Growing Up with Liver Disease

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Introduction

As the survival of children with liver disease has significantly changed over the last few decades, pediatric liver transplantation and improved medical and nutritional management have changed the outcome for children with liver disease and a large cohort of patients is now moving into adolescence and adulthood with a liver condition. Unfortunately, young people with liver disease have inferior health outcomes compared to younger and older age groups [1]. They face challenges inherent to their adolescent development, now known to carry on into the mid-20s, but also in particular adult healthcare professionals might not be familiar with childhood liver diseases and their management [2, 3]. The current setup of healthcare systems sees young people looked after by either pediatric or adult services, irrespective of whether this is developmentally appropriate and the current provision of support during the transition from one service to the other is limited [4].

In this chapter we, as physician and clinical psychologist, will give an overview of the interaction of physical development during puberty and liver disease, as well as the psychosocial and health behavior aspects of adolescence. We will share our experience of running an integrated multidisciplinary care model for young people with liver disease aged 16–25 years.

Young People

The World Health Organization recognizes that "young people" aged between 10 and 24 years are a population who require dedicated care [5]. Having a chronic condition or disability has multiple effects on adolescent development including biological, psychosocial, and social effects that can in turn contribute to poor adherence and risk-taking behaviors [6]. Non-adherence to medication is a particular challenge in the adolescent population as it is difficult to measure, often multifactorial however relatively developmentally appropriate. Its prevalence is reported to exceed 50% in the post-transplant population and effects long-term outcome in this patient population [7]. Adolescence coincides with transfer of medical care from pediatric to adult-centered services hence the importance of defining a dedicated, individualized transition care pathway for young people. This will be discussed in more detail further in the chapter.

Medical Aspects of Growing Up with Liver Disease

Within pediatrics, liver disease is a relatively new specialty within which the last few decades have seen a significant change in the diagnosis and management of conditions. Patients tend to present in infancy or later childhood with a variety of genetic and incidental conditions, either in an acute, often life threatening, or more chronic setting. Lifelong specialist follow-up and treatment are usually required. The development of pediatric liver transplantation has had a significant impact on the outcome and prognosis of children developing end-stage liver disease or presenting with acute liver failure, and the majority of the patients are now moving into adolescence and adulthood. This emerging population is a challenge for both pediatric and adult hepatology teams.

Information on the long-term outcome of patients with liver disease presenting in infancy, such as biliary atresia (BA) and Alagille syndrome, is becoming available but is still scarce and more focused on survival data. It is estimated that 14–44% of patients with biliary atresia survive into adulthood without needing liver transplantation. In our experience 28%

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of BA patients survived with their native liver up to 16 years with a quarter requiring liver transplantation during adulthood. Abnormal serum bilirubin levels, evidence of portal hypertension with varices on endoscopy, and having an episode of cholangitis during adolescence were associated with the need for liver transplantation in adulthood [8]. Of note is that listing criteria vary significantly between pediatrics and adults, and the use of mathematical models based on adult liver diseases disadvantages young people. We found that when comparing a group of young people with BA (median age 15.5 (range 13.8–18.6) years) either listed by the pediatric ($n = 22$) or adult team ($n = 14$), those listed by the adult team waited significantly longer on the waitlist and more likely to require intensive care support at time of listing (29% vs 5%; $P < 0.05$), and this was independently associated with poorer patient and graft survival. The mathematical models used by adult teams as listing criteria did not correlate with waiting times or outcomes. What did improve survival was the support from the multidisciplinary young people's liver service with all young people in this group ($n = 11$) surviving compared to 88% in the rest of the group [9].

In Alagille syndrome, extrahepatic aspects of the syndrome related to vascular or renal involvement are becoming more relevant and can impact the long-term prognosis [10, 11].

The advances in molecular genetics are now enabling us to diagnose genetic liver conditions such as familial intrahepatic cholestasis and other rarer metabolic conditions such as mitochondrial cytopathies, etc. The implications of dealing with a genetically based condition can have further long-term implications on adult life and prognosis [4].

Other conditions such as autoimmune liver disease, Wilson disease, and nonalcoholic fatty liver disease tend to present more frequently during adolescence, and patients will have to come to terms with their condition and management during an already challenging time in their life.

Finally, some young people will present to adult services with liver-related complications related to conditions such as complex congenital heart disease or childhood cancers and will require specialized care. In a series of 95 patients who had underwent a Fontan operation during infancy, 23% developed Fontan-associated liver disease which has shown to be linked with morbidity and premature mortality [12]. Regular screening for adolescents and adults has now been recommended.

