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Invited Review

PGHN

Long Term Outcomes after Pediatric Liver Transplantation

Nada A. Yazigi

MedStar Georgetown Transplant Institute, Georgetown University Hospital, Washington DC, USA

Long term outcomes after liver transplantation are major determinants of quality of life and of the value of this heroic treatment. As short term outcomes are excellent, our community is turning to take a harder look at long term outcomes. The purpose of this paper is to review these outcomes, and highlight proposed treatments, as well as pressing topics needing to be studied. A systemic review of the English literature was carried in PubMed, covering all papers addressing long term outcomes in pediatric liver transplant from 2000-2013. Late outcomes after pediatric liver transplant affect the liver graft in the form of chronic liver dysfunction. The causes include rejection particularly humoral rejection, but also de novo autoimmune hepatitis, and recurrent disease. The metabolic syndrome is a major factor in long term cardiovascular complication risk. Secondary infections, kidney dysfunction and malignancy remain a reality of those patients. There is growing evidence of late cognitive and executive function delays affecting daily life productivity as well as likely adherence. Finally, despite a good health status, quality of life measures are comparable to those of children with chronic diseases. Long term outcomes are the new frontier in pediatric liver transplantation. Much is needed to improve graft survival, but also to avoid systemic morbidities from long term immunosuppression. Quality of life is a new inclusive measure that will require interventions and innovative approaches respectful not only on the patients but also of their social circle.

Key Words: Children, Liver, Transplants, Patients outcome

INTRODUCTION

Liver transplantation is now a well-established treatment for end stage liver disorders in pediatrics. Over the last decade advances in surgical techniques, immunosuppressive therapies and infectious monitoring and treatment have revolutionized patient and graft survival. Short term complications are at all times low, and 1 year survival is solidly above 95% across all pediatric cholestatic disorders. A correlate of this success is that long term complications are becoming more apparent as patient survival is now reaching over 20 years.

Long term complications likely for some originate in the early post-transplant period, but others reflect long term and cumulative side effects of immunosuppressive medications as well as compliance hurdles. All are in addition affected by the individual

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Corresponding author: Nada A. Yazigi, MedStar Georgetown Transplant Institute, Georgetown University Hospital, 3800 Reservoir Rd, NW, Main bld, 2nd floor, Washington, DC 20007, USA. Tel: +1-202-329-3603, Fax: +1-202-444-0336, E-mail: nada.a.yazigi@gunet.georgetown.edu

genetic and general health background.

When Ng et al. [1] looked in the studies in pediatric liver transplant (SPLIT) registry at the health status of children alive 10 years after liver transplant, of 167 survivors, only 32% achieved an "ideal profile" as defined by first allograft, stable on mono therapy, normal growth and absence of common immunosuppression-induced sequelae. Impaired growth was seen in 23%, renal dysfunction in 9%, post transplant lymphoproliferative disease (PTLD) in 5%, and patients had a lower health-related quality of life score than matched healthy children.

These outcomes defer slightly from those reported from other areas in the world, but the general themes are constant. An excellent review of long term outcomes was included in the recently published American Association for the Study of Liver Diseases guidelines for the management [2].

In this review we will briefly go over common outcomes. We will detail some of the novelty and controversy areas. We will also review emerging topics of interest.

GRAFT HEALTH

Liver graft health is clearly affected by the integrity of its vascular and biliary systems, as well as by the immunologic responses along the spectrum of its life affecting parenchymal, but also vascular and biliary structures. Improving surgical techniques and operative support, as well as treatment modalities have helped improve dramatically those outcomes.

Vascular complications

While they reach up to 10% in some series in the first 90 days, de novo late onset hepatic artery thrombosis (HAT), or portal vein (PV) or hepatic vein (HV) stenosis/thrombosis are growing in recognition. They are often found on monitoring US or with manifestation of related morbidities. The onset of these vascular complications is likely still to have been in the early post-operative time, but chronic immunologic and ischemic insults are also at play. The long term effect on the graft can result in progressive scarring and/or bile duct disease, leading to morbidities and in rare cases to a need for re-transplantation. In addition pro-thrombotic disorders need often to be rule out as part of their work up.

