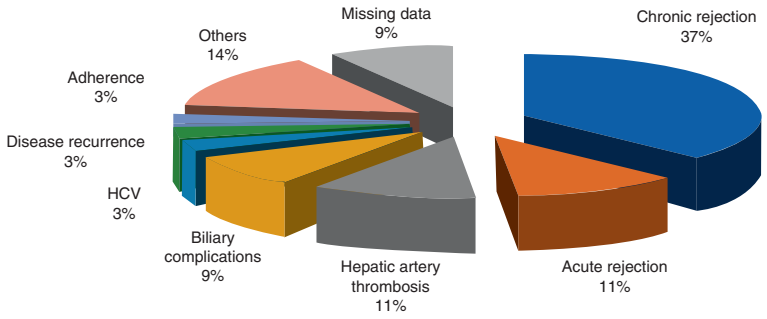

Fig. 15.4 Causes of graft loss after paediatric LT, from SPLIT DATABASE (1995–2004) [2]

158 patients, the most common features were graft inflammation and fibrosis [25]. In particular, chronic hepatitis was very common: 22%, 43% and 64% at 1, 5 and 10 years, respectively, whereas fibrosis was evident in 52%, 81% and 91% at 1, 5 and 10 years, respectively. By 10 years, 15% of children developed cirrhosis [25]. An increase in graft fibrosis from 30% to 65% was also reported after transplantation from 1 year to 5 years after LT. Despite no severe graft fibrosis was noted at 10 years, the proportion of patients with any degree of fibrosis raised up from 10% at 5 years to 29% at 10 years from LT [29, 30]. In the evaluation of 157 protocol liver biopsies in paediatric recipients of liver transplantation, Feng et al. [31] found that lymphocytic inflammation was very common in the portal and periportal area (59% mild, 5% moderate) whereas a minority showed interface activity (21% mild, 1% moderate), lobular (23% mild, 1% moderate) or perivenular inflammation (17% mild). Inflammation and fibrosis occurred together and were spatially associated.

Biopsies with portal inflammation and interface activity had higher Ishak fibrosis stages, while biopsies with perivenular inflammation had higher perivenular fibrosis score [32]. Furthermore, late cellular rejection (LCR) has been reported in 8% of LT paediatric recipients [33] and it plays an important role in graft and patient survival, with a rate of progression to chronic rejection and graft loss reported between 8% and 27% [34] (Fig. 15.5). In addition, a common complication of LCR is *de novo* autoimmune hepatitis, also labelled as idiopathic post-transplant hepatitis. *De novo* AIH seems to be a low grade form of chronic rejection, and may be related to scarce adherence to the treatment, molecular mimicry or oversuppression of T cells [12, 35, 36]. A recent long term analysis of failed liver grafts at time of re-transplantation has shown rare aspects of chronic rejection but common features of chronic idiopathic hepatitis associated with progressive fibrosis leading to graft failure [37]. Furthermore, C4d expression in endothelial cells of portal or central veins has been described as an indirect sign of antibody response and it may play a role in humoral liver rejection (Fig. 15.6).

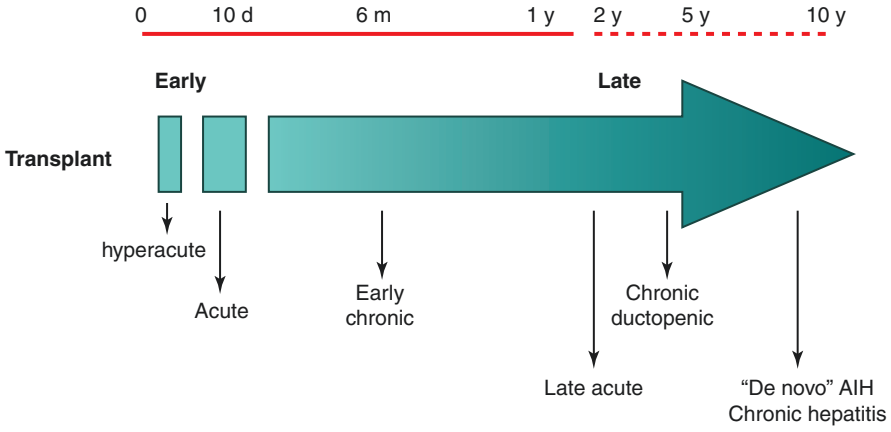

Fig. 15.5 Approximate timing of different types of rejection

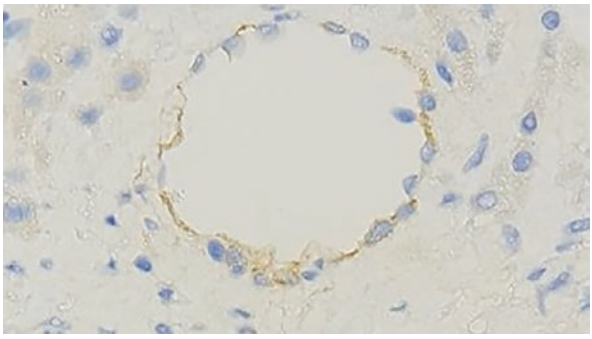

Fig. 15.6 C4d expression in post liver transplant biopsy. Complement deposits (C4d) in the endothelium of a portal vessel (brown stain)

Remarkably, we have recently found that an isolated cholangiolar proliferation (Fig. 15.3) detected on cytokeratin-7 stained liver biopsies, even in the absence of any other clinical or imaging sign, was the best tool to predict a subclinical biliary stricture with a positive predictive value (PPV) of 86.4%. If diagnosed early during the follow up, biliary stricture can be managed successfully in order to prevent a long-term allograft dysfunction [16].

Taking into consideration that liver tests are known to be insufficiently sensitive in several liver diseases, performing routine protocol liver biopsies seems to be an essential part of long term post liver transplant management, especially at 5–10 and 20 years after LT.

Patient Outcome Including Medical Complications: Infections, Malignancies, Renal Failure, Nutrition, Social Aspects

Although excellent outcomes over the last three decades have been achieved, long term complications still affect 30% to 50% of paediatric liver transplant recipients (Table 15.1).

Table 15.1 Long term complications

Graft
– Late acute rejection
– Chronic rejection
– Portal hypertension
– Biliary complication
– Recurrent disease
– Need for re-transplantation
Infections
– Enteric gram-negative bacteria
– Fungal infections (Candida species, Aspergillus)
– Viral infections (EBV. CMV)
– Opportunistic (Pneumocystis jirovecii)
– Community acquired pathogens (respiratory syncytial virus and influenza viruses, rotavirus and adenovirus)
Malignancies
– Posttransplant lymphoproliferative disease (PTLD)
– Skin tumours
Chronic Disease
– Renal dysfunction
– Hypertension
– Growth and development
– Psychological and social aspects, quality of life

Infections

Immunosuppressive agents play a critical role in dampening the immune response, thereby increasing infection risks in transplanted patients [38]. Infections have been categorized into 3 periods, according to their highest incidence rate: early (0–30 days), intermediate (1–6 months), and late (>6 months) [39] (Fig. 15.7). Early infections are mostly related to surgical procedures, technical complications and indwelling catheters. Intermediate infections (such as CMV) are more attributable to immunosuppression. Children with uncorrected surgical complications (bile duct stenosis and obstructions) may suffer recurrent bacterial cholangitis. In the late period, recipients are on lower level of immunosuppression and can handle the exposure to community–acquired infections similarly to age-matched immunocompetent children.

Cytomegalovirus (CMV) infection remains the most significant opportunistic infection in liver transplant recipients [40, 41]. Primary CMV infection is associated with the highest morbidity and mortality rates. The reactivation of a latent infection or a superinfection with a new CMV strain tends to result in milder illness. Late CMV may be associated with longer periods of chemoprophylaxis, but some cases occur during late rejection. CMV disease may manifest as a nonspecific viral syndrome or tissue-invasive disease. Nowadays, the best diagnostic method is CMV-DNA detection via quantitative PCR [38]. The goal of anti-CMV management in the LT setting is to prevent overt disease and related complications. To

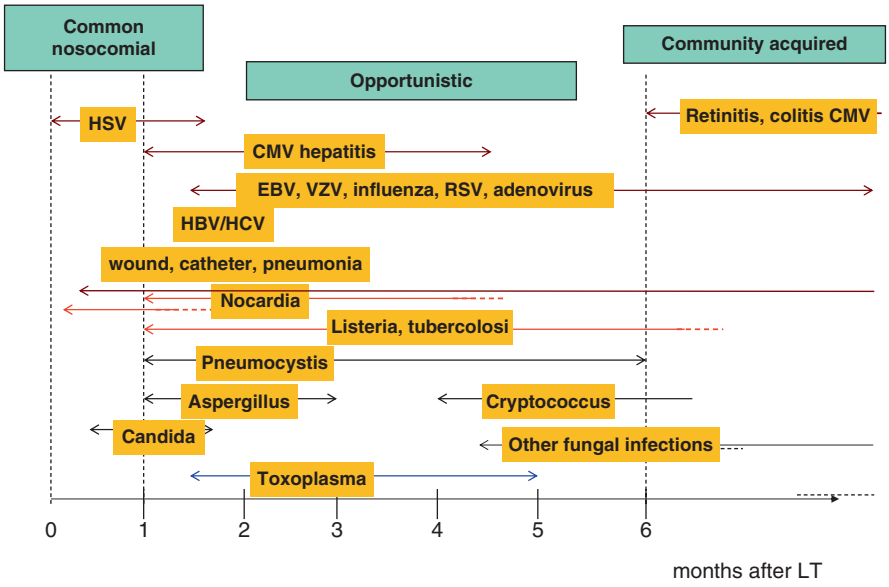

Fig. 15.7 Infectious complications after LT

achieve this, two major strategies are currently employed: prophylaxis and pre-emptive therapy. In the past, prophylaxis has been the most widely used approach and still remains the most used strategy by both the North American and the European paediatric transplant networks [42]. It consists of administering an antiviral agent (mainly ganciclovir or its orally absorbed prodrug valganciclovir) soon after LT to all, or only to high-risk recipients regardless of the development of viremia for a certain period of time. Pre-emptive therapy (PET) consists of administering the antiviral agents only in children with documented replication at an established viral load cut-off and continuing until CMV-DNA clearance [43, 44]. In a recent study performed in our centre, PET did not differ from prophylaxis, but it was associated with lower antiviral drug exposure and cost per patient [43]. Other agents, such as foscarnet or cidofovir, are restricted to cases of suspected or confirmed resistance [15].

Epstein-Barr virus (EBV) is the second most frequent viral infection affecting paediatric liver transplant recipients which occurs as either a reactivation of previous infection or as a primary infection. About 60–80% of seronegative children are expected to acquire EBV infection within 3 months from solid organ transplant, either from primary oropharyngeal EBV infection or via donor passenger lymphocytes in the transplanted organ from a seropositive donor. Symptomatic EBV infection occurs in 8–22% of the cases and is not different from that of the immunocompetent host [45]. It is commonly defined in the presence of IgM against the viral capsid or positive viral load in the peripheral blood by Real-Time Polymerase Chain Reaction (RT-PCR) along with either the histological evidence of an EBV infection or specific symptoms (fever, flu-like illnesses, leukopenia, atypical lymphocytosis, exudative tonsillitis and/or lymphadenopathy, or hepatitis). Pre-emptive approach consists of reducing immunosuppression if EBV RT-PCR is greater than 10,000 copies/10^5 PBMC until EBV viral load decreased below 1000 copies/10^5 PBMC [46]. The most important and potentially fatal complication related to EBV is the post-transplant lymphoproliferative disorder (PTLD) [47].

Malignancy

Two thirds of late mortality is directly attributed to immunosuppression complications such as infections or malignancy [2, 48]. A population based study from 4 Nordic countries reported that children with liver transplants experience nearly ten-fold higher standardized incidence ratio for all cancers [49]. The cumulative incidence of cancers rises steeply in young adulthood, increasing from 2% to 6% and 22% at 10, 20 and 25 years, respectively, after transplant [49]. PTLD is the most common, representing >50% of malignancies in this population [47], and it comprises of a wide spectrum of atypical lymphoid proliferations, ranging from benign lymphoid hyperplasia to malignant lymphomas [50]. In most cases, PTLD is of B-cell origin (only 10% of cases being of T-cell immunophenotype), and EBV-driven, though EBV-negative PTLDs have been reported in 10–48% of cases. The

pathogenesis of EBV-negative PTLD is less clearly understood. PTLD is most commonly seen within the first year following transplantation, though a subset of PTLDs, especially those that are EBV-negative, can occur later on. Classical Hodgkin Lymphoma type PTLD can occur, especially late after transplant [51]. Treatment of PTLD begins with decreasing the intensity of immunosuppression. In cases where the tumor cells express CD20, rituximab (anti CD 20 chimeric monoclonal antibody) is administered. In most cases the tumor will regress with these treatments. However some tumors of monoclonal origin may not respond to these therapies and require the administration of other chemotherapeutic regimens used also for non-Hodgkin lymphomas (CHOP). Prevention of PTLD is based on keeping reduced immunosuppression levels and on surveillance for EBV viremia by serial EBV-polymerase chain reaction determinations in peripheral blood [52].

Cutaneous tumors are the second most-common malignancy: these include squamous cell carcinoma, basal cell carcinoma, melanoma; anogenital cancers and Kaposi sarcoma have also been described. The mainstay of treatment for the majority of these lesions is surgical excision and the prognosis is generally good [53].

Renal Failure

Chronic kidney disease (CKD) is a very well recognised complication of LT, impacting on morbidity and mortality. The percentage of patients presenting with CKD after LT varies between 26% and 86% depending on the definition used, and up to 8% of children are estimated to develop end-stage renal disease at 10–20 years from LT [54]. The exposure to calcineurin inhibitors (CNI) is considered the main culprit for post-transplant CKD, and the nephrotoxic effect correlates with the drug serum levels. Risk factors associated with CKD post LT are presence of renal disease prior to transplant, indication for LT (such as Alagille syndrome) or hepato-renal syndrome before LT [55]. Some authors found that elevated blood pressure at 1 year after LT is associated with deterioration of native kidney function by 5 years post-transplantation. This effect was found to be independent of patient age, sex, type, dose or trough level of CNI therapy [56]. Other studies have found that older age and male sex are risk factors for CKD in recipients of non-renal organ transplants, with diabetes mellitus, pretransplant renal dysfunction or post-operative acute renal failure cited as additional risk factors [57, 58].

Although commonly used, the measurement of serum creatinine and the calculation of creatinine clearance are not very reliable tools in cirrhotic patients undergoing LT, since some aspects of the liver patient (reduced muscle mass, decreased creatinine biosynthesis, high blood bilirubin levels) and post-LT treatment can lead to inaccurate results [59]. Remarkably, cystatin C (a low molecular weight polypeptide) have been found to be useful in monitoring renal function especially in cirrhotic patients in the immediate perioperative period after LT [60, 61].

In conclusion, as the development of renal failure is still associated with considerable mortality and morbidity, it is extremely important to use highly sensitive

GFR, in order to identify renal dysfunction early, assess its severity and adjust the dose of drugs having renal excretion and toxicity [60, 62]. Regular monitoring of blood pressure is also recommended as well as screening for proteinuria [63]. Collaboration with paediatric nephrologists is advisable, especially in those patients who are at risk of developing CKD post LT and those who develop evidence of decreasing GFR during the follow-up [62, 64]. Attempts at reducing or withdrawing CNI with the introduction of other non-nephrotoxic but effective immunosuppressive agents (such as mycophenolate mofetil and mTOR inhibitors) can be considered during follow up in selected patients [64, 65].

Nutrition

Growth failure is common in children with cirrhosis because of malnutrition secondary to fat malabsorption and increased energy expenditure and possibly growth hormone resistance [66]. After successful LT and nutritional restitution, growth hormone and insulin-like growth factor 1 levels return to normal level and linear growth improves [67]. Catch up growth is influenced by steroid therapy and may not occur until the second year [68, 69]. The prevalence of linear growth failure decreases after LT (19.5% vs 33.5%), but remains above the expected for a normal population (5%). In a clinical study linear growth impairment was common in both sexes; however, the proportion of boys affected increased in the 16–18 years age range [70]. The largest series come from the studies of Pediatric Liver Transplantation (SPLIT) registry, showing that 20% of LT pediatric recipients had linear growth impairment at their last follow-up. Growth failure was more frequent in patients with metabolic disease and steroid exposure for longer than 18 months [70]. Higher percentiles for weight (OR 0.8) and height (OR 0.62) at LT were protective and weight and height Z-scores at transplant best predicted catch up growth at 5 years post LT [68]. Remarkably, children with more severe growth were found to be less likely to achieve normal growth percentiles post LT, underscoring the importance of appropriate pre-transplant growth and nutrition [71].

Viner et al. showed a catch up growth lasting up to 7 years post LT, with mean height on 11th percentile at LT and 27th percentile when they reached final height [72]. In agreement with these results, Australian and Japanese authors found a mean height on the 26th percentile at 15 years from LT; the final height was determined by height at LT [73]. Up to 50% of recipients have a final adult height 1.3 standard deviations below their genetic potential, and patients with Alagille syndrome may not have improved growth despite these measures [74, 75].

In children and adults with chronic liver disease, standard measurements of height and weight are known to underestimate the degree of malnutrition compared to body analysis. Notably, body mass cell in children was reduced after LT despite normalization of height and weight, suggesting weight increase was related to increase in fat mass rather than body cell mass [73]. Of interest, the proportion of obese adult LT recipients currently approaches 30% and is associated with the

development of metabolic syndrome after LT [76]. On multivariable analysis, older age at LT significantly predicted body cell mass, and linear growth impairment was associated with reduction of body cell mass [15]. The psychological impact of growth delay should not be overlooked, and the use of recombinant growth hormone could be considered in the post-transplant setting. It is extremely likely that the effect of growth in patients with liver disease and post LT will have a long standing impact on their outcome once they outgrow the pediatric age [77].

Social Aspects

Studies suggest that paediatric LT patients have lower physical and psychosocial function [78, 79]. A multicenter study involving more than 800 recipients found that psychosocial function was more affected than physical function, and psychosocial health was affected by school function, especially in case of cognitive impairment or significant school absence. A systematic review summarized that health-related quality of life (HRQoL) is impaired in paediatric LT recipients compared to the general population [80]. Medication concerns and treatment anxiety were found to be significantly increased among paediatric recipients [81]. Children reported that medications had a negative impact on their physical appearance, and their parents nagged them about adherence. Non-adherence has been associated with lower physical quality of life, limitations in social and school activities, increased parental emotional distress and decreased family cohesion [82]. Several studies have suggested intellectual quotient delays, differential impairment of language and verbal skills [83, 84]. Low executive functions and quality of life markers were found similar in LT recipients and in other chronic disease conditions [85]. Up of 16% of adolescents reported symptoms consistent with post-traumatic stress disorder, and parents also reported symptoms of post-traumatic stress disorder with significant anxiety related to the child's medical condition [86, 87]. In addition, transition from paediatric to adult setting may represent an abrupt change in care (different providers, heightened expectations for autonomy and changes in medical insurance) and is considered a risk factor for non-compliance in long term. In this setting, it is important to address adolescent psychosocial health issues with the patients and their families, and provide counselling on smoking, illicit drug use, alcohol use, birth control and sexually transmitted disease, in order to improve adherence and maximizing long term outcome [88] (see Chaps. 17–19).

Long Term Immunosuppression and Tolerance

As more and more recipients enter adulthood, more attention is paid to the potential harm of chronic immunosuppressive (IS) therapy and its side effects [1, 2]. The main goal of transplant clinicians is arguably acceptance of the graft by the recipient

without any long term pharmacological help [89]. It is estimated that 20% to 25% of pediatric LT recipients could be operationally tolerant without immunosuppression [90]. Unfortunately, contradictory literature regarding the optimal immunosuppression and its withdrawal has been published so far in this setting [31]. The clinicians have been managing stable patients with consistently normal liver function tests with modest immunosuppression. In fact, spontaneous tolerance initially came from the incidental clinical observation of stable liver tests despite immunosuppression withdrawal due to poor compliance, infections, or post-transplant lymphoproliferative disease (PTLD). In 1993, Reyes et al. reported that 8 LT recipients with poor compliance ceased immunosuppression (IS) from 0.5 to 11 years after LT but unexpectedly developed operational tolerance (OT). Since then, many liver transplant centers have conducted clinical trials of IS withdrawal (ISW) in both adult and paediatric LT recipients. Adams and Sanchez-Fueyo conducted a prospective multicenter ISW clinical trial in 98 adult LT recipients. In this group 41 (41.8%) achieved clinical tolerance and 57 (58.2%) developed mild rejection. No significant histological damage was found in liver biopsies of the tolerant recipients during the 3 year follow up after IS withdrawal. A longer time post LT correlated positively with tolerance induction and was the strongest predictor of withdrawal success [91]. Levitsky showed that operational tolerance rate of sirolimus was comparable to CNI withdrawal studies [92]. An interesting paediatric study showing the efficacy and safety of IS withdrawal in stable LT recipients on CNI monotherapy has been published very recently [93]. The authors conducted a multicentre, single arm trial of immunosuppression withdrawal over 36–48 weeks. No death, graft loss or chronic refractory or severe rejection occurred. They concluded that 37.5% of selected paediatric liver transplant recipients were operationally tolerant. Allograft histology did not deteriorate for either tolerant or non-tolerant subjects [93]. The time after LT was significantly longer in the tolerance group than in the non-tolerance group suggesting that longer time after transplant is an important predictor of tolerance induction [94]. Although *de novo* donor-specific antibodies (DSA) are associated with injury and diminished graft survival for non-liver allografts [32, 95], a negative impact on liver allograft health is less well established [96, 97]. Some authors found that pre-existing or *de novo* DSA does not portend inevitable or aggressive structural deterioration [93, 94, 96]. A substantial number of subjects with class II DSA had healthy allografts at trial entry, and remained healthy after attempted ISW, irrespective of outcome [93]. DSA presence seems not to preclude ISW and does not contradict operational tolerance [93, 94, 96]. However the development of DSA during ISW was associated with non-tolerance [93]. A trial of ISW involving adults early after LT reported that *de novo* DSA predicted acute rejection [98]. These findings raise the question as to why, after immunosuppression reduction, some subjects develop DSA while others do not. In a pilot trial, an inverse association was observed between portal inflammation at enrolment and operational tolerance [94]. An adult center has also reported that increased numbers of CD8+ cells correlated with failed ISW [99]. While some authors have speculated that allograft infiltrates may facilitate the tolerance [100], other data indicate that ISW might activate the few scattered inflammatory cells and precipitate rejection [93].

There is a wide area of research for the development of induced liver tolerance, including various cell therapies such as Tregs, regDCs, mesenchymal stem cells, regulatory macrophages, regulatory B cells and bone marrow derived immunosuppressive cells [101]. Further trials exploring the best timing and patient selection for immunosuppression minimization and withdrawal are needed.

Key Points for Adult Hepatologists

- Paediatric liver transplantation has dramatically changed the prognosis of end-stage liver disease.
- However, long term complications still affect up to 50% of paediatric liver transplant recipients.
- Protocol liver biopsies seem to have become an essential part of long term post liver transplant management.
- There is a wide area of research for immunosuppression withdrawal in paediatric stable liver transplant recipients approaching transition to adults.

