The Health Care Transition of Youth With Liver Disease Into the Adult Health System: Position Paper From ESPGHAN and EASL

*Pietro Vajro, †Björn Fischler, ‡Patrizia Burra, §Dominique Debray, ||Antal Dezsofi, *Salvatore Guercio Nuzio, ¶Nedim Hadzic, #Loreto Hierro, **Joerg Jahnel, ††Thierry Lamireau, ‡‡Patrick McKiernan, §§Valerie McLin, ||||Valerio Nobili, ¶¶Piotr Socha, ##Francoise Smets, ***Ulli Baumann, and †††Henkjan J. Verkade

ABSTRACT

Background: Medical advances have dramatically improved the long-term prognosis of children and adolescents with once-fatal hepatobiliary diseases. However, there is no generally accepted optimal pathway of care for the transition from paediatric care to the adult health system.

Aim: The purpose of this position paper is to propose a transition process for young people with paediatric onset hepatobiliary diseases from child-centred to adult-centred healthcare services.

Methods: Seventeen ESPGHAN/EASL physicians from 13 countries (Austria, Belgium, France, Germany, Hungary, Italy, the Netherlands, Norway, Poland, Spain, Sweden, Switzerland, and United Kingdom) formulated and answered questions after examining the currently published literature on transition from childhood to adulthood. PubMed and Google Scholar were systematically searched between 1980 and January 2018. Quality of evidence was assessed by the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system. Expert opinions were used to support recommendations whenever the evidence was graded weak. All authors voted on each recommendation, using the nominal voting technique.

Results: We reviewed the literature regarding the optimal timing for the initiation of the transition process and the transfer of the patient to adult services, principal documents, transition multi-professional team components, main barriers, and goals of the general transition process. A transition plan based on available evidence was agreed focusing on the individual young people's readiness and on coordinated teamwork, with transition monitoring continuing until the first year of adult services.

We further agreed on selected features of transitioning processes inherent to the most frequent paediatric-onset hepatobiliary diseases. The discussion highlights specific clinical issues that will probably present to adult gastrointestinal specialists and that should be considered, according to published evidence, in the long-term tracking of patients.

Conclusions: Transfer of medical care of individuals with paediatric onset hepatobiliary chronic diseases to adult facilities is a complex task requiring multiple involvements of patients and both paediatric and adult care providers.

Key Words: children, hepatobiliary disease, transition, young adults, young people

(*JPGN* 2018;66: 976–990)

What Is Known

- There is no generally accepted optimal pathway of care for the transition from paediatric care to the adult health system.
- Proposed transition programs have not yet included paediatric-onset hepatobiliary diseases.

What Is New

- The first agreed intersocietal transition pathway for patients with paediatric-onset liver diseases.
- Specific evidence-based recommendations on when/who/what/how to initiate and implement the transition process.
- Focus on new onset issues expected during the follow-up of transitioning youth with hepatobiliary diseases requiring special attention by adult providers.

Transition is an active and evolving process that addresses the medical, psychosocial, and educational needs of young people as they prepare to move from child- to adult-centred health care (1–4). Although recent medical advances have dramatically improved the long-term outcomes of once-fatal chronic diseases (5), adult medicine practitioners still focus differently on issues beside the immediate medical management such as family interaction or patient development and self-management skills. These divergences that have a direct impact on medical outcome variables, as well as an unfinished debate on transition modes, result in continued uncertainty about optimal transition strategies (6–8) regardless of the specific medical condition (9–18). Published evidence specific to patients with hepatobiliary disease only exists for liver transplanted children (19–23). Lack of guidelines for best practice management during transition of adolescents with

Received November 6, 2017; accepted February 25, 2018.

From the *Department of Medicine, Surgery and Dentistry, ''Scuola Medica Salernitana'' Paediatric Section, University of Salerno, Baronissi (Salerno), Italy, the †Department of Paediatrics, Karolinska University Hospital, CLINTEC, Karolinska Institutet, Stockholm, Sweden, the ‡Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Padova, Italy, the §Paediatric Centre, Hepatology, and Transplantation AP-HP, Hôpital Necker Enfants Malades, Paris, France, the ||First Department of Paediatrics, Semmelweis University, Hungary, the ¶Paediatric Gastrointestinal, Liver and Nutrition Centre Variety Children's Hospital King's College Hospital NHS Foundation Trust, London, UK, the #Hospital Infantil Universitario La Paz, Madrid, Spain, the **Department of

paediatric onset-liver diseases has only recently been outlined and partially addressed (24). We have identified five relevant areas that may benefit from a unified approach in young people with these conditions:

1. A proportion of patients have diseases that are highly specific to childhood. Exposure of these entities to adult-centred physicians may have been minimal.
2. Adherence to prescribed treatment in young adults cannot be automatically expected and may be difficult to monitor.
3. About 50% of all paediatric liver transplant patients have been transplanted in the first 2 years of life. These patients have no memory of life without a transplant.
4. Living-related transplantation with donor and recipient coming from the same household may lead to complex family interaction in case of that is chronic graft failure.
5. Some side effects of treatments/drugs or hepatic/extrahepatic complications may only become apparent in adult life.

Accordingly, health care providers for adult patients may benefit not only from a profound understanding of the basics of adolescent transition (25) but also from medical communication on common causes of so-called paediatric liver disease and their long-term outcomes and perspectives. Although these disorders (eg, biliary atresia and progressive familial intrahepatic cholestasis) are relatively rare, thanks to improved management measures, affected survivors with native or transplanted livers will in fact be increasingly represented in future adult hepatology practice. Furthermore, young adults with liver disorders who are leaving the paediatric wards continue to have substantial medical problems, which are complicated by individual behavioural, social, and educational difficulties. Adult providers need to acknowledge and respond to these new trends (26).

Experienced health care providers for adult patients understand the differences in management hitherto, which have only partially been reviewed by paediatric (27,28), or adult (29) hepatologists without a grading of the existing evidence. Data from an ESPGHAN survey on this subject (30) indicated that approaches of health care providers for adults were often perceived as of limited focus towards the specific needs of young patients during transition. This survey also demonstrated a lasting relationship and commitment between patient, family and their paediatric caregiver(s) and the frequent wish of the patient for an ongoing parental involvement.

The purpose of this position paper is to delineate basic requirements for multidisciplinary professional and bilateral approach to transition of young people with paediatric-onset hepatobiliary disease. On the paediatric side, we suggest developments facilitating the transition (ie, patient preparation); on the adult side, we emphasize the need for ongoing communication between adult and paediatric care providers on specific medical needs of young patients during and after transition (ie, physician/staff preparation).

METHODS

The Writing Panel is an international Panel of 17 physicians from 13 countries (Austria, Belgium, France, Germany, Hungary, Italy, the Netherlands, Norway, Poland, Spain, Sweden, Switzerland, and United Kingdom) with paediatric (ESPGHAN Hepatology Committee) and adult (European Association for the Study of the Liver, EASL) medical liver expertise.

In Part 1, the Writing Panel formulated questions addressing main features of a standard transition process (timing, documents, strategies, barriers) and presented answers obtained from a thorough search by topics and/or relevant authors between 1980 and January 2018 in the adult and paediatric English-language literature on transition in 2 search engines (PubMed and Google Scholar). The following search algorithm was used (''transition of care'' or ''transition of management'' or ''continuity of care'') AND ''adolescence'' or ''paediatrics'' or ''young adults'') AND (''paediatric-onset hepatobiliary disease'' or ''liver diseases'') and identified appropriate references. They also explored the literature on transitional issues in other paediatric fields and additional relevant literature. Successively, the Writing Panel developed recommendations and rated the quality of evidence.

The Voting Panel coincided with the Writing Panel. The Voting Panel voted on each recommendation. Recommendations were only included if consensus of at least 75% was reached. The recommendations were based on evidence from existing publications and presentations at international meetings with published congress proceedings as far as possible. If evidence was unavailable, the experts provided personal experiences and opinion.

The evidence and recommendations were graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The principles of the GRADE system have been enunciated in Table 1 (31).

The Committee referred to the main features of a standard transition process based primarily on the 2002 and 2011 American Academy of Paediatrics (AAP) documents (32,33), various American and European programs as ''Got transition'' (34), recently satisfactorily applied (35,36), ON TRAC (Transitioning Responsibly to Adult Care) (37), Good 2 Go Transition Program (38), Stepping Up (39), a ''Health needs technical'' review (40) and the National Institute for Health and Care Excellence guidelines

Pediatrics, Division of Gastroenterology and Hepatology, Medical University Graz, Austria, the ††Paediatric Gastroenterology Unit, Children's Hospital, Bordeaux, France, the ‡‡Center for Rare Disease Therapy, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh Medical Center, Pittsburgh, PA, the §§Swiss Centre for Liver Disease in Children, Paediatric Gastroenterology Unit, Department of Paediatrics, University Hospitals Geneva, Switzerland, the ‖‖Unit of Hepato-Metabolic Diseases, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, and University ''La Sapienza'' Rome, Italy, the ¶¶Department of Gastroenterology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland, the ##UCL, Cliniques Universitaires Saint-Luc, Paediatric Gastro- Hepatology, Brussels, Belgium, the ***Medical School, Children's Hospital, Division of Paediatric Gastroenterology and Hepatology, Hannover, Germany, and the †††Department of Paediatrics, Center for Liver, Digestive, and Metabolic Diseases, University of Groningen, University Medical Center, Groningen, The Netherlands.

Address correspondence and reprint requests to Professor Pietro Vajro, MD, Department of Medicine, Surgery and Dentistry, ''Scuola Medica Salernitana'' Paediatric Section, University of Salerno, 84022 Baronissi (Salerno), Italy (e-mail: pvajro@unisa.it).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

Dr Guercio Nuzio is a paediatric expert invited to join this ESPGHAN Committee.

Disclaimer: ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians.