Hepatic artery thrombosis & hepatic artery stenosis

Early HAT occurs in around 8.3% of transplanted children and is more common in lower volume centers (performing less than 13 transplants a year). Risk factors include: less than 6 month old donor livers, small recipient vessels, whole liver graft, right split liver graft, need for arterial graft, prolonged cold ischemia time, and recipient massive ascites and hyper-coagulable state. The use of interrupted and fine sutures for arterial anastomosis, loupe or microscope, and attention to organ harvesting improved outcomes through the decades to a current 3.8% incidence in large transplant centers (inclusive of adult and pediatric transplants). Mortality in the case of early HAT can range from 30-40%, and is due to infections, severe bile ducts injury, and graft dysfunction. Treatment with heparin or aspirin, and the use of micro-vascular surgeries do not show clear preventive advantage in published literature. Thrombectomy, surgical revision of the arterial anastomosis, and thrombolysis are the prevalent treatment modalities. Children tend to do better than adults with a 92% good outcome if diagnosis and treatment are done early. Re-transplantation was performed in 62% of children [3].

Late HAT is rarer, as most cases arise in the first month post-transplant. It is often felt to represent more of a late recognition than late onset. The liver function is usually fairly preserved due to the presence of extensive collateralization, assured usually in pediatric recipients by the roux, the cut surface of the liver and the liver capsule. Non-specific transaminase elevations, de-novo biliary complications, and a finding of parvus tardus could point towards late HAT. Bile ducts complications are the defining morbidities. They typically consist of non-anastomotic strictures, often in the hilum and complex in nature. Bilomas and biliary sepsis are common.

Re-vascularization usually does not work. Re-transplantation is the better treatment when complications arise, but is very hard, fraud with substantial comorbidities and financially forbidding.

If hepatic artery stenosis is diagnosed, it is always worth treating conservatively usually with dilatation, but long and recurrent interventions are needed. It remains a high risk situation for long term graft dysfunction and biliary complications.

Portal vein thrombosis

PV thrombosis is estimated at 2-10% in all pediatric recipients. While often silent in early post transplant time, portal hypertensive clinical findings and hypersplenism are usually seen as time elapses. Portal hypertensive complications manifest mostly as hypersplenism, and gastrointestinal (GI) bleeding. GI bleeding is often clinically significant, sometimes requires surgical shunting and more rarely re-transplantation. Currently scarce systematic data is available on those patients' outcomes, the timing and appropriate vascular shunt type to use; a REX shunt (mesenterico-left portal bypass) is favored when technically feasible [4].

Hepatic vein/outflow stenosis

Late outflow obstruction is the least prevalent of vascular complications and is more commonly seen in the technical variant graft (less than 1% in most reports). It presents as a Budd-Chiari syndrome. Diagnosis is made by US, computed tomography (CT) angiography or magnetic resonance imaging (MRI). It is confirmed by direct venography that can also serve as first line treatment. Often those livers do end up failing with time unless corrective surgery can be done. Thrombotic tendencies need to be ruled out in such patients if technical issues are not at play.

Biliary complications

Bile ducts (BD) complications can arise at any time in the life of a graft. They average 5-25% incidence in pediatric liver graft recipients. Late biliary strictures are more frequent in anatomic variant liver grafts. The mean time to diagnosis is around 2 months from transpant.

Biliary complications are to suspect when cholestatic biochemical changes or cholangitis are present. The bilirubin level is often normal, and rarely anomalies are seen on US. Imaging the liver graft with CT and magnetic resonance cholangiopancreatography can be helpful in diagnosing dilated ducts in some patients. In the absence of radiologic findings, if the suspicion is high, a liver biopsy can document cholangitis and obstructive findings. Endoscopic or percutaneous cholangiography is often needed to confirm or rule out the diagnosis, and also serves as the most common treatment modality.

Bile duct stenosis tends mostly to be ischemic in origin. Anastomotic strictures are usually short and respond nicely to dilation and stenting for 6-8 weeks. Non-anastomotic strictures are harder to manage, often result from HAT or ischemia-reperfusion injury. Some can also be due to primary immune injury. Rarely in pediatrics, casts and stones are seen, but cholangitis remains the most common manifestation along with progressive liver graft scarring.

In adults, 30-50% with BD complications needs re-transplantation. In pediatrics, surgical correction or re-transplantation are rarely needed, and no studies are available about their long tern outcomes. In a recent abstract describing their single center series, J. Seal for the Toronto's group reported that 70% of their biliary complications resolved with endoscopic or interventional radiology interventions, but mortality and re-transplant rates were higher in patients with biliary complications than in ones without (SPLIT meeting 2013).