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Chapter 16
Liver Transplantation in Early Adulthood

Tim Mitchell and Deepak Joshi

Indications

Liver transplantation is the gold standard treatment for acute or chronic liver failure irrespective of age [1]. Recipients of liver transplantation in early adulthood (16–25 years of age) are a unique population including survivors of childhood liver disease, aggressive adult onset chronic liver conditions and acute liver failure [1]. The conditions that may require liver transplantation are listed in Table 16.1 [1].

As the number of individuals with childhood liver disease surviving into adulthood increases, diseases that were once thought to be only in the domain of paediatric hepatologists are now seen in adult services. As such, individuals diagnosed in childhood are now requiring referral for transplantation by adult hepatologists who may be unfamiliar with their clinical syndrome [2, 3]. A United Kingdom (UK) review found that a composite group of rare indications, including post-Kasai biliary atresia and inherited syndromes, comprised over 30% of elective liver transplants in the age 18–29 years group [4]. In combination with primary sclerosing cholangitis (PSC) and autoimmune hepatitis these three groups comprised over 90% of liver transplant indications for young adults [4]. A United States (US) review found that the leading indications for liver transplantation in 18–24 year old recipients were acute liver failure (29%), PSC (15.7%) and metabolic liver disease (13.1%) which are markedly different to adult aetiologies [2, 5].

Given the difference in transplant indications, understanding when is an appropriate time for a young adult to be considered for liver transplantation is a complex

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Table 16.1 Common indications for liver transplant in young adults [1]

Chronic liver disease typically presenting in childhood	Alagille syndrome Biliary atresia post Kasai Crigler-Najjar type I Cystic fibrosis related liver disease Fibropolycystic liver disease +/− Caroli syndrome Genetic cholestasis i.e. MDR3 deficiency, BSEP deficiency Glycogen storage disease type IV Primary oxalosis Tyrosinaemia type I
Chronic liver disease presenting at any age	Alpha-1-antitrypsin deficiency Autoimmune hepatitis Primary sclerosing cholangitis Viral hepatitis i.e. HBV, HCV Wilson disease
Acute liver failure	Autoimmune hepatitis Paracetamol overdose Viral hepatitis Wilson disease

Table 16.2 King's College criteria for poor prognosis in acute liver failure [7]

Paracetamol	One of the following: Arterial pH <7.3 after resuscitation and more than 24 hours since ingestion OR Lactate >3/5 mmol/L OR INR >6.5 AND creatinine >300 μmol/L AND hepatic encephalopathy grade III or IV
Non-paracetamol	INR >6.5 OR At least three of: Indeterminate cause or drug-induced hepatitis Age < 10 years or > 40 years Interval from jaundice to encephalopathy >7 days Bilirubin >300 μmol/L INR >3.5

process. In contrast to paediatric liver transplantation, growth failure, impact on cognitive development and quality of life are not considered in adult transplant listing criteria [6].

For transplantation in acute liver failure prognostic scores are well established (Table 16.2) [6, 7]. For chronic liver disease, adult patients can be listed for liver transplantation when their one year risk of death is higher than that without transplant [8]. In the UK this is estimated to be >9% and reflected in a United Kingdom End Stage Liver Disease (UKELD) score of ≥49, which is a statistical model encompassing serum sodium, creatinine, INR and bilirubin [8]. The aetiology of chronic liver disease is not considered in this calculation [6]. Patients can also be considered for transplantation with a UKELD <49 if they have refractory ascites or hepatic encephalopathy, hepatocellular carcinoma within transplant criteria or a variant syndrome (Table 16.3) [6].

Table 16.3 Accepted indications for adult liver transplantation in the UK [6]

Acute liver failure	Severe acute impairment of liver function with encephalopathy occurring within 8 weeks of the onset of symptoms without underlying liver disease
Chronic liver disease (cirrhosis)	Alpha-1-antitrypsin deficiency Autoimmune liver disease: PBC, PSC, AIH, overlap syndromes Chronic viral hepatitis (B, C, D) Congenital hepatic fibrosis Fatty liver disease: alcohol or non-alcohol related Genetic haemochromatosis Secondary biliary cirrhosis Wilson's disease
Hepatocellular carcinoma	≤5 tumours all ≤3 cm OR Single tumour ≤5 cm diameter OR Single tumour >5 cm and ≤ 7 cm diameter with stable tumour biology demonstrated over 6 month period
Variant syndromes	Familial amyloidosis Glycogen storage disease Hepatic epithelioid haemangioendothelioma Hepatopulmonary syndrome Hereditary haemorrhagic telangectasia Intractable pruritus Maple syrup urine disease Nodular regenerative hyperplasia Ornithine transcarbamylase deficiency Polycystic liver disease Porphyria Primary hypercholesterolaemia Primary hyperoxaluria Recurrent cholangitis

Unfortunately, qualifying scores such as UKELD do not accurately reflect the potential benefit of liver transplantation for young adults who tend to be disproportionately affected by complications of portal hypertension but may not have as advanced synthetic dysfunction [4]. As such, disease specific criteria for transplant consideration in young adults have been suggested. In adolescent patients with post-Kasai biliary atresia a minor elevation in bilirubin (>21 μmol/L) at age 16 years predicted the need for liver transplant when >16 years old with acceptable sensitivity and specificity [9]. Furthermore a reduced serum creatinine, possibly reflective of reduced muscle mass, was an independent predictor for the need for liver transplantation [9]. Application of UKELD to this cohort would clearly disadvantage these patients as it associates a higher creatinine with increased severity of liver disease [9]. The development of more sensitive models to assess the severity of liver disease in young adults and determine who will benefit from liver transplantation is needed.

When referring a young adult for liver transplantation, their comorbidities should allow a greater than 50% probability of surviving at least five years after transplant with an acceptable quality of life [8]. There are few absolute contraindications to liver transplantation when indicated in young adulthood [1]. These include extrahepatic sepsis at the time of surgery, malignant liver tumours with extrahepatic

spread and severe extrahepatic disease that is not reversible following liver transplantation. Transplantation for alcohol related chronic liver disease is rare in young adults [4]. Criteria regarding recency of alcohol consumption and episodes of non-adherence to abstinence are applied similarly across all adult age groups [6].

The assessment for liver transplantation in young adults is not too dissimilar to that for older adults. Depending on the indication for transplantation, specific assessment of cardiac, neurological or renal complications of the underlying disease may be required [1]. Psychological assessment and preparation of the patient and family is crucial and emphasis is placed on preparing the patient regarding the need for lifelong immunosuppression [1]. Cognitive functioning is also assessed as lower function may increase the risk of behavioural or adherence issues post-transplant [5].

Assessing patients with uncommon indications for liver transplantation such as sickle cell hepatopathy, can be particularly challenging. Although liver transplantation is rarely performed it can provide good outcomes in highly selected patients with chronic liver disease or acute sickle related hepatic crisis [10]. Involvement of the patient's haematologist to achieve good control of sickle fraction with exchange transfusion peri-transplantation is paramount [11]. Isolated liver transplantation for cholangiopathy may result in recurrent cholangiopathy in the graft however sequential liver transplantation followed by haemopoietic stem cell transplant has been suggested to prevent this in selected cases [12]. Unfortunately, liver transplantation does not affect the course of sickle cell disease and patients with significant extrahepatic complications should not be considered for liver transplantation [11]. Understandably, patients being considered for rarer transplant indications such as this should be managed in referral centres where the relevant sub-specialty expertise is available.

Understanding the indication for transplantation is another important consideration when discussing post-transplantation outcomes with patients. Whilst liver transplantation is curative for many inheritable liver conditions (e.g. Wilson disease), autoimmune diseases requiring transplantation in young adulthood have a relatively high rate of recurrence (i.e. PSC) and subsequent possibility of future graft failure [13]. This outcome should be discussed clearly with the potential recipient and their support network. Furthermore, adult hepatology post-graduate training curriculums need to address these aetiologies seen in young adulthood in sufficient detail. This need for improved education to care providers is further highlighted by the finding that one of the key barriers to a successful transition from paediatric to adult care is an inexperience or lack of knowledge in treating childhood diseases [14, 15].

Liver Transplant Waitlist

Waiting for a suitable donor graft can be challenging from a psychological perspective in young adulthood given the developmental changes that are taking place [1]. Patients should be involved in decision making where possible and a full

exploration of the knowledge and understanding of their liver disease, prior adherence and risk behaviours before listing is recommended [1]. The promotion of self-management tools such as creating a portable medical history, maintenance of medication prescriptions and control over clinic appointments have been shown to empower young adults and improve engagement with their medical team [3].

Each individual patient will respond to being placed on the waitlist differently. For some, this juncture may precipitate behavioural change as they realise the seriousness of the situation [16]. Concrete thinkers may focus on practical aspects of waiting, for example interpreting average waitlist times as a promised deadline to receive a transplant [16]. Risk taking behaviour and exploring boundaries are a component of young adult development [16]. Executive functions such as organisation, planning and self-regulation are the last aspects of neurocognitive development to mature, often taking place in the third decade of life [16]. Consideration of these developmental changes is needed when assessing a young adult's response to this monumental change [16].

Time on the waiting list should be spent on psychological preparation for liver transplantation and addressing any identified issues, which are commonly present pre- and post-transplantation [16, 17]. Common mental health conditions have been demonstrated to exist at a higher rate in young adults post-liver transplant than in their healthy peers [18]. Additionally, this psychological distress has been associated with medication non-adherence in young adults who underwent liver transplantation in childhood [18]. Given that most of these issues can be addressed in the clinic it is recommended that clinicians discuss psychosocial circumstances at every visit with their patients [18, 19]. The presence of a psychologist within the young adult team may further improve outcomes [19].

Information regarding the post-transplant period on the ward, postoperative pain management and the intensive care unit experience should be available in as much detail as wished [16]. A physical 'walk round' the wards and intensive care units may be of benefit for certain individuals. Implementing individualised care that includes addressing mental health issues and social circumstances improves engagement with the clinical teams following transplantation when clinic attendance is less frequent and increasing self-management is required [20].

Management of medical complications whilst on the waitlist remains paramount. Although young adults requiring liver transplantation were less likely to have symptoms of liver failure (e.g. ascites, encephalopathy) than older adults at time of transplantation 20% were an inpatient prior to transplantation indicating a high potential for sudden deterioration [4]. In particular, attention should be paid to portal hypertension management with patients requiring regular endoscopic surveillance and appropriate beta-blockade to avoid variceal haemorrhage. Malnutrition is common in chronic liver disease and associated with a detrimental effect on post-transplantation outcomes [5]. Nutritional support, such as high calorie supplements or nasogastric enteral feeding, may be required [1].

Young adults are best managed pre-transplant in dedicated young adult liver disease clinics with the support of a multidisciplinary team to improve post-transplant outcomes [5]. A study from Birmingham comparing outcomes between transitioned

paediatric patients and young adult recipients showed higher rates of re-transplantation for chronic rejection in the young adult group (4.5%) who did not have any dedicated clinic support, compared with the transitioned group (2.2%) who did [21]. Similarly in a US study, recipients aged 18–24 years with graft failure were less likely to be re-transplanted than younger age groups and had the highest proportion of deaths secondary to graft failure [2]. This may reflect a lack of specialised support and advocacy for the young adult group who are at high risk of non-adherence. The use of dedicated multidisciplinary clinics designed specifically for young adult liver transplant recipients provide a holistic, proactive approach addressing the psychological, physical and social needs of the young adult patient [22]. These clinics exist in some UK centres and are multidisciplinary, generally comprising of physicians with an interest in young people, clinical nurse specialists, transplant coordinators, clinical psychologist and social worker although the exact composition is not uniform [22]. Whilst specialised clinics are recognised as beneficial in both chronic liver disease and transplantation infrastructure to support them is lacking in most countries [22].

Allocation of donor organs in adult liver transplantation varies across the world and affects waitlist time. Recent data from the US shows that the overall median waiting time for adult liver transplant is 10.8 months [23]. In the US, a 'sickest first' system is utilised with the Model for End Stage Liver Disease (MELD) score determining the order of who receives an offer [24]. Whilst overall this has reduced waitlist mortality, patients with variant indications or intolerable quality of life tend to be disadvantaged [25]. Although overall waitlist mortality is lowest amongst young adults (aged 18–34 years) according to US data, when reviewed in more detail, non-super urgent recipients aged 18–24 have a higher waitlist dropout than those aged 0–17 years or 25–34 years [2]. This association is most notable in those with MELD scores <20 and is thought to reflect a lower likelihood of receiving MELD exception points for non-standard indications in the young adult group, despite similar indications for transplantation between 12–17 year old and 18–24 year old groups [2].

The UK has recently moved to a transplant benefit system that utilises donor and recipient variables to rank patients [25]. Theoretically this may benefit younger adult recipients and those with a curable disease (e.g. biliary atresia) [25]. However, it should be noted that descriptors of portal hypertension severity are not included amongst the recipient variables [26].

Liver Transplant Outcomes and Re-transplantation

Life-long immunosuppression is a prerequisite to liver transplantation to prevent graft rejection. The challenge for clinicians and patients is achieving a balance of immunosuppression that prevents rejection but minimises potentially debilitating long-term adverse effects (Table 16.4).

Table 16.4 Important side effects of immunosuppression used for liver transplantation [27]

Prednisolone	Cataracts Hirsuitism Hyperglycaemia Hyperlipidaemia Hypertension Mania/delirium Osteoporosis Weight gain
Calcineurin inhibitors e.g. Tacrolimus, Ciclosporin	Gingival hyperplasia (ciclosporin) Hirsuitism (ciclosporin) Hyperglycaemia Hypertension Infection Neurotoxicity/tremors/seizures Renal impairment
Azathioprine	Bone marrow suppression Hepatotoxicity Hypersensitivity reaction Pancreatitis
Mycophenolate mofetil	Bone marrow suppression Colitis Gastrointestinal upset Teratogenic
mTOR inhibitors e.g. Sirolimus, Everolimus	Hyperlipidaemia Impaired wound healing Oral ulcers Pedal oedema Pleural effusion Teratogenic

Although consensus is lacking on the optimum immunosuppression regimens, most centres will use a combination of prednisolone, a calcineurin inhibitor (CNI) and an antimetabolite e.g. mycophenolate [28]. Prednisolone is generally tapered and withdrawn within the first three months, depending on the aetiology of liver disease [28]. Steroid free immunosuppression regimens have been suggested as beneficial from a side effect perspective but have to be balanced against a potentially higher risk of acute rejection in young adults [5].

Tacrolimus is the backbone of most regimens, utilised by 92% of paediatric liver transplant recipients [29]. This has replaced ciclosporin as first line CNI due to its potency and preferred side effect profile [27]. The most recognised side effect of tacrolimus is nephrotoxicity which is dose dependent [27]. Unfortunately, up to 33% of long-term survivors of liver transplantation as children have been reported to show stage 3 renal disease at 15 years post-transplant [30]. Efforts to minimise renal function deterioration by utilising a low dose of CNI include the addition of an antimetabolite to the immunosuppression regimen [28]. Mycophenolate mofetil (MMF) has been demonstrated to allow CNI reduction with improvement in renal function in adults post-liver transplantation and has now largely replaced

azathioprine in the transplant armamentarium [31]. Crucially, MMF is highly teratogenic and female patients need to be made aware of this prior to its use [31]. mTOR inhibitors such as sirolimus have also been used in adult liver transplantation as a CNI sparing alternative [31]. A high proportion of patients will develop hypercholesterolaemia however and the potential long-term effects of this need to be considered in a young adult cohort [31].

Post-transplant lymphoproliferative disorders (PTLD) are an uncommon complication of immunosuppression following solid organ transplantation in adults, with an overall incidence of 2–3% [32]. In many cases PTLD is associated with Epstein-Barr virus (EBV) infection and develops when immunosuppression is at its highest, generally within the first year post-transplant [32]. The risk of PTLD is greatest in recipients who are EBV negative who receive an EBV positive graft, an occurrence that is most common in paediatric population where the incidence has been reported to be >10% in some series [23, 32]. Treatment ranges from immunosuppression reduction alone in early disease to immunochemotherapy for more aggressive or advanced disease [32].

Nonetheless, outcomes following liver transplantation in young adults are excellent with US data indicating one-year and five-year survival rates of >90% and > 75% respectively (Table 16.5) [23].

Despite this overall success, in one large database study young adults (18–24 years) have been shown to have comparatively lower rates of overall survival when assessed in narrower age ranges [2]. In this study adjusted hazard ratios for survival in comparison to the 18–24 years group were 0.70 (0.55–0.90) and 0.77 (0.64–0.93) for the 12–17 years and 25–34 years groups respectively [2]. Furthermore, death secondary to graft failure contributed to 38% of deaths [2]. In keeping with this finding, rates of late graft loss have been shown to be higher amongst young adults. Data from the UK has shown that young adults (aged 18–29 years) are almost 30% more likely to have graft failure compared to older adults at 10 years post-transplant, independent of liver disease aetiology [4].

Common reasons for late graft loss in young adults post-liver transplantation are chronic rejection and disease recurrence [4]. Chronic rejection at 10 years post-transplant has been reported in 5% of young adults receiving liver transplants in the UK [4]. Risk factors for chronic rejection in young adults include autoimmune aetiology, cytomegalovirus infection and low levels of immunosuppression [33]. In addition to chronic rejection, medication non-adherence has been shown to be potentially responsible for approximately 50% of late acute rejection episodes and

Table 16.5 Graft survival by age group (OPTN data) [23]

Age (years)	One year	Three years	Five years
18–34	91.86%	83.71%	77.85%
35–49	90.3%	84.33%	80.28%
50–64	88.45%	81.61%	76.96%
≥65	86.50%	77.15%	70.46%
Overall	88.62%	81.44%	76.48%

15% of graft loss [34]. Studies have estimated the rate of non-adherence amongst adolescents post-liver transplant upwards of 50% [35]. Non-adherence is not isolated to adolescence however, with a meta-analysis estimating non-adherence rates of 23% across all adult solid organ transplant recipients [36]. Non-adherence can exist despite normal graft function and is suggested by increased variability in immunosuppression drug levels [37]. Early recognition and intervention may prevent chronic rejection and ultimately graft loss [34].

With the advent of effective treatment for hepatitis C, disease recurrence post-liver transplant is seen most commonly in patients transplanted for autoimmune conditions, such as autoimmune hepatitis and PSC [13]. Although rates are variable across centres, estimated recurrence rates for autoimmune hepatitis range from 17–42% and PSC from 12–60% with increasing prevalence with time following transplantation [13]. Low dose maintenance steroid has been shown to decrease the likelihood of recurrent autoimmune hepatitis without increasing the risk of sepsis or osteoporosis [13].

Younger age at liver transplant is a risk factor for recurrent PSC [13, 38]. In addition, in patients with PSC and inflammatory bowel disease (IBD) it has been frequently observed that patients with more severe IBD at the time of transplant are at increased risk of graft failure [39]. Colectomy at the time of liver transplant has been performed in patients with severe or refractory IBD at the time of transplant with observational studies showing fewer episodes of PSC recurrence post-transplant [40, 41]. Whilst colectomy can be considered in patients with severe or refractory IBD at the time of transplant it should be noted that there is no randomised controlled trial data to guide decision making [42]. When feasible, the type of biliary anastomosis (primary duct-to-duct vs Roux-en-Y biliary reconstruction) has not been shown to impact the rate of stricture occurrence, PSC recurrence or graft failure, however higher rates of cholangitis are reported in patients with a Roux-en-Y biliary reconstruction [43–45]. To maintain IBD remission, 5-ASA should be continued post-transplantation [46]. Prednisolone continuation is recommended as the risk of IBD flare is increased in patients who cease prednisolone [47]. In adult literature, tacrolimus and MMF combination has been associated with higher rates of IBD flare post-transplant compared with ciclosporin and azathioprine [46]. However, tacrolimus containing regimens are associated with better graft function as such they continue to take precedence [46, 48, 49].

Re-transplantation can be considered for patients with graft failure in young adulthood who are expected to have a 5 year survival post-transplant of >50% [6]. However, data from adult cohorts demonstrate outcomes following re-transplantation are inferior to the initial transplant. US data for all adult liver re-transplantation showed one-year and five-year survival rates of 77% and 65% respectively [23]. Reasons for this include immunological sensitisation, increased surgical complexity, recurrent disease and in some cases persistent immunosuppression non-adherence.

Re-transplantation in the context of immunosuppression non-adherence is a complex dilemma facing transplant centres. Each decision to re-list a patient with graft loss due to non-adherence has to balance organ scarcity, knowledge of

inferior outcomes and the fact that past behaviour predicts future behaviour against principles of non-maleficence, evidence that behaviour change can occur and opinion that patients admitting to non-adherence should not be punished for their honesty [34]. The lack of consensus guidelines or robust evidence and differences in healthcare systems further complicates the decision making process for clinicians [34]. Anecdotally, assuming there are no contraindications to transplantation, most young adults with graft loss due to non-compliance would be considered for re-transplantation, taking into account their potential for behaviour change with cognitive development and the appropriate psychological support.

Conclusion

Young adults undergoing liver transplantation are a unique cohort of patients with particular medical and psychosocial needs. Clinicians caring for these patients need to be familiar with childhood liver disease yet understanding of the complex neurocognitive development that is taking place at this age. Empowering young adults to take control of their health-related interaction improves engagement, whilst addressing psychological distress early improves non-adherence and graft survival. Although, long-term outcomes post-transplant are good, they remain inferior to adjacent age groups. The utilisation of dedicated multidisciplinary young adult clinics will be critical for reducing non-adherence and improving post-transplant outcomes in the future.

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Part IV
Challenges for Adolescents and Young Adults with Liver Disease

Chapter 17
Adherence to Treatment and Substance Misuse

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Scope of the Nonadherence Problem

Medication nonadherence among adolescence with liver disease is common and often results in severe adverse outcomes [1, 2]. For example, in adolescents who have received a liver transplant, nonadherence can result in rejection of the organ and subsequent death [1]. In those with Wilson disease, medication nonadherence is associated with the development of disease-related neuropsychiatric symptoms and symptoms related to hepatic dysfunction [3]. Thus, addressing nonadherence is important if one wants to achieve optimal care for adolescents with liver disease. The risk of nonadherence is high during adolescence in part because it coincides with both the growing responsibilities of oncoming adulthood and the transition from pediatric to adult care [4, 5].

An essential point to understanding nonadherence is that it is not necessarily stable across time [1, 6]. Thus, just because a patient is adherent to medications at one point, does not necessarily mean that they will be adherent at another. One study of medication adherence among pediatric transplant recipients found that 18.5% of patients who were adherent during the first year of the study were not adherent in the second year [1]. Frequent monitoring of adherence is recommended throughout patient care.

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Some literature on medication nonadherence conceptualizes it as either intentional or nonintentional [7]. Unintentional nonadherence is defined as non-deliberate failure to take medication, with the most common reason being as simple as forgetfulness. Unintentional nonadherence is often linked to patients' cognitive capacities (such as age, cognitive impairment, health or literacy) to follow medication regimen as well as specific elements of treatment such as dose and complexity [8]. Conversely, intentional nonadherence refers to the deliberate failure to follow one's medication regimen and treatment plan. Intentional nonadherence can include behaviors such as purposefully skipping, delaying, or lessening prescribed dosages. Contributing factors to intentional nonadherence may include more intrinsic personal factors such as beliefs, subjective norms, or specific misconceptions related to disease and treatment [9, 10]. For example, in a study of 152 renal transplant recipients, intentional non-adherence was reported as far less common than unintentional adherence and it was associated with co-morbid medical complications and beliefs surrounding medication side effects [11].