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000001965

TABLE 1. Grading of evidence and recommendations according to the Grading of Recommendation Assessment, Development and Evaluation system

Grading of recommendation	Benefits versus risk and burdens	Methodological quality of supporting evidence	Implications
1A, strong recommendation, high-quality evidence	Benefits clearly out-weigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B, strong recommendation, moderate-quality evidence	Benefits clearly out-weigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/D, strong recommendation, low-quality or very low-quality evidence	Benefits clearly out-weigh risk and burdens, or vice versa	C: observational studies or case series, retrospective reviews, systematic reviews, survey. D: expert's opinion, case report	Strong recommendation but may change when higher quality evidence becomes available
2A, weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B, weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/D, weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk, and burden may be closely balanced	C: observational studies or case series, retrospective reviews, systematic reviews, survey. D: expert's opinion, case report	Very weak recommendations; other alternatives may be equally reasonable

Adapted from (31). The quality of evidence in the recommendations has been classified into one of four levels: high (A), moderate (B); low (C), or very low (D), according to the type of publication. The GRADE system offers two grades of recommendations: strong (1) or weak (2) reflecting the quality of underlying evidence. In general, the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted. GRADE = Grading of Recommendation Assessment, Development and Evaluation system, RCTs = randomized controlled trials.

(41). Finally, each author examined 1 or 2 specific sections related to specific paediatric onset hepatobiliary diseases.

Specific disease sections were subsequently discussed and the agreed issues relevant to the adult Gastroenterology (GI)/Hepatology provider are described in Part 2.

The manuscript has been reviewed and finally approved by the ESPGHAN and EASL Council and Governing Board members, respectively.

Clinical questions identified by the Writing Panel, inherent literature with intrinsic quality of evidence are summarized in Table S1 (Supplemental Digital Content 1, *http://links.lww.com/MPG/B325*).

PART 1: MAIN FEATURES OF A STANDARD TRANSITION PROCESS

There were no published studies experimentally designed and categorized as randomized controlled trials (level A of evidence) and very few studies categorized as well-controlled cohort studies (level B of evidence). Most of the evidence (approximately 85%) was from not well controlled studies, reviews (Level C of evidence) and expert opinions deriving from clinical experience only (Level D of evidence) (Table S1, Supplemental Digital Content 1, *http://links.lww.com/MPG/B325*).

WHEN: TIMING OF TRANSITION AND TRANSFER

In this manuscript the transition is defined as a period of several years aiming to prepare the young patient and its parents for the final transfer to adult care.

Chronological Age Versus Flexible and Individualized Approach

It is generally agreed that chronological age in itself is insufficient for decisions on the optimal timing of transition/transfer and that a flexible and individualized approach should be used instead (22,24,42,43). The timing of a correct transition should consider the young person's mental and physical development, the socioeconomic circumstances of the patient's family, and availability of the adult providers. Final transfer of responsibility should

occur after mental health stability evaluation (44) and when the young person has globally a stable emotional and physical functioning. Transfer most commonly occurs around 18 years of age but in some centres not until 25 years of age (45). The 25-year limit is sometimes suggested for those rarer conditions which have not available adult specialists (40).

Preparation/Training

The preparation must begin before the planned transfer, preferably by introducing the concept already in early adolescence (even as early as age 12 years) (33), with educational interventions by specialist paediatricians aiming to help the patients to understand their illness, treatment rationale, the origin of the symptoms and monitoring strategies (eg, occasional therapy adjustments for weight, liver function tests) (46). Although adolescents and young adults still today receive limited or no education and preparation regarding key elements of health care transition to adult-oriented healthcare (47), it is proved that training program (especially early, at least 3 years before the final transfer) is conducive to a successful transition (41,48).

Interventions that focus on youth and not on parents are insufficient for empowering transitioning youth (49). Explanations should be given in a way that is understandable, with language that is appropriate to the developmental level of the teenager. Treatment-related problems (health literacy, therapy adherence, side effects) should be discussed at regular intervals by patients and parents (trying to see health professionals individually). It should also be clear that if a treatment has to be stopped because of an adverse effect, another treatment will usually be needed to substitute the stopped medication under medical prescription. A program to report on the quality of health care transition preparation received from medical providers may be useful for 16- to 17-year-old youth (50).

Other important general issues to highlight such as healthy sexuality (eg, potential contagiousness in case of chronic infections, unintentional pregnancies, contraceptive methods), need for routine immunizations (eg, A and B viral hepatitis, human papilloma virus), avoiding weight excess, recreational drugs and excessive alcohol consumption, should also be approached early in order to minimise possible additional hepatotoxic injuries.

Readiness

According to other transition experiences coming from other chronic paediatric-onset diseases (51,52), only approximately 50% of the clinical programs that sought to promote the acquisition of transition skills perform an assessment of the young people readiness. This relatively low rate is primarily because of the lack of a validated, patient-centred tool that can be used to evaluate the ability of young people to make appointments, understand their medications and request help whenever necessary.

It is of interest that only 50% of parents report that they have discussed the transition with their paediatrician (53), and less than 40% of young people between 12 and 17 years of age with special health needs make a successful transition (54), also because of a lack of paediatric long-term planning.

Transition Process Versus Administrative Transfer

The incorrect assumption that the transition process represents a purely administrative transfer leads to inappropriate transition hand offs, resulting in young patients not yet ready to the step. If this mistaken view is applied insensitively, patients may feel ''lost in the system'' with less satisfactory results in terms of long-term follow-up and an ultimate increase in health costs (40,55).

The Committee recommends:

1. For optimal timing of transition/transfer, paediatric providers should take into account the young person's mental and physical development, disease activity, health literacy, autonomy in disease management and socioeconomic circumstances of her/his family, rather than mere chronological age (1C [22,45, Survey], [24, Guidelines] [42, 43, Reviews] [34, Transition Program]; agreed 100%).
2. Paediatric teams should start transition ''training'' well before the planned transfer, preferably already in early adolescence (12–14 years), or at least 3 years before the final transfer, whenever possible during a stable phase of the disease (1C [33, Expert Opinion] [41, Guidelines] [44, Retrospective review]; agreed 100%).
3. Treatment-related problems (medication nonadherence and/or side effects) as well as establishing a healthy lifestyle should be discussed with patients and parents (trying to see health professionals individually) at regular intervals (1B [46, RCT] [49, Prospective Cohort Study]; agreed 100%).
4. A program to report on the quality of health care transition preparation received from medical providers may be useful (2C [50, Survey]; agreed 100%).
5. In uncomplicated cases, actual transfer is recommended around the age of 18 years (1C [40, Review]; agreed 88.2%).
6. A prolonged period of transition up to age of 25 years, preferably under the observation of both paediatric and adult professionals, is recommended in complicated situations (1C [40 Reviews; 45 Surveys]; agreed 76.4%).
7. Depending on own countries and granted patients approval, parents' presence and involvement is (under certain conditions) in the best interest of the patient, also if 16 or above (1C [22, Survey], [24, Guidelines]; agreed 88.2%).

WHICH DOCUMENTS

Essential Documents and Instruments for Training

Taking into account several sources, we propose a list of documents (paediatric provider's letter with a synthesis of the patient's medical history, a transfer and emergency care plan, a transition checklist for self-evaluation of feasibility of the transition process and a transition roadmap easily accessible by patients and families) for young people smooth transition as summarized in Table 2 (34,40,56,57).

Ideally, each paediatric hepatology centre should develop a personalized booklet according to local available resources, including also information about the scope, meaning and rules of transition. A checklist helping the young people to self-assess readiness to navigate into Adult Health care system should be available as well. Table 3 shows a planning checklist produced by the Royal College of Nursing (58) and modified by our Committee. In this document, the evaluation of the young people occurs in three stages: early (12–14 years), middle (14–15 years), and late (15–16 years).

The Committee recommends:

1. The use of transfer documents, which should include a paediatric provider's letter with a synthesis of the patient's medical history, a transfer and emergency care plan, a transition checklist for self-evaluation of feasibility of the transition process, and a transition roadmap easily accessible by patients and families (1C [34, 58 Program/Review]; agreed 100%).

TABLE 2. Essential documents used/proposed during transition procedures

Paediatric provider's letter	Containing the first appointment with the adult's provider
Transition checklist	Evaluation of transition process's feasibility → skills assessment for self-management
	Indicates whether adolescents have or do not have particular knowledge or expertise related to the disease through dichotomous variables (yes/no) or ordinal scale (TRAQ) → identification of training areas and building greater autonomy
Emergency care plan	Paediatrician's indications in case of emergency
Synthesis of transfer	A medical summary aimed to the transfer of knowledge from paediatric to adult provider
	List of therapeutic indications, synthesis of present or past problems, mental health status, possible expected problems to monitor
Training skills for transition team	Interpersonal and communication skills for transition training of health professional figures
Transition plan (roadmap)	Written information as ''roadmap'' form → easily consulted by patients and families
	Scheduling own appointments and who to contact
	Opportunity to review any unclear topics and periodic guidance visits at the adult service
Educational skills for patients	Understand disease characteristics/evolution
	Understand possible differences between paediatric and adult approach (eg, upper/lower endoscopies, liver biopsy, MRI, etc without anesthesia)
	Learning about exemptions and legal rights

TRAQ = Transition Readiness Assessment Questionnaire.

WHO

Many young people and families continue to be reluctant to leave the familiar environment of their paediatric specialist because of a long-established relationship. They find difficult to initiate a long-term relation with a new specialist (57). In fact, paediatric care is often multidisciplinary and includes a holistic approach played by the paediatrician and centred around family (7).

In contrast, the attention of adult specialists tends to be focused more directly on the patient's disease. This context could encourage independent decisions by young people, for which, however, they may not necessarily be educated or prepared.