Immune complications

Late acute rejection (LAR): Although its exact definition is not formalized, it is often referred to as acute cellular rejection over 3 months post-transplant. The incidence of LAR has not changed with current immunosuppression, and it should always raise the question of compliance problems. As opposed to early acute rejection, LAR seems to be associated with a higher incidence of chronic graft dysfunction and loss estimated to be at 50% in some series. It remains

a not well defined and studied entity in pediatrics, and likely the new donor specific antibodies (DSA) and compliance data will shed more light on its immune mechanism and treatment potential.

Chronic rejection (CR): The incidence of CR has declined in most reported adult series from 20% to 3-8%, likely reflecting improved immunosuppressive regimens. In the SPLIT database, CR as defined by ductopenic findings of graft dysfunction, remains at a less than 5% incidence. The highest risk factors for CR are transplantation for CR, immune-mediated primary liver diseases, cytomegalovirus (CMV) infection, and low immunosuppression. In the early phases of chronic liver allograft rejection, there is usually no architectural distortion and the portal inflammation is mild. However, duct damage is usually severe and widespread, with or without bile duct loss. When present, duct loss involves over 50% of the portal tracts, inflammation concentrate around the small BD and more rarely around the central vein usually then with peri-venular hepatocyte dropout, cholestasis and/or hepatocyte ballooning.

Often clinical and histological pictures are not clear cut and CMV and Ebstein Barr virus (EBV) co-infections are often reported in pediatrics, raising the possibility of a causative relationship. Recurrent immune disease (auto-immune hepatitis [AIH], primary sclerosing cholangitis [PSC]) can also cloud the diagnosis and can independently lead to graft failure. Finally, the role of humoral immunity as a cause or complication of CR is gaining momentum.

No codified treatment is currently available for CR. The introduction of tacolimus-based immunosuppression decreased CR's incidence. Newer immunomodulatory agents, inclusive of some that better target the humoral and naïve immune systems, seem to help select patients. Timing of such therapies and the compliance profile, likely play a major role in their effectiveness.

Humoral rejection: Pre-formed and particularly de novo donor human leukocyte antigen (HLA) specific antibodies (DSA), while having not much effect on the incidence of early acute rejection, have now been shown in multiple retrospectively studies, to be associated with a higher incidence of chronic graft dysfunction, CR and graft loss. Emerging prospective data is building up, and helps to better interpret and validate those findings, as well as establishes their clinical relevance in the context of modern immunosuppressive regimens. New data is also now emerging on the possible role of non-HLA antibodies. Pediatric data remains at best scarce.

HLA immunity: Most of the literature on HLA immunity comes from the adult patients. Mazariegos, in a report on attempted immunosuppression withdrawal, found that: patients with negative DSA could be easily weaned off immunosuppression; most patients who failed weaning off immunosuppression were DSA positive [5]. De novo DSA was identified as an independent risk factor for late graft dysfunction and decreased patient and graft survival at 1 year [6]. Evans et al. [7] found a graft survival rate of 68% at 1 year, 45% at 5 years, 31% 10 years with the only predictor of graft loss being DSA positivity. Ekong et al. [8] and Scheenstra et al. [9] reported on the high incidence of liver fibrosis on protocol biopsies, associated with high de novo DSA.

While more reports are coming detailing the association of graft dysfunction with DSAs, we still in large do not know more details about their significance, how graft injury happens in their presence, nor how and when to treat them. This is promising to be one of the hottest topics in liver transplantation this coming decade. As adult studies a fine tuning the incidence and relevance of anti-HLA antibodies, retrospective and prospective studies are needed in pediatrics.

De novo auto-immune hepatitis: De novo AIH was first reported in pediatric liver recipients and remains since more prevalent in the pediatric age group averaging 2.35-6.2% depending on the series [10]. McDiarmid reported a similar incidence from the University of California Los Angeles transplant group; 40% of their patients having isolated anti-nuclear antibody positivity of still unknown significance; patients with de novo AIH were more likely to have experienced rejection and to be still on steroids on long term follow up (AASLD post-graduate

course 2013). The presence of high antinuclear antibody titers (1 : 1,600) was highly associated with progressive graft fibrosis, and children again were more commonly affected than adults [11]. In the SPLIT data, de novo AIH patients are older, females' predominance, more commonly diagnosed with LAR and/or cholestatic rejection, on higher immunosuppression, and more likely to belong to a minority ethnic group [12].