Nonadherence in the literature on liver disease is not regularly divided in this way but rather seen as one entity. Moreover, the line between unintentional and intentional may be somewhat ambiguous [12]. Further complicating this, patients may engage in both unintentional and intentional nonadherence at the same time. Thus, this chapter addresses interventions that address both dimensions of a unitary concept of nonadherence.

Measurement of Adherence

Measurement of medication adherence can be either direct or indirect [13]. Indirect measures of adherence include self-report, electronic monitoring, and pharmacy refill data [14]. Direct measures of adherence include biological drug indicators of adherence, such as blood levels, and observation of the patient taking the medication [14]. In much of the current research and clinical practice, medication adherence is measured by self-report [15]. However, this method of measurement may not be accurate [15]. In this section, we address current research on adherence measurement and offer suggestions for practice.

	Indirect	Direct
Measures	• Self-report • Clinician report • Refill data • Pill counts • Electronic monitoring	• Biomarkers • Direct observation of intake
Benefits	• Easier implementation • Sometimes cheaper	• Most accurate • Earlier recognition of nonadherence
Drawbacks	• May overestimate adherence • Overly dependent on clinical judgment	• Biomarkers may require additional specialized lab work • Direct observation of intake may be seen as intrusive

Indirect Measures of Adherence

Self-report Self-report measures of adherence are prone to overestimate adherence [16]. Commonly used self-reports methods include casual questioning about adherence as well as the use of standardized assessments [16]. A widely-used standardized assessment is the Morisky Adherence Medication Scale [17, 18]. However, research on the concurrent validity of these types of measures in measuring adherence in other populations is mixed [16–20]. These scales may be inaccurate since they are dependent on the truthfulness and accurate recollection of the patient [20]. Furthermore, such measures often have an arbitrary cutoff between what is considered adherent and what is not [20].

Clinician Report Clinician assessment of nonadherence may overestimate actual adherence. One study of German doctors' showed poor agreement between clinical judgment of patient nonadherence, self-report nonadherence, and variability in immunosuppressant serum levels [21]. An additional study of physician assessment of nonadherence found that in women taking osteoporosis medications, physicians believed that 62.7% of their patients were adherent while pharmacy refill data suggest it was only 40% [22]. A sample of patients aged 9 to 11 with chronic kidney disease reported similar results [23]. Physician report, as well as electronic monitoring of prescription bottle openings, categorized 34.5% of participants as nonadherent, while pharmacy refill data indicated that 60.9% of participants were nonadherent [23]. A study by our group also found that clinical impression did not predict graft outcomes in liver transplant patients, while the Medication Level Variability Index (MLVI), a biological measure of adherence was a significant predictor [24]. Moreover, in detecting nonadherence before obvious physical effects, clinical judgment may only be as good as the ability of the clinician to build rapport and trust with patients.

Prescription Refill Data One of the more objective measures of nonadherence is using pharmacy prescription refill data. Refill data can involve using refill claims made to insurance companies and/or reports from pharmacies. The tell-tale sign of nonadherence is that the patient is not filling or picking up their refills on time. There are several methods of computing adherence using refill data, including the medication possession ratio [25] and the proportion of days covered [26]. Briefly, the medication possession ratio is the sum of the days supplied in prescription refills in a given period divided by the amount of the days in the period [25, 26]. This method can result in an adherence rate of over 100% if patients refill their prescriptions early [26]. The proportion of days covered method is similar but uses the number of days in the period covered rather than the numerical supply amount [26].

Research on this method of measurement is generally favorable. A study of clinical outcomes and diabetes pharmacy claims found that adherence, as measured by pharmacy claims, was a significant predictor of diabetes-related outcomes [27]. Another study of kidney transplant patients in the Veteran's Affairs Hospital System

found that prescription refill data was a significant predictor of graft outcomes [28]. However, refill data is also apt to overestimate adherence since patients may engage in conflicting behaviors such as throwing away or losing medication doses. Increasingly, pharmacies automatically fill and send medications to patients making this data unreliable as measure of adherence. In that vein, having the medications in possession does not always translate to actualized adherence. Furthermore, pharmacy data and insurance claim data, may not always be readily available to physicians.

Pill Counts Pill counts are often done by asking patients bring their bottle to the clinic for a pill count or calling patients for random check-in counts. The accuracy of this measure is reliant on factors such as whether the patient remembers to bring their prescription to the clinic and that they did not lose or toss pills that were not taken [29]. Pill counts are considered to be a more accurate method of measurement than self-report data [30].

Electronic Monitoring Electronic monitoring often consists of using an electronic pill cap that records openings and closings. This method has several limitations [31]. First, since it is dependent on bottle openings and closings, it may be affected by patients leaving the bottle open for extended periods after taking their dose [31]. Secondly, patients may also open the bottle without taking their dose. Third, it may be inconvenient for patients to have always to use bottles fit for the cap, especially if they typically carry a small number of doses in a small container for convenience [31]. Lastly, patients may be unable or may not agree to use electronic monitoring devices leading to a selection bias in which only adherent patients are monitored since those are likely the patients who agree and are able to use such devices. This selection bias is counter-productive since the goal of measuring adherence is to identify patients that are nonadherent. Commonly used electronic monitoring prescription caps may include the SmartCap®, which can track bottle opening time and dates, and certain models may be able to provide medication reminders [32].

More recent electronic methods of measuring nonadherence are those that can connect to cell phones or computers to both measure adherence and provide patients feedback on adherence [33]. This feedback may act as an intervention in and of itself [33]. The effectiveness of this method as an intervention has thus far yielded mixed results [33, 34]. In transplant recipients, we reported that the use of electronic monitors was associated with lack of ability to show medical improvement in interventions geared to improve adherence, possibly because patients who use those methods consistently are adherent anyway and do not stand to benefit from an intervention to improve adherence [15]. Electronic monitoring may thus underestimate nonadherence since some prior studies have not found more favorable outcomes despite seemingly increased adherence [33, 35–37].

Direct Measures of Adherence

Biomarkers The most accurate of the medication adherence measures are those that utilize objective measures of assessment. In liver transplant recipients, the Medication Level Variability Index (MLVI) is a feasible to use and accurate metric for assessing immunosuppressant adherence [38]. The MLVI is computed by calculating the standard deviation (SD) of consecutive blood levels of a medication over time [38]. Since this method utilizes blood levels of medication that are likely already in medical charts, the burden on patients is minimal [38]. MLVI is a good predictor of graft loss and liver injury [15]. Similarly, in patients with Wilson disease treated with zinc therapy, fluctuating urine copper values, and increased in circulating non-caeruloplasmin copper values may indicate nonadherence [39, 40].

Direct Observation of Intake Direct observation of medication intake has been successfully used in achieving medication adherence in patients with tuberculous [41]. However, given the long-term nature of medication usage for liver disease in adolescents, this is not a practical measure of adherence.

Adolescent Vulnerabilities and Interventions

Transition from pediatric to adult care typically occurs at the end of the adolescent years. Most commonly, this is between 18 and 21 years old, but preparations for transition should occur much earlier [42]. Adolescence involves changes in responsibilities for individuals independent of their health concerns. For adolescents with liver disease, the typical stresses of having the disease in the first place now also include the added stresses of changing responsibilities in the management of their care, a new healthcare team, and the environment of adult care. Yet, despite the vulnerabilities of this period, one survey of adult transplant hepatologists reported that 32.4% of providers do not employ a transition strategy [43]. Thus, though transition to adult care is a vulnerable period, there is a lack of transition services in practice. This section explores transition-related and general vulnerabilities, as well as, interventions relevant to adherence during this period.

Mental Health

Mental health disorders may be a critical risk factor for nonadherence among adolescents. In behavioural medicine, depression consistently has been shown to be a risk factor for nonadherence [44, 45] while evidence for anxiety as a risk factor is

more mixed [45–47]. In adolescent transplant recipients, post-traumatic stress symptoms (PTSS) are related to nonadherence [48]. However, few studies have directly looked at the effects of treatment PTSS symptoms on increasing adherence [48]. One small pilot study of post-traumatic stress disorder (PTSD) in liver transplant recipients describes the increase of adherence in three of the patients after the treatment of their PTSD symptoms [49]. Importantly, psychosocial risk factors prior to transplantation have not effectively been shown to be significant predictors of nonadherence after transplant [50, 51]. However, given of the rising prevalence of mental health disorders among adolescents with chronic medical conditions, detection and treatment are essential in this population [52].

Role of Caregivers

Though it may seem as though adolescence is a period growing independence, parents and caregivers can still play an important role [53]. To this point, a study of adolescents with cystic fibrosis found that increased parental monitoring was associated with increased adherence outcomes [54]. However, few studies specific to liver disease have incorporated interventions that involve caregivers. One pilot study [55] in liver transplant recipients utilized an intervention focused on helping parents and adolescents transition responsibilities. Patients who completed the intervention had increased adherence [55]. Furthermore, similar interventions have shown promise for use in adolescents with other chronic health problems such as epilepsy [56], diabetes [57–59], and asthma [60], among others. Caregivers and adolescents may have different beliefs about ability and the share of responsibility [61]. Thus, interventions focused on communication between caregivers and adolescents about responsibilities of care are useful in a successful transition. Such interventions will likely also address self-management skills.

Transition Readiness

An essential part of successful medication adherence during adolescence is the building of both transition readiness, which involves both the concrete skills and the self-efficacy of adolescents to take on greater responsibility in their care as they transition to adult services. Transition readiness should be taken into account when deciding on the timing of the transition to adult care. Importantly, perceived transition readiness does not always translate into actualized increased adherence [61]. Thus, it is likely still useful for caregivers to be involved in helping adolescents manage their own care. The decrease of caregiver responsibility is best accomplished at a pace that is consistent with the actual skills of the adolescent.

Transition Coordinators

Interventions that have utilized a transition coordinator or navigator are promising. This coordinator is most often a psychologist or a related professional but can be a different member of the clinical team [62, 63]. The transition coordinator role is most effective when it is someone who works with the adolescent before and through the transition [62, 63]. One study [63] utilized a transition coordinator to help adolescent liver transplant recipients transfer from pediatric to adult care. The coordinator was a licensed psychologist specializing in pediatric psychology who started working with patients one year before the transition until the end of the first year of adult care. The coordinator helped prepare patients for the transition to adult care, served as a liaison between pediatric and adult care teams, aided with care coordination between adult and pediatric services, helped outreach efforts between families and care teams, and implemented outcome assessments. Patients in the transition coordinator group had significantly decreased rates of nonadherence as measured by MLVI. Although small, this study suggests that a transition coordinator procedure may be a useful intervention. Other studies utilizing a transition coordinator reported similar positive results in adolescents with diabetes [64] and haemoglobinopathies [62] among others.

Programmatic Interventions

Transition coordinators may also be part of larger transition programs, such as those that use dedicated clinics [62]. Transition clinics may include various components such as educational and skills-based interventions as well as opportunities to meet adult providers before the transfer of care. There are no standard definitions of what such clinics should or must do. Few studies have assessed the use of transition clinics in patients with liver disease, and findings from transition clinic programs for other chronic health concerns have yielded mixed results [62, 65–67]. Importantly, these mixed findings may be a result of the different types of programs implemented.

Of the more positive findings, one study [68] looked at the use of a transition clinic in young adult kidney transplant recipients. The transition clinic consisted of meetings between patients and families with the pediatric and adult care teams, a joint case review, and separate patient and family groups. The groups talked about issues such as the differences between pediatric and adult care, adherence, and broader topics like education and career planning, among others. Compared with a historical control, patients who attended the transition clinic were significantly more adherent as measured by calcineurin inhibitor levels.

Another study [66] in adolescent heart transplant patients utilized seven quarterly educational interventions over two years in the context of a pediatric heart

transplant transition program. The sessions were two hours each and focused on topics like medications, medical conditions, and risky behaviors. Caregivers went to support groups that discussed similar topics. Similar to the prior study [68], this study used a retrospective chart review. When compared to patients who did not receive the intervention, they found a significant decrease in nonadherence measured by the percentage of calcineurin inhibitor levels [66].

However, other studies on transition clinics have found more mixed results [67]. One study [67] utilized a similar type of transition clinic as those described earlier for patients with juvenile idiopathic arthritis, but the intervention did not address adherence. Though the intervention improved some clinical outcomes, including perceived rheumatic-specific health status and psychosocial functioning, it did not have a significant effect on adherence [67].

Technology-based Interventions

Other interventions not yet adequately addressed in the current literature include the use of technology-based interventions, such as mobile phone applications. One study of text message reminders for adolescents with liver transplant found significantly increased adherence as measured by MLVI [69]. Studies that have used text message-based adherence interventions for other health concerns have found more mixed results [36, 70, 71]. Research in this area is still in its infancy, and most published data are from pilot studies and planned research projects [72].

Limitations

The current research on adherence interventions during adolescence is limited by less-than-ideal study design and a paucity of successful approaches to draw from. Thus, while current research suggests some general recommendations, no firm conclusions can be drawn. Many studies utilize a retrospective design, such as historical controls or a chart review. Finally and importantly, some studies have noted increased adherence, but not better outcomes [15]. This challenge is likely also indicative of a design flaw in methods used to measure adherence and recruiting patients who were adherent at baseline [15].

Recommendations

Despite the limits of current data, there are several converging findings that can be translated into practice. The transition from pediatric to adult care is a difficult time for adolescents when it comes to medication nonadherence. Starting this process

earlier may allow patients to be less overwhelmed and more prepared to take on more control over their care. It is also critical to measure nonadherence frequently throughout care using objective measures whenever possible. Parents, caregivers, and family members can be valuable contributors to successful adherence. The extent and pace of transition of responsibilities from caregivers to adolescents should not be based on age, but rather the self-care skills of the individual. Interventions to build these skills, such as those frequently found in transition clinics, may be useful. The implementation of a transition coordinator role in clinics, may also be an effective intervention. It is likely even more beneficial when the transition coordinator can work with families both prior and through the transition. Lastly, providers should be attuned to mental health aspects of transition and intervene accordingly.

Substance Use

The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) [73] conceptualizes a substance use disorder as the as the presence of symptoms related to substance use that cause a significant impairment in functioning. Symptoms must be present for at least twelve months. Severity of substance use disorder in DSM-5 can be either mild (endorsement of two symptoms), moderate (endorsement of four to five symptoms), or severe (endorsement of six or more symptoms). Before the release of DSM-5, DSM-IV-TR [74] conceptualized substance use disorder as substance abuse and substance dependence. The criteria for substance abuse are similar to that of mild substance use disorder in the newer classification. The criteria for substance dependence are similar to those of moderate to severe substance use disorder [73, 74].

This section provides an overview of substance use disorders in this population and then examines some of the most common substance used by adolescents and their effects on those with liver disease.

Alcohol Use

Studies of the effects of alcohol on liver transplant outcomes in adults indicate that the adverse effects of alcohol use are more likely to be seen over the long-term [75]. Yet, recent small studies of adolescents who engage in binge drinking have provided some evidence that this behavior can have impacts on immune function [76, 77], which is highly relevant to liver transplant recipients. In the short term, adolescent excessive drinking is associated with increased risk for medication nonadherence, risky behavior, and accidental injury or death. In the long term, chronic alcohol use can have a more protracted and severe effect including the development of alcoholic liver disease [78].

Marijuana Use

Marijuana use is common among adolescents with one recent survey of American youth, finding that 21.7% of high school students used marijuana in the last 30 days [79]. The effects of marijuana on liver disease outcomes are unclear [80], especially in adolescents. One review of marijuana use in individuals with liver disease that was not specific to adolescents found that there was only a weak effect of marijuana use on worsening symptoms related to liver disease [80]. A study of women with both chronic hepatitis C (HCV) and human deficiency virus (HIV) found no effect of marijuana use as measured by the mean number of uses per week or daily on worsening liver fibrosis [81], while a retrospective study of adult marijuana users assessed for liver transplantation also found that that patients with a positive marijuana toxicology screen had similar survival rates to non-users [82]. Other studies have found comparable results [83, 84]. However, there is a lack of consensus about how transplant centers should address marijuana use in the context of transplant eligibility [85–88].

Opioid Use

Opioids, such as oxycodone and morphine, may be prescribed by medical professionals, but are sometimes used for recreational purposes. The rate of opioid misuse and dependence in those prescribed them were once erroneously considered extremely low [89]. For example, one influential editorial in 1980 from the *New England Journal of Medicine* cited a rate of opioid abuse of 4 out of 11,882 patients [89]. However, more recent studies have found rates of misuse and abuse of prescribed opioids to be much higher than this initial estimate [90]. Among adults prescribed opioids, rates of misuse are around 21.7–29.3%, and rates of dependence are around 7.8% to 11.7% [90]. Thus, opioid misuse is common among those prescribed, and some of those individuals go on to develop an opioid use disorder. These findings are similar to rates of opioid use disorder found in the general population [91].The incidence of opioid use amongst adolescents with liver disease is unknown.

In the general population, opioid use among adolescents is on the rise [92, 93]. In adults, one study found that patients who used higher levels of opioids before and after liver transplantation had higher rates of adverse outcomes [94]. Other studies demonstrate worsening outcomes in chronic opioid users with cirrhosis [95] and suggest that opioid prescriptions may be associated with psychiatric symptoms and not only pain [96]. Prescribers should assess for opioid misuse when prescribing opioids [97].

Other Substances

Rates of any form of tobacco use in adolescents have steadily declined worldwide [98]. The rate of tobacco use among adolescents with liver disease is unknown. In adults, tobacco usage is associated with worsening outcomes in various liver diseases, such as in patients with liver transplants [99, 100] and hepatitis C [101]. There is mixed evidence of the effect of smoking on non-alcoholic fatty liver disease (NAFLD) [102–104]. This equivocal finding could reflect that the effects of smoking on NAFLD may be too early to detect in younger people [104]. Regardless, tobacco use in general is an important risk factor in worsening general health outcomes and early death [105].

Summary and Implications

There is a general dearth of research on the long-term outcomes of substance use in adolescents suffering from liver diseases. Larger and more rigorous studies are necessary to better understand the prevalence and consequences of substance use disorders. Adolescents with liver disease may be at a higher risk for the adverse side effects related to substance use and worsening of liver disease status. This may be due to the compounded effects of substances, specifically alcohol and opioid use, on an already vulnerable liver.

Substance use is a modifiable risk factor for poorer outcomes in adolescents suffering from liver disease. Though more research is necessary on this topic, the assessment and treatment of substance use in this population may help to prevent adverse outcomes. Clinical impressions of substance abuse by healthcare providers may not be accurate when compared to standardized assessments [106]. Thus, it is useful for providers to use standardized assessments, such as the Alcohol Use Disorder Identification Test (AUDIT) [107] or the Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD) [108], to screen for substance use [109]. The National Institute on Drug Abuse (NIDA) also provides paediatric providers with two brief online versions of the BSTAD and Screening to Brief Intervention (S2BI) [110] for use with adolescents aged 12 to 17 [111]. Both measures can be administered in under two minutes, providing a feasible and quick way to integrate assessment for substance use into patient visits [111].

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Chapter 18
Mental Health

Jemma Day

Introduction

Mental health problems are one of the main causes of the burden of disease worldwide [1] with one in four individuals in the general population experiencing a mental health problem in any given year. Around 10% of children and young people in the United Kingdom have a clinically diagnosable mental problem at any one time [2] but mental health services are overstretched, and have long waiting lists. The mental health budget is largely spent on coping with crisis rather than prevention [3] and the vast majority do not receive appropriate interventions at a sufficiently early age [4].

Recent medical advances have reduced disability associated with physical health problems, yet comparable mental ill health indices have not caught up [5]. Analysis of the 1990–2010 data collected by the World Health Organisation global burden of disease showed that disability-adjusted life years of major physical illness have fallen, while almost every mental health condition had increased its burden of disease [6]. There are strong links between our physical and mental health, although the two are often managed by completely separate services and hospitals with limited liaison between the two.

A 2012 report by The King's Fund [7] found that 30% of people with chronic illness also had a co-occurring mental health problem. Suicide mortality is also high (close to 800,000 deaths per year globally), which disproportionately affects young people under 30 years. Teams set up specifically for the needs of younger adults, such as early intervention in psychosis services, are more effective than traditional care and have proven to be cost effective [5], however, typically young people are

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looked after by paediatric services until the age of 16 or 18 years, and separate adult services thereafter. This applies to most physical and mental health provisions.

Mental health difficulties and adverse psychosocial circumstances have been associated with poorer health outcomes in young people with liver conditions, including non- adherence to medication [8] and subsequent graft rejection [9, 10]. They have been found at an elevated rate in young people with liver conditions [11]. Adolescence and early adulthood is the peak age of onset for mental health problems [12] whereas physical illness onset peaks in the fifth or sixth decades of life. Clinically this means that younger patients with physical illness are relatively more likely to have co-existing psychological difficulties in comparison to older patients [5].

On liver wards, adolescent and young adults are quite rare and their unique mental health needs can be overlooked. Symptoms of chronic illness, restrictions on functioning, and the need for complicated treatment regimens are likely to interfere with many aspects of adolescent life and are considered to cause frustration in young people [13]. Treating mental health conditions is 'every doctor's business' and should be given equal priority when attending to physical health needs [14].

Prevalence

Qualitative research indicates that young people with chronic illness experience additional worries relative to their healthy peers, due to the demands of living with and managing a health condition during adolescence [13, 15]. Previous research [16–18] has indicated higher levels of depression and anxiety in children and young people with chronic conditions, particularly those impacting upon energy levels (chronic fatigue syndrome and fibromyalgia), those with severe symptoms (migraine/tension headache) and those resulting in a visible difference (cleft lip and palate), all of which can apply to young people with CLD. Symptoms of chronic illness, restrictions on functioning, and the need for complicated treatment regimens are likely to interfere with many aspects of adolescent life and to cause frustration. Larger effect sizes are found for studies using parent rather than child ratings of mental health [16–18].

A cohort study at our centre (n = 187, [11]) found elevated rates of depression and anxiety in adolescents with CLD relative to general population norms. Brief, standardised questionnaires were used to investigate the levels of depression and anxiety (The Patient Health Questionnaire, PHQ9 and Generalised Anxiety Disorder Assessment, GAD7) as part of a battery of questionnaires completed by young people as part of a pre-transplant work up. Across conditions, 17.7% of YP screened positively for anxiety or depression, with no differences between diagnoses groups, which matches our experience clinically. As these data were collected as part of routine practice, the opt-in rate is much higher than might otherwise be expected (82%) increasing the representativeness of the sample and generalisability of the findings. Levels of depression and anxiety were higher than those found in the

general adolescent population [2] but comparable to data in other chronic illness populations [16–18], highlighting the need to address these issues in all young people with CLD.

Studies in adult CLD populations have also indicated elevated levels of depression and anxiety relative to the general population [19]. However, there are difficulties with generalising adult CLD data to young people with CLD- for example, due to differences in presenting conditions. No other studies have systematically examined mental health in young people with CLD, and most studies investigating quality of life (QoL) report only on young people post-liver transplant or specific conditions such as biliary atresia (e.g. [20]) rather than adolescents with CLD as a group. Collectively, these studies indicate lower QoL than healthy controls but comparable QoL to children with chronic diseases (or other organ transplant recipients). Across studies [21], identified predictors of poor QoL included transplantation in adolescence (as well as sleep problems and medication adherence), which were similar factors highlighted by our mental health study, discussed in more detail below.