Outcome Data

Whereas long-term outcome following pediatric liver transplantation is significantly better compared to adult cohorts (21–52%) with up to 20-year patient and graft survival of 79% and 64%, respectively, those transplanted between the ages of 12 and 17 years have inferior patient and graft survival, and this is similar for other solid organ transplants as heart, kidney, and lung transplants [13, 14]. Young adults, aged 18–24 years, experience disparities both while waiting for transplantation and with regard to outcome [15].

Young people (12–25 years) hence constitute a unique and vulnerable cohort who deserves special attention by health professionals in order to improve survival.

In the non-transplant setting, a recent report on predictors of poor outcome in a cohort of 133 patients with autoimmune hepatitis aged 14 and over found that presentation between the ages of 14 and 20 years was a significant independent predictor of liver-related death or requirement for liver transplantation, suggesting that their condition was more challenging to manage compared to the older population [16].

Impact of Liver Disease on Physical Development

Growth retardation is common in children with chronic liver conditions and more common in cholestatic liver disease, where some degree of catch-up growth is noted after liver transplantation. In an analysis of growth following liver transplantation, risk factors for poor linear growth were prolonged steroid exposure, lower weight percentiles at time of transplantation, linear growth impairment pre-transplantation, and metabolic disease as primary diagnosis [17]. More recently, out of a total of 892 liver transplant patients between 8 and 18 years, 20% had linear growth impairment at their last follow-up and, where available, height z-scores were significantly lower than the calculated mid-parental height z-scores. Linear growth impairment at transplant, re-transplantation, non-white race, and primary diagnosis other than biliary atresia were found to be independent predictors of growth impairment. In the same study, the authors reported that on the pubertal development of 353 children, 61% of girls and 58% of boys aged 16–18 years reached Tanner 5 compared to 100% of a normative population with growth impairment occurring in 11% of Tanner 5 subjects [18]. Growth impairment has also been described in genetic conditions such as Alagille syndrome and can also be associated with the treatment. Further data is needed to establish the prevalence of growth failure and pubertal delay in chronic liver disease but is available in other chronic conditions such as inflammatory bowel disease, nephrotic syndrome, asthma, and cystic fibrosis. Growth failure and pubertal delay can have a significant psychosocial effect on quality of life and long-term outcomes; hence treatment of recombinant human growth hormone in this population has been reported to be associated with improvement in psychosocial functioning as well as linear growth [19]. Larger studies are needed to assess its safety in this patient population.

In girls with chronic liver disease, menstrual cycles can be irregular, and amenorrhea and anovulation are common. Menorrhagia can occur in patients with advanced liver disease with portal hypertension. Estrogens, and typically the synthetically produced ethinylestradiol used in the combined hormonal preparations, are more potent and have a potential effect on the liver irrespective of the route of administration. Progestogens do not have receptors on the liver cells and are commonly given at a lower dose and well tolerated.

Although not contraindicated in patients with compensated cirrhosis, both in pre- and post-liver transplant setting, current contraceptive recommendation is with progesterone-only preparations such as minipill (e.g., Cerazette), medroxyprogesterone injection or etonogestrel implants, and, if sexually active, levonorgestrel releasing intra-uterine system [20]. Successful pregnancy outcomes have been reported both in chronic liver disease and liver transplantation settings, although there is an increased risk both for mother and baby. Treatment with calcineurin inhibitors, steroids, and azathioprine is recommended to be continued during pregnancy to avoid graft dysfunction or relapse in autoimmune liver disease; however, mycophenolic acid and rapamycin are contraindicated because of the increased risk of birth defects. In patients with portal hypertension, an upper GI endoscopy during the second half of the second trimester is indicated to assess the degree of portal hypertension and the need for further management to avoid GI bleeding during the course of pregnancy [21]. Obstetric follow-up by an experienced team in a hospital setting is required. Adolescent girls should be informed timely of the various contraceptive options, the potential complications of pregnancy and childbirth, as well as the possible genetic implications of their underlying condition.

Cosmetic side effects of medical treatment such as steroids and currently less commonly use, cyclosporine, can have an impact on body image and adherence to treatment in the adolescent population (see later), and health professionals should keep this in mind when prescribing treatment.

In order to effectively manage young people's care, it is crucial to successfully address their wider "medical, psychosocial and educational/vocational needs" [22]. In order to do this, professionals need to be familiar with the unique developmental stage of adolescence and recognize that young people are neither just "big children" nor "small adults." This developmental perceptive is discussed in the next section, along with the psychosocial elements of growing up with liver disease.

Adolescent Development and Its Interaction with Liver Disease

The biopsychosocial changes associated with adolescence interact with how young people manage their illness and treatments and accordingly with how their healthcare should be approached. For an excellent review of this area, please see Suris, Michaud, and Viner [6].