Aguilera et al. [13] showed that some patients with de novo AIH have circulating antibodies to glutathione S-transferase T1, that is present in the graft but not in the donor. Thus, if the graft-damaging immune response seen in de novo AIH is directed against graft rather than host antigens, then this would surely fit the criteria for rejection rather than autoimmune disease. The question of autoimmune, versus allo-immune disorder remains therefore unclear as non-liver directed auto-immune phenomena are also seen more commonly in some of those patients, namely immune cytopenias and hypothyroidism.

De novo post-transplant AIH responds to classical AIH treatment with steroids and purine analogues per most series. Earlier reports had worse outcomes, possibly due to base immunosuppression and late diagnosis, confusing this entity with rejection [10]. For cases where the classical treatment is not possible, Gibelli et al. [14] reports are promising.

RECURRENT DISEASE

Recurrent disease is understandably more frequently reported when protocol biopsies are done. As disease phenotypes are changing with the availability of new medications, particularly in viral hepatitis, the data remains in flux, but continuously improving.

Infectious

Hepatitis C virus (HCV) and hepatitis B virus infections are rare indications for liver transplantation in pediatric age patients in the western hemisphere. Current preventive measures for recurrent disease mirror those in adult experience, and newer antivirals are likely to revolutionizing this field.

Immune liver disease

Recurrent AIH in kids is estimated to be up to 33% in pediatrics, with up to.

Recurrent AIH ranges form 12-46% depending on the immunosuppression used. While its mean time to recurrence is 4.6 years it can be as early as a month post transplant. The diagnosis relies on the typical histologic appearance and positive auto-antibodies. Successful treatment relies on early diagnosis and consists mostly of re-introducing steroids and azathioprin [10]. Death rate in that subgroup of patients is high and approaches 10-11%.

Transplant for PSC remains rare in pediatrics, and data on recurrence is not available. In adults, while recurrent PSC seems to be frequent, it rarely leads to graft lost, but is a diagnostic challenge as has common pathologic and imaging features as CR.

Steatohepatitis

Sutedja et al. [15] examined the post-transplant histology of 39 patients transplanted for cryptogenic cirrhosis who survived for longer than 1 year. Steatosis and steatohepatitis were present in 37.6% of patients (vs. 16.7% in control); 18.8% had moderate steatosis at 1year, and half progressed to cirrhosis at 4 years.

Pediatric data is currently unavailable in this select group of patients. As the obesity epidemic is spreading across borders and age groups, this is likely to become a prime topic of study and focus in the future as more adolescents are meeting criteria for non-alcoholic steatohepatitis advanced liver disease. Clearly this remains a major opportunity for prevention, and liver transplant should be reserved as a last treatment option.

Cancer

More pediatric patients are going through transplantation for hepatoblastoma and other pediatric liver tumors than in the past. This field was revolutionized by a multi-disciplinary approach to these complex patients resulting in fine tuning of peri- and

post- transplant chemotherapy and medical support, and in a better and evolving understanding of the distinct biological behavior of these tumors in pediatric hosts. Long term outcomes for primary transplants are excellent for both patient and graft survival. Caution remains for possible primary tumor recurrence.

KIDNEYS, METABOLIC SYNDROME, AND CARDIO-VASCULAR HEALTH

Renal dysfunction is reported at ~30% in a cross sectional study of SPLIT [16], and the Birmingham's group reported a 15% incidence in their >15 years survivors, likely reflecting different immunosuppressive regimens (AASLD post-graduate course 2013). In addition, it is accepted that albuminuria and decreased GFR independently increase cardiovascular risk. As a result of this data, much effort has been put the last decade to decrease and palliate the risk of kidney injury both short and long term, with the use of less nephrotoxic agents, induction regimens allowing minimization of calcineurin inhibitors exposure, treating hypertension and glomerular hyper-filtration in order to avoid early glomerulosclerosis, and closely monitoring kidney health with implementation of nephron-sparing immunosuppression regimens. Future populations outcomes will judge of the success of these preventive and treatment strategies that seem to be having already great effects on short term kidney outcomes.