Factors Associated with Poorer Mental Health

Sleep and Fatigue

In our cohort study almost half of young people cited fatigue and nearly a third cited sleep difficulties as contributing to their distress. Sleeping difficulties and associated problems with fatigue have also been highlighted in the QoL literature, with studies linking poor sleep to lower QoL (e.g. [22]) even post-transplant. Although liver disease undoubtedly can cause problematic sleep [23], in our clinical experience, this can be further exacerbated by general factors contributing to poor sleep as found in the healthy population. For example, young people often report inconsistent sleep schedules (e.g. napping and long weekend lie-ins to compensate for periods of little sleep), a poor bedtime routine and sleep hygiene (e.g. excessive screen time and mobile phone use before bed), unhelpful sleep environments (e.g. bedding, temperature, lighting), lifestyle factors (e.g. alcohol use, excessive caffeine, large meals before bed) and psychological factors (‘racing mind’, intrusive thoughts, anxiety about not sleeping, problem-solving). Asking young people about their sleep satisfaction and routine should be routine in adolescent health settings. Brief assessment and intervention for sleep hygiene can easily be incorporated into standard clinical practice and is discussed in the final section of this chapter. In addition, problematic sleep is strongly associated with depression [24], with some evidence that interventions directly targeting sleep improve mental health outcomes [25, 26]. Including a question about young people’s sleep in routine clinical practice may also help identify those at risk of poorer mental health as well as identify areas of intervention.

Illness Beliefs

Young people's mental health appears to be linked with their beliefs about their illness and treatment rather than simply coexisting, meaning that their beliefs should be targeted within routine liver care rather than treating the mental health difficulties in isolation. Specifically, young people reporting a greater number of symptoms, a higher level of concern about their condition and a greater impact of the condition on their emotional health and general life, reported higher levels of distress. Young people reporting a significant emotional impact of their illness, a high degree of concern regarding their illness and a reporting a high number of symptoms and a significant impact on their life, should be considered at higher risk for co-occurring mental health problems and should be evaluated. It is interesting to note that perceived understanding of illness and how much young people believed treatment could help their condition had no relationship to distress. Further work in our centre has also found no relationship between 'understanding' and adherence in young people with AILD… The findings that young people's understanding of illness did not have an impact on their level of distress, suggesting that their concerns are not related to a lack of knowledge, indicating that further information about their condition (often a significant component of transition care) does not ameliorate their distress.

Cognition and Employment

The relationship between chronic liver disease and cognitive development is attracting increased attention and is discussed in Chap. 3. Problems with school and/or employment were cited as contributing to distress in almost a third of young people. This echoes findings from qualitative studies where, despite striving for normality, the transplant was perceived to have a negative impact on their schooling in adolescence [27, 28] and on relationships in young adulthood [29]. The long-term impact of reduced cognitive functioning cannot be underestimated. Employment is a concern in the liver transplant setting with unemployment rates of 50% in adults post-transplant [30] and 20% for young adults who underwent liver transplantation in childhood [31]. In a recent study of patients aged 16–35 years old post-transplant for biliary atresia, 22% were unemployed at the time of their last follow-up [32]. These are all higher than the current UK rate in young people of 13.7%.

Such concerns should be preempted and taken seriously by clinicians within the routine clinic review, both to engage the young people in discussing their most pertinent concerns and to facilitate appropriate onward referrals.

Screening and Management of Mental Health Problems (Difference in Access to Mental Health Services)

Given poor mental health is linked to worse physical health via increased non-adherence to medication and disengagement from services it is important that mood and emotional wellbeing in young people post-liver transplant is considered routinely, as part of good clinical care [33, 34] even when embedded psychosocial support is unavailable.

The Five Year Forward View for Mental Health from NHS England has identified parity of esteem between mental and physical health as an essential goal. Healthcare for young people with liver conditions should be proactive, holistic, preventive and patient-centred. Young people typically remain under paediatric services until the age of 16 or 18 years, and then move to adult services during this already tricky time. Our young adult liver service aims to meet the needs of young people aged 16–25 years by providing developmentally appropriate multidisciplinary care specifically targeted to this age group. Our patients have full and open access to the multidisciplinary team as needed. There is a core team of paediatric and adult doctors, clinical nurse specialists, social workers and a clinical psychologist.

Standardised Screening Questionnaires

The use of standardised screening mental health questionnaires can be helpful to both identify young people warranting further review, as well as support referrals to local mental health services by using the same tools used by these services in monitoring patients. For services without embedded clinical psychology, it may be helpful to liaise with clinicians in local mental health services to discuss referral pathways and to seek their advice regarding appropriate methods of screening and signposting. Our multi-disciplinary clinic screens for mental health difficulties in our young patients as part of all routine appointments, using standardised mental health questionnaires followed by use a semi-structured interview tool within the clinic appointment. Here in the UK, The Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder Questionnaire (GAD-7) are widely used to diagnose and monitor symptoms of depression and anxiety. We implement an informatics system that facilitates collection of these patient-reported outcomes ('IMPARTS'). The questionnaires are completed on an iPad in the waiting room prior to patients' clinic appointments. These are scored automatically and link up with medical notes to generate instant alerts regarding likelihood of depression/anxiety, as well as suicidality alerts. Our young people have reported [11] that completing the electronic screening is acceptable, a positive experience and that routine mental health screening in this manner would not affect the way they felt

about coming to clinic. Responses to these questionnaires are reviewed by the clinicians before seeing young people, and a semi-structured psychosocial interview is completed within the appointment. Clinician judgement has been shown to corroborate those who screened positively for anxiety/depression in most (31/33) cases. This means those presenting with probable depression or anxiety can be assessed in clinic and signposted to our embedded clinical psychologist as part of the same appointment, or to external agencies as appropriate. A similar pathway can be created with the use of pen-and-paper questionnaires providing there is support in the clinic to immediately review responses and incorporate these into the general liver review. Such assessment is only undertaken in our clinic when multidisciplinary support is available (clinical psychology for mental health support). Pathways can be developed with the input of local services but forward planning is required.

The HEEADDSS Tool

Further information regarding a young person's psychosocial needs within the clinic setting can be identified with the use of the HEEADDSS tool, a short psychosocial screening interview instrument which was initially conceived by Berman in 1973 and then more regularly used from 1982 in a High Risk Youth program in LA, USA [35].

The acronym HEEADDSS stands for:

- **H**ome
- **E**ducation & **E**mployment
- **A**ctivities
- **D**rinking Alcohol/**D**rugs/Medication Adherence
- **S**exuality/Relationships
- **S**uicidality & Mood/Anxiety

The HEADSS interview addresses the major areas of adolescent psychosocial stress and is a useful screening profile in any clinical setting with young people. This interview addresses the major areas of adolescent psychosocial stress and is a useful screening profile in the liver clinic and transplant setting, especially given the potential contribution of psychosocial stressors to treatment non-adherence. Considering living and psycho-social circumstances of young people can help health professionals to identify barriers to adherence and provide guidance for further practical and emotional support. Enquiring about education and employment often facilitate communication with young people in the clinic and can help to identify those young people with learning difficulties who could benefit from additional support to manage their condition. In addition to understanding more about a young person's

psychosocial background, reviewing these areas can give pertinent information regarding a young person's condition self-management potential. For example, a young person reporting that they are moving out of the family home to go to University may require additional support adjusting their medication regimen without parental input. Information about loss of employment may prompt questions about affordability of prescriptions, and young patients reporting new relationships may require information about appropriate contraception.

It can be helpful to see young people on their own, at least for part of the consultation. Sometimes young people are more comfortable talking about relationships, alcohol and drug use when not accompanied by their parents or carers. We find that asking about these issues routinely in all young patients is helpful and can 'plant the seed' for future consultations. For example, asking young people if there are times they struggle to take their medicine, or how much alcohol/drugs are around in their social circles reassures them that it is okay to talk about these issues in clinic and in our experience, makes it more likely that young people will discuss these factors in subsequent clinic appointments. It can be helpful to remind young people of confidentiality arrangements (usually that anything discussed in clinic is confidential and can be kept private other than in the rare instance that they tell you something that makes you worry about their safety or that of someone else). The use of open and non-presumptive questioning (e.g. 'are you in a relationship?/ have you been in a relationship before?' rather than 'do you have a boyfriend/girlfriend?') is also likely to lead to more honest responding (Fig. 18.1).

Young people are most likely to talk openly and honestly if they feel they are **treated with respect, listened to, and taken seriously** and spoken to using non-judgmental, and age-appropriate language.

As described above, it is really important to **talk about Confidentiality** early on (including explaining the limits of confidentiality). Young people are often worried that information shared in the consultation will be shared with others without their permission.

Ask the young person about their background using the HEADSS tool (described above), which is helpful in both identifying risk factors as well as support.

As well as asking the young person if they have any concerns about their mood or mental health, ask about their sleep, appetite and how they spend their spare time, which will give you more **information about their general wellbeing**. Some phrases you might find helpful to start a conversation include: *"How have you been feeling [in yourself]? How have you been coping [with everything that is going on]? Have you or anyone else noticed any changes in your mood?"*

Fig. 18.1 Top tips in assessing mental health

Assessing Suicidality

If young people report significant problems with their mood, don't be afraid to **ask about suicide directly**. There is no evidence that asking about suicide increases the risk, and asking could save someone's life. You could say something like: "*You mentioned that you have been feeling very low lately. Sometimes when young people feel very sad, they tell me that they experience thoughts about hurting themselves or even taking their own lives: have you had thoughts like that?*"

Please note that suicidal ideation is not uncommon, and it does not necessarily mean the young person will attempt take their own life, however, it is very important that they are asked about it. If young people acknowledge that they have been experiencing these thoughts, **ask if they have specific plans** (and if they have acted on these plans previously). *"Have you made plans for how you would do it?", "Do you have the means to carry this out?", "Have you considered what might stop you?/ "Is there anyone you can turn to for support?"* It can be helpful to ask the young person how things have been recently, and **if there is anything that has triggered the thoughts/how they are feeling.**

Young people reporting suicidal intent will need access to timely support.

- If there are immediate concerns about the patient's safety, contact urgent care mental health services (paediatric liaison/the duty liaison psychiatrist for discussion about the patient and advice.
- Think with the patient about ways they might be able to keep themselves safe, e.g. being with people, calling a friend or using other coping strategies if they are feeling low.
- Advise patient to attend their local Accident and Emergency Department if feeling in crisis; let them know they will see an experienced team who us used to helping people in similar situations.
- If the patient declines to go to A&E, please contact their GP to let them know what has happened.

- **When to Refer**

Anxiety and depression are amenable to intervention, this could dramatically improve patient care and optimize YP's health, well-being, and educational/occupational outcomes. An immediate response is required if patients report suicidality and intent. In our cohort study of n = 187, 4 (2%) reported suicidal ideation. Whilst suicidal ideation is not uncommon, suicidal intent needs careful review with these patients in order to determine whether they need access to urgent mental health support to ensure their safety. Sometimes physical healthcare clinicians can be hesitant to ask about mental health needs due to feeling unsure about how best to respond, particularly to disclosures about suicidality and self-harm. Young people disclosing suicidal intent do require immediate action and if embedded support is unavailable (either in the form of embedded clinical psychology or outpatient liaison psychiatry), should be supported to attend their local Accident and Emergency Service where psychiatric assessment is available 24/7.

Patients reporting milder symptoms of depression/anxiety but where there is an interaction with their physical illness should be referred to the embedded clinical psychologist. Embedded psychosocial professionals also ensure mental health difficulties are managed as part of routine liver care, and that the impact of current psychosocial stressors on young people's self-management is considered and supported. In addition to timely input from a mental health professional within clinic appointments, it is likely that YP benefit from being cared for by a medical team who are capable and confident in conducting psychosocial assessments. The team's experience is that this integrated approach also ensures that co-occurring difficulties are managed in a complementary way. For example, having a shared understanding of the relationship between a YP's depression, adjustment to illness and adherence behaviours and subsequently working together to improve these concurrently.

If the mental health concerns reported are unconnected to their health condition (or where embedded support is unavailable) young people can be directed to primary care mental health services. Care pathways can incorporate the use of local healthcare providers (such as Child and Adolescent Mental Health Services, Community Adult Mental Health Services and Primary Care Counselling and Emotional Wellbeing Teams) and General Practitioners to activate referrals to local mental health services. In the UK, primary care services such as Improving Access to Psychological Therapies (IAPT) typically accept GP referrals and many now accept self-referrals as well.

Some problems may also be amenable to immediate intervention within the clinical consultation without the need for specialist support, for example, by writing support letters to school, discussing concerns about medication side effects, and advising on sleep hygiene strategies (eg. consistent sleep schedule, bed for sleeping only, avoid blue light from screens, sugar and caffeine).

Another promising strategy to promote better mental health is to embed peer support into service models [36]. Peer-mentoring for liver transplant recipients was recently examined by Jerson et al. who found improved adherence (measured by mean tacolimus standard deviation levels) in both mentees and mentors [37]. The authors suggested that this may be attributable to the increased emotional support from attending the mentor training workshop. We have a small mentor programme, established in 2014, in which a group of young mentors are trained to support their peers. Positive feedback has been received (including several comments akin to "*I wish I had something like this when I was younger*").

Relationships with relevant third sector and charity organisations can be useful; for example, we regularly refer our young patients to a charitable organisation which supports young people with getting into employment, education and training. This can be particularly helpful for patients who have missed a large portion of education due to a period of ill health and/or transplant recovery. Attending to patients' mental health and psychosocial needs can dramatically improve patient care and optimize young people's health, well-being, and educational/occupational outcomes. Psychosocial distress has been correlated with nonadherence in both adolescents and younge people and so, addressing these issues is likely to also have a positive impact on their physical health [9, 33].

Key Points for Adult Hepatologists

1. Younger patients with physical illness are relatively more likely to have co-existing psychological difficulties in comparison to older patients. These can impact on how they look after themselves and their condition.
2. Asking about mental health ensures that co-occurring difficulties are managed in a complementary way. For services without embedded psychology, patients can be directed to and linked in with local services.
3. Asking the young person about their general background, for example, using the HEADSS tool (described above), can be helpful in identifying support as well as risk.
4. Some problems are amenable to intervention within the clinical consultation without the need for specialist support (e.g. writing support letters to school, discussing concerns about medication side effects, and advising on sleep hygiene strategies) but can be very helpful for young patients.
5. Making links with relevant third sector and charity organisations can also be useful in supporting young people's wellbeing

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Chapter 19
Health Related Quality of Life, Education and Employment

Mar Miserachs and Vicky Lee Ng

Introduction

Transition from childhood to early adulthood is surrounded by a number of physical, emotional, social and cognitive development changes, and challenges, all of which are likely to be amplified in the context of a health condition such as hepatobiliary disease. Hepatobiliary diseases in the adolescent encompass a broad range of disorders, ranging from congenital or genetic liver diseases presenting during early infancy to diseases that are typically diagnosed during adolescence, such as Wilson disease, autoimmune liver disease and non-alcoholic fatty liver disease. All these conditions can be associated with significant morbidity which, added to the unique challenges faced by adolescents, may negatively impact key outcomes such as quality of life, education, and employment. Quality of life broadly refers to the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns, complementing the World Health Organization's definition of health as a "state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity" [1]. While the constructs of quality of life and health-related quality of life are often used indistinguishably, health-related quality of life best represents the individual's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life [2, 3]. Quality of life assessment can be evaluated using both generic and disease-specific patient reported outcome measures. Commonly used generic quality of life measures include the Pediatric Quality of

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Life Inventory (PedsQL) Generic Core scale 4.0, the Child Health Questionnaire-Parent Form 50 (CHQ-PF50), and the Child Health Questionnaire-Child Form 87 (CHQ-CF87). These generic tools are limited by inadequate capture of unique and distinct clinical issues confronting adolescents and young adults with different liver diseases. Disease-specific health-related quality of life measures have the advantage of capturing treatment- and disease-related challenges [4]. To date, validated disease-specific tools are only available for liver transplant recipients, in whom both the PedsQL Transplant Module and the Pediatric Liver Transplant Quality of Life (PeLTQL) may be used [5, 6].

Incorporating and gaining a better understanding of key outcomes in young people such as health-related quality of life, education and employment is necessary to fully capture impact of disease in this population, enhanced and enabled by a dedicated and expert multidisciplinary team. In doing so, we will be able to develop best practices towards improving overall outcomes of chronic liver disease during adolescence, a critical phase of growth and development. This chapter will examine health-related quality of life outcomes in the adolescent with liver disease and the adolescent liver transplant recipient, discuss risk factors for impaired quality of life outcomes, and review what is known on the impact of liver disease on education and employment outcomes.

Health-Related Quality of Life in the Adolescent with Liver Disease with Native Liver

With advances in the diagnosis and treatment of liver diseases and, improved access to and survival after liver transplantation, assessing the quality of a patient's life has become an important outcome measure in clinical research and medical care. In 2007, a literature search was undertaken to identify all publications addressing quality of life in children and adolescents with gastrointestinal and liver disease. From 70 included studies published until the end of 2005, 11 were assigned to the category of liver transplantation (n = 9), chronic viral hepatitis (n = 1) and non-alcoholic steatohepatitis (n = 1) [7]. Since then, a growing number of publications have provided further insight into health-related quality of life outcomes across liver transplantation and other conditions; biliary atresia, Alagille syndrome, progressive familial intrahepatic cholestasis and autoimmune liver disease. Studies published over the last decade exploring health-related quality of life outcomes in children, adolescents and young adults with liver disease with their native liver, have been summarized in Table 19.1.

An important area to consider is how adolescents with liver disease fare when compared with healthy peers and other chronic illnesses. To make these comparisons, generic HRQOL tools need to be employed. These have been used in several studies investigating quality of life outcomes in patients with **biliary atresia**, which is a rare progressive, fibro-obliterative disorder of the intra and extrahepatic bile

ducts with onset in the first 3 months of life. Unfortunately, most affected children will eventually develop end-stage liver disease, with biliary atresia historically being the leading indication for pediatric liver transplantation. In a multi-center study including 221 subjects with biliary atresia (age 2–25 years), Sundaram et al. showed that biliary atresia subjects surviving with their native liver self-reported significantly lower PedsQL 4.0 scores when compared to the healthy population, but similar to that of patients with biliary atresia who had previously undergone liver transplant. The most significant differences between patients with biliary atresia surviving with their native livers and their healthy peers occurred in school functioning [13].

Using the Short Form 36 Health Survey in a cohort of young adults with biliary atresia, Wong et al. observed lower General Health and Physical Component summary scores in young adults with biliary atresia with native livers compared to a healthy control group, but similar to biliary atresia controls after liver transplant [17]. Other studies have failed to corroborate these findings and have shown that

Table 19.1 Summary of studies exploring health-related quality of life in patients with chronic liver disease in the last decade

Reference	Cohort characteristics	QoL instrument	Results
Autoimmune hepatitis (AIH)			
Bozzini et al. 2019 [8]	80 children with AIH (median age, 13 years; range 5–18 years) (Brazil)	PedsQL 4.0 (0–100)	Total PedsQL scores were significantly lower in AIH patients compared to healthy controls (78.2 vs. 85.6; P <0.001). Abdominal pain and corticosteroid dose negatively influenced the HRQOL in children and adolescents with AIH. Disease severity and disease remission status did not influence the HRQOL in the AIH pediatric population.
Trevizoli et al. 2018 [9]	43 children, adolescents, and young adults with AIH up to the age of 21 years (mean age 15 ± 3.9 years), mean follow-up time 6.3 years ±3.9 years (Brazil)	PedsQL 4.0 (0–100)	Total PedsQL scores were significantly lower in AIH patients compared to healthy controls (77.9 vs. 84.4; P = 0.016). Presence of symptoms (e.g. abdominal pain, arthralgia, diarrhea) negatively affected total PedsQL scores. Total PedsQL scores were not influenced by advanced liver disease, type of AIH, and association with sclerosing cholangitis.

(continued)

Table 19.1 (continued)

Reference	Cohort characteristics	QoL instrument	Results
Gulati et al. 2013 [10]	30 children (mean age 11.6 ± 4.5 years) with autoimmune liver disease (AIH, 16; PSC, 18; AIH/PSC overlap, 6) diagnosed for an average of 4.6 ± 4.3 years (North America)	PedsQL 4.0 (0–100)	Children with autoimmune liver diseases reported lower total PedsQL scores compared to healthy controls (71.6 vs. 83.9; P = 0.002). PedsQL scores in children with autoimmune liver disease were comparable other chronic health conditions such as moderate asthma, rheumatologic disease and obesity but worse than children with type 1 diabetes mellitus or pediatric liver transplant recipients. Abdominal pain, fatigue, and mood symptoms were associated with reduced significant HRQOL scores across many domains.
Alagille syndrome			
Kamath et al. 2015 [11]	98 children with Alagille syndrome (mean age 9.4 ± 3.1 years) 95 alpha-1-antitrypsin deficiency controls and 49 chronic intrahepatic cholestasis controls (25/49 progressive familial intrahepatic cholestasis) (North America)	PedsQL 4.0 (0–100)	Children with Alagille syndrome self-reported lower PedsQL total scores compared to healthy controls (69.9 vs. 83.9; effect size 1.12). Participants with Alagille syndrome reported worse quality of life than children with alpha-1-antitrypsin deficiency but similarly impaired to those with chronic intrahepatic cholestasis. Growth failure, total bilirubin, elevated INR and an intra-cardiac defect were predictive of poor self-reported or parental scores on univariate analyses, with only weight z-score remaining significant for child and parent-reported scores on multivariate analyses.

Table 19.1 (continued)

Reference	Cohort characteristics	QoL instrument	Results
Elisofon et al. 2010 [12]	71 patients with Alagille syndrome (median age 9.4, years; range 5–18 years); 8 liver transplant controls; 74 juvenile rheumathoid arthritis controls and 83 attention-deficit/ hyperactivity disorder controls (North America)	CHQ-PF50 (0–100)	Children with Alagille syndrome had lower CHQ-PF50 scores compared with a normative sample. Children with Alagille reported lower physical function scores than a liver transplant population; lower psychosocial function scores compared to children with juvenile rheumatoid arthritis and lower physical function scores but higher psychsoocial scores compared to children with attention-deficit/hyperactivity disorder. Cardiac catheterization or surgery, mental health diagnoses, and poor sleep were associated with lower CHQ scores.
Biliary Atresia			
Sundaram et al. 2013 [13]	221 patients aged 2–25 years with biliary atresia with their native liver (mean age 9.75 +/– 5.25 years) (North America)	PedsQL 4.0 (0–100)	Patients with biliary atresia self-reported lower PedsQL total scores compared to healthy controls (76.9 vs. 84.7; effect size 0.62), but similar to post-transplant biliary atresia patients (76.9 vs. 75.2; effect size 0.12). On multivariate regression analysis, black race and elevated total bilirubin were associated with lower total PedsQL scores.
Lee et al. 2016 [14]	36 children with biliary atresia with their native liver (median age, 7.4 years; range 2–18 years); 81 healthy controls and 44 other chronic liver disease controls (Malaysia)	PedsQL 4.0 (0–100)	Children with biliary atresia reported a mean PedsQL score of 85.6, which was similar to those of healthy children as those with chronic liver disease by other aetiologies.