Although most of the literature focuses on adolescence, research demonstrates that structural and functional changes continue to take place in the brain into young adulthood [23]. This is mirrored by changing societal norms with young people increasingly delaying many of the traditional "tasks" of adulthood, such as financial independence and starting a family. Furthermore, health outcomes are poorer for young adults into their mid-twenties, so it is more helpful to think about young adult development more broadly [24].

Adolescence is traditionally defined by the onset of puberty. Delayed puberty, reported in young people with liver disease, can impact on how the young person views themselves, their illness, and their wider world. For example, an adolescent who looks younger may be treated differently by people and have reduced social opportunities. Common stories from patients include being asked by adult clinic staff whether they are there with their mum, being stopped by the police when driving to check their age, and being refused entry to 18-rated films or pubs.

Alongside the physical changes are changes in how young people think and feel and in the nature and importance of their social world. In order to become an independent adult, the adolescent needs to separate from their parents. They start to develop a more independent sense of identity, and their peer group typically takes over from family as being their main social world [25]. Peer acceptance becomes key, with a strong desire to feel normal. Self-consciousness increases. The typical adolescent has an increased sense of invincibility, poorer abstract thinking, and reduced thoughts of the future [26]. An increasing body of research demonstrates ways in which the structure and function of the adolescent's social brain is distinctly different from that of children or adults [27].

As part of this adolescent profile, risk-taking behaviors peak, with high levels of alcohol and drug use, smoking, and unsafe sex [28]. In the UK, "binge-drinking" is widespread and synonymous with certain rites of passage for young people, such as the introductory "freshers' week" at university. Young people growing up with liver disease have the same needs as other young people, with the additional challenge of trying to balance their health needs against their social and psychological needs. The way to meet these can often seem to be opposition. Indeed, research suggests that alcohol and drug use is similarly prevalent in young people with chronic illnesses as compared to their healthy peers [29] and they are equally as likely to be sexually active [30]. This adolescent profile and tendency to take risks helps young people to develop independence but can present significant challenges for successfully managing a chronic illness. This is discussed further below under adherence.

Impact of Family

All of the above changes happen within a family context. To enable the young person to develop into an adult, their family also need to adapt their roles, for example, by giving their child more freedom and privacy [31]. Parents/carers of children with chronic illness have often dedicated much of their lives to caring for their sick child and have their own relationships with the illness and hospital teams. Young people's relationships with their family may be impacted by their liver disease, for example, having less independence. Parents/carers might also have had to change other roles in their lives, such as giving up work, in order to successfully care for them. This can result in some parents seeming to be more overprotective, for example, worrying about their adolescent taking their medication, abstaining from alcohol at parties, monitoring for symptoms, or appropriately seeking help [32].

There are also significant challenges for families of young people who are diagnosed with a liver disease during their adolescent years, as is common, for example, in autoimmune liver disease or Wilson disease. At a time when adolescents should be becoming more independent, the acute stage of illness forces them into a state of dependence on others. This can present challenges for the whole family that may not be expected at this stage of development [33], such as parents needing to take time off work, physically caring for their child and spending concentrated time together that might not otherwise have been expected from being the parent of a teenager or be normal among their peers.

Wider Influences

The above processes occur within a wider set of systems still, such as schools, workplaces, friendships, and other relationships; how the liver disease is managed in any of these contexts will interact with the young person's adjustment and management of it. Furthermore, this is within a societal context in which the general public hold certain beliefs, assumptions, and prejudices. As public perception of people with liver disease and transplant is most commonly associated with drug and alcohol use, young people struggle to develop a positive self-identity if they associate (or other people associate them) with this stigmatized group. Our patients often grapple with the dilemmas about who to tell about their condition and how to tell, as many have experienced bullying or prejudiced comments in the past. It can be beneficial to discuss these dilemmas with patients and help support them in communicating their needs to schools and workplaces.

Given the importance of peer relationships during this period, it is worrying that peer networks are often disrupted in young people with chronic illness [34]. Among young people, post-transplant peer support has been found to be an effective means of engaging young people in services and improving their health outcomes and well-being [35]. In a small recent study in which young people were trained to act as mentors for younger post-transplant patients, the mentors themselves benefited from improved adherence as well as the mentees (measured by lowed mean tacrolimus standard deviation levels) [36]. The authors suggested that this may be attributable to the increased emotional support from attending the mentor training workshop. As part of the liver transition service at King's College Hospital, we run peer support days and peer mentoring for young people with chronic liver disease and post-transplant. Preliminary feedback suggests numerous benefits of this for both young people and their mentors, including feeling more positive about having a liver condition due to increased hope and feeling less alone, feeling more prepared for transition, and several comments akin to "I wish I had something like this when I was younger" [37].