The incidence of diabetes is around 10% in pediatric recipients, and is more common in older patients and those with cystic fibrosis. Underlying kidney dysfunction seems in addition to predispose to insulin resistance in most patients, and is revealed often at times of stress or steroids exposure [17]. In a cross sectional data from the SPLIT registry [1-18], obesity was seen in 12% of 461 five year survivors, and hyperlipidemia in 7%. Hyperlipidemia from the same group was at 23% in >10 years survivors, and hypertension was at 20%.

Diabetes, hyperlipidemia and obesity form the basis of the metabolic syndrome; it was shown to be an independent predictor of poor outcomes in heart transplant recipients. In a meta-analysis of liver transplant recipients, Madhwal et al. [19] found that the cardiovascular risk is increased by 64%. The Toronto group shared an abstract at the 2013 SPLIT meeting where they found a 20% incidence of metabolic syndrome in their liver recipients, much higher than the median predicted prevalence of 3.3% in the general population, raising of course concerns about significant cardiovascular risk in the future of those pediatric aged recipients.

Prevention remains the cornerstone of the metabolic syndrome treatment. It includes minimizing steroids exposure, encouraging healthier eating habits, and optimizing physical activity. Looking forward, at least in this arena, the pediatric community has made big thrives. But the obesity epidemic is still reaching our patients, and poses another level of challenge to our community of care.

PREVENTION

More attention is now given across programs to assure that accelerated and updated vaccines are given before transplantation, and to vaccinate patients after transplantation. The Center for Disease Control and Prevention vaccinations guidelines were recently updated, and serve as the guideline for our patients' vaccination regimen [20].

Secondary cancer awareness and prevention is an integral part of post transplantation follow up. Dramatic decrease in PTLD incidence to less than 3% in the pediatric population is likely due to the vigilant EBV viremia monitoring by PCRs and minimization of immunosuppression when possible.

Skin and gynecologic cancer risks are to be emphasized and screened for, in particular in adolescents.

While mostly improved after transplant, nutrition and growth face now the hurdle of the obesity epidemic [1-18]. Vitamin D nutritional deficiency is commonly seen and tends to mirror its incidence in the general pediatric population, reflective of prevalent diet habits.

Sexual maturation and fertility are also noted to be

normal in pediatric liver recipients [21]. Pro-active family planning and contraception are encouraged to all transplant recipients. Special attention needs to be given to prevention of sexually transmitted diseases in adolescents.

Perhaps the single most important prevention move in pediatric liver transplantation over the past decade is a move away from the transplant center-centric care, to an effort to re-integrate the primary care pediatrician in the treating team, assuring a more comprehensive and anticipatory look at the general health of pediatric liver recipients.

CHRONIC FIBROSIS

The emergent reports on silent fibrosis in long term grafts is raising concerns about long term outcomes, in particular in an era of aggressive attempts at immunosuppression minimization.

Desai and Neuberger [11] looked retrospectively at 667 annual protocol biopsies in 335 patients: despite normal liver biochemistry, 49.8% had abnormal histology; only 4.9% had normal histology suggesting poor correlation between liver tests and liver histology. However, in only a minority did the findings result in a change of treatment (usually amending the immunosuppression).

Sebagh et al. [22] showed histologic abnormalities in 80% of 143 patients at 10 years follow up. In 52%, liver tests were normal, suggesting protocol biopsies were justified annually.

Diagnosis of liver graft fibrosis still requires a liver biopsy. The platelet count can be useful as a secondary marker. The aspartate aminotransferase to Platelets Ration Index (APRI) score has a good predictive value for cirrhosis in HCV hepatitis but not for earlier stages of fibrosis. Along with serum markers of collagen (European liver fibrosis and fibro test), and MRI elastography, these tests still need validation in a transplanted graft, but could prove to be useful as non-invasive screens in the future.

Patients transplanted for acute liver failure of indeterminate origin seem to be at higher risk for progressive graft fibrosis than the control group. This finding still needs to be validated in pediatrics, but can prove to be particularly relevant in pediatric age recipients where indeterminate acute liver failure (ALF) predominates in the patients requiring transplantation.