(continued)

Table 19.1 (continued)

Reference	Cohort characteristics	QoL instrument	Results
Lind et al. 2015 [15]	25 young adults with their native liver (median age 23.2 years) (Netherlands)	WHOQOL-100 (0–20) RAND 36-Item Health Survey	Patients surviving biliary atresia into adulthood with their native liver had comparable WHOQOL-100 scores compared with healthy peers, except for higher scores on the social domain (17.2 vs. 15.7, P = 0.002). Young adults with biliary atresia reported similar RAND 36 scores in all the domains when compared with healthy peers, except for lower scores in health perception domain (63.2 vs 77.1, P = 0.002).
de Vries et al. 2016 [16]	25 young adults with their native liver (median age 23.2 years; range, 18–30) and 15 young adults post-transplant with biliary atresia (median age 22.4 years; range, 18–30) (Netherlands)	RAND 36-Item Health Survey	RAND-36 physical and mental summary scores in young adult patients with biliary atresia with native liver were comparable to that of transplanted biliary atresia controls and an age-matched reference group, except for decreased general health domain scores among non-transplanted biliary atresia young adults, particularly in females. RAND-36 summary scores correlated moderately to strongly to Liver Disease Symptom Index 2.0 total scores, which measure symptom severity and hindrance of these symptoms in daily activities.
Wong et al. 2018 [17]	26 patients older than 20 years: 16 with native liver and 10 with transplanted liver (median ages were 26.8 years and 25.6 years (China)	Short Form-36 Health Survey (0–100)	In subjects with native liver, scores were comparable to that of transplanted biliary atresia controls. When compared to a healthy control group, subjects with biliary atresia achieved lower scores in the General Health scale (42.9 vs 49.6, P = 0.029, CI 0.8–12.6) and the Physical Component (summary) scores (49.6 vs 54.4, P = 0.037, CI 0.3–9.2)

Table 19.1 (continued)

Reference	Cohort characteristics	QoL instrument	Results
Chronic viral hepatitis			
Abdel Hady et al. 2014 [18]	33 children treated for chronic infection with hepatitis C virus (median age of entire cohort of 71 patients at commencing treatment was 10 years; range 3–17.2 years) (United Kingdom)	Modified CHQ-PF28	The impact of treatment on QoL was evident at 12 weeks of treatment: the child's general health was perceived to be poorer, physical activities were more limited and frequency of pain was rated higher. Subsequent scores at 24 and 48 weeks of treatment and follow-up at 24 weeks declined to nearer the base level.
Annunziato et al. 2017 [19]	10 children treated for chronic infection with hepatitis C virus (mean age 11.62; range 7–17) (United States)	PedsQL 4.0 (0–100)	At baseline, patients displayed poorer quality of life than population norms, (PedsQL = 76.7). After treatment, PedsQL scores were 67.8
Schwarzenberg et al. 2017 [20]	161 children 10–18 years with chronic hepatitis B (mean age 14 years ± 2.1) (North America)	CHQ-CF87 (0–100)	Physical symptom-reporting, lower maternal education, and non-adoptee status were associated with lower CHF scores
Nonalcoholic fatty liver disease (NAFLD)			
Kistler et al. 2010 [21]	239 children 5–17 years with biopsy-proven NAFLD (mean age 12.6 ± 2.5) (United States)	PedsQL 4.0 (0–100)	PedsQL total scores were lower in children with NAFLD when compared to healthy children (72.7 vs. 83.8) with greatest discrepancies noted in school functioning. PedsQL scores did not differ by histological severity of disease. Symptoms significantly associated with lower QOL included: fatigue, sadness, and trouble sleeping
Pediatric Acute Liver Failure (PALF)			
Sorensen et al. 2015 [22]	36 children with PALF (median age 9.9 years, range 6–16.6): 23 liver transplant and 13 without liver transplant (North America)	PedsQL 4.0 (0–100)	PedsQL total scores (self-report) were significantly lower in PALF survivors compared with a matched healthy sample matched for age (72.2 vs 84.2)

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Table 19.1 (continued)

Reference	Cohort characteristics	QoL instrument	Results
Progressive Intrahepatic Familial Cholestasis (PFIC)			
Wassman et al. 2018 [23]	32 subjects with PFIC: 22 with transplanted liver and 10 with partial external biliary diversion (PEBD) (mean ages were 18.9 ± 7.5 years in the transplanted group and 15.3 ± 6.5 years in the PEBD group) (Germany)	PedsQL 4.0 (0–100)	PedsQL total scores of patients with PFIC after PEBD were similar to those after liver transplantation (80 vs 77). Children in the liver transplant group but not those after PEBD reported lower mean scores in the school functioning domain when compared to healthy controls (72 in transplant group vs 80 in healthy children)
Miscellaneous			
Gritti et al. 2013 [24]	25 children with compensated and clinically stable chronic liver disease (mean age 11.9 years, SD ± 3) compared to 33 liver transplant recipients (mean age 12.8 years, SD ± 3.6 years) (Italy)	CHQ-CF87 and CHQ-PF50	General Health Perception scores of liver transplant subjects resulted significantly lower than those of stable chronic liver disease, with comparable HRQoL in other areas

CHQ-PF Child Health Questionnaire Parent Form, *CHQ-CF* Child Health Questionnaire Child Form, *PSC* primary sclerosing cholangitis, *PedsQL* Pediatric Quality of Life Inventory generic core scale, *WHOQOL* World Health Organization Quality of Life assessment instrument

quality of life in young adults with biliary atresia is comparable to their healthy peers, when the RAND 36-Item survey and WHOQOL-100 generic instruments where used [15, 16]. Interestingly, when the WHOQOL-100 tool was used, young adult biliary atresia patients surviving with their native scored higher on the social domain of the WHOQOL-100 compared to the healthy population. The authors of the study postulated that their finding might relate to different experiences and expectations concerning their friends and family in subjects with biliary atresia to that of healthy controls due to their chronic illness or that family and friends are more concerned and helpful toward them [15]. When comparing the findings of the studies conducted by Lind et al. and de Vries et al. to those of Sundaram's study in a younger group of patients, it may appear that that over time, children seem able to adjust more to their health situation, and thus are coping better to living with biliary atresia [15]. However, the extent to which this is possible is unknown, as findings may also relate to survivor selection bias. Alternatively, the inconsistency in reported quality of life outcomes in biliary atresia populations could simply rely on the notion that the different tools used to assess quality of life may capture different quality of life aspects, and that direct comparison between studies is not possible.

Using the PedsQL generic health-related quality of life tool, Kamath et al. compared quality of life in children and adolescents with **Alagille syndrome** to that of healthy controls and other chronic liver diseases. Selecting a cohort of children with Alagille syndrome ascertained on the basis of the presence of cholestatic liver

disease, Kamath et al. showed that Alagille syndrome patients report lower PedsQL scores compared to healthy controls and children with alpha-1-antitrypsin deficiency, but similar to those with chronic intrahepatic cholestasis [11]. Similar findings were reported by Elisofon et al. in a previous multi-center North-American study. Using the CHQ-PF50, Elisofon et al. compared quality of life in children and adolescents with Alagille syndrome to that of a normative sample and those with liver transplantation and other chronic diseases. In their study, the authors found that children and adolescents with Alagille syndrome had significantly lower CHQ-PF50 scores compared to a healthy normative sample with decrements seen in all CHQ-PF50 subscale scores except for Family Cohesion. Children with Alagille showed lower physical function scores in comparison with liver transplant population and lower psychosocial function scores compared to children with juvenile rheumatoid arthritis. When compared children with attention-deficit/hyperactivity disorder, children with Alagille syndrome showed lower physical function scores but higher psychosocial function scores [12]. Both studies found that children and adolescents with Alagille syndrome fare lower quality of life than healthy children, likely related to the complexity of this multisystemic disease with multiple disease manifestations potentially impacting health-related quality of life.

It is possible that growing into adolescence with a chronic liver disease diagnosed during infancy may impact quality of life and patients´ perspective differently than when a new diagnosis is made during an already challenging time such as adolescence. As far as we know, no previous research has been able to assess the impact of age at liver disease diagnosis or disease duration in quality of life outcomes. However, few studies have explored quality of life outcomes in populations with liver diseases often diagnosed around adolescence. Three recent studies conducted in Brazil and North-America explored quality of life in adolescents with **autoimmune liver disease**. In these studies, adolescents with autoimmune liver disease reported lower PedsQL scores compared to healthy controls, with largest differences seen in the school functioning domain [8–10]. In their study, Gulati et al. also compared PedsQL scores in their cohort with autoimmune liver disease with other chronic conditions. They observed that health-related quality of life in their cohort was comparable with moderate-to-severe asthma, juvenile rheumatoid arthritis and obesity but worse than in pediatric liver transplant recipients or type 1 diabetes mellitus [10]. Others have explored health-related quality of life in populations with **non-alcoholic fatty liver disease**, which has now become the most common liver disease in adolescents. In a large North-American study in more than 200 children (mean age 12.6 years) with non-alcoholic fatty liver disease, individuals with non-alcoholic fatty liver reported lower total, physical and psychosocial health PedsQL scores compared with healthy children, with greatest discrepancies again noted in the school functioning domain. Overall, quality of life scores in children and adolescents with non-alcoholic fatty liver disease were comparable with the range of scores reported by age-matched populations with other chronic diseases such as asthma or diabetes [21]. When taken in aggregate, these limited studies, using the PedsQL generic instrument, demonstrate moderate impairment of quality of life in children and adolescents with autoimmune hepatitis and non-alcoholic

fatty liver disease. These findings highlight that the care of adolescents with liver disease should be broadened to include evaluation of quality of life.

The biology of chronic liver disease, and our clinical experience with adolescents and young adults, is such that we would anticipate a relation between severity of liver disease and worsening quality of life outcomes. While such relation has been described in adults with chronic liver diseases in whom the deterioration of health-related quality of life appears with increasing age and severity of chronic liver disease, such findings have not been identified in the adolescent and young adult populations [25, 26]. In children and adolescents with autoimmune hepatitis, no association was found between quality of life outcomes and disease remission status based on biochemical parameters or disease severity defined as previous history of complications (portal hypertension, upper gastrointestinal bleed, ascites, and/or spontaneous bacterial peritonitis) [8]. Similar results were shown by Gulati et al. in their small-sample size study in children and adolescents with autoimmune liver diseases diagnosed for an average 4.6 years, in whom the presence of advanced disease (present in 73% of subjects) was not associated with impairments in health-related quality of life but with debilitating liver disease-related symptoms [10]. A similar conclusion was reached by Kistler et al. in young individuals with non-alcoholic fatty liver disease in whom quality of life did not differ by histological severity of liver disease but was negatively affected by symptoms, in particular the symptom of fatigue, reported by 68% of participants [21]. These results support the notion that the subjective disease state seems to be a more important determinant of health-related quality of life than clinical disease state. To maintain or improve the quality of life of the adolescent with liver disease, it thus seems important for health-care professionals to focus treatment on liver disease–associated debilitating symptoms.

Several studies have linked liver disease-associated symptoms with decreased quality of life, even in diseases previously thought to be relatively asymptomatic such as non-alcoholic fatty liver disease. Symptoms reported to have a detrimental effect on the quality of life in children, adolescents and adults with liver disease include fatigue, irritability, abdominal pain, pain in the right upper quadrant, muscle aches, decreased appetite, memory problems, sleeping problems and itching [12, 21, 27]. In children with Alagille syndrome, itching was identified as a significant issue, with close to 60% of patients having some form of scratching, and 25% having destruction of the skin, bleeding or scarring [12]. Other symptoms reported by individuals with Alagille syndrome included sleep problems in 30%, bone fractures in 39% and xanthomas in 36%, the latter affecting physical appearance mobility, and pain [12]. Growth failure, common in children with cholestatic liver disease and genetic conditions, has also been described as a major determinant of impaired health-related quality of life [11]. Whether growth failure is a marker of poor overall health or there are specific effects of short stature that impact quality of life remains unknown. Other factors may contribute to poor health-related quality of life in growth failure, including pronounced cholestasis which is a more visible sign of disease, nutritional deficiencies, need for nutritional support and more frequent

medical visits. Another important consideration is that liver disease in childhood and adolescence often occurs in the context of a multisystemic disorder (e.g. cardiac and renal disease in Alagille syndrome) or in association with other conditions (e.g. obesity in non-alcoholic liver disease, inflammatory bowel disease in autoimmune liver disease), all of which also appear to negatively impact quality of life.

The course of liver disease can be chronic and unpredictable, with debilitating symptoms, visible signs of disease, complications, monitoring and interventions that can leave the adolescent patient worried about many aspects of their life. Factors leading to low quality of life may include worries about the need for liver transplantation, occurrence of malignancy or death. Decreased quality of life may also be a consequence of factors such as disruption to usual life activities, the dislike of taking medications, limitations to in both individual and group activities or concerns regarding physical appearance and worry about stigmatization, education and employability. All these issues certainly put patients with liver disease at risk for developing psychological problems similar to other adolescents and young adults with chronic diseases. Elisofon et al., described the psychosocial burden associated with Alagille syndrome, and reported a higher prevalence of mental health diagnoses (18% vs. 5–10%), depression (10% vs 5%) and attention problems (32% vs 19%) in children with Alagille syndrome compared to a healthy normative sample [12]. This preliminary data highlights the importance of recognizing the nature and extent to which adolescents with liver disease experience difficulties in various quality of life domains, including mental health.

Last, with advances in clinical trial designs and the influence of regulatory agencies seeking patient-reported outcomes, quality of life measures are of often used to inform on the impact of therapeutic interventions. In early research in this field, Iorio et al. informed on the impact of alpha-interferon therapy in pre-adolescents with **chronic viral hepatitis**. In their study, using the Sickness Impact Profile instrument, the authors described that quality of life was good before treatment, deteriorated during treatment, and returned to baseline within 3 months of stopping treatment [28]. Recent studies exploring the effect of pharmacological treatment on the quality of life of children with chronic infection with hepatitis C virus showed poorer quality of life at baseline compared with population normal and corroborated a decline in quality of life with treatment [18, 19]. In the study by Abdel Hady et al., the impact of treatment with PEG-interferon alpha and ribavirin on quality of life was evident at 12 weeks of treatment and this was thought be related to the side effects experienced during this period, which tended to improve later during the course of treatment [18]. In adolescents with autoimmune liver disease, the use of prednisone at a dose of ≥0.16 mg/kg/day was associated with poorer quality of life [8]. Weight gain, acne, stretch marks, hypertrichosis and growth disturbances associated with the use of corticosteroids have been described as determinants of health-related quality of life. Other studies have shown beneficial aspects of treatment, such as described in a small pilot study using metformin in children ages 10–17 years with biopsy-proven nonalcoholic steatohepatitis in whom PedsQL scores significantly improved following treatment compared to baseline [29].

Health-Related Quality of Life in the Adolescent Liver Transplant Recipient

Reflecting improved survival after liver transplantation, the literature on the impact of liver transplantation on quality of life has grown substantially in recent years. Liver transplantation replaces a chronic liver disease for another medical condition, requiring life-long immunosuppression and monitoring. While the expectation is that liver transplantation will lead to improved quality to life, results from two systematic reviews published in 2007 and 2017 reveal that paediatric liver transplant recipients report a poorer health-related quality of life in comparison to healthy population, but equal or better than those with other chronic diseases or other solid organ transplant recipients [7, 30, 31].

In their systematic review on health-related quality of life after paediatric liver transplant, Parmar et al. identified biggest impacts on the school functioning domain when the PedsQL was used and on the general health perception domain when using the CHQ, which were the two most used generic quality of life instruments in this population [30]. Several factors have been associated with lower quality of life after liver transplant. Interestingly, older age at time of paediatric liver transplantation has been associated with worse quality of life outcomes, with a pronounced effect in the adolescent period [32]. Whether quality of life outcomes in liver transplant recipients differ based on their primary disease, remains an area of controversy as discrepant results have been obtained. Similar to children and adolescents with liver disease, sleep problems and fatigue have been associated with worse quality of life in adolescent transplant recipients.

Adolescence is a particularly high-risk period for non-adherence to therapeutic regimens, particularly immunosuppressive agents, which are needed to prevent acute rejection, liver graft failure or death [33]. Non-adherence has been identified as potentially modifiable risk factor affecting health-related quality of life in adolescent liver transplant recipients [30, 34]. Previous studies described poor health-related quality of life across domains of physical, school and social functioning among those with poor adherence to immunosuppressant medication. Additionally, an association between non-adherence and psychological distress (poorer health perceptions, self-esteem, mental health, family cohesion, and more limitations in social and school activities) have also been described [34]. The described association between quality of life and non-adherence is of particular importance and suggests that empirically-based assessment of quality of life in the routine post-transplant monitoring of the liver transplant recipient may help identify those at highest risk for non-adherence. Equally important, adolescence appears to be the peak time for mental health problems. Rates of anxiety and depression appear to be higher among those with physical health problems and adolescents and young adults after liver transplantation are no exception to this [5, 35, 36]. Using the PeLTQL tool, a disease-specific quality of life instrument, lower quality of life scores were seen in participants with possible clinical depression and anxiety. Hence, routinely assessment of quality of life in the adolescent transplant recipients using the PeLTQL has

been suggested as a non-stigmatizing tool to begin discussions with adolescents related to the often sensitive issue of mental health [5].

Education and Employment

Previous studies indicate that youth with chronic illness may be at increased risk for poorer school functioning. Limited research suggests that liver disease interferes with school functioning in young people after liver transplant and in those with non-alcoholic fatty liver disease and autoimmune hepatitis [9, 21, 30]. School functioning, a construct that measures missed days of school and school-related cognitive functioning is reflective of current development and independent functioning into adulthood, and is associated with well-being and self-esteem. It is also an important functional outcome associated with occupational and economic outcomes in adulthood. Yet, little is known on the burden of liver disease on school functioning, educational and professional outcomes. More data are necessary to obtain a more accurate and complete assessment of the impact of disease on the individual.

Chronic liver disease during adolescence may compromise school functioning across attendance, participation and performance domains. Adolescents with liver disease and those after liver transplantation require frequent blood work and ongoing medical care, often at distant specialized healthcare facilities. Medical care includes multi-disciplinary clinic visits, radiology tests, procedures or hospitalizations, all of which may cause adolescents to miss a significant amount of school. A comparative study in the Netherlands revealed that adolescents with chronic liver disease missed more school than other children. In this study by Calsbeek et al. adolescents with chronic liver disease, were more often absent from school due to illness than age and gender matched healthy controls (7.5 ± 13.8 vs. 1.6 ± 6.0 weeks during total school time), similar to adolescents with inflammatory bowel disease [37]. Similarly, in a large study conducted through the through the Society of Pediatric Liver Transplantation research consortium, one third of liver transplant recipients reported missing at least 2 weeks of school after a mean interval from transplant of 5.42 ± 2.79 years [38]. Impairments in the physical and psychosocial functioning domains might lead to decreased participation in physical activity activities, after-school sports or other school-related activities. Fatigue, sleep disturbances and medication side effects reported by individuals with liver disease and after transplantation may impact on their ability to concentrate. Additionally, physiological complications of liver disease, such as profound cholestasis, hepatic encephalopathy and malnutrition may impact on school performance via a combination of mechanisms including altered cognitive function [39, 40]. A recent systematic review of the literature was conducted to determine to neurodevelopmental outcome if children with liver diseases [40]. Cognitive deficits, predominantly low IQ scores, were reported in 67% of children with liver disease with their native livers and in 82% of children after liver transplant [40]. Whether lower school attendance, reduced participation, and cognitive deficits and not to mention other important familial and social factors,

lead to educational underperformance in individuals with liver disease remains unknown. Among liver transplant recipients, the need for special educational services in more than a third of patients has been described for a broad range of academic difficulties. Interestingly, a risk factor for special education services after transplantation is the requirement for special education pre-transplant [38, 41, 42]. Perhaps more encouraging findings were those reported by Duffy et al. in a cohort of 20-year survivors of liver transplant, more than 90% of whom completed high school [43]. This suggests that academic difficulties in liver transplant recipients were, to some extent, already present before transplant. Challenges in elucidating this include the wide array of disease-related (type, duration, severity), demographic and psychosocial determinants of school performance to be considered. Until a better understanding in this area of knowledge will be gained, attention must be placed to identify those at risk for impaired school functioning so that they can receive the proper educational and social support in order to achieve the expected success in school.

Preliminary data in adolescents with chronic illness suggests that adolescents with chronic liver disease are less often employed than their age and gender matched healthy controls (67.6% vs 77.5%) [37]. More contemporary data from a single-centre study describing long-term medical and social outcomes in a cohort with juvenile autoimmune liver disease, suggests that success can be achieved in the educational and employment systems [44]. Among 54 of 70 patients (10 liver transplantation) individuals followed up for more than 10 years, 28% were still in education, 65% were employed (80% of liver transplantation patients) and 7% unemployed. Higher education degrees were achieved in 42% [44]. Clearly, education and employment outcomes have been understudied and further work is needed to understand the impact of disease in adolescents and young adults.

Summary

Traditional metrics of succesful management of liver disease have improved but such metrics alone are no longer sufficient to capture the full burden of disease. Data such as quality of life, education and employment are necessaty to obtain a more accurate and complete assessment of the impact of disease on the individual.

Most studies to date have focused on quality of life in children after liver transplantation, although a growing number of studies are now taking a closer look at other hepatobiliary diseases. When taken in aggregate, these studies demonstrate impairments in the quality of life of children and adolescents after liver transplantation and those with liver disease when compared to healthy controls, except for subjects with biliary atresia with their native liver in whom findings have been inconsistent. Findings suggest that the subjective disease state seems to be a more important determinant of health-related quality of life than clinical disease state, and that liver disease is associated with a significant psychosocial burden. These findings highlight that the care of adolescents with liver disease should be

broadened to include evaluation of symptoms and quality of life, and barriers to identifying and achieving academic and professional goals.

While increasing attention has been given to capturing the full burden of disease in children, adolescents, and young adults, much remains to be done, particularly in the adolescent group. First, impact of disease on quality of life of adolescents and young adults with chronic disease is not being routinely assessed nor adequately comprehensively addressed, something than can only be enhanced and enabled by a dedicated multidisciplinary team. Second, outcomes of education and employment have been rarely studied and further work needs to be done to understand the impact of disease across the wide array of hepatobiliary diseases occurring in adolescents and young adults. Finally, evidence-based strategies to improving the medical and psychosocial outcome in young individuals with chronic conditions are needed. This will allow us to effectively intervene in supporting young people in reaching their full social, academic and professional potential.

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Chapter 20
Fertility and Pregnancy

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Introduction

The incidence of chronic liver disease and cirrhosis in young people is increasing [1], primarily due to increasing prevalence of alcohol-related liver disease (ARLD) and non-alcoholic fatty liver disease (NAFLD) [2]. While pregnancy in chronic liver disease was previously considered a rare event, recent epidemiological studies have demonstrated that rates of successful pregnancies in patients with cirrhosis are increasing by 8% per annum over the last two decades [3, 4]. Despite fertility being often impaired in cirrhosis, there remains a risk of unplanned pregnancy without appropriate contraception, which accounted for a third of cases in one study [5]. Another increasingly frequent scenario faced by physicians is the liver transplant recipient seeking advice regarding either conception or an established pregnancy.