Most of the developmental models are based upon Western notions of adolescence. It is unclear how this may differ in other cultures, for example, where adolescence may not exist as a construct or notions such as independence from family are not expected or endorsed. How culture interacts with chronic illness management and transition is an under-researched area that demands further attention [38]. It is important for professionals to be curious about what the adolescence and their family expect at this stage of development rather than making assumptions about how these constructs may or may not apply.

Psychological Aspects of Growing Up with Liver Disease

Adolescence is a period of rapid change, full of opportunities and challenges. Young people growing up with chronic liver disease have the same aspirations in life as their healthy peers but have additional stresses and restrictions to manage, including hospital visits, time off school, medication, and lifestyle restrictions. Rather than focusing purely on the presence of psychological distress, it is important to consider how all young people and families adapt to their changing health needs at different stages of development. Most young people, with or without liver disease, strive to be normal [39]. Those who have difficulties adjusting to their illness/treatment and integrating it into a positive self-identity are at increased risk of developing psychological difficulties and are less likely to manage their physical health needs effectively. Routine questions about the adolescent's wider world are crucial for engagement and in order to assess how they

are adjusting to the demands of their condition and areas that may require intervention [40].

There has been relatively little research into the psychological needs of young people growing up with liver disease, and most of this limited research has focused on those post-transplant. Research conducted with adults with liver disease is unlikely to be generalizable as the populations are different on multiple levels, including age and developmental stage, age at diagnosis, type of liver disease, and/or reason for transplant. A brief overview of some key areas is given below, citing research specific to liver disease where it exists and otherwise extrapolating from other chronic childhood diseases.

Quality of Life

Quality of life is a broad term that encompasses a range of physical, psychological, and social factors. Most studies investigating quality of life in young people with CLD report only on those post-liver transplant, rather than adolescents with CLD as a group. Health-related quality of life is found to be poorer in children and young people post-liver transplant as compared with the general population, but similar to young people with other chronic conditions, including other solid organ transplants [41, 42]. Across studies, Ohnemus identified predictors of poor QoL included transplantation in adolescence (as well as sleep problems and medication adherence) [43]. A study of children and adolescents with autoimmune liver disease found a similar trend, with poorer quality of life being associated with the presence of symptoms such as ascites, abdominal pain, and fatigue [44].

In a qualitative study aiming to understand how liver transplant affects young people's quality of life, adolescent participants spoke about the impact of transplant on their relationships, schooling, fatigue, burden of medication, communication with healthcare professionals, and thinking about the future [41]. These are key areas to explore when working with young people and demonstrate the importance of fostering good collaborative relationships with young people, in which they feel listened to and valued and their wider needs and hopes are respected.

School Achievement

A young person growing up with a chronic liver disease or transplant is more likely than healthy peers to take time off school for hospital appointments and ill health. This can have a significant impact on their school attainment and subsequent employment opportunities in adulthood. There is also some evidence that a portion of the poorer QoL documented in this population relates to poorer cognition and school performance. For example, Ohnemus and colleagues [43] found adolescent liver transplant recipients reported QoL 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.

Data available on cognitive development in the context of pediatric liver conditions, and mainly in the post-liver transplantation setting, confirms an increased incidence of learning disability in this population. Out of 144 patients from the SPLIT registry children aged between 5 and 7 years and more than 2 years post-transplant, 26% were found to have a mild to moderate, and 4% a serious, learning disability with 25% having impaired performance with reading and math skills and a relevant executive functioning deficit which would potentially affect independent management of their health condition in adult life [45]. Further research identified height centile at transplantation and genetic-metabolic conditions as having a high impact on long-term cognitive functioning [46].

The literature relating to cognition in our young people is in its infancy. The limited evidence so far does indicate that cognition is poorer in children and young people with CLD [47] 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 and not those surviving with their native liver [48–50]. Studies are also heterogeneous due to sample size, age, condition, areas examined, and tests used.

A recent systematic review of the available literature identified a total of 25 studies which have investigated cognition in children and young people with liver conditions (n = 1913) [47]. The majority of these (19/25 studies examined) described individuals post-transplant (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 [51–53]. These studies did collectively indicate that the poorer cognition observed persisted 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) [54]. There is also evidence of poorer educational attainment, which is likely to be related to lower cognition, and at levels over and above those with comparable school absence due to hospitalization for other forms of chronic illness [55]. With poor quality of life and job performance seen into adulthood, the importance of interventions to target these impairments becomes increasingly clear.

The longer-term impact of these childhood difficulties also needs to be further researched, as in clinical practice we frequently see the long-term consequences such as in Case Study 77.1.