The actual cause of progressive liver graft fibrosis remains unclear, and therefore no treatment can be specifically recommended. Further, of concern is a reported 15% rate of progression to cirrhosis documented over time in some patients [7]. In this single center report on 117 survivors over 15 years, fibrosis was diagnosed in 33% of patients with graft dysfunction. Interestingly, maintenance steroids seemed to have a protective effect, raising the possibility of an immune cause underlying the fibrosis. This is further enforced by experienced improvement in fibrosis found in trials of immunosuppressive withdrawal or minimization, once tacrolimus goal levels were raised.

FOCAL NODULAR HYPERPLASIA

Reports of focal nodular hyperplasia are increasing. They are particularly found in patients with prolonged vascular occlusions, and in those with exposure to chemotherapy. Close follow up for possible portal hypertensive complications is warranted in those patients. In addition, specific imaging techniques and agents are sometimes required for diagnosis. No primary treatment is available.

RE-TRANSPLANTATION

Liver graft survival is currently at 80% at 5 years and 60% at 10 years, resulting in a 1/2 life of a liver of roughly 13 years.

Improved surgical techniques and immunosuppressive regimen clearly improved graft health, but little dent was placed in long term graft outcomes that are likely due to humoral-based immune responses, compliance issues and higher risk recipients. For those patients, re-transplantation remains a viable option when possible.

Re-transplantation incidence decreased from 20%

to 10 % over the years, but is seeing a more recent increase again likely reflecting the adoption of new surgical techniques for transplantation, but also an increased number of pediatric transplant recipients going through adolescence and early adulthood with significant compliance problems.

Survival after re-transplant varies with timing of re-transplant. The Scientific Registry of Transplant Recipients data shows a survival of 61% in re-transplants vs. 85% after first liver transplant. In a single center study, Heffron et al. [23] found comparable 3 year survival rates between those groups.

In a seminal paper reviewing pediatric data from the SPLIT registry, Ng et al. [18] in 2008 identified the following as risks for death after re-transplantation were: <1 year old, donor age increase and high international normalized ratio. In a single center data report, Lao et al. [24] added as death risk predictors: intensive care unit, small recipient, bilirubin >19.

Clearly more work is needed to prevent the need for re-transplantation, but also to improve the health of those candidates, and define the optimum timing for re-transplantation. Of course also, re-transplantation has to reconcile the realities of organ availability and financial hurdles, to optimize its value to the individual patient and society.

IMMUNOSUPPRESSION

The most common causes of death after transplantation remain: malignancy, infection, graft failure, multi-organ failure, and cardio-vascular. They all seem to mostly peak in the second decade post transplantation. They are vastly associated with immunosuppressive medications side effects. So the goal of transplantation in this era is in large to decrease/eliminate the need for immunosuppression therapy in order to achieve a state that best balances graft and host health: functional tolerance.

Many immunosuppressive withdrawal and minimization trials are on the way. Major work is carried also to define tolerance footprints, so to be able to monitor those patients.

The Pittsburgh group reported failure of withdrawal in patients who were younger than 50 years and less than 5 years post-transplant; they found that no rejection in the first post-transplant year seems to be a good marker for success (Oral Presentation SPLIT meeting, Sep 2013). Feng et al. [25] achieved a 1 year functional tolerance in a highly selected group of pediatric recipient of living related liver. Slow withdrawal of immunosuppression was carried only in patients with normal histology, and who were at least 1 year out of transplantation and with no history of rejection in the preceding year. Ongoing monitoring of this successful group is pending, and includes blood immune parameters and liver biopsies.

Liver genes microarrays seem to be more reliable than serum, in predicting tolerance, and Bohne et al. [26] found that mostly iron metabolism gene panels distinguish tolerant from non-tolerant patients.

The withdrawal studies have also shed a light on the presence of sub-clinical inflammation and fibrosis in a subset of patients with normal liver biochemical profiles, prompting the proposal of protocol liver biopsies to better define and understand this problem. Importantly, the very concept of whether withdrawal improves long term outcomes remains debated: while Tryphonopoulos et al.'s data [27] supports a benefit, the Immune Tolerance Network data so far shows none.

Therefore, much needed to advance this field are retrospective disease-specific data and immunosuppressive protocols to pave the ground for prospective work, and the development and validation of immune testing to help guide and tailor therapy. One fact is clear: while we still know little, there is an enormous interest in learning more and from patients to participate. In the meantime, messages of caution for patients enrolled in those trials come from Abdelmalek et al. [28] about long term morbidities.