Clear strategies and guidance for both patients and healthcare professionals are increasingly important to optimise maternal and foetal outcomes. This chapter discusses fertility and pre-conception planning in cirrhosis and liver transplant recipients, management of an established pregnancy and contraception options for both groups.

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Table 20.1 Childbirth rates by aetiology of cirrhosis (Adapted from [4])

Aetiology of cirrhosis	Live deliveries per 1000/PY
HBV	63.7
NAFLD/NASH	57.6
PBC/PSC/other	55.6
AIH	45.7
HCV	40.8
ALD	27.2

Chronic Liver Disease and Cirrhosis

Fertility

As described above, rates of pregnancy are increasing in patients with chronic liver disease and in cirrhosis [4, 6], although there is some variation depending on aetiology of liver disease (see Table 20.1). With compensated cirrhosis and minimal portal hypertension, regular menstrual cycles and fertility appear to be preserved, however, in patients with decompensated cirrhosis and portal hypertension, menstrual dysfunction is commonly reported [7], with 30% to 48% of patients reporting amenorrhoea and 28% oligomenorrhea [8]. Reasons for this are multifactorial. The hypothalamic-pituitary dysfunction observed in cirrhotic patients results in impaired production of sex hormones. This is compounded by impaired hepatic metabolism and porto-systemic shunting in advanced disease. These result in high rates of anovulation and amenorrhoea [9]. Aetiology of liver disease is likely to have a contributory role e.g. poor nutritional status in patients with ARLD is associated with a evidence of primary gonadal failure [10]. Successful pregnancy is therefore relatively uncommon in decompensated liver disease.

Pregnancy

There is limited high quality evidence regarding the management of cirrhosis and portal hypertension during pregnancy due to relatively small numbers of patients reported. Aetiology of liver disease also has a role in likelihood of successful pregnancy (Table 20.1). However all such cases ideally require careful management in a multi-disciplinary setting with hepatology, obstetrics and foetal medicine input.

Monitoring

In all patients with established cirrhosis, risk of variceal bleeding as a complication of portal hypertension must be addressed. Up to 30% of cirrhotic women will bleed from oesophageal varices during pregnancy, increasing to 50–78% if known to have

varices prior to conception [11]. The risk is highest in the second trimester and at time of delivery, likely related to increased intravascular circulating volume, compression from the gravid uterus and repeated Valsalva manoeuvre [12]. Each variceal bleed is associated with maternal mortality rates as high as 20–50%, with significant risk of fetal loss. A screening gastroscopy at 20–24 weeks gestation is recommended [13], timed after completion of organogenesis at first trimester. While risks of sedation to enable screening endoscopy are documented, the benefit of early diagnosis and primary prophylaxis of oesophageal varices outweighs the risks. Key points during the procedure are to maintain haemodynamic stability and oxygenation, with particular care to avoid over-sedation. The patient should be positioned in the left lateral position to avoid IVC compression [14] and therefore maintain uterine blood flow to reduce risk of fetal hypoxia.

Treatment modalities of primary prophylaxis include use of endoscopic band ligation or beta-blockade, with limited data on safety. Propranolol is listed as Category C drug and has been used in other maternal conditions such as arrhythmias and hyperthyroidism, with documented low risk of neonatal bradycardia and IUGR, but overall appears to be safe.

Treatment of actively bleeding oesophageal varix follows similar principles to the non-pregnant patient, aiming to achieve haemostasis with endoscopic therapy. Terlipressin is listed as a Category D drug and is therefore not recommended due to risks of causing uterine contractions and concerns of reduction of uterine blood flow. Octreotide (Category B drug) has been shown to be safe as adjunctive therapy. Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) has been described as a salvage therapy for uncontrollable bleeding [15].

Splenic artery aneurysms are associated with portal hypertension both in the setting of cirrhosis and non-cirrhotic portal hypertension. While the true prevalence is unknown, an autopsy series demonstrated an incidence of 7.1% in patients with cirrhotic portal hypertension. These have been shown to be up to 4 times more common in multiparous women, which can be attributed to oestrogen and relaxin-related changes to the endothelium as well as increased cardiac output and blood volume affecting the vessel wall. Acute rupture in pregnancy is associated with high maternal and fetal mortality of up to 75% and 95%, respectively. As such, aneurysms greater than 2 cm should be treated prophylactically with radiologically-guided coil embolization [16].

Protein malnutrition is common in patients with established cirrhosis and needs to be careful managed from early in the pregnancy, ideally with specialist dietetic input. Fat-soluble vitamins are also often low and require replacement. Vitamin K is of particular importance towards delivery in view of its role in synthesis of clotting factors.

Complications

Efforts have been made to stratify risk of complications within pregnancy in patients with cirrhosis. A retrospective review of 62 pregnancies in patients with cirrhosis from King's College Hospital demonstrated that the model for end-stage liver

disease (MELD) score of 10 or above or a United Kingdom end-stage liver disease (UKELD) score of 47 or above is predictive of a significant liver-related complication, while a MELD score of 6 was suggestive that risks of complications were minimal [5]. Risks of hepatic decompensation in patients with relatively low MELD scores (<10) are relatively high in this patient group, with rates of clinical deterioration of up to 24% in some studies, often triggered by a variceal bleed. Hepatic encephalopathy has been reported after general anaesthesia provided for Caesarean section, and is treated similarly to the non-pregnant patient with laxatives and antibiotics. Table 20.2 summarises commonly prescribed medications in cirrhosis and evidence regarding their use in pregnancy. Risk of flare of specific diseases in the context of pregnancy are discussed at the end of this chapter.

Outcomes

Overall, maternal and fetal outcomes are improved by optimising management of the underlying maternal liver disease. Recent studies looking at these outcomes are summarised in Table 20.3.

Maternal outcomes: While maternal mortality in cirrhosis has previously been quoted with a wide range of 10% to 61% (reflecting the variation in severity of liver disease), these were mostly related to variceal haemorrhage which is now electively screened for and treated with primary prophylaxis. As a result, more recent studies quote improved outcomes with mortality at <2% [3].

Fetal outcomes: As illustrated in the table below, data from the UK, North America and Sweden reflect increased rates of fetal growth restriction and preterm birth.

Mode of Delivery: There is no large-scale data comparing safety and outcomes of vaginal delivery vs. Caesarean delivery in this patient group. Observational studies report increased rates of Caesarean section compared to control groups, which may be related to greater risk of obstetric complications in patients with cirrhosis. If opting for vaginal delivery, ideally there should be a relatively short second stage of labour as prolonging this stage with repeated Valsalva may increase risk of variceal bleeding. However, Caesarean section may have an increased risk of bleeding from surgical site related to portal hypertension. Decision regarding the safest mode of delivery needs to made on an individualised basis, depending on preferences of the patient and physician, as well as severity of liver disease. Care needs also to be taken regarding correction of underlying coagulopathy. Should regional anaesthesia be required, care needs to be taken to minimise risk of epidural haematoma. In general, platelet count above 80,000 and INR of less than 1.5 are considered safe for anaesthetic and surgical procedures.

Table 20.2 Commonly prescribed medications in cirrhosis and their effects on the fetus/breast feeding [17]

Drug	FDA pregnancy category	Potential effects on the fetus	Potential effects regarding breastfeeding
Variceal bleeding therapy			
Propranolol	C	Overall appears safe but can cause decreased placental perfusion, intrauterine growth restriction, fetal and neonatal bradycardia, and hypoglycaemia.	Low level excretion in breast milk, not expected to cause adverse effects in infant but recommend delaying feeds for 3 hours
Carvedilol	C	Use in third trimester may increase risk of hypotension, bradycardia, hypoglycaemia, and respiratory depression in the neonate. If used during pregnancy, it should be stopped 3 days before birth.	Unknown effects on the infant, not recommended unless benefits outweigh risks
Octreotide	B	No evidence of fetal harm in animal studies, although occasional reports of spontaneous abortions in first trimester in human cases.	Unknown effects on the infant, not recommended unless benefits outweigh risks
Terlipressin	D	Not recommended during pregnancy; shown to induce uterine contractions with potential risks of spontaneous abortion. Teratogenicity in animal studies has also been demonstrated.	Unknown effects on the infant, not recommended unless benefits outweigh risks
Diuretics			
Spironolactone	C	Possible reduced uteroplacental perfusion. Reduced live birth rates in animal studies.	Unknown effects on the infant, not recommended unless benefits outweigh risks
Furosemide	C	Possible reduced uteroplacental perfusion. Reduced live birth rates in animal studies.	Unknown effects on the infant, not recommended unless benefits outweigh risks
Hepatic encephalopathy therapy			
Rifaximin	C	Teratogenicity in animal studies (cleft palate, incomplete ossification, facial deformities, abnormal ocular development)	Unknown effects on the infant, not recommended unless benefits outweigh risks

(continued)

Table 20.2 (continued)

Drug	FDA pregnancy category	Potential effects on the fetus	Potential effects regarding breastfeeding
Lactulose	B	No evidence of harm in animal studies	Unknown effects on the infant, not recommended unless benefits outweigh risks
L-Ornithine L Aspartate	NA	Insufficient data	Unknown effects on the infant, not recommended unless benefits outweigh risks
Prophylactic antibiotics			
Ciprofloxacin	C	No evidence of teratogenicity in animal studies, although possible bone development anomalies as well as increased rates of spontaneous abortion and intrauterine death have been reported. In view of availability of safer alternatives, not recommended in first trimester	Acceptable with monitoring of infant for side effects (diarrhoea/candidiasis)
Norfloxacin	C	No evidence of teratogenicity in animal studies but evidence of fetal death at high doses. In view of availability of safer alternatives, not recommended in first trimester	Acceptable with monitoring of infant for side effects (diarrhoea/candidiasis)
Neomycin	D	Aminoglycosides considered potentially ototoxic and nephrototic to the fetus.	Not recommended unless benefits outweigh risks
Cholestasis therapy			
Ursodeoxycholic acid	B	Used widely in clinical practice with minimal effects. Animal studies have demonstrated evidence of teratogenicity and fetal death	Unknown effects on the infant, not recommended unless benefits outweigh risks
Cholestyramine	C	Used widely in clinical practice with minimal effects. May need supplementation of fat soluble vitamins due to impaired absorption	Acceptable
Rifampicin	C	Congenital malformations and embryotoxicity reported in animal studies	Not recommended unless benefits outweigh risks

Table 20.3 Outcomes of pregnancies in patients with cirrhosis (Adapted from [17])

Study	Shaheen et al. 2010 [3]	Westbrook et al. 2011 [5]	Hagstrom et al. 2018 [18]	Gonsalkorala et al. 2019 [6]	Flemming et al. 2020 [4]	
Population	339 obstetric-related admissions in women with cirrhosis	62 pregnancies in 29 women with cirrhosis	103 pregnancies in 76 women with cirrhosis	80 pregnancies in 48 women with cirrhosis vs 85 pregnancies in 52 women with chronic liver disease without cirrhosis	2022 pregnancies in women with cirrhosis compared to healthy controls	76 pregnancies in women with decompensated cirrhosis compared to healthy controls
Maternal outcomes						
Decompensation	15% Ascites: 11% VH: 5%	10% VH: 4.8% Ascites: 3.2% HE: 1.6%	VH: 1%	13% during pregnancy 21% within 6 months post partum VH: 5% Ascites: 2.5% Flare of underlying liver disease: 23%	1.6% Of which VH: 62% Ascites/HRS: 38% Risk of decompensation of 13% in women with pre-pregnancy decompensation compared to 1.2% in compensated disease	
Maternal mortality	1.8% vs 0% 6% in women with decompensated cirrhosis 18% in VH	1.6%	0%	1.2%	0.3%	
Pre eclampsia	6.8% (vs 3.9%)	No data	3.9% (vs 2.8%) (RR 1.39)	1.2%	Hypertensive disorders 11.2% (vs 8.8%)	13.2% (vs 8.4%)
Gestational diabetes	6.5% (vs 6%)	No data	3% vs 1%	No data	5.9% (vs 5.8%)	<7% (vs 7.4%)
Intrahepatic cholestasis of pregnancy	No data	No data	No data	1.8%	4.6% (vs 0.5%)	7.9% (vs <2%)

(continued)

Table 20.3 (continued)

Study	Shaheen et al. 2010 [3]	Westbrook et al. 2011 [5]	Hagstrom et al. 2018 [18]	Gonsalkorala et al. 2019 [6]	Flemming et al. 2020 [4]	
Population	339 obstetric-related admissions in women with cirrhosis	62 pregnancies in 29 women with cirrhosis	103 pregnancies in 76 women with cirrhosis	80 pregnancies in 48 women with cirrhosis vs 85 pregnancies in 52 women with chronic liver disease without cirrhosis	2022 pregnancies in women with cirrhosis compared to healthy controls	76 pregnancies in women with decompensated cirrhosis compared to healthy controls
Fetal outcomes						
Live birth rate	No data	58%	No data	75% vs 85%	No data	No data
Premature birth (gestational age < 37 weeks)	38.7% (vs 10%)	64%	19% vs 5% (RR 3.5)	45% vs 25%	Preterm birth: 11.3% (vs 7%)	14.5% (vs 6.3%)
Growth restriction	5.3% (vs 2.1%)	No data	15% vs 3%	No data	10.5% (vs 10.2%)	21.1% (vs 8.5%)
Neonatal mortality	5.9% (vs 2.1%) 12% mortality in cases with maternal decompensation	No data	1% vs 0.2%	0% vs 1.2%	0.7% (vs 0.3%)	0%
Obstetric outcomes						
Caesarean section rate	42 (vs 28%)	No data	36% (vs 16%)	No data	32.4% (vs 30%)	40.8% (vs 26.6%)

Key: *VH* variceal haemorrhage

Liver Transplantation

Fertility

Long-term outcomes for liver transplant recipients continue to improve with 5-year survival for adults currently at 83% [19]. Female patients of reproductive age increasingly look towards return to normal quality of life including starting a family. The first successful pregnancy post transplant was reported in 1978 [20]. Since then overall favourable outcomes have been documented with increasing live birth rate to 84% in the King's College Hospital patient cohort between 2007 and 2016 [21].

Menstruation is in most cases restored within 1 year post transplantation [7], suggesting reversal of previously described imbalances in endocrine axis. Patient education regarding potential restoration of fertility is crucial during the transplant assessment phase (or post-transplant in the case of emergency listing and transplantation). While menstruation may return to normal rapidly, without appropriate counselling regarding contraception, there is a risk of unplanned pregnancy.

In consideration of pregnancy post transplantation, current guidance from the National Transplantation Pregnancy Registry and other sources suggests delaying pregnancy for at least 1 year [21–23]. Multiple studies have demonstrated that conception within the first year post transplantation is associated with increased acute cellular rejection rates and lower live birth rates [24–27]. It is also suggested that up to a quarter of post-transplant recipients report sexual dysfunction for some time postoperatively [28, 29]. Reasons for this include side effects of medications, other medical co-morbidities such as co-existing endocrine dysfunction, organic pathology and psychological reactions.

Pre-pregnancy Counselling

It is never too early to discuss fertility and contraception with potential transplant recipients. The initial discussion should be held as early as at transplant assessment for patients being considered for elective liver transplantation, including education around immunosuppression and timing of pregnancy (as discussed earlier). This should be reinforced at routine post-transplant clinic visits.

Immunosuppression and Pregnancy

All women of child-bearing age must be counselled on the potential effects of immunosuppression during pregnancy, both for mother and fetus. These are summarised in Table 20.4. It is preferable that drug regimens are established and stable prior to conception.

The only absolutely contraindicated immunosuppressant during pregnancy is MMF, due to significant reported teratogenicity rates of up to 27% [22, 30]. Patients

Table 20.4 Immunosuppressive therapy used in transplant recipients and safety in pregnancy (Adapted from [9])

Drug	FDA Pregnancy Category	Proportion crossing the placenta	Potential maternal side effects relevant to pregnancy	Potential fetal side effects	Breast feeding safety information
Corticosteroids	C	10%	Hypertension Cushingoid symptoms Gestational diabetes Poor wound healing	Malformations (rate 4%) Premature rupture of membranes Adrenal insufficiency IUGR if requiring prolonged courses	At lowest dose possible and avoiding feeding for 4 hours post to minimise exposure to infant
Azathioprine	D	Crosses readily but the fetus is not able to convert to active metabolite	Leukopenia	Malformation (rate 7%) Preterm delivery Anaemia Leukopenia Thrombocytopenia Immune deficiency Infection Low birth weight IUGR Thymic hypoplasia	No
Cyclosporin	C	30–60%	Hypertension Gestational diabetes Pre-eclampsia Renal dysfunction	Malformation (rate 3–5%) LBW IUGR (moderate risk)	No
Tacrolimus	C	70%	Hypertension Gestational diabetes Renal dysfunction Neurotoxicity	Malformation (rate 4–6%) Pre term delivery LBW IUGR	Yes—with careful monitoring of infant for toxicity
Mycophenolate mofetil	D	Readily	Leukopenia	Malformation (rate 22%: cleft palate, ears, limbs, heart, oesophagus and kidneys) Spontaneous abortion (49%)	No
mTOR inhibitors	C	Limited data	Mucositis Infection	Limited data Animal models: reduced fetal weight, delayed ossification of skeletal structures,	No

started on MMF must have a negative pregnancy test and should be advised to use two methods of contraception before, during and for 6 weeks following completion of treatment. The effects of MMF on spermatogenesis are poorly reported. Current guidance from the UK Medicines and Healthcare products Regulatory Agency recommends that in absence of definitive safety data, male transplant recipients on MMF should use reliable contraception while on treatment and for 90 days after cessation [31].

Monitoring

These patients should be considered at "high risk" and ideally be managed in a centre with relevant experience. If any changes to immunosuppression are made (such as switching to tacrolimus from MMF), monitoring of graft function is essential. Antenatal imaging should be performed as per local policy. In view of increased risk of intrauterine growth retardation, the guidance recommends additional imaging at weeks 28, 32 and 36 [9].

Outcomes

Maternal Outcomes

Maternal mortality has not shown to be higher in the post-transplant population compared to the general population. Rates of graft dysfunction and rejection have been reported to be between 0 to 20% in a variety of studies, but this is confounded by lack of standardisation of diagnostic criteria for rejection. Discontinuation of immunosuppression by patients to minimise perceived risk to the fetus has been reported as a cause of rejection in this population, and highlights the need for careful pre-conception counselling regarding the importance of adherence to medications throughout pregnancy. Another common cause for low immunosuppression levels is related to increased plasma volume and haemodilution effect in the latter stages of pregnancy. In terms of treatment, acute cellular rejection responds well to optimisation of immunosuppression [22, 32, 33].

Pregnancy induced hypertension (defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg after 20 weeks gestation without development of proteinuria or new onset renal/hepatic abnormalities) has been shown to be more common in post-transplant patients than the general population (16–30% vs. 9%).

Pre-eclampsia remains the most common reason for preterm delivery in post-transplant patients. While rates in the post-transplant population have reduced with better medical management, it remains higher than the general population (7–12% vs. 4%), with likely multifactorial aetiology, including CNI-related vascular remodelling and increased pregnancy-induced hypertension. Further risk factors include vitamin D deficiency and are illustrated in Fig. 20.1. Recent data suggests that

	Unadjusted relative risk in pregnant women	95% Confidence interval
Previous pre-eclampsia	8.4	7.1 - 9.9
Chronic hypertension	5.1	4.0 - 6.5
Pre-gestational diabetes	3.7	3.1 - 4.3
Multifetal pregnancy	2.9	2.6 - 3.1
BMI pre-conception > 30 kg/m^2	2.8	2.6 - 3.1
Anti phospholipid syndrome	2.8	1.8 - 4.3
SLE	2.5	1.0 - 6.3
Previous stillbirth	2.5	1.7 - 3.4
Nulliparity	2.1	1.9 - 2.4
BMI pre-conception > 25 kg/m^2	2.1	2.0 - 2.2
Previous placental abruption	2	1.4 - 2.7
CKD	1.8	1.5 - 2.1
Anti retroviral therapy	1.8	1.6 - 2.1

Fig. 20.1 Risk factors for pre-eclampsia in the non-transplant population (Adapted from [34])

aspirin at doses of 75–150 mg/day until week 36 of gestation improves placental haemodynamics and therefore reduces risk of preterm pre-eclampsia (although not term pre-eclapmpsia) [35, 36].

Fetal Outcomes

Live birth rate has been shown to be improving over the last 30 years from 60% in late 1990s to 77–84% in most recently published cohorts. This likely reflects fewer unplanned pregnancies and recognition that these patients are high risk and should be cared for by a specialist multi-disciplinary team. Stillbirth rates have been reported as high as 12%, with similar rates of spontaneous abortion to the general population (16% vs. 17%).

Preterm birth remains more common in post-transplant recipients, with recent studies reporting rates from 32–39% (vs. 14% in general population) [32, 37], with an association with pre-eclampsia. A further risk factor has also been shown to be impaired renal function (eGFR <90 ml/min/1.73 m^2 prior to conception) [21].

Low birth weight has been shown to be lower than in the general population, which is likely related to higher preterm birth rates. However, IUGR rates have also been shown to be more common in post-transplant patients than in the general population, possibly related to vascular abnormalities within the placenta.

Congenital malformations are reported as less frequent in the latest cohorts, ranging from 0–4% (compared to 3–5% in general population). There is a wide variation in types and severity of malformations, making it difficult to attribute to side effects of immunosuppression.

While risks of vertical transmission of infections such as hepatitis B/C, HIV and toxoplasmosis remains similar compared to the general population, primary or recurrent maternal CMV infection needs to be monitored for and treated as it can

lead to congenital CMV infection. Untreated congenital CMV infections can have severe fetal complications including stillbirth, congenital malformations and death.

Mode of Delivery

There are no specific contraindications to vaginal delivery in post-transplant recipients, although there are often higher rates of obstetric complications which lead to increased rates of Caesarean section, e.g. pre-eclampsia. Rates of Caesarean delivery are reported between 20–63% (vs. 32% in general population).

Contraception/Breast Feeding

Recommendations from the WHO (2015) and UK (2019) publications on Medical Eligibility Criteria for Contraception Use offer guidance on safety of different forms of contraceptive therapy according relevant medical conditions. These are summarized in Table 20.5.

Chronic Liver Disease

There is limited data on safety and efficacy of contraception in established chronic liver disease. As described earlier, fertility is generally impaired but unplanned pregnancies, while uncommon, carry significant risk for both mother and fetus. Contraception options in cirrhosis are broadly similar compared to the general population.

Current recommendations from WHO 2015 guidance on Medical Eligibility Criteria for Contraception use are that there are no restrictions on use of hormonal contraception for women with stable compensated cirrhosis. However, in severe decompensated disease, combined hormonal therapy is deemed to be an unacceptable health risk (MEC Category 4), although combined injectable contraception therapy has been assessed as MEC Category 3 (where theoretical or proven risks

Table 20.5 Definition of Medical eligibility for contraception use (MEC) categories [38]

MEC	Definition of category
Category 1	A condition for which there is no restriction for the use of the method.
Category 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks.
Category 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method.
Category 4	A condition which represents an unacceptable health risk if the method is used.

usually outweigh the advantages of using the method). Progesterone only contraception has been assessed as MEC Category 3 in both oral and implant/injectable forms. Intrauterine devices are the most effective option and are deemed safe in compensated disease. The copper-IUD is deemed to be only safe option in this group in decompensated liver disease, whereas levonorgestrel-IUD has been assessed as MEC Category 3. Barrier methods are safe in this group of patients but less effective as a single method of contraception [39].