Case Study 77.1 Harry was diagnosed with biliary atresia shortly after he was born. Following a Kasai procedure, he required regular visits to hospital for appointments and sometimes needed admission for treatment with antibiotics or endoscopy procedures as he developed portal hypertension. He was a bright, sociable child who was well liked by patients and staff. Aged 11, his health deteriorated and the decision was made to list him for liver transplantation. A year later Harry was transplanted and he recovered well after surgery. Due to time spent in hospital, he missed most of his formal education and left school without any qualifications. Harry is now 22 years old. He lives with his parents and is unemployed. He has held a number of causal jobs, but struggles to find permanent employment due to his lack of qualifications and relevant experience. Harry feels left behind by his friends, most of whom who have now been to university and started good jobs.

Mood Difficulties

Research investigating psychological well-being in adolescents with chronic illness more broadly suggest that there are higher rates of depressive and anxiety symptoms relative to healthy controls, but the rates vary across studies and illness group (see meta-analysis by Pinquart & Shen [56]) and were particularly common in young people with conditions impacting upon energy levels, those with severe symptoms, and those resulting in a visible difference, 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.

Post-traumatic Stress Disorder

Young people with chronic liver disease are likely to have had some unpleasant experiences in hospital and times which may have been felt confusing, scary, or upsetting. High rates of post-traumatic stress disorder (PTSD) have been found in adolescents who have had transplants. For example, in 104 adolescents (aged 12–20 years) post solid organ transplant, 16% met full criteria for PTSD, with an additional 14% reporting 2 of the 3 necessary symptom clusters at a level that was causing them clinically significant distress [57, 58] reported similar prevalence rates of PTSD (13%) in 76 children post-transplant; these PTSD symptoms were significantly under-reported by parents.

In addition to the distress associated with PTSD, in a small study of 19 adolescents post-liver transplant [59], a significant association was found between presence of PTSD symptoms and non-adherence (as measured by blood levels and clinician judgment). This is likely to be due to medication serving as a reminder of the transplant and non-adherence therefore being a form of avoidance. Functional outcomes are also found to be lower, for example, adult survivors of childhood cancer who had PTSD were found to have lower functioning in areas such as school, work, and personal relationship [60].

Failure to identify PTSD compromises the young person's well-being, impacts on their functioning as adults, and is associated with non-adherence. As parents tend to underestimate rates of PTSD and there is no relationship between the objective characteristics of the trauma and the risk of PTSD [61], it is impossible to predict who will have difficulties. Detection therefore relies upon directly asking the young person. Research has not addressed rates of PTSD in young people with chronic liver disease more generally, but as these young people also encounter situations where they perceive their life to be threatened, then it is reasonable to assume that their rates of PTSD may also be elevated.

One of the most significant challenges of caring for adolescents is the high rates of non-adherence. This is outlined below.

Adherence

As highlighted earlier, rates of non-adherence to medication are found to be as high as 50% in adolescents post-transplant, with significant negative implications for their health. Although non-adherence to treatment, medical advice, and clinic appointments is considered developmentally appropriate in this population, it is a concern for clinicians working with young people and is often challenging to manage.

It is easy to see that a typically developing adolescent as described in the earlier section might not take all their medications or attend appointments correctly. Increases in impulsivity, delay discounting (the extent to which consequences decrease in effectiveness to control behavior as a function of there being a delay to their occurrence), reward-seeking, and emotional reactivity are noted in adolescence, which make this period a time of heightened vulnerability to taking risks with their health. Adherence in liver disease or transplant requires the patient to trust their doctor that the treatment is

required, buy into the notion that the status of their liver disease may not correspond with symptoms, be motivated by a long-term outcome of improved health, and be able to plan and organize themselves to maintain a good routine. This directly contrasts with the developmental profile of young people, as illustrated in Case Study 77.2.

A full review of the factors associated with non-adherence is outside the scope of this chapter, but a number of comprehensive reviews exist (e.g., Drotar, 2009; Shemesh et al., 2008, Kyngas, Kroll & Duffy 2000) [62–64]. Many of the characteristics known to make adherence more difficult are present for young people with liver disease; for example, the treatment is seemingly preventative rather than curative, does not have any immediate tangible benefits, and needs to be taken for life. Knowledge is generally necessary, but not sufficient for adherence (e.g., Macquaid, Kopel, Klein & Fritz, 2003 [65]), and requires particular attention as young people grow up and each with different understandings.