Despite the fact that this seminal and important work remains too young to be translated in clinical practice, it is clearly promising of a different future for immunosuppressive regimens and monitoring. Tolerance is the ultimate goal in organ transplantation, and the liver as an immunomodulatory

organ in his own rights, might very well be the best organ to allow this goal to come true.

PEDIATRIC LIVER DISORDERS IN ADULTS

A particular challenge emerging from successful pediatric liver transplantation is the survival of patients with disorders that never in the past made it past early childhood. Many of those are actually systemic disorders, and their phenotype is maturing as children are surviving into the second decades post transplantation. Being on the lookout for known and suspected outcomes, but also keeping a pro-active approach for unknown ones is crucial to optimize our patients' long term outcomes and health. Eventually also, updating our adult transplant hepatology peers about such disorders is crucial to help with a successful transition to adulthood.

While patients with biliary atresia, still constituting the majority of pediatric transplant indications, have a liver focused problem, this defers for others: alpha one anti-trypsin, tyrosinemia and other metabolic patients can have primary kidney problems and some have increased immune problems.

Alagille's patients are at risk for kidney disease, primary renal artery stenosis, primary bone disease, pancreatic insufficiency, progressing pulmonary artery stenosis and pulmonary hypertension, progressive retinopathy and vascular anomalies putting them at risk among others for strokes and bleeding.

Cystic fibrosis patients remain at risk for progressing lung disease, severe infection, pancreatic insufficiency, pancreatic and colon cancers.

AIH and PSC patients are at risk for recurrent disease, but also for increased auto-immune disorders affecting other organs, typical of such disorders presenting in the pediatric age. Ongoing monitoring and screening is recommended for those patients.

It became clear that transplant for progressive familial intra-hepatic cholestasis (PFIC 2), while curative for the disease, does trigger a unique form of humoral rejection targeted to the new protein made by the graft.

Children transplanted for liver tumors (particularly if hepatoblastoma) require monitoring for secondary tumors due to innate or chemotherapy induced risk.

Finally, neonatal liver failure requiring transplantation exemplifies the "SPLIT black box", as the vast majority of those patients have no clearly indentified cause for their liver failure. Close monitoring for metabolic and immune anomalies are particularly needed in such recipients.

TRANSITION OF CARE AND ADHERENCE

Perhaps one of the most challenging outcome post pediatric liver transplantation is that of achieving a successful transition into adult care.

Berquist et al. [29] documented a risk of non- adherence up to 50 % of their single center adolescents. Of the 37 non-compliant patients, 6 needed re-transplantation during the study period and 3 died. Shemesh et al. [30,31] reported the strong incidence of post trauma stress disorder (PTSD) in non-adherent SPLIT recipients, and the psychological hurdles to successful transition to adult care in those patients. Diagnosing non-adherence has proven hard till a problem happens. Tacrolimus standard deviation seems to be a helpful marker for non-compliance [32]. Diagnosis factors that increase non-adherence risk like health literacy, PTSD, depression, psychosocial and economic hurdles are crucial to identify and treat. Of course all these factors are a moving target and reassessment, as well as specific interventions and treatment tools need to be readily available. Such an intervention can only be made in a structured multidisciplinary clinic and requires extensive staffing and economic resources.

These adherence factors ironically are the same that can lead to a successful state of health sufficiency that can assure a successful transition to adult care [33]. The preparative work for transition needs to start many years before its due time, and should involve both patient and family. Dedicated multidisciplinary transition clinics have proven so far to be the best forum for a successful and safe transition to adult care. Successful transition implementation includesz early involvement of the adult transplant

hepatologist, follow up after transition with the pediatric team to review the process including the risk of not taking medications, simplifying medication regimen, counseling and support groups, and preferably an involved primary care physician.

While work continues to consolidate and implement these principles in most pediatric transplant programs, there is a need for a specific multi-center data base to capture those young adults transitioning care to better track their outcomes and challenges.

QUALITY OF LIFE

Quality of life (QOL) matters. Liver transplant has proven to be a life-saving operation. We now have the luxury to explore QOL as an ultimate goal.