Viral Hepatitis

With the advent of direct antiviral agents (DAAs, hepatitis C treatment has changed dramatically in the last decade. However, there is no large scale safety data on use of DAAs in pregnancy. Ribavarin is known to be teratogenic, with potential effects lasting up to 6 months post cessation of treatment. Contraception is therefore strongly recommended during treatment with DAAs and for 6 months after if treatment regimen includes ribavirin. Co-administration of combined oral contraceptives with certain DAAs (glecaprevir and pibrentasvir, as well as PrOD ± ribavirin) has been associated with rise in serum transaminases, and alternative forms of contraception are recommended.

Post Transplantation

Choice of contraception in the post transplantation population is important, particularly in the context of our earlier recommendations to defer planned conception for at least 1 year postoperatively. Current evidence has not shown that a particular form of contraception is safest or unequivocally contraindicated in post-transplant patients.

While post-transplant recipients are not specifically discussed in the WHO 2015 guidance on Medical Eligibility Criteria for Contraception, the UK guidance from the Faculty of Sexual and Reproductive Healthcare and US guidance from the CDC state that use of IUDs (copper and levonorgestrel) are deemed to be safe to continue if already established (MEC Category 2) in the stable transplant recipient. In terms of hormonal contraception, the UK MEC guidance recommends progesterone-only therapy as safe for use in all transplant recipients (MEC Category 2), although combined therapy is also deemed safe in stable recipients only (Category 3–4 in patients deemed higher risk e.g. previous graft rejection). These recommendations are summarized in the Table 20.6 [38].

Table 20.6 Potential contraception methods in patients who have undergone transplantation (adapted from [9, 38, 40])

Contraceptive Method	UK and USA MEC Category of Use		Comments
	Stable graft function	Complicated graft function (rejection or graft failure)	
Barrier method	1	1	No drug-drug interactions Higher failure rates
Intra uterine device			
– Copper – Hormonal (levonorgestrel)	2 2	3 for initiation as new treatment (2 for continuation) 3 for initiation as new treatment (2 for continuation)	Theoretical risks of infective complications
Progesterone only			
– Depot – Implant – Progesterone only pill	2 2 2	2 2 2	No protection against sexually transmitted disease
Combined hormonal contraception (pill, patch, ring)	2	4 in CDC guidance 3 in UK guidance	No protection against sexually transmitted diseases. May interact with immunosuppressive medications

Specific Considerations Dependent on Aetiology of Liver Disease

Hepatitis B Virus

Antenatal screening in the UK includes testing for hepatitis B virus (HBV) via surface antigen (sAg). Patients found to be HBsAg positive at screening should be referred to a specialist clinic including hepatology input for further assessment of viral status including full HBV serology profile (HBV core antigen/antibody, HBV e antigen/antibody), HBV DNA, and assess for co-existent hepatitis D virus infection.

Chronic HBV infection remains a significant cause of cirrhosis and hepatocellular carcinoma with associated morbidity and mortality. Mother-to-child transmission is a key route of infection, thought to occur mainly at delivery.

The risk of developing chronic HBV is strongly associated with age of exposure, ranging from 90% in infants to 50% in young children and 5% in adults [41]. Risk of vertical transmission also depends on maternal Hepatitis B e-Antigen (HBeAg)

status, with 70–90% transmission rate in cases where the mother is HBeAg-positive compared to 10–40% in cases where this is negative. Current recommendations for prevention of perinatal transmission from EASL Clinical Practice Guidelines (2017) are for Hepatitis B Immunoglobulin and vaccination within 12 hours of birth, which reduces rate of transmission from 90% to 10% [42]. Failure of this prophylaxis is almost exclusively in HBeAg positive mothers with high DNA levels above 200,000 IU/ml ([43]) or high HBV surface antigen (HBsAg) levels >4 $\log^{10}$ IU/ml [44]. EASL guidance therefore also recommends that these patients should be offered nucleoside or nucleotide analogue prophylaxis. Tenofovir disoproxil fumarate has been safe in both human and animal studies, and has been shown to reduce perinatal transmission in this higher risk group to 0% at 28 weeks post-partum, compared to 7% with immunoprophylaxis alone [45]. Timing of cessation of antiviral therapy in cases where it was only initiated to reduce risk of perinatal transmission remains unclear. Careful monitoring is required due to risk of HBV flare upon cessation.

In terms of mode of delivery, there is no clear evidence that elective Caesarean section reduces risk of transmission compared to immunoprophylaxis alone.

Breastfeeding is associated with a low risk of transmission particularly if the infant has received immunoprophylaxis. WHO guidance recommends continuing breastfeeding. In patients who have received antiviral prophylaxis, tenofovir disoproxil fumarate been detected in breast milk but only in small concentrations, for which there is limited data on implications for the infant.

Hepatitis C Virus (HCV)

All patients who are pregnant should be screened for HCV. The main intra-partum risk is premature rupture of membranes and gestational diabetes. As pregnancy is a state of immune tolerance followed by immune reconstitution post-partum (breakage of immune tolerance), AST tends to fall in second and third trimester with rebound post-partum. However, no post-partum HCV flares have been described in the literature.

There remains a 3–10% risk of HCV transmission at birth, which accounts for the majority of childhood HCV. Risk of transmission increases in co-infection with HIV at a rate of 2–4 fold compared to HIV-negative patients [46, 47]. There is no clear perinatal management strategy to reduce this risk. Invasive procedures such as amniocentesis and invasive fetal monitoring are not recommended although there is very low level of evidence for this. There is no evidence for selection of Caesarean section over vaginal delivery although rupture of membranes for greater than 6 hours may increase risk of transmission [48], nor is there any evidence to recommend against breastfeeding unless there is evidence of skin breaks/damage to nipples [49].

In terms of treatment options for chronic HCV, the current recommendations are to start treatment of mother after delivery. IFN and ribavirin are strictly

contraindicated and there is limited evidence regarding safety of DAAs, although in vitro studies have been shown DAAs to be safe [50]. Preliminary results of a Phase I clinical trial treating chronic HCV with sofosbuvir/ledipasvir in the second and third trimester suggest similar efficacy and safety compared to non-pregnant patients [51]. A case report of treating a HIV/HCV co-infected mother with sofosbuvir monotherapy prior to delivery, followed by addition of velpatasvir post partum to complete 12 weeks of therapy, resulted in successful sustained virological response at 12 weeks, with negative HCV viral load in the baby and no evidence of teratogenicity at 2 years [52].

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) has a prevalence of 16–18 cases per 100,000 in Northern Europe [53], with a significant female predominance (71–95% [54]. In patients with known AIH, flares of disease were reported in 33% of pregnancies [55], with a statistically significant association with poor disease control in the year preceding pregnancy and absence of active treatment during pregnancy. This is in turn associated with a significantly increased risk of hepatic decompensation and neonatal high dependency admissions. 78% of these episodes were post-partum, in keeping with previously reported data. Flares of disease post-partum are presumably due to immune reconstitution; in AIH, regulatory T-cell number and function are impaired, leading to loss of immune tolerance and resulting in an uncontrolled effector autoimmune response. During pregnancy, the number of regulatory T-cells increases to allow the mother to tolerate paternally derived antigens from fetus, thereby theoretically enabling relatively stable disease until delivery. Patients should therefore be monitored closely for 6 months post-partum for such flares.

Standard immunosuppression with corticosteroids, thiopurines or calcineurin inhibitors should be continued during pregnancy. Mycophenolate Mofetil is contraindicated and patients should ideally be converted to an alternative immunosuppressant 12 weeks prior to planned conception. Best outcomes are achieved by continuing therapy to maintain a well-controlled disease throughout. If cirrhosis is present, stratification according to its presence is appropriate. Outcomes in pregnancy in AIH are good overall.

Fetal Outcomes

Live birth rates from case series have been reported at 73%, with stillbirth rates of 27% (general population 7–15%), with strong association between worse outcomes and active disease. Prematurity is associated with flares of active disease. Antiphospholipid antibodies are strongly associated with AIH, and they may be a separate, but related, cause of preterm delivery (20%).

Maternal Outcomes

Serious maternal adverse events are reported as 7–11% (including hepatic decompensation, hospitalisation and death), associated with active disease, absence of therapy and cirrhosis. As a new condition, AIH is rarely diagnosed in pregnancy, but should strongly be considered in the differential diagnosis of liver dysfunction, particularly accompanied by hypergammaglobulinemia with selective IgG elevation, in the post-partum period as well as during pregnancy.

Primary Biliary Cholangitis

There is limited data due to initial diagnosis/presentation with PBC being at a median age of 65 years [56]. However, 25% of patients will be of child-bearing age, and younger age at diagnosis (< 45 years) is associated with a more aggressive disease course [57]. Patients with ductopenic variant of PBC are at increased risk for significant cholestasis and should be discussed at pre-conception counselling.

Recent data demonstrated good outcomes both from maternal and fetal perspective [58]. Main clinical finding reported is worsening of pruritus during pregnancy (71%), requiring symptom-specific treatment, ranging from cholestyramine monotherapy to plasmapheresis [58]. Close monitoring in the post-partum period is recommended for cholestatic flares (up to 70%) [58], which in this study was not related to disease activity pre-conception. Screening for anti-Ro and anti-La antibodies is also recommended, as their presence would affect obstetric practice regarding fetal screening for bradycardia.

Evidence-based advice regarding the use of UDCA in pregnancy is lacking, but expert clinical practice generally includes safe use throughout all trimesters. Indeed, a good safety profile stems from its common use in intrahepatic cholestasis of pregnancy. Cholestyramine and rifampicin are also considered safe.

Primary Sclerosing Cholangitis (PSC)

This chronic inflammatory and fibrosing disease of intra/extra hepatic biliary tree frequently presents in child-bearing age, with a median age of diagnosis between 30–50 years. Two separate studies from Sweden and the UK both demonstrated increased rates of preterm birth, but no increase in maternal or fetal mortality or other adverse outcomes [59, 60]. Correlation was also noted between lower gestational age and elevated ALT at pregnancy booking bloods, as well as serum bile acids during the pregnancy. An earlier case series from Germany also reported 2 out of 21 mother developing intrahepatic cholestasis of pregnancy, which can be

difficult to distinguish clinically from a flare of PSC [61]. Treatment of the former with ursodeoxycholic acid and expedited delivery of the fetus may account partially for the increased rates of preterm birth in this patient group.

Wilson Disease

Although it can present at any age, the majority are diagnosed between age of 5 and 35 [62], with therefore a significant proportion of patients of child bearing age. Preconception counselling should include genetic screening, with likelihood of homozygote amongst children of 0.5%, and consideration of testing of the partner including haplotype analysis. There is a theoretical reduction of fertility due to copper deposition within endometrial lining affecting embryonic implantation and increased risk of pregnancy loss. Successful chelation treatment improves likelihood of conception.

Discussions with the patient should highlight the importance of continuing chelation treatment throughout pregnancy due to risk of acute liver failure upon cessation. Alongside chelation, close monitoring and treatment of copper deficiency minimises risks of birth defects.

D-penicillamine is currently listed as FDA Category D drug, with documented concerns over teratogenicity and risk of birth defects. Dosage reduction is recommended during first trimester (period of highest risk for birth defects) to 25–50% and monitor LFTs/copper levels during rest of pregnancy [62, 63]. Trientine is listed as FDA Category C drug due to possible risks of teratogenicity. Similarly to D-penicillamine, dosage reduction by 25–50% is recommended (by 25–50%) ([63]. Lower dose chelation at term also reduces risk of impaired wound healing and supports increased fetal copper requirement towards end of pregnancy. Breast feeding is not recommended whilst on chelation therapy.

If liver biochemistry is stable, a daily dose of 150 mg of elementary zinc could be maintained during pregnancy in almost all cases. It is not recommended whilst breast feeding due to potential risks to the infant of zinc-induced copper deficiency. There needs to be regular clinical controls and assessments of liver function tests and copper parameters in blood and urine during and after pregnancy, particularly if any of the above medication changes are made.

In terms of disease activity, in a study of 282 pregnancies in 136 patients, maternal disease course does not appear to be worsened by pregnancy. Fetal outcomes are also acceptable, with live birth rate of 74% and 3% birth defect rate [64]. No detailed studies regarding contraception in this patient group have been performed so far. Oestrogens may interfere with biliary copper excretion, as in the general population, with observed increase in serum copper and urinary copper excretion. Guidance therefore suggests that only barrier contraceptives and progesterone-only contraception are safe [62].

Biliary Atresia

Biliary atresia has been discussed in detail elsewhere (Chapter 4). The implications for fertility and successful pregnancy for these patients depend on whether the patient has secondary chronic liver disease, or is in the post-liver transplantation phase. The only additional consideration is in the former group, where cholangitis and associated risk of significant sepsis can further complicate the pregnancy. Otherwise, the patient should be managed as previously discussed in this chapter.

Alagille Syndrome

Alagille syndrome and its features have been well described elsewhere (Chapter 5) [65]. Few successful pregnancies have been described in this patient group. Severity of chronic liver disease, as discussed earlier in this chapter, can have significant implications in terms of reduced fertility and potential worsening of portal hypertension during the pregnancy. Cardiac dysfunction, particularly degree of pulmonary hypertension, can also complicate the pregnancy further. Finally, genetic counselling and consideration of screening via chorionic villus sampling for relevant gene mutations (*JAG1* or *NOTCH2*) should be considered in view of the autosomal dominant inheritance pattern [66].

Key Points for Adult Hepatologist

Incidence of reported pregnancies in CLD and post-transplant patients are rising. Patients of childbearing age should be offered early contraceptive and/or pre-pregnancy counselling. Choice of contraception may vary depending on aetiology of liver disease and concurrent medications. Successful conceptions should be managed in a multi-disciplinary setting with appropriate monitoring of both maternal and fetal health as outlined above.

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Chapter 21
Social Media and Technology

Jonathan Hind

Introduction

The definition of social media is broad and evolving as media evolves. It is commonly defined as a group of Internet-based applications that build on the ideological and technological foundations of Web 2.0 (the dynamic web rather than static web pages), and that allow the creation and exchange of User Generated Content [1].

Use of patient-facing technologies such as telehealth, digital devices and mobile phone applications (apps) is increasing. Mobile health or mHealth is now a huge field with many thousands of apps available. A report by the UK communication services regulator Ofcom in 2018 found that 95% of 16–24 yr. olds had access to a smartphone, and the smartphone was the device that people said they would miss the most [2]. In the US, the Pew Research Centre found similar results (Fig. 21.1*)*.

Social Media in Healthcare

As the web evolved (Web 2.0), the use of this for healthcare became known as Health 2.0. It may be defined as the use of a specific set of Web tools (blogs, Podcasts, tagging, search, wikis, etc.) by actors in healthcare including doctors, patients, and scientists, using principles of open source and generation of content by users, and the power of networks in order to personalise health care, collaborate, and promote health education [3]. The key concept of Health 2.0 is that patients themselves can have greater input, knowledge and control of information and data

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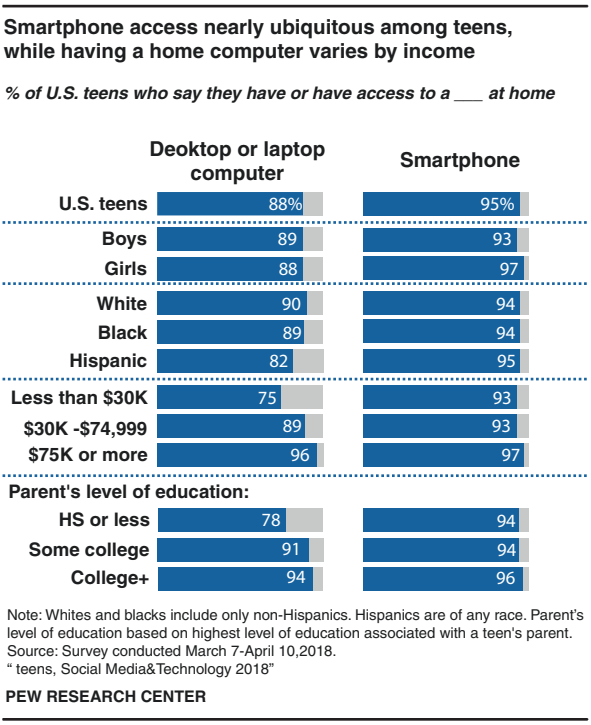

Fig. 21.1 Anderson, M and Jiang J. Teens, social media and Technology 2018, Pew Research Centre. May 2018. Permissions: the Center provides you with a personal, revocable, nonexclusive, nontransferable license to use the Services, to the extent attribution is to the Center or is not attributed to another, and the text, graphics, information, and other content made available through or from the Services (collectively, "Content"), including without limitation, Content obtained through widgets, RSS feeds, APIs or other similar means

generated about their health. This may be particularly useful in chronic diseases where patients require coordinated care from different specialties and in different locations.

The possibilities for social media in healthcare are huge, for example:

- Health-related information—awareness, promotion and education
- Online platforms with moderated health-related conversations
- Peer communities for disease support and management
- Clinical trial recruitment through online communities
- Personal health records with patients uploading their data
- Online HCP training, and collaborations to manage difficult cases
- Treatment, doctor and hospital reviews, ratings and comparisons

Young People and Social Media

Understanding how social media influences young people's knowledge and behaviour is complex [4]. It is a space where communication, friendship, play, self-expression, and learning occur [5, 6]. The pervasiveness of social media and the need to be continuously connected challenge the separation between "real" and online life [7–9]. The Pew Research Centre found that in 2018 45% of US teens said they were online "almost constantly" (Fig. 21.2).

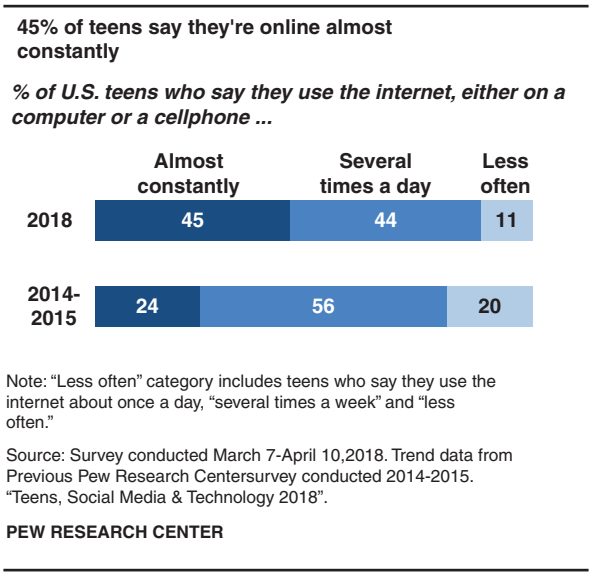

Fig. 21.2 Anderson, M and Jiang J. Teens, social media and Technology 2018, Pew Research Centre. May 2018. Permissions: the Center provides you with a personal, revocable, nonexclusive, nontransferable license to use the Services, to the extent attribution is to the Center or is not attributed to another, and the text, graphics, information, and other content made available through or from the Services (collectively, "Content"), including without limitation, Content obtained through widgets, RSS feeds, APIs or other similar means

Social media is a space where learning can happen as a result of observing and communicating with peers [8]. Traditional teaching and learning concepts are difficult to apply [10–13] and understanding of the health-related risks and opportunities of social media has been constrained by methodological weakness [14]. Evidence has been limited to one-off, short-duration intervention studies, analysis of parent/guardian and teacher perspectives, survey data or observational methods [15–17]. Therefore, health-related impacts of digital media engagement have been associated with time spent on social media, or the dissemination of information [18, 19] rather than changes in health outcomes.

The process of testing and validating interventions needs to be streamlined and include collaboration with young people with the aim of an engaged and informed patient population using evidence-based social media sites seamlessly integrated into their care.

Engaging Young People in Their Health Using Social Media

Adolescents and young people are difficult to engage in their health and are low healthcare users but they value the accessibility of information from social media, and they increasingly turn to it for health-related information [9, 17, 20]. They

have also reported on the benefits of social media in other areas such as socialisation, support and creativity [9, 20, 21].

Healthcare Delivery

Social media offers the opportunity to better understand the patient's perspective on their healthcare or its quality [22]. Information on the usefulness or delivery of a healthcare service for young people can be found from their social media posts, reviews and ratings.

Social media can be used to supplement face-to-face care. Rather than covering a long list of topics or guidance during a visit, the HCP could direct young people to social media platforms where they can explore, comment and ask their own questions in advance, allowing a focused physical visit [23].

Between visits, social media can be used to follow patients and motivate them to increase compliance with peer support and gamified tools [24]. People can be connected regardless of language and cultural barriers [25] and there are examples of using mobile technology including social media in the management of chronic disease [26] though the evidence base for widespread use is not strong [27].

There are challenges in using social media to deliver healthcare. The most obvious is confidentiality, which is especially relevant to adolescents who may be less aware of the risks of sharing personal data online, and at risk of cyber bullies [28]. HCPs must be particularly aware not to post anything through which it may be possible to identify an individual patient without their explicit consent as confidentiality must be protected.

Another challenge is professionalism in HCP-patient interaction. Friend requests, following patients, and maintenance of professional social media identities are concerns for the HCP [29]. Guidelines have been developed to assist professionals [30]. HCPs remain HCPs on social media—ethical and professional standards still apply. Boundaries between HCP and patient should be maintained. With health 2.0 social media is part of medical practice and resources to help HCPs navigate it and use it to best advantage whilst protecting themselves and their patients from risk are available [31].

Health Education

There is evidence that peer-to-peer healthcare is an important information source [29]. For adolescents in particular they find social media particularly useful for receiving health information that may be sensitive [32].

Social media as a platform for adolescent health education has the ability and capacity to disseminate information widely including to difficult to reach groups.

Thus, it has the potential to reduce disparities in health [33]. HCPs can also be reached on social media. For example, Cochrane child health evidence was disseminated using daily tweets, weekly blogs and a monthly journal club "tweet chat". It was found that a geographically and professionally diverse audience viewed the posts [34].

Social media for health education is not without challenges, in particular that information may be inaccurate or misleading. There are well-governed sites and moderated forums, but user-generated content is constantly being added and modified sometimes with little provenance [35].

Social Media and Liver Disease

Searching social media platforms for liver disease brings up information on therapies, diets, complementary medicine, research articles, symptoms and support groups. The difficulty is ensuring that useful, reliable content is available and shared widely.

One way in which gastroenterologists are trying to moderate the vast amounts of information on social media is by developing a universal hashtag ontology though this does have its difficulties [36].

Liver transplant patients have benefited in terms of engagement and satisfaction using a Facebook support group created by a team in Cincinnati [37]. Patients posted, commented and reacted on the platform and reported in a survey that the group had a positive impact in their care.

Social media can also be used to discover current or emerging themes in liver disease, or highlight areas of interest for future research. Da et al. looked at Twitter activity data for HBV, HCV and NAFLD/NASH from 2013–2019 [38]. HCV activity peaked in 2015 with 243,261 tweets before declining, whereas both NAFLD/NASH and HBV have continued to increase (Fig. 21.3). Treatment was the most popular content for HCV and NAFLD/NASH, whereas prevention was the most popular for HBV.