For the above reasons, it has been well documented that the implementation of an effective transition program may require an integrated and multidisciplinary effort by both paediatric and adult staff, ideally working as a well-coordinated multi-professional team (8,57,59) (see Supplementary Figure S1, Supplemental Digital Content 2, *http://links.lww.com/MPG/B326*). For optimal outcomes, the team should send a uniform message to adolescents and their families, namely one that encourages increased health-

TABLE 3. Multidisciplinary staff transition checklist

Issue	Early stage transition	Middle stage transition	Late stage transition
Self advocacy	Educate pts in describing their health condition and ask questions during each visit. Parents' participation	Know how to access information about pts' condition (support groups, internet or condition-specific organizations)	Explain all the available adult care options and differences between paediatric and adult care Help pts to choose an adult provider, possibly close to their home
Independent health care behaviour	Understand medication and potential problems/barriers → where to get help?	Personal health record book for appointments, information, treatments, and health providers	Personal health record book Pts meet with adult specialist nurse before discontinuing paediatric care
Sexual health	Talk through the changes associated with puberty, and the implications of pts condition	Questions about impact of the condition and/or medications → will the condition affect fertility?	Discuss pts sexual capabilities (physical capability, fertility, genetic, infection issues) and impact of pregnancy, delivery and breastfeeding on pts condition
Psychological support	Discuss about parents' feelings and future, pts friends and relationships	Encourage to join a social group, such as a club or youth group	If pts condition is potentially life shortening, identify any need for help in dealing with this.
Educational and vocational planning	Talk about pts responsibilities at home, restrictions affecting pts's education and amusing activities	Talk about school, favorite subjects, and any career idea Set up a meeting with a work counseling service	Discuss about an opportunity for a work experience placement If pts plan to go to college or university, discuss the implications of this
Health and lifestyle	Discuss issues surrounding sexuality, smoking, overweight, alcohol, and drugs	Discuss any restrictions caused by pts condition, body images, weight gain or loss;	Discuss any feelings of low blue mood, depression, etc → identify people they can contact for help

Adapted and modified from Royal College of Nursing (58). pts = patients.

care knowledge and self-management skills (60). Specifically, parents require support during this time for adolescent developmental issues, such as negotiating independence for treatment (61,62).

Trained nursing staff could play a central coordinating/contact role in the proper delivery of effective transition programs. The supportive role of parents is, of course, essential, although occasionally they may show some ambivalence. Whenever possible, the young person should be given opportunity to establish a leading role in his/her own health care (60).

The Committee recommends

1. A transition multidisciplinary professional team is composed by essential components as paediatric and adult providers together with a coordinator (any transition involved or dedicated professional) (2C [7 Guidelines, 85,759, Reviews]) (agreed 100%).

TRANSITION STRATEGIES (HOW)

Transition strategies vary from country to country according to the respective health systems.

Medical Home Principles

In United States, the AAP suggests that an effective transition process of children with special needs should be coordinated, comprehensive, individualized, and patient-centred, as well as able to increase self-control and independent health care (32), following the Patient-Centred Medical Home (PCMH) principles. In the Medical Home, the medical care of infants, children, and young people is delivered or directed by well-trained physicians who provide primary care (63). Within PCMH, it is usual that the specific activities of the transition begin after discussion and periodic revision/updating of a shared protocol (33).

Especially for genetic syndromes and metabolic diseases, access to a Medical Home may be significantly affected by the severity and clinical instability of the patient's health condition (64) because the primary care system may be less accustomed to providing the coordinated, time-consuming medical and social care that these patients need or because of poor reimbursement for care coordination (65). US Medical Home transition model, therefore, is not easily applicable to young people with rare liver diseases and may be, furthermore, quite difficult to implement according to the specific country where she/he is living.

It is still necessary to adapt this suggested model to different health systems in European countries where- with few exceptions- there is no specific transition staff, and where certain key aspects are extremely variable, for example, the maximum age allowed for hospitalization in a paediatric ward.

Transition Plan

A transition plan should be based on the young people's readiness and on coordinated multi-professional team-work, with transition monitoring until the completion of the first year in the adult service. The paediatric provider should inform the patients about the transition program: this preliminary phase should be followed by a number of joint visits (in attendance of both paediatric and adult providers) if possible at a dedicated centre (Transition Unit), or alternating between the adult and the paediatric care centres over 12 months (66). After a further transition feasibility evaluation, the final paediatric visit should be planned.

By minimizing complication rate, the establishment of a transition program is likely to improve prognosis and reduce long-term medical costs.

As shown in Figure S2 (Supplemental Digital Content 3, *http://links.lww.com/MPG/B327*), the transition program includes several phases:

1. preliminary phase, with the aid of a specific register redacted for early young people' identification and involvement. If patient is 12 to 14 years, the Committee suggests paediatric providers to assess transition feasibility and specific checklist issues (67,68);
2. combined visits phase: preliminary phase might be followed by several combined visits if possible at a dedicated centre (Transition Unit), or alternating between the adult and the paediatric care centres (66);
3. transition feasibility evaluation: when a teenager is not ready, he/she should repeat transition feasibility checklist evaluation until he proves to be well prepared (although some young people may never fully achieve this level of independence) (33);
4. final paediatric visit: the final paediatric visit without parents, should happen preferably around 18 years, and in any case, no later than 25 years of age (37,40,45).

The Committee recommends

1. The first phase of a transition plan should be a preliminary phase for early young people identification, involvement and assessment of transition feasibility (1C, [67 Survey 2C, 68 Review C]; agreed 100%).
2. Transition plan should provide a phase composed by several combined visits if possible at a dedicated centre (Transition Unit), or alternating between the adult and the paediatric care centres (1D [66, Expert opinion]; agreed 88.2%).
3. When a teenager is not ready, he/she should repeat transition feasibility checklist evaluation (transition feasibility re-evaluation phase) until he proves to be well prepared (1D [33, Expert Opinion]; agreed 94.1%).
4. Transition paediatric monitoring should continue until the completion of the first year in the adult service (1C [37 Transition Program, 40 Review, 45 Survey]; agreed 82.3%).

MAIN TRANSITION GOALS: SURMOUNTING THE BARRIERS!

Preventing young people becoming lost in the transfer between paediatric and adult health services is a major challenge for healthcare providers (69). When the paediatric and adult liver centres are not within the same hospital, a strong collaboration with regional adult referrals with preferential pathways for patients in transition must be established. If a dedicated and specialized service is not available near the patient's home, efforts should be made in order to find the closest available and accessible gastroenterology/hepatology unit.

Most Significant Transition Barriers, Related Consequences and Strategies to be Adopted

Unfortunately, a number of barriers could impede the transition process. The most significant recognized barriers and the related consequences upon paediatricians and adult providers, patients and family members are summarized in Table S1, section E (Supplemental Digital Content 2, *http://links.lww.com/MPG/B325*) (70–74). Accordingly, clinicians should use transition skills and specific adolescent medicine programs for transition training of health professional figures (29). Regular meetings, and also

suitable technological connection (eg, sms, mailing list, smartphone) for interaction among patients and paediatric/adult providers, should be arranged to improve the effectiveness of the transition program (57,75–79). Websites including lists of specialists who are prepared to work with paediatric problems associated with transition, civic education campaigns by national societies, mass media collaboration (67) (eg, *www.gottransition.org*) have been proposed to significantly help to create nationally based transition networks. Specific networks for transition of some GI disease (eg, IBD) have been recently proposed (80). According to adult hepatologists, the greatest barriers to optimal care are often patients' poor adherence and their limited knowledge and management of their condition (81). The presence of relatives and their strong control on everything that happens to their kids is more frequent with a greater impact on the outcome of transition, than the poor adherence of young patients (81) Factors that might negatively affect medical adherence include not only age but also severity of illness, that is, asymptomatic periods during chronic liver disease may create the risk of poor adherence, and the long duration of treatment. In addition, nonadherence in adolescence is often part of a constellation of risk behaviours, including alcohol and drug use, unintentional pregnancy, mental health diagnoses and legal issues (44). If a formal transition program exists, negative consequences such as patient's inability to discuss the impact of their condition on their overall daily life, fitness, and sexuality are reported as less common (82) (Table 4).

TABLE 4. Main transition barriers and their consequences

Main transition barriers	For patients and families
	Poor knowledge on health care system
	Poor information → rights to services, treatments
	Difficulties in identifying the right adult's specialist
	Lack of knowledge of disease
	For paediatric providers
	Little time for the transition care
	Lack of financial reimbursement
	Young adults with different level of care
	Lack of experienced adult- specialists.
	For adult's providers
	Little time for the transitional care
	Low economic reimbursement assistance
	Lack of training in congenital/paediatric onset diseases
	Lack of communication with paediatric colleagues
Consequences of an inappropriate transition	For patients and families
	↑Hospitalizations and non-adherence to treatment
	↓Education and/or working training of the adolescent
	↓Success and productivity in adulthood
	Contact with medical profession only in emergency
	For paediatric providers
	Difficult parent's involvement in the chronic disease
	Transition felt as a punishment/refusal to follow pts
	Parents behave in opposite ways
	For adult's providers
	↓Experience on child's diseases continuing into adulthood
	Transition training difficult to integrate into workflow
	Approach perceived quite unfriendly by new pts

Transition Outcomes

Past studies focused on transition examined a variety of health (83), or psychosocial outcomes (84), although without uniformity in measurement both in terms of timing and standardization of measurement (85,86). Betz et al (87) assessed the health care transition literature from the triple perspective of health care reform examining outcomes of population health, patient experience, and costs concluding that persons experiencing the transition desire to be a part of the process and want providers who will listen and be sensitive to their needs, which are often different from others receiving health care at the same facility. A recent study (88) is consistent with this conceptual mode.

The Committee recommends

1. Regular meetings, suitable technological connection interaction among patients and paediatric/adult providers, should be arranged to improve the effectiveness of the transition program (1B [76–79, RCTs]; agreed 94.1%).
2. Websites including lists of GI/Hepatology specialists who are prepared to work with problems associated with transition, civic education campaigns by national societies, mass media collaboration may be proposed to help to create regionally/nationally based transition networks (2C [67, Survey]; agreed 94.1%).
3. Transition programs should aim to assure individual quantifiable outcomes (quality of life, knowledge of medication, self-management, adherence to medication, dietary adherence, understanding health insurance, complications) (1C [85–87 Reviews]; agreed 100%).
4. Transition programs might consider adolescent's social tools (eg, having a social network; 2C [87, Review]; agreed 82.3%).
5. Transition programs may also englobe health services (attending medical appointments, having a transition team as reference, and avoidance of unnecessary hospitalization; 2C (87, Review; agreed 88.4%).