In and analysis of the United Network for Organ Sharing database Huda et al. [34] found that only 1/4 of adult recipients are employed. This is in contrast to recent pediatric data from Birmingham showing that the majority of their pediatric recipients are in school or working, drawing some attention to geographic and societal as well as age differences.

Burra et al. [35] looked at adherence post liver transplant in both adults and children in a center cohort: non-adherence to drugs was 15-40%, and to clinic appointments 3-47%. In addition non-adherence in pediatrics was 4 times higher than in adults. Risk factors in adults were high cost, psych disorders and side effects, conviction that medications are harmful. Risk factors in pediatrics were psychological distress, family functional status, and impact of medications on their physical appearance.

Limbers et al. [36] looked at health related quality of life (HRQOL) in pediatric transplant recipients compared to other chronic disease groups. He found a similar HRQOL to children s/p renal transplant and cancer treatment in remission, better HRQOL than kids on dialysis except for school functioning, worse HRQOL than kids with type 1 diabetes except for emotional functioning. The study concluded that liver transplant recipients manifest impaired HRQOL and face ongoing challenges that warrant monitoring and indicate a need for interventions to improve their HRQOL.

Mohammad et al. [37] looked at health status in young adults 2 decades after SPLIT (1988-1992): 85/171 patients were alive, 56 were contacted, with a response rate of 66%. Of those who answered, 62% attended college, and 80% of those older than 23 years were employed. Patients had lower HRQOL than non-liver transplant age matched controls. Patients' health utilities were lower than normal and correlated with unemployment and hospitalizations. The authors concluded that physical and psychological sequelae continue to affect health status up to 2 decades post liver transplant.

Sorensen et al. [38] examined cognitive and academic outcomes after SPLIT. In 144 kids over 2 years post liver transplant enrolled in the SPLIT study group: 26% (vs. 14 expected) had mild to moderate intelligence quotient (IQ) delays (in 71-85 range), 4% (vs. 2% expected) had serious IQ delay (<70), reading and math score were weaker than IQ in 25% (vs. 7%) suggesting learning disabilities, executive deficits were also noted.

Based on the available data we clearly have ways to go to improve ultimate QOL and function of SPLIT survivors. Improving medical and general health outcomes will obviously help achieve this goal. Disease-specific HRQOL instruments will likely help map the road for us. Identifying and palliating to the cognitive, and socioeconomic hurdles remain crucial interventions and hold true across societies and systems of health care delivery.

CONCLUSION

While there is still a lot to conquer in transplantaion in scientific and medical knowledge, the real pressing cornerstones of care are: better management of our current treatment tools to avoid and treat toxicity, and adressing psycho-social and economic hurdles that affect every aspect of long term outcomes, through poor compliance and/or poor access to care.

Long term outcomes after pediatric liver transplantation are the true new frontier in this ev-

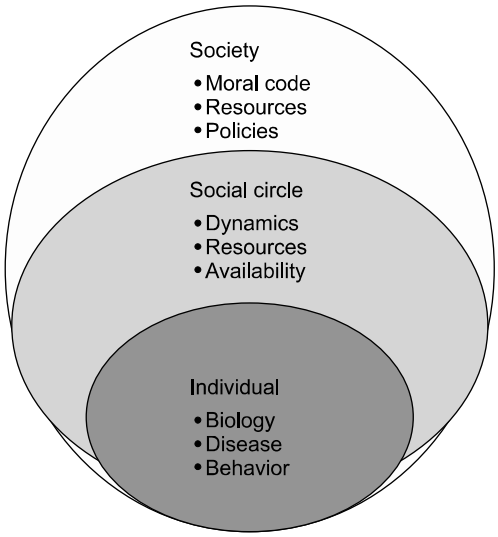

Fig. 1. The vulnerable population model: chronic life-long disease with both controllable and un-controllable elements.

er-evolving field. They will no doubt improve as we as a community: 1) Accept the fact that liver transplantation is a chronic disease state, no matter how healthy and functional our recipient patients are–we should therefore be cognizant to use the Chronic Care Model of health care delivery along the Institute Of Medicine rules of redesign; 2) Adopt upfront a model of health care delivery along the Ohio State Project 4 model: predictive, personalized, preventive and participatory; 3) Build a system around our patients that accommodate their state as a "vulnerable population" public health model, allowing us to address not only patient-based but social circle- and society-based issues relevant to their care (Fig. 1).

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