Negative Impacts of Social Media

Self-Esteem

The perception of self-value is a predictor of psychological wellbeing [39]. Seventy-six percent of adolescents believe that using social media has no effect on their confidence and 20% believe it makes them more confident [40]. However, there is evidence that greater time spent on social media is correlated with decreased body

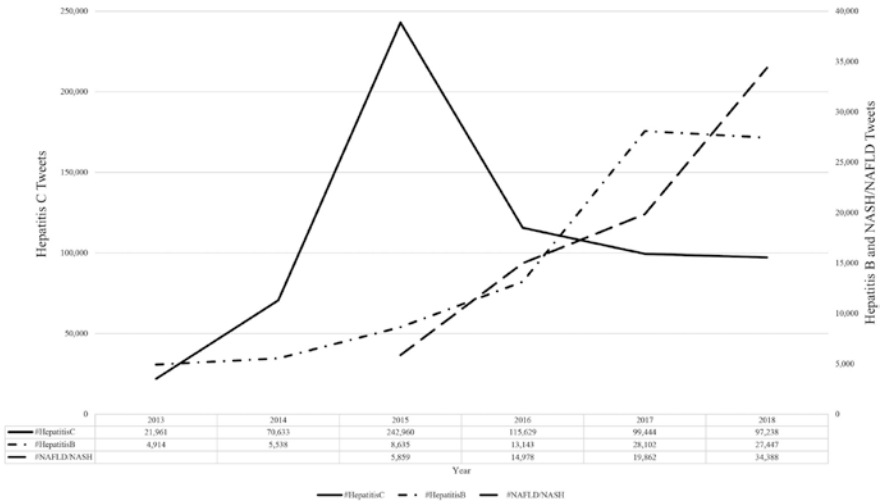

Fig. 21.3 Trend of tweet activity. The three CLDs evaluated: HBV versus HCV versus NAFLD/NASH. Hashtags used for HBV included #hepatitisb, #hepb, #hbv; HCV included #hepatitisc, #hepc, #hcv; NAFLD/NASH included #fattyliver, #nash, #nafld. Source: Ben L. Da, Pallavi Surana, Samuel A. Schueler, Niloofar Y. Jalaly, Natasha Kamal, Sonia Taneja, Anusha Vittal, Christy L. Gilman, Theo Heller, and Christopher Koh. Twitter As a Noninvasive Bio-Marker for Trends in Liver Disease. Hepatol Commun. 2019 Sep; 3(9): 1271–1280

satisfaction, and that adolescents with already low self-esteem are predisposed to finding validation through social media [41, 42]. Image enhancement and the reinforcement of beauty standards places teenagers at increased risk for developing body image concerns [40]. It may follow that those with a chronic disease which alters appearance are at heightened risk. The HCP must discuss and help adolescents recognise that social media images are often enhanced and not representative of the whole spectrum of bodies.

Cyber-Bullying

Cyber-bullying is the wilful and repeated harm inflicted through the use of electronic devices [43]. Victims of bullying are most often targeted for looks and body shape [44]. Again, it may follow that those with chronic disease can fall into these groups and thus be at heightened risk. Cyber-bullying has been associated with increased risks of depression, paranoia, anxiety and suicide [45].

Use of Technology in Young People's Healthcare

Mobile technologies and apps are increasingly used in healthcare to support personal condition management, remote monitoring, medication adherence and transition to adult services. These apps have much potential for young people with chronic conditions, whereas tailored strategies are required to help the development of self-management and personal responsibility.

Despite this potential, the evidence base in adolescents is limited. A systematic review of apps supporting development of self-management in adolescents published between 2003 and 2014 was able to include only 4 studies and was unable to come to any conclusions about their usefulness [46]. Studies that do exist tend to be proof-of-concept or small and with short follow-up times. Therefore, generalising findings or comparing studies is difficult and developers produce apps which are not based on empirical evidence [47], or may not involve HCPs or patients (Fig. 21.4). A meta-analysis on mHealth technology interventions did show that they could be effective in improving paediatric health behaviour and outcomes, but the average age was young and many interventions focused on caregivers. Conclusions around adolescents and chronic disease were therefore limited [48]. Nevertheless, there is the basis for future development and evaluation of app intervention.

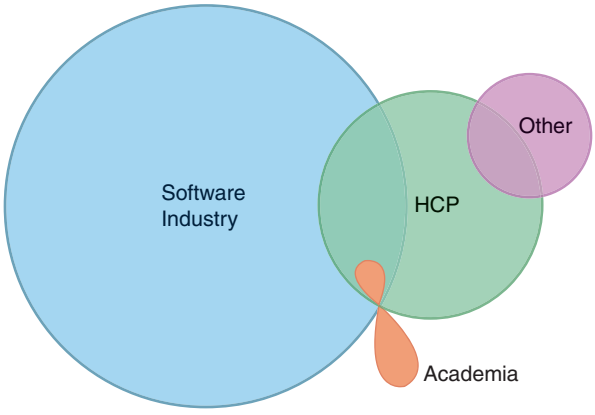

Fig. 21.4 Diagram illustrating the distribution of different authors involved in the development of the medication management apps. The overlapping regions indicate the apps codeveloped by 2 or 3 different author affiliations (combinations). Source: Katarina Tabi, Abnashi Singh Randhawa, Fiona Choi, Friederike Albers, Maren Schnieder, Mohammadali Nikoo, Daniel Vigo, Kerry Jang, Regina Demlova, Michael Krausz. Mobile Apps for Medication Management: Review and Analysis. JMIR Mhealth Uhealth. 2019 Sep; 7(9): 13608. Published online 2019 Sep 11. doi: 10.2196/13608. Permissions: This is an open-access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR mhealth and uhealth, is properly cited. The complete bibliographic information, a link to the original publication on http://mhealth.jmir.org/, as well as this copyright and license information must be included

Transition, and Self-Management

A systematic review in 2019 looked at mobile and web-based apps that may help young people during the vulnerable period transitioning between paediatric and adult services [49]. Six articles published between 2015 and 2018 met the review criteria. The apps used a variety of different means such as reminders, treatment plans, gamification, adherence graphics, logbooks, automatic data transfer and education modules. Patients reported high satisfaction with the apps and found them useful for support and education. Significantly increased treatment adherence was reported, but few apps reached statistical significance in any health outcome.

Adherence

Significant decline in treatment adherence is observed during adolescence [50]. Interventions such as monitoring, goal setting, rewards, contracting, problem solving and routines have been tried with some small degrees of success [51]. Uses of technology in this area include collecting and delivering information, facilitating communication, social networking, capturing real-time data, monitoring physiological parameters, automated feedback, clinical alerts and decision-making tools [52].

Medication management is one area where mHealth may be utilised and there is some evidence that adherence to treatment is improved when the patient is engaged [53]. A review and analysis in 2019 looked at apps available for people of all ages to help with medication management [54]. Android and apple app stores were searched and 328 apps were found and categorised. 73% were developed by industry and most were general rather than disease specific. The most prevalent app features were a medication reminder in almost all followed by a symptom tracker, and the ability to share data and reports with others.

Another review looked at text messaging and mobile phone apps specifically to improve adherence in young people [55]. Studies varied in design, sample size and methods of adherence assessment so there was no opportunity for meta-analysis. Most studies did report efficacy of the text message or app to improve adherence, although none reported on long-term outcomes. Those that looked at feasibility and acceptability outcomes found high levels of satisfaction despite high frequency of messaging. The authors concluded that there was only modest evidence to support the efficacy of this type of intervention.

Mobile Technology and Liver Disease

Searching for liver disease apps in the main app stores brings up a large number of results—apps offering education, liver diets or home remedies, a few for specific diseases, and many for HCPs. However, it is clear from the outset that many of the

apps may not be credible and that there is little to offer adolescents. Young people with liver disease have reported that they would welcome a mobile phone app as a supportive tool through transition [56]. The viability of mobile phone technology to support young people who have received a liver transplant transitioning from paediatric to adult healthcare services has been explored [57]. Ways in which technology could help the transition process were to provide educational material and to promote self-management and independence.

Young people want evidence from HCPs with whom they have built up a professional relationship. Information from online sources may not be trusted [58]. One way of providing this information and self-management skills is by web-based and text message intervention such as in the programme MD2Me. In the evaluation of this intervention the authors concluded that those who used the system demonstrated greater improvements in health-related self-efficacy [59].

In young liver transplant recipients a text messaging medication reminder system has been used with a text being sent to the young person followed by a reminder to the caregiver if confirmation was not received. Although 41% of the participants in the study dropped out and some of the intervention was aimed at caregivers, the authors did demonstrate an improvement in tacrolimus level standard deviation as a marker of improved adherence [60].

Research focusing on transition in liver transplant recipients has emphasised the importance of a long-term structured approach moving towards self-management. Technology has been used to assist with education, and mHealth applications or web-based systems offer quick ways to gain this information. They also offer possibilities for communication and patient empowerment though there is no suggestion that a mobile application could replace standard care.

Summary

For young people use of mobile technology and social media is so embedded that there may no longer be a life online and a life off. Despite this, evidence that social media or mHealth interventions in healthcare change outcomes is limited. There are hundreds of thousands of apps yet few have been scientifically evaluated. Most are designed by industry without HCP, academic or young person involvement. There is often no information on author credentials of apps. There is little specific to young people or liver disease. To understand how to better support young people's engagement with mHealth and health-related social media, there is a need to learn from the experiences of young people. Any proposed interventions must be relevant for young people's needs and be designed for the ways in which they use the media. Concerns remain around misleading information, data privacy, HCP standards, the effect of social media on self-esteem, and exposure to cyber bullying. Detailed and longer-term evaluations of mHealth and social media interventions are required to build an evidence base and help design better tools for the future.

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Chapter 22
The Social Aspects of the Adolescent in Transition

Paul McKie

From the poets we can explore the concept of transition. In *"Blackberry Picking"* Seamus Heaney evokes the innocence of childhood, initially starting from the joy of picking fruit on a late August day, but later on this joy soon turns to disappointment and despair when confronted with the rotting hoard [1]. This is a poem representing the transitions in life, in particular the transition from childhood into adulthood and the inherent challenges that one endures; *"Once off the bush the fruit fermented, the sweet flesh would turn sour"*. Life occurs in the small transitions, and no other transition can be so formative than the period between adolescence and adulthood.

It is on the brink of childhood that the adolescent at 17-years-old edges ever closer to a new claim, a claim that is solely based upon the amount of years spent in existence, and in turn, to be rightly recognised by the state as an adult. Yet we know from a physiological perspective that there are challenges to this inherent claim [2]. We know that human development does not recognise such distinct junctures but instead adolescent development can reach beyond our eighteenth year and continue into our early twenties. On this basis, adolescence into adulthood cannot be so easily demarcated by an arbitrary number but represents a transitional stage filled with nuance and fraught with complexity.

In understanding the components that make up this specific transitional stage, the World Health Organisation [3] identifies specific categories that includes transitioning to higher education, or from education into the workforce or indeed unemployment. There is also the transition from family living to autonomy, the challenges of traversing a housing market, as well as the inner workings of personal relationships, issues of sexuality and identity, and ultimately an attempt at being a responsible citizen. In addition to a young person's navigation into adulthood, there is also health and associated responsibility. Adding a layer of complexity that is chronic ill health

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can further colour the emotional landscape of the adolescent on the cusp of adulthood, and presents unique challenges that may compromise the ability to thrive within their environment. Ideally, both informal and formal resources and support networks combine to ensure that a young person's needs are addressed and nurtured but in some circumstances these resources may not be accessible or working in tandem together.

The adolescent facing adulthood is to be seen as an individual part of a larger system that may sometimes hinder rather than support. It is good practice to explore the social and environmental components involved in a young patient's life to help reveal the inherent challenges and barriers in maintaining good liver health. As a health professional, it is important that we are aware of the layers of social complexity that the young patient are ensconced within, so that we can effectively respond to patient need in a more holistic manner.

In delving further into what constitutes social complexity, it helps to identify the social determinants that may impact on poor health for the adolescent on the brink of adulthood. There are six aspects of note: (i) money and resources, (ii) the living environment, (iii) the family and support system, (iv) peer groups, (v) education, (vi) work and worklessness [4]. Each and all of these aspects could be beset by disadvantage and it is important to understand that there are links between such disadvantage and certain health outcomes; to view that young people in situations of disadvantage have poorer health outcomes and these aspects needs to be considered as part of any health care provision.

> By measures we know are associated with later health, it has been demonstrated that significant proportions of today's young people aged 12–24 are experiencing disadvantage that is likely to be associated with poorer long term health outcomes. [4]

What of the system, what does the health and social care interface look like for the young patient? Healthcare focuses on providing medical care to individuals and communities and the social care sector deals with the daily activities of living to help maintain independence, promoting social interaction, as well as protection from vulnerable circumstances. Two statutory bodies, and traditionally separate entities, but now aiming to work together.

Looking at social care today in the UK [5], we learn that funding is lower, there is a growing trend and prevalence of long-term conditions and the future care trends edge towards wider gaps in care provision as well as increasing the chasm between care needs and the support available. All of this is taking place whilst the inevitable trajectory points towards young people now forming a major part of the UK social care system. Current patterns of service delivery that are fragmented will ultimately fail to meet young people's specific needs, leaving many young people struggling to resolve their difficulties alone or falling through the gaps between children and adult services. Holistic and integrated approaches are crucial to improving access, service quality and better outcomes. Key characteristics of an integrated approach comprise of complementary interventions that are embedded. This enables a degree of flexible provision as well as help incorporate a more socially minded approach into clinical practice. For the young liver patient, the right components of good

practice for transition planning are to include a specific service provision that is multidisciplinary in its approach and can provide a continuity of care. For the latter constituent, continuity is one of the key drivers for services to work effectively together, providing seamless connections so that young people do not have to navigate complex external referral systems [6]. It is under one roof that health challenges can be explored alongside the travails of education, housing, or employment; to name but a few of the challenging junctures encountered by the young patient in transition.

The Patient Experience

In drawing from patient experience, and for a successful transition to occur, import is placed upon maintaining "relationships with healthcare professionals" and "the continuity of care", two main ingredients of good service provision [7]. Interventions are needed to support young people in transition, particularly in ending relationships in paediatric care and in the forming of new relationships in both medical and social care settings. Communication is thematic of effective service provision, a medium that can now be broadened out to include smartphone technology as well as engaging non-professionals in the guise of embedded peer support [8]. Adopting versatility provides the young patient with more access points; it minimises the one-dimensional approach, increasing the chances of helping the young person navigate their transitional experience through a variety of settings and media platforms. Flexibility being key, and representing the creative attempt at meeting the patient halfway to ultimately improve their experience and interface with health institutions.

The Perspective of a Young Adult in Transition

Introducing Chanceline, a 27-year-old liver transplant patient, Chanceline has been subject to a variety of environmental stressors that has made her life difficult but not insurmountable. Along with a personal resilience and an openness to work with her health and social care professionals, Chanceline journeyed through the transition pathway in its entirety, from the age of sixteen up until she was twenty-five years old. This is a snapshot of her personal journey.

Q. What were the challenges faced as a young adult with liver disease?

I was living in a hostel, trying to do my A levels, deal with my family and trying to have normal relationship with my boyfriend at the time. I would worry about money, having food, basic essentials. Having a social worker really helped me because I could actually speak to someone who understood about my struggles outside of liver disease and could offer me to help. I was given advice on how to budget, a mobile and shown how I could apply for grants. Money worries remain an

issue for me, finding a job that was understanding of my condition, still dealing with relationship issues.

Q. What was helpful to you as a transition patient?

The social workers in the team have been amazing, they've been beyond supportive. They've helped me apply for grants, get help in my local community, been the middle person between me and other health professionals and the DWP. I've even had someone visit my flat and facilitate with a mental health assessment through local services. I feel like my social worker knows more about me than some of my other health professional people. They understand me a lot more. It's good to know that my social worker is still there if I need any support at the difficult points in my life.

Q. What did you find helpful if you were looked after by the transition team?

I think you actually need to like working with young people. You need to be able to see things from their side. Be willing to listen to them. Having people that actually listen to me, and don't talk down on me is important. I also think the team differs for others in that I like the diversity of the team. Its feels great to have a social worker, a psychologist, nurses and doctors that all communicate with each other, so you don't have to repeat yourself.

Q. What would your recommendations be for health professionals outside our team?

They treat the young people in their care with respect and as individuals with feelings. That all of us deal with this condition in different ways. Some of us have been diagnosed since childhood, some of us have been diagnosed at a later stage so the way we process things about this condition is different. For example some might have never had alcohol and might want to try it, whereas others might have had it and might find it difficult to stop. Also just because we hit a certain age, it doesn't mean suddenly adherence to medications suddenly improves or that we're not taking them on purpose.

Q. What is important to you?

Clear and continuous communication, having someone that will liaise on your behalf because at times it feels like doctors will only listen to other health professionals and not the patient especially young people. In transition I would see a regular doctor and I liked it like this because in paediatrics I felt like each time I came, there was a new doctor who I had never met, also doctors in transition didn't talk at me, they talked to me.

The Perspective of a Young Peer Mentor

Another element that proves to be successful in meeting the needs of the young adult patient is to not only draw from the professional pool but to also access young peer mentor support. This is an alternative and creative way to try and engage younger patients and to help minimise the feelings of isolation associated with their liver experience. Health professionals can encourage peer groups that promote and support physical and mental health. The inclusion of young mentors/expert patients

can help highlight the benefits of improved adjustment to condition and preparedness to transition, increase confidence in talking with professionals, improve their adherence, and a reduced a sense of isolation.

The expert patient is one who is living though their own unique liver experience but is also trained by liver health professionals to be a mentor to other young patients. Beth is a 39-year-old liver patient that has been a young peer mentor for ten years and has been a point of contact and support for many of our young patients over this time period. What is different for Beth is that she never had the experience of being involved in a transition team and at the time of her transplant, she only just turned 19 years-old; the experience of waking up on an adult ward was understandably jarring and scary. Beth has kindly provided her own perspective.

Q. What do you believe is important for a health professional to be aware of when working with a young person with liver disease?

Individualised care, as one size does not fit all. Listen and be sensitive to their needs. Know who is important in their life. Don't assume what they might be thinking or feeling, instead ask and be open-minded. Recognise that a young person's world view may not match your world view. Don't make judgements, rather explore their world view in order to inform yourself. Consider that their world views may change and evolve over time as they age, learn and have experiences, so perhaps consider every encounter as a blank canvas. Consider that their lives will change and therefore their individualised needs may change. Recognise that they may be processing loss at different points in time, even if you can't understand their loss, acknowledge it's important to them. If they are an inpatient, explore what might help them to feel like themselves (e.g. wearing their own clothes, putting up photos, seeing friends…).

What are your thoughts on the challenges associated with non-adherence?

Avoid applying labels to individuals as this causes the persistence of stereotypes, negatively affecting future interactions and relationships, and limiting your ability to understand the situation from the young person's point of view. When a young person is non-compliant, don't assume they don't have the knowledge, understanding or motivation or that they have behavioural or mental health issues. There is a multitude of reasons why they might be finding it difficult to adhere to a treatment regimens for example where it is direct conflict with their personal needs and the life they are trying to live. Rigid, protocolised management can leave one feeling disempowered in the sense that their life revolves around the disease and its management. Rather than negatively judging or lecturing them, rather engage in exploratory dialogue to try to reveal and understand the issues, and consider alternatives. For years I struggled to adhere to taking Tacrolimus as prescribed because I had been instructed to take it on an empty stomach, so I would choose to eat breakfast with the honest intention of taking it later, but then life happens. Consequently my levels fluctuated, and every clinic appointment I would be told the same thing again and again, to essentially 'be better'. Until one day my consultant changed, and he explored the issue and was able to propose alternative options and adaptations. Being granted permission to take my tablets differently, and to have other options available to me was life-changing.

Q. What would you find helpful about a Young Adults Liver Service?

I particularly like that there now exists a multi-professional and holistic service for young adults, as I didn't have that. Following my period of illness and transplant, it was not only difficult emotionally and psychologically, but I also experienced difficulties with managing my finances and returning to both work and study. I'd like to think young adults are able to access help and support with all aspects of their life that have been impacted by the disease through your service now. While, I've not attended to the Young Adults clinic, I can imagine it might be a more comforting waiting environment. On the rare occasion when I do cross paths with someone of similar age in clinic, it is nice to be able to socially chat while waiting, which is in contrast to when I interact with older people in clinic who are usually more interested in talking about the service and health-related topics.

Being able to communicate with my care providers by other means. Such as video consultation? Or Whatspp? I do very much appreciate now being able to email the outpatient clinic (for appointments), the liver pharmacist (for prescriptions), my consultant and the liver co-ordinator for all other non-urgent issues. Rather than finding time at work to make a phone call, waiting on the phone for ages, or having to keep trying because it's engaged. I appreciate this convenience as I can email anytime (such as evenings), and it's easier to ask embarrassing questions via email than in person. While I see the need for face to face clinic appointments, I also value to option of telephone or video appointments as having to take a half day off work for the round trip to the hospital is disruptive. If you are a young person in an hourly paid job, that could be a significant loss of income. And it sort of backs you into a corner of having to explain to many of your colleagues about your illness.

Q. What would your recommendations be for health professionals outside this specific service?

Please don't say you can drink on special occasions. I was told this a countless number of times and I think that is meaningless to a young adult, during a time of our lives when we are experiencing many milestones and firsts with friends, and therefore regular occasions we want to celebrate including graduations, jobs, promotions, first homes, engagements, weddings etc.

Q. Practical suggestions on how to manage young people when admitted, what is important for them?

Take time to get to know who they are and what is important to them. Be willing to collaborate as they may have some useful ideas or suggestions as to what will help. Facilitate connection with those people who are important to them, family and even visits from friends. Consider this might mean being flexible and enabling access before or after school, university, working hours etc. Enable contact to practitioners by email or phone which is useful, convenient and sometimes less awkward than asking questions in person. It is also a good way to share information that I can review later in my own time. Consider providing short bite-size videos e.g. 1 min which is easier to engage with when feeling unwell, compared to reading materials. Taking advantage of apps and technology might also be of benefit. It is so helpful to be able to access information or ask questions in the palm of your hands and with only a few clicks. Provide a 'shopping' list of what is available and how to

access it, including who's who and what they can help with. It is so hard to remember many different names and faces.

Q. If you were asked to be involved in setting up a young adult service what do they want for it to contain with regard to set up, health professionals, and facilities?

Foster access to different professionals for holistic support. Psychology, mental health and social work are vital. I think maybe even offering access to a youth worker or peer support worker and sexual health adviser or GP could be beneficial. If you already need to visit the hospital a lot which can be time-consuming, you can feel less keen going to other services. So a 'one-stop shop' clinic would be preferable. Also create opportunities for young people to be able to meet each other such as through the purposeful design of the facilities and the process, provision of events, forums and access to peer mentors and social media groups etc. Be innovative and creative.

Lastly, it would be great to see the joint education day for patients and parents that focusses on the experience of transitioning from child to adult services recommenced. One of the things that was striking about that programme is the impact it has on the parents to meet other autonomous, well-adjusted young adults with liver disease/transplant and to ask questions. This seemed to be the most valued part of the transition programme by the parents. I like to think this might have helped to reframe the fears and worries they must have and the nature of their relationship with their quickly growing child. So I believe a transition service that considers and addresses the needs of parents/carers (or significant person in their life) is just as important as this will no doubt benefit young adults.

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