PART 2: SELECTED FEATURES OF TRANSITION PROCESSES OF YOUNG ADULTS WITH SPECIFIC PAEDIATRIC-ONSET HEPATOBILIARY DISEASES

Long-term clinical outcomes of patients with a number of hepatobiliary disorders starting during childhood have recently been summarized (25,89).

In general, specific available retrospective multicentre studies show that most cases of long-term survivors with native livers:

1. may have a decreased therapy adherence;
2. require lifelong care because of the possibility of hepatic deterioration and/or progressive portal hypertension, sometimes ending up into the need for liver transplantation (22,23).

Regarding specifically liver transplanted (LT) patients, the causes for nonadherence to medication and for poor confidence in hospital visits following transfer to adult clinics, leading to graft

TABLE 5. Agreed specific new onset issues during the follow-up of transitioning youth with hepatobiliary diseases well known by adult providers requiring special attention

Condition	Liver issues	Other organs/systems	Social/sexuality/pregnancy/newborns
Hepatitis B (95–103)	Cirrhosis and HCC Portal hypertension Liver failure No treatment (if in the tolerance phase) Discuss treatment with new direct antivirals (tenofovir, entecavir) after transition, if indicated		Antiviral therapy during the 3rd trimester of pregnancy → maternal viral load Neonatal rapid active/passive immunization Breast feeding yes Partner vaccination and/or care of safe sexuality
Hepatitis C (102,104,105)	Rates of fibrosis ↑ during late adolescence Rare clearance if in newborn period acquired Treatment with new direct antivirals	Cryoglobulinaemia	Antiviral treatment before a planned pregnancy Breast feeding accepted Perinatal HCV risk Care of safe sexuality
AIH (106–110)	Consider alternative medical treatment in unresponsive or relapsing cases (eg, cyclosporine, tacrolimus, mycophenolate) Progress to end-stage liver disease despite therapy Poor compliance to cortisones and IS therapy Overlap with autoimmune sclerosing cholangitis Recurrence after LT, especially with overlap syndrome	Monitor possible emergence of other AI diseases (celiac disease, thyroiditis) Monitor IBD Monitor APECED	Increased risk of preterm delivery and neonatal complications Not stop therapy during pregnancy/ breast-feeding (AZA) Not stop therapy during pregnancy/ breast-feeding (AZA) Avoid MMF in pregnancy
PSC (93,111–114)	Liver cirrhosis and liver failure. Risk of recurrence after OLT Cholangiocarcinoma PSC/ASC/AIH-PSC overlap	Monitor IBD development before or after LT	Pregnancy not be discouraged. Associated to preterm birth and caesarean section but not to congenital malformations.
NAFLD (26,115–118)	Potential evolution to cirrhosis and HCC Lower long-term survival described in a tertiary care setting	Metabolic syndrome and renal/ cardiovascular diseases Plan bariatric surgery after transition, in selected cases	Maternal gestational diabetes, metabolic syndrome Neonatal NAFLD
LT (75,119–135)	Possible recurrence of previous liver disease (eg, AIH; PFIC 1–3) and *de novo* AIH Insulin resistance → de novo NAFLD post LT→ liver fibrosis Hepatic artery thrombosis, rejection Poor adherence to IS and hospital visits: → graft loss and need for re-transplantation → need to simplify the therapy (reducing number of drugs) Be aware that usually there is a Roux en Y loop, piggy-back of cava, usually pts are appendicectomized	Linear growth impairment; delayed Tanner 5 pubertal stage Obesity, arterial HT, IR, diabetes, met. syndrome Poor renal function EBV-PTLD	Lower school performances Lower physical health related QOL Feelings of limitation of freedom, loneliness Negative thoughts, problematic relationships- Good maternal and neonatal outcome described if it is followed by a multidisciplinary and high-risk obstetrical team

AIH = autoimmune hepatitis, APECED = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, ASC = autoimmune sclerosing cholangitis, AZA = azathioprine, EBV = Epstein-Barr Virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HT = hypertension, IBD = inflammatory bowel disease, IR = insulin-resistance, IS = immunosuppressive, LT = liver transplantation, NAFLD = nonalcoholic fatty liver disease, NTBC = nitisinone, LT = liver transplantation, PFIC = progressive familiar intrahepatic cholestasis, PSC = primary sclerosing cholangitis, PTLD = posttransplant lymphoproliferative disease, QOL = quality of life.

TABLE 6. Agreed specific new onset issues expected during the follow-up of transitioning youth with specific paediatric age onset hepatobiliary diseases requiring special attention by adult providers

Condition	Liver issues special recommendations	Other organs/systems	Social/sexuality/pregnancy/newborn
Biliary atresia (93,136–140)	PH, including endoscopic follow up for variceal screening and prophylaxis If still with native liver, increased risk of decompensation upon pregnancy Lifelong care for possible hepatic deterioration if still with native liver Lifelong posttransplant care if indicated (see ''LT'', liver transplantation, below in this Table), including monitoring long-term consequences of LT	Post-transplant: bone density, malignancies (skin, other organs), hypertension, kidney function, if relevant: corticosteroid induced ocular abnormalities	School and work: satisfying career In case of native liver, pregnancy may lead to increased risk of decompensation of until then compensate cirrhosis After transplantation, pregnancy possible under close monitoring of multidisciplinary obstetrics/hepatology teams
A1AT deficiency (27,28,141,142)	Cirrhosis HCC Look for new therapy	Avoid obesity, alcohol, tobacco smoking Pursue vaccinations (influenza, pneumococcus) Pulmonary involvement may benefit from recA1AT High variability of disease symptoms presentation	
Alagille syndrome (93,143–149)	Liver failure/portal hypertension (during pregnancy) Hepatic nodular/HCC Hypercholesterolemia/Xanthomas Intractable pruritus	Kidney problems up to renal failure Heart /vascular anomalies (abdominal, neurological level) Problems with external stomas Hypertension	Good maternal and fetal outcome Genetic counselling Familial screening
Ciliopathies (150–153)	Cholangiocarcinoma Cholelithiasis Worsening portal hypertension (not cirrhotic) Recurrent cholangitis/ Sepsis Consider LT (liver failure or complications /severe PH)	Polycystic kidney disease associated Risk of kidney related-systemic hypertension	Uncomplicated pregnancy or transient worsening of renal function
Crigler-Najjar (154)	Phototerapy: regular assessment of the frequently decreased efficacy with increasing age Type 2: Enzyme inducers Indication and optimal timing of LT Awareness of the continuous risk on bilirubin toxicity, including the lifelong risk on kernicterus (if no transplanted)	Possible kernicterus with permanent neurological damage at any age	Normal pregnancy described during PB treatment or after LT Social and psychological burden of phototherapy need: effects on relationship and family life
CF (155–161)	Combination of CF liver and lung disease Cirrhotic or non cirrhotic, portal hypertension/hypersplenism Liver failure Decision about timing for LT, possibly before irreversible lung disease	Lung/cardiovascular disease management Pancreatic insufficiency/Diabetes/Osteoporosis	Normal pregnancy possible if multidisciplinary care Genetic counseling Social/couple problems
GSD (162–165)	Type I: hepatic adenomas → dysplasia and HCC Type III and IV → cirrhosis and cardiomyopathy	Type Ib → neutrophil deficiency-based chronic IBD colitis Specific Diet	Normal pregnancy described

TABLE 6. (Continued).

Condition	Liver issues special recommendations	Other organs/systems	Social/sexuality/pregnancy/newborn
Hereditary tyrosinemia type I (166,167)	Acute or chronic liver failure if unresponsive to NTBC HCC Plan LT if liver failure or HCC	Renal tubular dysfunction Hypophosphataemic rickets at all age Specific Diet	Normal pregnancy in NTBC-treated patients
Mitochondrial disorders (168–173)	LT only after accurate evaluation Genetic counselling	Multiorgan dysfunction → CNS disease may precede or follow hepatopathy	Significant risk of MLD if fetuses have short, medium, and long-chain FAOD (eg, HELLP syndrome in LCHAD deficiency) and mother is heterozygous; AFLP when fetuses have CPT I deficiency, a Reye-like syndrome typically between 8 and 18 months of age Innovative therapies
PFIC/BRIC (174–180)	PFIC1&2: gallstones, PH, cirrhosis, HCC Biliary diversion → problems with external stomas PFIC-1 pts post LT: liver steatosis PFIC-2 pts relapse post LT PFIC 3: rarely transplanted/BRIC: milder course	PFIC1&2: diarrhea PFIC-1 pts post LT: diarrhoea	Pregnancy complicated by variable exacerbations of jaundice and cholestasis (BRIC/PFIC) Newborn hyaline membrane disease
Urea cycle disorders (181,182)	Poor adherence → metabolic decompensation, acute liver injury or liver failure LT if recurrent metabolic decompensation	Diet for avoiding serious acute metabolic decompensations Hyperammoniaemic neurological signs or psychiatric signs Avoid valproic acid and steroids	High-risk pregnancy; should be closely followed by a multidisciplinary and high-risk obstetrical team
Portal cavernoma (183–185)	Portal hypertension and complications (hypersplenism) Consider surgery	Pulmunar shunts	Elective CS seems necessary in cases with digestive varices OEGD every 1 year
Wilson disease (186–190)	Poor adherence → liver failure, behavioural changes, neurological signs Liver failure after spontaneous interruption of treatment Consider to switch from Penicillamine to Zinc	Fanconi syndrome and progressive renal failure Irregular periods and multiple miscarriages → hormonal changes WD behavioural changes need to be differentiated from physiological adolescent changes Possible nutritional deficiencies (Fe, Zn) Elastosis perforans serpiginosa after long term D-penicillamine therapy Necessity of a multidisciplinary team Genetic counselling	Pregnancy should be closely followed by a high-risk team GE varices may be aggravated by pregnancy Irregular periods and miscarriages if liver not functioning well Pursue medication to avoid mother/newborn health problems

