



# **Report on Growth and Development in Pediatric Transplantation of the Kidney, Liver, and Heart**

**Prepared by the EMMES Corporation**

January 22, 2002

**Contacts:**

Robert E. Gore-Langton, Ph.D.

Rebecca A. Enos, M.P.H.

# Table of Contents

<b>EXECUTIVE SUMMARY .....</b>	<b>5</b>
<i>Introduction.....</i>	<i>5</i>
<i>The literature review.....</i>	<i>6</i>
Renal.....	6
Liver .....	7
Heart .....	9
<i>Recommendations.....</i>	<i>10</i>
General recommendations for cognitive research.....	10
Specific recommendations for growth, cognitive, and psychosocial research .....	13
Kidney: growth studies.....	13
Kidney: cognitive studies.....	14
Kidney: psychosocial studies.....	16
Liver: growth studies.....	18
Liver: cognitive studies.....	19
Liver: psychosocial studies.....	25
Heart: growth studies.....	27
Heart: cognitive studies.....	28
Heart: psychosocial studies.....	30
<b>INTRODUCTION.....</b>	<b>33</b>
<b>I. GROWTH LITERATURE REVIEW AND RECOMMENDATIONS.....</b>	<b>36</b>
<i>Growth: Some notes on terminology.....</i>	<i>36</i>
<i>Growth: Kidney.....</i>	<i>37</i>
Pre-transplant risk factors for growth impairment and strategies for growth improvement.....	38
Catch-up growth following renal transplantation.....	39
rhGH therapy and the GH/IGF axis .....	41
Impact of renal function on growth.....	47
Steroid use and alternative immunosuppression protocols.....	47
Other risk factors for impaired growth following renal transplantation.....	53
Pediatric renal transplant recipients compared to pediatric cardiac and hepatic transplant recipients .....	54
Summary (Kidney – growth).....	54
Recommendations from the panel of experts (Kidney – growth) .....	55
Recommendations from expert-selected studies from the literature (Kidney – growth).....	56
Clinical recommendations based on individual studies (Kidney – growth).....	59
<i>Growth: Liver.....</i>	<i>61</i>
Pre-transplant risk factors and strategies for growth improvement.....	61
Catch-up growth following liver transplantation .....	62
rhGH therapy .....	63
Steroid-sparing strategies.....	63
Summary (Liver – growth).....	65
Recommendations from the panel of experts (Liver – growth) .....	65
Recommendations from expert-selected studies from the literature (Liver – growth).....	66
Clinical recommendations based on individual studies (Liver – growth).....	66
<i>Growth: Heart.....</i>	<i>66</i>
Catch-up growth following heart transplantation.....	66
Steroid-sparing strategies.....	67
Summary (Heart – growth).....	68
Recommendations from the panel of experts (Heart – growth) .....	68
Recommendations from expert-selected studies from the literature (Heart – growth).....	69
Clinical recommendations based on individual studies (Heart – growth).....	69

## II. COGNITIVE DEVELOPMENT LITERATURE REVIEW AND RECOMMENDATIONS.....70

### GENERAL RECOMMENDATIONS ON METHODOLOGY .....70

Three-pronged approach .....	70
Choosing measures .....	71
Learning Disabilities.....	73
Use of sibling controls – some caveats .....	74
Comparisons across kidney, liver, and heart transplant patients .....	74
<i>Cognitive development: Kidney</i> .....	75
A note on acronyms, technical terms, and standardized measures.....	75
Introduction .....	75
Factors in ESRD affecting cognitive development .....	76
Does renal transplantation lead to improved cognitive development? .....	76
Specific cognitive abilities affected by uremia .....	80
Neurological sequelae of uremia/transplantation .....	82
School achievement among pediatric renal transplant recipients.....	83
Summary (Kidney – cognitive development) .....	84
Recommendations from the panel of experts (Kidney – cognitive development).....	85
Recommendations from expert-selected studies from the literature (Kidney–cognitive development) .....	86
Clinical recommendations based on individual studies (Kidney – cognitive development) .....	87
<i>Cognitive Development: Liver</i> .....	88
A note on acronyms, technical terms, and standardized measures.....	88
Pre-transplant cognition.....	88
Neurological sequelae.....	90
Overall cognitive functioning after liver transplantation .....	90
Risk factors.....	94
Specific cognitive abilities .....	96
Hearing loss .....	97
School achievement.....	97
Summary (Liver – cognitive development) .....	98
Recommendations from the panel of experts (Liver – cognitive development).....	99
Recommendations from expert-selected studies from the literature (Liver – cognitive development) .....	104
Clinical recommendations based on individual studies (Liver – cognitive development) .....	106
<i>Cognitive Development: Heart</i> .....	107
A note on acronyms, technical terms, and standardized measures.....	107
Introduction .....	107
Do pediatric heart transplant recipients have normal neuro/cognitive development? .....	107
Specific cognitive abilities in pediatric heart transplant recipients .....	110
Does pediatric heart transplantation lead to improved cognitive capability? .....	111
School achievement.....	112
Factors in pediatric heart disease and transplantation affecting cognitive development.....	113
Summary (Heart – cognitive development) .....	118
Recommendations from the panel of experts (Heart – cognitive development) .....	119
Recommendations from expert-selected studies from the literature (Heart – cognitive development).....	120
Clinical recommendations based on individual studies (Heart – cognitive development) .....	121