Case Study 77.2 Jake is 18 years old. He was well throughout his childhood until being diagnosed with autoimmune liver disease when he was 14 years old. When he was first diagnosed, Jake felt quite unwell and spent a week in hospital, but since then he has been well and only has to go to an outpatient clinic appointment every few months. Jake does not think of himself as being sick and doesn't really think about it except for when he goes to hospital. He is most bothered about the way he looks, in particular about his acne, which started when he was commenced on steroid treatment and lack of muscle tone. He feels very self-conscious around other people his age and often feels quite down about his appearance. Jake is told to take daily medications to prevent him from getting ill again in the future - but when he stops taking his medications, nothing bad happens; he actually feels better because he isn't bothered by side-effects, his skin gets better and his face looks more defined. Jake feels happier because he feels more similar to his friends, and doesn't feel so self-conscious about having to remember to take his meds or risk having to explain his condition to others. Jake's been told he shouldn't drink alcohol, but all of his friends do and it's really hard to explain why he can't. When he started drinking recently at a party it was really fun and nothing bad happened, so he thinks it must be alright. Jake doesn't really get on very well with his parents and teachers at the moment, so doesn't tell them because he knows they will nag him about it. When he goes to hospital his mum does most of the talking. His doctor tells her about some blood tests numbers that he doesn't really understand, and then he gets to go home.

Exploring non-adherence should be part of the routine management of all patients (irrespective of age) and approached in a non-judgmental fashion to encourage disclosure and engagement. Health professionals should know that in young people non-adherence is considered to be relatively developmentally appropriate and not suggestive of distrust in healthcare professionals or equally rejection on the part of the adolescent. Individual education, which is tailored to the young person's needs and repeated and checked regularly, is important, to ensure the young person has a good understanding of their condition and rationale for treatment recommendations. It is important to understand the young person's priorities and encourage them to have open conversations about the barriers to adherence for them; for example, discussions may enable medication regimes to be simplified or altered to fit in with the person's routine, encouraging use of alarms and reminders, taking medication on sleepovers, and more broadly how to manage the handing over of responsibility from parents to their child. Simplifying medical treatment and conversion to once daily preparations of immunosuppression have been reported to improve adherence and treatment satisfaction [66]. An overview of strategies for improving adherence can be found in Table 77.1.

Non-adherence has also been found to be associated with psychosocial distress, such as PTSD [59] and other psychosocial stressors [67]. 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 well-being in young people post-liver transplant is considered routinely, as part of good clinical care [68, 69]. Social difficulties such as financial restrictions should also not be overlooked. For example, in the UK at the age of 18 years, young people have to start pay-

Table 77.1 Adherence management strategies

Barrier to adherence	Strategies
Naive about the risks of non-adherence	Individualized education about illness and medication
Burden of medication regime: too many tablets or too many times a day	Simplify medication regimes Ensure young person understands rationale for each medication and anticipated course
Non-intentional non-adherence: forgetting or organizational difficulties	Pill boxes, blister packs Medication charts and apps Alarm reminders Visual reminders
Intentional adherence: choosing not to take it due to the meaning of the medication	Explore beliefs about illness and medication, including the benefits of non-adherence for the young person. Assess mood Referral to psychologist
Intentional adherence: practical barriers	Assess barriers such as housing, finances, parental support Referral to social worker

Table 77.2 Routine assessment and management of adherence

Task	Rationale	Example questions
Engage the young person	Young people are more likely to be actively involved in their healthcare and more adherent if they have a good relationship with their healthcare provider Screen for psychosocial difficulties Gather information about how the illness and treatment fit into the young person's life	See HEADSS (Goldenring and Cohen [40]): ask about home, school/college, friendships, activities, and interests
Assess who is responsible for medication	Responsibility needs to be handed over from parents to young person: difficulties often arise during this transition	"Who is in charge of medication at home? How long have you been taking charge of your medication? Who organizes the prescriptions?"
Assume non-adherence and routinely assess with every patient	Rates of non-adherence exceed 50% – most young people will be non-adherent some of the time Impossible to predict who will be non-adherent so need to ask everyone Asking questions in a non-judgmental way that assumed some non-adherence is more likely to increase disclosure	"In a normal week, how often do you tend to miss your medication? How often do you take it at a different time?"
Normalize: full adherence is difficult; very few people are adherent all of the time	More likely to increase honest disclosure and willingness to discuss the barriers to their adherence Trying to scare or tell off your patient is unlikely to improve their adherence but will ensure that they don't disclose it to you again!	"Most young people we see struggle to take all of their medication all of the time. We know that it can be a really hard thing to have to take medication every day."
Check understanding of illness and risks of non-adherence	Knowledge is necessary (but not sufficient) for adherence Need to ensure that the young person understands why they need to take medication and fully understand the risks of not taking it	"How would you explain your condition to someone who hadn't heard of it before? What do you think the medications do? What do you think would happen if you didn't take your medication? How many doses of medication do you think you could get away without taking?"
Assess intentionality of non-adherence	Different determinants of non-adherence require different interventions	"Are there times that you remember your medication, but choose not to take it for some other reason? How often do you forget your medication compared to choosing not to take it? When you miss it, do you always miss all of your medication or just some of them?"
Identify barriers	Different determinants of non-adherence require different interventions.	"What gets in the way of taking medication? What is the worst/hardest thing about (having to take) medication?"