AFLP = acute fatty liver of pregnancy, BRIC = benign recurrent intrahepatic cholestasis, CF = cystic fibrosis, CNS = central nervous system, CPTI = hepatic carnitine palmitoyltransferase, CS = caesarean section, FAO = fatty-acid oxidation disorders, HCC = hepatocellular carcinoma, HELLP = haemolysis, elevated liver-enzyme levels, and a low-platelet count, IBD = inflammatory bowel disease, IT = immunosuppressive therapy, LCHAD = L-3-hydroxyacyl-CoA dehydrogenase deficiency, MLD = maternal liver disease, NTBC = nitisinone, LT = liver transplantation, OEGD = oesophagus-gastro-duodenoscopy, PB = phenobarbital, PFIC = progressive familiar intrahepatic cholestasis, PH = portal hypertension, recA1AT = recombinant alpha1-antitrypsin.

loss, and the need for retransplantation (90) are complex and include the difficulties young people experience in the development from childhood to adulthood, their need to become self-reliant, and the different medical approach of paediatric and adult care (91–93). Other relevant issues, which the Committee feels need to be taken into special consideration, regarding young adults with paediatric onset hepatobiliary diseases, refer to:

1. effects of pregnancy/lactation/associated illnesses on exacerbations of specific chronic liver disease and vice versa (eg, BRIC-pregnancy);
2. obesity-related nonalcoholic fatty liver disease (NAFLD) and effects of alcohol during adult life;
3. surveillance for neoplastic changes and other nonhepatic organ-related diseases (eg, autoimmune conditions).

Similarly, important aspects specific to each condition are considered:

1. parenthood, maternal, and fetal outcomes (eg, in hepatitis B/C);
2. long-term effects/complications of some chronic treatments on patients and/or their offspring (for detailed information on how to use the lowest risk drug possible, with attention to the appropriate level of efficacy, readers are addressed to a specific AGA document) (94);
3. education, professional occupation, and career.

In Table 5, the Committee summarizes relevant available references and/or Committee considerations specific for the most common conditions. The Committee focused on a number of common disease-specific clinical, psychological, and social problems that an adult GI/hepatologist/internist may encounter once the young adult patient with chronic liver disease has been transferred.

Some information on a number of rare paediatric onset hepatobiliary disorders and liver transplantation is provided as well (Table 6).

Overall, advances in medical and surgical therapy mean that significant numbers of children with previously fatal liver disease are surviving into adult life. Adult physicians need to be aware of the clinical management and complications of diseases originating in infancy such as biliary atresia, Progressive Familial Intrahepatic Cholestasis, Alagille's syndrome, and metabolic diseases such as Tyrosinemia Type 1. They also need to be familiar with the long-term consequences of childhood liver disease or liver transplantation performed in childhood (eg, psychological, cognitive/growth/pubertal delay, renal failure, recurrent disease, osteoporosis, and posttransplant malignancies, especially posttransplant lymphoproliferative disease) (90).

The Committee concludes that a multiprofessional team, trained to detect, treat or even prevent several disease-specific complications encountered during/after transition of adolescents affected by paediatric-onset hepatobiliary conditions, could definitely improve outcomes, and quality of life.

FINAL CONSIDERATIONS

Transition from childhood to early adulthood is surrounded by a number of physical, emotional, social and cognitive developmental changes and challenges, many of them being ''physiological.'' The issues hitherto discussed highlight that the presence of a chronic disease in general and of some hepatobiliary diseases in particular, represents an additional challenge. The transition process—in addition to pharmacological therapies, side effects, and hepatic disease-related complications should include a number of general subjects such as education, counselling, career, social education, sexuality. Detailing most of these aspects, however, was beyond the scope of this position paper, while some of them have already been well addressed in existing comprehensive guidelines (33,34).

Although there is broad agreement that preparation is needed to help adolescents and young adults during transition process, there is no consensus regarding what constitutes a successful health care transition. A successful transition process should create independent young adults who are capable of living independently and in balance with their chronic condition and to make informed decisions about their future health. Special attention is required for young patients with additional learning needs because of or associated with liver disease where transition process could be even more challenging and requires specifically planned pathways (89).

The key elements for an effective transition include correct timing, preparation, and education. A joint structure including paediatric and adult staff would be the ''ideal'' introduction for young people to the adult medical world. For this purpose, it should be advised to select and contact well in advance adult clinics for strict cooperation in the transition program.

An evidence-based implementation of a systematic transition policy on paediatric-onset hepatobiliary diseases is still limited by a lack of solid evidence. Different models of transition have, therefore, been developed also locally. It is still unknown if a standardized protocol-driven transition process as the one here proposed is superior to a process that varies both nationally and internally. Existing models of transition proposed also for other organs/systemic paediatric onset diseases have rarely been evaluated in randomized controlled trials with accurate measurements of patients' outcomes. It will be crucial to evaluate to what extent a well structured and planned transition remove barriers, influences medical adherence, reduces the prevalence and severity of complications, and improves health-related quality of life.

Acknowledgment: The authors wish to acknowledge Dr Tom Karlsen, EASL Secretary General for his kind support.

REFERENCES

1. Blum RWM, Garell D, Hodgman CH, et al. Transition from child-centred to adult health-care systems for young people with chronic conditions *J Adolesc Health* 1993;14:570–6.
2. Sawyer S, Blair S, Bowes G. Chronic illness in young people: transfer or transition to adult services? *J Paediatr Child Health* 1997;33:88–90.
3. Ladores S. Concept analysis of health care transition in adolescents with chronic conditions. *J Pediatr Nurs* 2015;30:e119–29.
4. Rosen DS, Blum RW, Britto M, et al. Transition to adult health care for young people and young adults with chronic conditions: position paper of the Society for Young people Medicine. *J Adolesc Health* 2003;33:309–11.
5. Kennedy A, Sloman F, Douglass JA, et al. Young people with chronic illness: the approach to transition. *Intern Med J* 2007;37:555–60.
6. Bensen R, McKenzie R, Fernandes S, et al. Transitions in paediatric gastroenterology: results of a national provider survey. *J Pediatr Gastroenterol Nutr* 2016;63:488–93.
7. Mazur A, Dembinski L, Schrier L, et al. European Academy of Paediatric consensus statement on successful transition from paediatric to adult care for adolescents with chronic conditions. *Acta Paediatr* 2017;106:1354–7.
8. de Silva PSA, Fishman LN. The transition of the gastrointestinal patient from paediatric to adult care. *Pediatr Clin North Am* 2017;64:707–20.
9. Young N, McCormick A, Mills W, et al. The transition study: a look at youth and adults with cerebral palsy, spina bifida, and acquired brain injury. *Phys Occup Ther Pediatr* 2006;26:25–45.

10. Marcer H, Finlay F, Baverstock A. ADHD and transition to adult services—the experience of community paediatricians. *Child Care Health Dev* 2008;34:564–6.
11. Peters A, Laffel L. American Diabetes Association (ADA) Transition Working Group. Diabetes care for emerging adults: recommendations for transition from paediatric to adult diabetes care systems: a position statement of the ADA. *Diabetes Care* 2011;31:2447–85.
12. El-Matary W. Transition of children with inflammatory bowel disease: big task, little evidence. *World J Gastroenterol* 2009;30:3744–7.
13. Baldassano R, Ferry G, Griffiths A, et al. Transition of the patient with inflammatory bowel disease from paediatric to adult care: recommendations of the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2002; 34:245–8.
14. Bryant R, Young A, Cesario S, et al. Transition of chronically ill youth to adult health care: experience of youth with hemoglobinopathy. *J Pediatr Health Care* 2011;25:275–83.
15. Lyon ME, Kuehl K, McCarter R. Transition to adulthood in congenital heart disease: missed young people milestones. *J Adolesc Health* 2006;39:121–4.
16. Houtrow AJ, Newacheck PW. Understanding transition issues: asthma as an example. *J Pediatr* 2008;152:453–5.
17. Shrewsbury VA, Baur LA, Nguyen B, et al. Transition to adult care in young people obesity: a systematic review and why it is a neglected topic. *Int J Obes (Lond)* 2014;38:475–9.
18. Ludvigsson JF, Agreus L, Ciacci C, et al. Transition from childhood to adulthood in coeliac disease: the Prague consensus report. *Gut* 2016;65:1242–51.
19. Kelly D, Wray J. The young people liver transplant patient. *Clin Liver Dis* 2014;18:613–32.
20. Fredericks EM. Nonadherence and the transition to adulthood. *Liver Transpl* 2009;15:S63–9.
21. Burra P. The young people and liver transplantation. *J Hepatol* 2012;56:714–22.
22. Junge N, Migal K, Goldschmidt I, et al. Transition after paediatric liver transplantation -perceptions of adults, adolescents and parents. *World J Gastroenterol* 2017;23:2365–75.
23. Kamath BM, LThoff KM. Liver transplantation in children: update 2010. *Pediatr Clin North Am* 2010;57:401–14.
24. Brooks AJ, Smith PJ, Cohen R, et al. UK guideline on transition of adolescent and young persons with chronic digestive diseases from paediatric to adult care. *Gut* 2017;66:988–1000.
25. Guercio Nuzio S, Ann Tizzard S, Vajro P. Tips and hints for the transition: what adult hepatologists should know when accept teens with a paediatric hepatobiliary disease. *Clin Res Hepatol Gastroenterol* 2014;38:277–83.
26. Hadžić N, Baumann U, McKiernan P, et al. Long-term challenges and perspectives of pre-adolescent liver disease. *Lancet Gastroenterol Hepatol* 2017;2:435–45.
27. Rook M, Rosenthal P. Caring for adults with paediatric liver disease. *Curr Gastroenterol Rep* 2009;11:83–9.
28. Vajro P, Ferrante L, Lenta S, et al. Management of adults with paediatric-onset chronic liver disease: strategic issues for transition care. *Dig Liver Dis* 2013;46:295–301.
29. Joshi D, Gupta N, Samyn M, et al. The management of childhood liver diseases in adulthood. *J Hepatol* 2017;66:631–44.
30. Vajro P, Tizzard SA, Fischler B, et al. Paediatric onset liver diseases transitioning to adult care: preliminary data on a still orphan area requiring a consensus. XXI SIGENP Annual Meeting, Sorrento (Italy) October 2014. *Dig Liver Dis* 2014;46:e102.
31. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. *Chest* 2006;129:174–81.
32. American Academy of Paediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. Consensus statement on health care transitions for young adults with special health care needs. *Paediatrics* 2002;110 (6 Pt 2):1304–6.
33. American Academy of Paediatrics, American Academy of Family Physicians, American College of Physicians; Transitions Clinical Report Authoring Group, Cooley WC, Sagerman PJ. Supporting the health care transition from adolescence to adulthood in the medical home. *Paediatrics* 2011;128:182–200.
34. Centre for Health Care Transition Improvement. Got transition program. 2014. Available at: *www.gottransition.org*. (last assessed February 2018).
35. Gold JI, Boudos R, Shah P, et al. Transition consultation models in two academic medical centers. *Pediatr Ann* 2017;46:e235–41.
36. Jones MR, Robbins BW, Augustine M, et al. Transfer from paediatric to adult endocrinology. *Endocr Pract* 2017;23:822–30.
37. ON TRAC (Transitioning Responsibly to Adult Care). Available at: *http://ontracbc.ca/*.(last assessed February 2018).
38. Good 2 Go Transition Program. Available at: *http://www.sickkids.ca/good2go/*.(last assessed February 2018).
39. Stepping UP: A GUIDE to enabling a good transition to adulthood for young people with life limiting and life-threatening conditions. Available at: *http://www.togetherforshortlives.org.uk*. (last assessed February 2018).
40. McPheeters M, Davis AM, Taylor JL, et al. Transition care for children with special health needs Rockville (MD): Agency for Healthcare Research and Quality; 2014. Available at: *http://www.ncbi.nlm.nih.gov/books/NBK222123/* PubMed PMID: 25057736.
41. National Institute for Health and Care Excellence. Transition from children's to adults' services for young people using health or social care services. February 2016. Available at: *https://www.nice.org.uk/guidance/indevelopment/gid-scwave0714*. (last assessed February 2018).
42. Binks JA, Barden WS, Burke TA, et al. What do we really know about the transition to adult-centered health care? A focus on cerebral palsy and spina bifida. *Arch Phys Med Rehabil* 2007;88:1064–73.
43. Watson R, Parr J, Joyce C, et al. Models of transitional care for young people with complex health needs: a scoping review. *Child Care Health Dev* 2011;37:780–91.
44. Harry R, Fraser-Irwin C, Mouat S, et al. Long-term follow up of paediatric liver transplant recipients: outcomes following transfer to adult healthcare in New Zealand. *Intern Med J* 2015;45:580–2.
45. Bensen R, McKenzie RB, Fernandes SM, et al. Transitions in paediatric gastroenterology: results of a national provider survey. *J Pediatr Gastroenterol Nutr* 2016;63:488–93.
46. Betz CL, Smith K, Macias K. Testing the transition preparation training program: a randomized controlled trial. *Int J Child Adolesc health* 2010;3:595–607.
47. Dwyer-Matzky K, Blatt A, Asselin BL, et al. Lack of preparedness for paediatric to adult-oriented healthcare transition in hospitalized adolescents and young adults. *Acad Pediatr* 2018;18:102–10.
48. Sebastian S, Jenkins H, McCartney S, et al. The requirements and barriers to successful transition of adolescents with inflammatory bowel disease: differing perceptions from a survey of adult and paediatric gastroenterologists. *J Crohn Colitis* 2012;6:830–44.
49. Gorter JW, Stewart D, Cohen E, et al. Are two youth-focused interventions sufficient to empower youth with chronic health conditions in their transition to adult healthcare: a mixed-methods longitudinal prospective cohort study. *BMJ Open* 2015;5:e007553.
50. Sawicki GS, Garvey KC, Toomey SL, et al. Preparation for transition to adult care among Medicaid-insured adolescents. *Paediatrics* 2017;140:pii: e20162768.
51. McLaughlin SE, Diener-West M, Indurkhya A, et al. Improving transition from paediatric to adult cystic fibrosis care: lessons from a national survey of current practices. *Paediatrics* 2008;121:1160–6.
52. Schwartz LA, Tuchman LK, Hobbie WL, et al. A social-ecological model of readiness for transition to adult-oriented care for adolescents and young adults with chronic health conditions. *Child Care Health Dev* 2011;37:883–95.
53. Lotstein DS, McPherson M, Strickland B, et al. Transition planning for youth with special health care needs: results from the National Survey of Children with Special Health Care Needs. *Paediatrics* 2005;115: 1562–8.
54. Data Resource Centre for Child and Young People Health. National Survey for Children with Special Health Care Needs 2009/2010. Available at: *www.childhealthdata.org*. (last assessed February 2018).
55. Beresford B, Moran N, Sloper T, et al. Transition to adult services and adulthood for young people with autistic spectrum conditions (working paper no DH 2525). York: Social Policy Research Unit, 2013. Available at: *https://www.york.ac.uk/inst/spru/pubs/pdf/TransASC.pdf*. (last accessed February 2018).

56. Sawicki GS, Lukens-Bull K, Yin X, et al. Measuring the Transition readiness of youth with special healthcare needs: validation of the TRAQ—Transition Readiness Assessment Questionnaire. *J Pediatr Psychol* 2011;36:160–71.
57. Kime N, Bagnall AM, Day R. Systematic review of transition models for young people with long-term conditions: a report for NHS Diabetes. Available at: *http://eprints.leedsbeckett.ac.uk/606/* (last assessed February 2018).
58. Royal College of Nursing. Adolescent transition care, RCN guidance for nursing staff. Available at: *www.rcn.org.uk* (last assessed February 2018).
59. Mencin AA, Loomba R, Lavine JE. Caring for children with NAFLD and navigating their care into adulthood. *Nat Rev Gastroenterol Hepatol* 2015;12:617–28.
60. Kovacs AH, Cullen-Dean G, Burchill LJ, et al. The multidisciplinary transition team. In: Schwerzmann M, Thomet C, Moons P, eds. *Congenital Heart Disease and Adolescence. Congenital Heart Disease in Adolescents and Adults.* Cham: Springer; 2016.
61. Bryon M, Madge S. Transition from paediatric to adult care: psychological principles. *J R Soc Med* 2001;94(Suppl 40):5–7.
62. Chandra S, Luetkemeyer S, Romero, et al. Growing up: not an easy transition-perspectives of patients and parents regarding transfer from a paediatric liver transplant center to adult care. *Int J Hepatol* 2015;2015:9.
63. American Academy of Paediatrics. Medical Home Initiatives for Children With Special Needs Project Advisory Committee, The Medical Home. *Paediatrics* 2002;110:184–6.
64. Van Lierde A, Menni F, Bedeschi MF, et al. Healthcare transition in patients with rare genetic disorders with and without developmental disability: Neurofibromatosis 1 and Williams–Beuren syndrome. *Am J Med Genet Part A* 2013;161A:1666–74.
65. Strickland BB, Singh GK, Kogan MD, et al. Access to the medical home: new findings from the 2005–2006 National Survey of children with special health care needs. *Pediatrics* 2009;123:e996–1004.
66. Elli L, Maieron R, Martelossi S, et al. Transition of gastroenterological patients from paediatric to adult care: a position statement by the Italian Societies of Gastroenterology. *Dig Liver Dis* 2015;47:734–40.
67. Huang JS, Gottschalk M, Pian M, et al. Transition to adult care: Systematic assessment of young people with a chronic illness and their medical teams. *J Pediatr* 2011;159:994.e2–8.e2.
68. Gleeson H, McCartney S, Lidstone V. Everybody's business': transition and the role of adult physicians. *Clin Med(Lond)* 2012;12:561–6.
69. McDonagh JE, Viner RM. Lost in transition? Between paediatric and adult services. *BMJ* 2006;332:435–6.
70. McManus M, Fox H, O'Connor K, et al. Paediatric perspectives and practices on transitioning young people with special health care needs to adult health care. Fact Sheet No. 6. National Alliance to Advance Young people Health, Washington, D.C. 2008. Available at: *www.thenationalalliance.org* (last assessed February 2018).
71. Peter N, Forke C, Ginsburg K, et al. Transition from paediatric to adult care: internists' perspectives. *Paediatrics* 2009;123:417–23.
72. Goodhand J, Hedin CR, Croft NM, et al. Young people with IBD: the importance of structured transition care. *J Crohn Colitis* 2011;5: 509–19.
73. Antosh AA, Blair M, Edwards K, et al. A Collaborative Interagency, Interdisciplinary Approach to Transition from Adolescence to Adulthood. Silver Spring, MD: Association of University Centres on Disabilities; 2013.
74. Adams RJ, Smith BJ, Ruffin RE. Impact of the physician's participatory style in asthma outcomes and patient satisfaction. *Ann Allergy Asthma Immunol* 2001;86:263–71.
75. Dommergues JP, Letierce A, Gravereau L, et al. Current lifestyle of young adults after liver transplantation during childhood. *Am J Transplant* 2010;10:1634–42.
76. Powers L, Geenen S, Powers J, et al. My life: effects of a longitudinal, randomized study of self-determination enhancement on the transition outcomes of youth in foster care and special education. *Child Youth Serv Rev* 2012;34:2179–87.
77. Lee Y, Wehmeyer ML, Palmer SB, et al. The effect of student-directed transition planning with a computer-based reading support program on the self-determination of students with disabilities. *J Spec Educ* 2011;45:104–17.
78. Huang JS, Terrones L, Tompane T, et al. Preparing adolescents with chronic disease for transition to adult care: a technology program. *Paediatrics* 2014;133:e1639–46.
79. Patrick K, Raab F, Adams MA, et al. A text message-based intervention for weight loss: randomized controlled trial. *J Med Internet Res* 2009;11:e1.
80. Gray WN, Resmini AR, Baker KD, et al. Concerns, barriers, and recommendations to improve transition from paediatric to adult IBD care: perspectives of patients, parents, and health professionals. *Inflam Bowel Dis* 2015;21:1641–51.
81. Fischler B, Dezsofi A, Dhawan A, et al. Paediatric and adult hepatologists views upon the transition of adolescents with chronic hepatobiliary disease: preliminary data of a European survey. XlVIII ESPGHAN Annual Meeting, Amsterdam (The Netherlands) May 2015. *J Gastroenterol Hepatol* 2015;60:e607.
82. Heldman MR, Sohn MW, Gordon EJ, et al. National survey of adult transplant hepatologists on the paediatric-to-adult care transition after liver transplantation. *Liver Transpl* 2015;21:213–23.
83. Reed-Knight B, Lewis JD, Blount RL. Association of disease, adolescent, and family factors with medication adherence in paediatric inflammatory bowel disease. *J Pediatr Psychol* 2011;36:308–17.
84. Bloom SR, Kuhlthau K, Van Cleave J, et al. Health care transition for youth with special health care needs. *J Adolesc Health* 2012;51:213–9.
85. Coyne B, Hallowell SC, Thompson M. Measurable outcomes after transfer from paediatric to adult providers in youth with chronic illness. *J Adolesc Health* 2017;60:3–16.
86. Rachas A, Lefeuvre D, Meyer L, et al. Evaluating continuity during transfer to adult care: a systematic review. *Paediatrics* 2016;138:pii: e20160256.
87. Betz CL, Lobo ML, Nehring WM, et al. Voices not heard: a systematic review of adolescents' and emerging adults' perspectives of health care transition. *Nurs Outlook* 2013;61:311–36.
88. Fair C, Cuttance J, Sharma N, et al. International and interdisciplinary identification of health care transition outcomes. *JAMA Pediatr* 2016;170:205–11.
89. Dhawan A, Samyn M, Joshi D. Young adults with paediatric liver disease: future challenges. *Arch Dis Child* 2017;102:8–9.
90. Ferrarese A, Germani G, Lazzaro S, et al. Short-term outcomes of paediatric liver transplant recipients after transition to Adult Healthcare Service *Liver Int* 2017. (Epub ahead of print).
91. Gritti A, Pisano S, Salvati T, et al. Health-related quality of life in paediatric liver transplanted patients compared with a chronic liver disease group. *Ital J Pediatr* 2013;39:55.
92. Gritti A, Sicca F, Di Sarno AM, et al. Emotional and behavioral problems after paediatric liver transplantation: a quantitative assessment. *Pediatr Transplant* 2006;10:205–9.
93. Gritti A, Di Sarno AM, Comito M, et al. Psychological impact of liver transplantation on children's inner worlds. *Pediatr Transplant* 2001;5:37–43.
94. Mahadevan U, Kane S. American Gastroenterological Association Institute Medical Position Statement on the use of gastrointestinal medications in pregnancy. *Gastroenterology* 2006;131:278–82.
95. Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after antigen seroclearance: final report of a 29-year longitudinal study. *Hepatology* 2006;43:556–62.
96. Sokal EM, Paganelli M, Wirth S, et al. Consensus of an expert committee on behalf of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines. *J Hepatol* 2013;59:814–29.
97. Vajro P, Veropalumbo C. Treating children with HBeAg-positive chronic hepatitis B: no small accomplishment. *Dig Liver Dis* 2014;46:1064–5.
98. Murray KF, Szenborn L, Wysocki J, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in young people with chronic hepatitis B. *Hepatology* 2012;56:2018–26.
99. Chen HL, Lee CN, Chang CH, et al., Taiwan Study Group for the Prevention of Mother-to-Infant Transmission of HBV (PreMIT Study); Taiwan Study Group for the Prevention of Mother-to-Infant Transmission of HBV PreMIT Study. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. *Hepatology* 2015;62:375–86.