ing for their prescriptions and travel to hospital; when money is limited, these can be very real barriers to adherence for which support is available. Within our service, we adopt a multidisciplinary approach to identifying and managing adherence, which begins with a stance of assumed non-adherence, and reinforcing disclosures as rates are known to be around 50%, we normalize that most young people will struggle to take all of their medication all of their time. Please see Table 77.2 for details of our approach for routinely assessing in this age group. From conducting a case note review of the more complex cases seen by our Clinical Psychologist and Specialist Social Worker, we found that a significant minority had entrenched relational difficulties and had experienced childhood abuse [70]. We hypothesized that non-adherence can be related to attachment difficulties and in some cases can require long-term specialist input to treat. Effective identification of non-adherence and the factors contributing to it are essential to ensure access to the appropriate services.

Self-Management

As described earlier, adolescence and young adulthood for young people with liver conditions can be associated with poor health outcomes related to non-adherence and graft loss. Self-management relies on the engagement of individuals in order to manage their health effectively, in a pediatric setting implying support from the parents/carers. From a behavioral perspective, one of the simplest explanations for difficulties during transition is that some young people are just not yet good at managing their own healthcare [71]. Annunziato et al. demonstrated that in a cohort of young adult pediatric liver transplant recipients, self-management skills appeared to develop with age with lower scores for those transplanted before the age of 10 years compared to older age at liver transplant. Further work from the same authors raised some concerns that young adults post-liver transplant reporting greater self- management were being less adherent to treatment, and this impacted on their medical condition as it was

found to be associated with rejection. They concluded that universal promotion of self-management in young adult patients was inadvisable and that acquiring self-management skills should be viewed as a gradual process. Input from a multidisciplinary team lasting well into the mid-twenties was recommended [72–74].

With the delayed timing of role transitions in today's society, such as completion of education, marriage, and parenthood, many of our young people may continue to rely on parental support well into the period of "young adulthood." This may be especially true in our population, considering almost 50% of children post-liver transplantation require special educational support [47]. Our young patients may be more likely to struggle with the development of the appropriate skills to manage their condition during adolescence and may continue to rely on carer support. Indeed, most young people with childhood liver disease have a long history with the pediatric care providers, with many relationships starting in infancy. Transition of healthcare to adult services can therefore be just as challenging for carers themselves, who have their own relationships with clinicians and healthcare providers. In practice, many patients may physically transfer from receiving services at pediatric to adult-oriented facilities before they manage the requirements of their particular medical illness. It is important that self-management is viewed as a process rather than a one-off conversation, especially in patients with additional learning needs (found at an elevated rate in our patients). It is recommended that clinicians periodically assess developmentally appropriate skills of health management in order to understand patient education needs and their skill acquisition over time.

Also of relevance here is the evidence that almost 50% of children after liver transplantation and with chronic liver disease require specialist educational support hence one can expect this to impact on the development of the skills expected when moving on to adult services [62]. In addition, with evidence that adolescent development is continuing into the mid-twenties, expectations that 16- and 18-year-olds might be capable of managing their condition independently could be unrealistic (Lancet adolescence). We recently explored the self-management skills and adherence patterns in a cohort of 156 patients attending our multidisciplinary young adult clinic. Results: There was a trend toward increased mastery of self-management skills over time, with those ≥19 years reporting being more confident in behaviors related to arranging appointments and organizing medications compared to those ≤18 years.

Non-adherence is thought to be related to both the adolescent stage of development [6] and the process of transitioning into adult services at this risky period [67]. It is therefore crucial for every center to carefully consider how to transition their young people. This is reviewed below.

Transition from Pediatric to Adult-Centered Health Services

The adolescent health society defined transition in 1993 as a "Purposeful, planned process that addresses the medical, psychosocial and educational/vocational needs of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-orientated healthcare systems."

In 2002 American Academy of Pediatrics published the following consensus: "The goal of transition in health care for young adults with special health care needs is to maximise lifelong functioning and potential through the provision of high-quality developmentally appropriate health care services that continue uninterrupted as the individual moves from adolescence to adulthood" [75]. Several reports, mainly in the transplant setting, have since been published, with worse outcomes for patients transplanted during adolescence and a decrease in 12-month mortality in renal transplant recipients as patients age from 20 to 30 years. This supports the concept that maturation and complete development occur after the age of 18 years [2]. It seems that to date the development of dedicated programs to optimize transition from pediatric to adult-centered care has mainly been driven by pediatric specialists, with currently no consensus as to how to implement or measure this or even define what a successful outcome is. A national survey of adult transplant hepatologists on transitional care after liver transplantation in the USA in 2015 provided interesting information on the perception of adult healthcare providers [76]. We subsequently carried out a similar survey in the UK, and the results are summarized in Table 77.3 [3]. Thirty-two percent of respondents did not have a transition strategy at their center and only 16% had a formal transition program. Not having ade-