100. Jonas MM, Chang MH, Sokal E, et al. Randomized controlled trial of entecavir versus placebo in children with HBeAg-positive chronic hepatitis B. *Hepatology* 2016;63:377–87.
101. Clemente MG, Vajro P. An update on the strategies used for the treatment of chronic hepatitis B in children. *Expert Rev Gastroenterol Hepatol* 2016;10:649–58.
102. Sogni P. Pregnancy and viral hepatitis B and C. *Presse Med* 2015;44 (6 pt 1):654–9.
103. Lamberth JR, Reddy SC, Pan JJ, et al. Chronic hepatitis B infection in pregnancy. *World J Hepatol* 2015;7:1233–7.
104. Jara P, Resti M, Hierro L, et al. Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. *Clin Infect Dis* 2003;36:275–80.
105. Wirth S, Rosenthal P, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin in adolescents 12 to 17 years old with hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2017;66:1102–10.
106. Strassburg CP, Manns MP. Transition of care between paediatric and adult gastroenterology. Autoimmune hepatitis. *Best Pract Res Clin Gastroenterol* 2003;17:291–306.
107. Radhakrishnan KR, Alkhouri N, Worley S, et al. Autoimmune hepatitis in children – impact of cirrhosis at presentation on natural history and long-term outcome. *Dig Liver Dis* 2010;42:724–8.
108. Floreani A, Liberal R, Vergani D, et al. Autoimmune hepatitis: contrasts and comparisons in children and adults - a comprehensive review. *J Autoimmun* 2013;46:7–16.
109. Stokkeland K, Ludvigsson JF, Hultcrantz R, et al. Increased risk of preterm birth in women with autoimmune hepatitis - a nationwide cohort study. *Liver Int* 2016;36:76–83.
110. Charlagorla P, Sublett S, Sy F, et al. Fetal intestinal perforation and meconium peritonitis associated with maternal autoimmune hepatitis. *J Neonatal Perinatal Med* 2014;7:71–4.
111. Miloh T, Anand R, Yin W, et al. Paediatric liver transplantation for primary sclerosing cholangitis. *Liver Transpl* 2011;17:925–33.
112. Liu R, Cox K, Guthery SL, et al. Cholangiocarcinoma and high-grade dysplasia in young patients with primary sclerosing cholangitis. *Dig Dis Sci* 2014;59:2320–4.
113. Ludvigsson JF, Bergquist A, Ajne G, et al. A population-based cohort study of pregnancy outcomes among women with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2014;12:95.e1–100.e1.
114. Feldstein AE, Perrault J, El-Youssif M, et al. Primary sclerosing cholangitis in children: a long-term follow-up study. *Hepatology* 2003;38:210–7.
115. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, et al. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to20 years. *Gut* 2009;58:1538–44.
116. Schwimmer JB, Pardee PE, Lavine JE, et al. Cardiovascular risk factors and the metabolic syndrome in paediatric nonalcoholic fatty liver disease. *Circulation* 2008;118:277–83.
117. Pardee PE, Lavine JE, Schwimmer JB. Diagnosis and treatment of paediatric non-alcoholic steatohepatitis and the implications for bariatric surgery. *Semin Pediatr Surg* 2009;18:144–51.
118. Nobili V, Vajro P, Dezsofi A, et al. Indications and limitations of bariatric intervention in severely obese children and Young people with and without non alcoholic steatohepatitis: the ESPGHAN Hepatology committee position statement. *J Pediatr Gastroenterol Nutr* 2015; 60:550–61.
119. Rothbaum Perito E, Lau A, Rhee S, et al. Post-transplant metabolic syndrome in children and young people after liver transplant: a systematic review. *Liver Transpl* 2012;18:1009–28.
120. Burra P, Germani G, Gnoato F, et al. Adherence in liver transplant recipients. *Liver Transpl* 2011;17:760–70.
121. Annunziato RA, Emre S, Shneider B, et al. Adherence and medical outcomes in paediatric liver transplant recipients who transition to adult services. *Pediatr Transplant* 2007;11:608–14.
122. Mohammad S, Hormaza L, Neighbors K, et al. Health status in young adults two decades after paediatric liver transplantation. *Am J Transplant* 2012;12:1486–95.
123. Soanes C, Timmons S. Improving transition: a qualitative study examining the attitudes of young people with chronic illness transferring to adult care. *J Child Health Care* 2004;8:102–12.
124. McDonagh JE, Kelly DA. Transitioning care of the paediatric recipient to adult caregivers. *Pediatr Clin North Am* 2003;50:1561–83.
125. Viner RM. Transition of care from paediatric to adult services: one part of improved health services for young people. *Arch Dis Child* 2008;93:160–3.
126. Shemesh E, Shneider BL, Savitzky JK, et al. Medication adherence in paediatric and young people liver transplant recipients. *Paediatrics* 2004;113:825–32.
127. Fredericks EM, Dore-Stites D, Lopez MJ, et al. Transition of paediatric liver transplant recipients to adult care: patient and parent perspectives. *Pediatr Transplant* 2011;15:414–24.
128. Annunziato RA, Parkar S, Dugan CA, et al. Brief report: deficits in healthcare management skills among young people and young adult liver transplant recipients transitioning to adult care settings. *J Pediatr Psychol* 2011;36:155–9.
129. Kelly DA, Bucuvalas JC, Alonso EM, et al. Long-term medical management of the paediatric patient after liver transplantation: 2013 practice guideline by the American Association for the study of liver diseases and the American Society of Transplantation. *Liver Transpl* 2013;19:798–825.
130. Bell LE, Bartosh SM, Davis CL, et al. Young people transition to adult care in solid organ transplantation: a consensus conference report. *Am J Transplant* 2008;8:2230–42.
131. La Rosa C, Glah C, Baluarte HJ, et al. Solid-organ transplantation in childhood: transitioning to adult health care. *Paediatrics* 2011;127:742–53.
132. Webb N, Harden P, Lewis C, et al. Building consensus on transition of transplant patients from paediatric to adult healthcare. *Arch Dis Child* 2010;95:606–11.
133. Ramirez CB, Doria C. Pregnancy after liver transplantation. *Best Pract Res Clin Obstet Gynaecol* 2014;28:1137–45.
134. Yazigi NA. Long term outcomes after paediatric liver transplantation. *Pediatr Gastroenterol Hepatol Nutr* 2013;16:207–18.
135. McLin VA, Allen U, Boyer O, et al. Early and late factors impacting patient and graft outcome in paediatric liver transplantation: summary of an ESPGHAN Monothematic Conference. *J Pediatr Gastroenterol Nutr* 2017;65:e53–9.
136. Shneider BL, Abel B, Haber B, et al. Portal hypertension in children and young adults with biliary atresia. *J Pediatr Gastroenterol Nutr* 2012;55:567–73.
137. Shinkai M, Ohhama Y, Take H, et al. Long-term outcome of children with biliary atresia who were not transplanted after the Kasai operation: >20-yearexperience at a children's hospital. *J Pediatr Gastroenterol Nutr* 2009;48:443–50.
138. Bijl EJ, Bharwani KD, Houwen RH, et al. The long-term outcome of the Kasai operation in patients with biliary atresia: a systematic review. *Neth J Med* 2013;71:170–3.
139. O'Sullivan OE, Crosby D, Byrne B, et al. Pregnancy complicated by portal hypertension secondary to biliary atresia. *Case Rep Obstet Gynecol* 2013:421386.
140. Chiengthong K, Somboonnithiphol K, Kittipinyovath P, et al. Pregnancy in biliary atresia after kasai operation complicated by portal hypertension. *J Med Assoc Thai* 2006;89:1961–4.
141. Pinto RB, Schneider ACR, da Silveira TR. Cirrhosis in children and adolescents: an overview. *World J Hepatol* 2015;7:392–405.
142. Bakula A, Pawlowska J, Niewiadomska O, et al. Liver transplantation in Polish children with ((1)-antitrypsin deficiency: a single-center experience. *Transplant Proc* 2016;48:3323–7.
143. Lykavieris P, Hadchouel M, Chardot C, et al. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut* 2001;49:431–5.
144. Kamath BM, Spinner NB, Emerick KM, et al. Vascular anomalies in Alagille syndrome: a significant cause of morbidity and mortality. *Circulation* 2004;109:1354–8.
145. Ferrarese A, Senzolo M, Burra P. Successful pregnancy in Alagille Syndrome. *Dig Liver Dis* 2015;47:86–7.
146. Salem JE, Bruguiere E, Iserin L, et al. Hypertension and aortorenal disease in Alagille syndrome. *J Hypertens* 2012;30:1300–6.
147. Tsai S, Gurakar A, Anders R, et al. Management of large hepatocellular carcinoma in adult patients with Alagille syndrome: a case report and review of literature. *Dig Dis Sci* 2010;55:3052–8.
148. Kayhan A, Ilkhchoui Y, Venu N, et al. Multiple abdominal vascular anomalies in a patient with Alagille syndrome. *J Vasc Interv Radiol* 2010;21:937–40.

149. Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet* 2012;20:251–7.
150. Suchy JF, Sokol RJ, Balistreri WF. Liver Disease in Children. 3rd ed. Cambridge: Cambridge University Press; 2007.
151. Mindikoglu AL, Regev A, O'Sullivan MJ, et al. Multiple normal deliveries in a woman with severe portal hypertension due to congenital hepatic fibrosis: the importance of preserved hepatocellular function. *Am J Gastroenterol* 2005;100:2359–61.
152. Byrd LM, Bullen P. Congenital hepatic fibrosis and portal hypertension in pregnancy. *Int J Gynaecol Obstet* 2005;88:142–3.
153. Banks N, Bryant J, Fischer R, et al. Pregnancy in autosomal recessive polycystic kidney disease. *Arch Gynecol Obstet* 2015;291:705–8.
154. Wilson JH, Sinaasappel M, Lotgering FK, et al. Recommendations for pregnancies in patients with Crigler-Najjar syndrome. *JIMD Rep* 2013;7:59–62.
155. Colombo C, Battezzati PM, Crosignani A, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors and outcome. *Hepatology* 2002;36:1374–82.
156. Debray D, Lykavieris P, Gauthier F, et al. Outcome of cystic fibrosis-associated liver cirrhosis: management of portal hypertension. *J Hepatol* 1999;31:77–83.
157. Milkiewicz P, Skiba G, Kelly D, et al. Transplantation for cystic fibrosis: outcome following early liver transplantation. *J Gastroenterol Hepatol* 2002;17:208–13.
158. Fischer R, Nährig S, Kappler M, et al. Cystic fibrosis care in transition from adolescence to adult age. *Internist (Berl)* 2009;50: 1213–4.
159. Tuchman LK, Schwartz LA, Sawicki GS, et al. Cystic fibrosis and transition to adult medical care. *Paediatrics* 2010;125:566–73.
160. Witters P, Libbrecht L, Roskams T, et al. Noncirrhotic presinusoidal portal hypertension is common in cystic fibrosis-associated liver disease. *Hepatology* 2011;53:1064–5.
161. Michl RK, Mues S, Mainz JG, et al. Pregnancy and cystic fibrosis - an overview. *Z Geburtshilfe Neonatol* 2015;219:170–5.
162. Yamaguchi T, Ihara K, Matsumoto T, et al. Inflammatory bowel disease-like colitis in glycogen storage disease type 1b. *Inflamm Bowel Dis* 2001;7:128–32.
163. Karabul N, Berndt J, Kornblum C, et al. Pregnancy and delivery in women with Pompe disease. *Mol Genet Metab* 2014;112:148–53.
164. Ferrecchia IA, Guenette G, Potocik EA, et al. Pregnancy in women with glycogen storage disease Ia and Ib. *J Perinat Neonatal Nurs* 2014;28:26–31.
165. Sechi A, Deroma L, Lapolla, et al. Fertility and pregnancy in women affected by glycogen storage disease type I, results of a multicenter Italian study. *J Inherit Metab Dis* 2013;36:83–9.
166. Lindstedt S, Holme E, Lock EA, et al. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. *Lancet* 1992;340:813–7.
167. McKiernan PJ. Nitisinone in the treatment of hereditary tyrosinaemia type 1. *Drugs* 2006;66:743–50.
168. Finsterer J. Central nervous system manifestations of mitochondrial disorders. *Acta Neurol Scand* 2006;114:217–38.
169. Ramsay KW, Hanson C, Asplund K. Mitochondrial replacement–potential therapy method with ethical implications. Severe disease may be prevented, but knowledge gaps exist. *Lakartidningen* 2014;111:1240–3.
170. Goel A, Jamwal KD, Ramachandran A, et al. Pregnancy-related liver disorders. *J Clin Exp Hepatol* 2014;4:151–62.
171. Ibdah JA, Bennett MJ, Rinaldo P, et al. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med* 1999;340:1723–31.
172. Innes AM, Seargeant LE, Balachandra K, et al. Hepatic carnitine palmitoyltransferase I deficiency presenting as maternal illness in pregnancy. *Pediatr Res* 2000;47:43–5.
173. Browning MF, Levy HL, Wilkins-Haug LE, et al. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. *Obstet Gynecol* 2006;107:115–20.
174. Pawlikowska L, Strautnieks S, Jankowska I, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. *J Hepatol* 2010;53:170–8.
175. Egawa H, Yorifuji T, Sumazaki R, et al. Intractable diarrhea after liver transplantation for Byler's disease: successful treatment with bile adsorptive resin. *Liver Transpl* 2002;8:714–6.
176. Keitel V, Burdelski M, Vojnisek Z, et al. De novo bile salt transporter antibodies as a possible cause of recurrent graft failure after liver transplantation: a novel mechanism of cholestasis. *Hepatology* 2009;50:510–7.
177. Jankowska I, Czubkowski P, Kaliciński P, et al. Ileal exclusion in children with progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr* 2014;58:92–5.
178. Czubkowski P, Jankowska I, Pawlowska J. Successful pregnancy after ileal exclusion in progressive familial intrahepatic cholestasis type 2. *Ann Hepatol* 2015;14:550–2.
179. Pataia V, Dixon PH, Williamson C. Pregnancy and bile acid disorders. *Am J Physiol Gastrointest Liver Physiol* 2017;313: G1–6.
180. Catzola A, Vajro P. Management options for cholestatic liver disease in children. *Expert Rev Gastroenterol Hepatol* 2017;11: 1019–30.
181. Kersale A, Jacob C, Egreteau PY, et al. Psychiatric symptoms during pregnancy: don't forget metabolic diseases! *Presse Med* 2014;43: 1015–6.
182. Gallagher RC, Lam C, Wong D, et al. Significant hepatic involvement in patients with ornithine transcarbamylase deficiency. *J Pediatr* 2014;164:720.e6–5.e6.
183. De Ville de Goyet J, D'Ambrosio G, Grimaldi C. Surgical management of portalhypertension in children. *Semin Pediatr Surg* 2012;21: 219–32.
184. Savoia F, Ferrara C, Sansone A, et al. Portal cavernoma during pregnancy. *Case Rep Obstet Gynecol* 2013;2013:396083.
185. Ducarme G, Plessier A, Thuillier C, et al. Pregnancy and delivery in patients with portal vein cavernoma. *Gynecol Obstet Invest* 2009;68:196–8.
186. Beinhardt S, Leiss W, Stättermayer AF, et al. Long term outcomes of patients with Wilson's disease in a large Austrian cohort. *Clin Gastroenterol Hepatol* 2014;12:683–9.
187. Taddeo D, Egedy M, Frappier JY. Adherence to treatment in young people. *Paediatr Child Health* 2008;13:19–24.
188. Zegarac Z, Duić Z, Stasenko S, et al. Wilson's disease in pregnancy. *Acta Clin Croat* 2013;52:529–32.
189. Socha P, Janczyk W, Dhawan A, et al. Wilson's disease in children: a position paper by the ESPGHAN Hepatology Committee. *J Pediatr Gastroenterol Nutr* 2018;66:334–44.
190. Pfeiffenberger J, Beinhardt S, Gotthardt DN, et al. Pregnancy in Wilson disease - management and outcome. *Hepatology* 2018; 67:1261–9.