Table 77.3 Comparison of survey of transition service in the USA and UK

Comparison of USA and UK Survey results	USA (%)	UK (%)
Formal transition programme	16	61
No transition strategy	32	22
Characteristics of YP attending clinic appointment		
Have adequate knowledge about their condition	70	62
Arrived to the appointment with parent/guardian	66	76
Barriers to transition		
Inadequate communication with paediatric provider	61	11
Patient/family dependence on paediatric provider	46	67
Poor adherence	72	56
Patients lack the capability to discuss the impact of their condition independently without the help of their parent/guardian	54	28
Parents/guardians manage their child's condition without engaging their child	49	44

quate knowledge about their condition was found to be present in a third of the patients. The majority of adult transplant hepatologists were confident with their own skills to manage young people but were concerned about the lack of ability of the young people to independently manage their condition and their poor adherence to treatment with similar observations in the UK. Both in the USA and UK, concerns were raised about dependence of families on the pediatric provider and their interference with the patient's management as a barrier to transition and were concerned as well as the prevalence of non-adherence to treatment.

The care for young people with liver disease should focus on providing appropriate care for young people with liver disease irrespective of whether they are looked after in pediatric or adult services.

Different models of transition programs have been described and will need to be developed depending on the setup and needs of the individual centers. Pediatric teams should focus on developing strategies to overcome barriers to an adequate transition including learning difficulties, social factors, patients in care, and patients with mental health problems and aim for an integrative process. With regard to congenital and rare conditions typically presenting in childhood, where adult teams might be less familiar in managing these conditions, management in specialized centers with pediatric expertise is recommended.

What about the success of adequate young people care? Experience in the renal transplant setting demonstrated that the introduction of an integrated pediatric/young adult joint transition clinic and care pathway improved outcome over a 4-year period, with no episodes of late acute rejection or graft loss compared to 35% graft loss in a group of patients who did not benefit from this service [35]. In our UK survey, we found that those centers with formal transition programs perceived young people to have better knowledge of their condition, have better adherence, and rely less on the pediatric providers (Table 77.4) [3]. It is relevant to include parents and carers in the process, to give them realistic expectations of adult healthcare services and help them to transition from care provider to a more supportive role for the young person. This entails nourishing the development of self-management skills which are essential to navigate within an adult healthcare setting. [77]. In this respect, it is important to use transition readiness tools to define a patient's individual needs and for a multi-professional team to address these.

A recent small pilot study in a group of 20 liver transplant recipients whose care was coordinated by a transition coordinator showed, compared to a historic group of 14 patients, improved adherence to treatment during the year before transfer to adult services. After transfer, tacrolimus standard deviation scores (SD) remained stable in the group supported by the transition coordinator compared to the historic group where the tacrolimus SD increased, suggesting poorer adherence [78].

Table 77.4 Comparison between centers with and without transition services

Comparison between centres with and without transition service	Transition service *N* = 9 (%)	No transition service *N* = 9 (%)
YP has adequate knowledge about their condition	76	50
Poor adherence	44	67
Patient/family dependence on paediatric provider	56	78

Ideally the timing of the transition process should be flexible and aimed at the patient's needs and readiness; however in practice, lack of age-appropriate inpatient facilities or pediatric and adult setting being on different sites often means that patients over 18 years cannot be admitted to pediatric inpatient facilities, raising the importance of starting the transition process early enough. This is particularly relevant in patients with special healthcare needs where the transition process becomes more complicated as the patient might not be able to advocate for their care, consent for procedures, and manage an inpatient stay on an adult ward independently. In these cases, the multiprofessional team should ensure a well-documented care pathway is discussed prior to transition to adult services [79, 80].

Summary and Conclusions

- With advances in medicine, more patients with liver conditions are growing into adulthood.
- Adolescence is a period of biological, psychological, and social changes, and the impact of a chronic condition on this process can be significant.
- Outcome data suggest that young people are a unique and vulnerable cohort who deserves special attention by health professionals, focusing on better outcome and survival.
- Growth failure and pubertal delay are prevalent, and sexual health advice should be offered standard during the consultation with the young person.
- Psychological aspects of growing up with liver disease are increasingly being recognized and identified and require management by specialized healthcare professionals.
- Non-adherence to all aspects of care is common, multifactorial, and often underestimated however impacts on outcome and survival. A non-judgmental approach aimed at identifying barriers to adherence and developing an individualized strategy is recommended.

- Successful transition programs have shown improvement in outcome and quality of life and should be developed according to the facilities of the individual center and focus on self-management, keeping in mind the special needs patients might have.

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