## III. PSYCHOSOCIAL DEVELOPMENT LITERATURE REVIEW AND RECOMMENDATIONS.122

<i>Psychosocial development: Introduction</i> .....	122
<i>Psychosocial development: Kidney</i> .....	123
A note on acronyms, technical terms, and standardized measures.....	123
Introduction .....	123
Psychosocial adjustment .....	123
Psychiatric adjustment and behavior.....	125
Body image, self-esteem and non-compliance.....	126
Social interaction .....	127
Quality of life.....	128

Rehabilitation.....	128
Family structure and environment .....	128
Theoretical models.....	129
Incorporation of foreign organ.....	130
Summary (Kidney – psychosocial development).....	130
Recommendations from the panel of experts (Kidney – psychosocial development).....	130
Recommendations from expert-selected studies from the literature (Kidney – psychosocial development) .....	131
<i>Psychosocial Development: Liver</i> .....	<i>133</i>
A note on acronyms, technical terms, and standardized measures .....	133
Introduction .....	133
Psychosocial adjustment .....	133
Psychological/Psychiatric adjustment and behavior .....	133
Body image, self-esteem and non-compliance.....	134
Social interaction .....	134
Quality of life.....	134
Rehabilitation.....	135
Family structure and environment .....	136
Incorporation of foreign organ.....	136
Summary (Liver – psychosocial development).....	136
Recommendations from the panel of experts (Liver – psychosocial development).....	137
Recommendations from expert-selected studies from the literature (Liver – psychosocial development) .....	138
<i>Psychosocial development: Heart</i> .....	<i>140</i>
A note on acronyms, technical terms, and standardized measures .....	140
Introduction .....	140
Psychosocial adjustment .....	140
Body image, self-esteem and non-compliance.....	145
Family structure and environment .....	147
Other risk factors .....	150
Summary (Heart – psychosocial development) .....	152
Recommendations from the panel of experts (Heart – psychosocial development).....	152
Recommendations from expert-selected studies from the literature (Heart – psychosocial development) .....	154
Clinical recommendations based on individual studies (Heart – psychosocial development) .....	154
<b>APPENDIX A – GLOSSARY OF ACRONYMS AND TECHNICAL TERMS .....</b>	<b>156</b>
<b>APPENDIX B – STANDARDIZED MEASURES FOR ASSESSMENT OF COGNITIVE ABILITY AND ACHIEVEMENT .....</b>	<b>161</b>
<b>APPENDIX C – STANDARDIZED MEASURES FOR ASSESSMENT OF PSYCHOSOCIAL FUNCTIONING .....</b>	<b>192</b>
<b>REFERENCES .....</b>	<b>214</b>

# Report on Growth and Development in Pediatric Transplantation of the Kidney, Liver, and Heart

Prepared by the EMMES Corporation

January 22, 2002

---

## Executive Summary

### INTRODUCTION

Medical strides in solid organ transplantation, begun in adults in the 1950s, were extended to the pediatric population in the mid-1960s. In the early 1980s, survival among pediatric organ recipients was greatly enhanced with the development of more effective immunosuppression, particularly in the form of cyclosporine in 1983. The great strides toward resolving short-term, medical problems, such as organ rejection soon after transplantation, led to increased focus on long-term, less biomedical issues. Thus, as more of these children survived for longer periods, with many entering adulthood, investigators began to turn their attention to the growth and developmental challenges faced by pediatric recipients of solid organ transplants.

Whereas the research on growth in pediatric recipients of solid organ transplants is quite strong and extensive, the research on cognitive and psychosocial development still has many gaps and various methodological deficiencies. A summary of what has been accomplished in the research and what still needs accomplishing is provided in the “Literature Review” section, below. Specific recommendations for future studies are provided in the following section.

A panel of experts guided the progress of the literature review, which covered all relevant publications for the period 1966–2001:

- *Richard N. Fine, M.D.*, Professor and Chairman in the Department of Pediatrics at Stony Brook Health Sciences Center, State University of New York at Stony Brook, New York. One of the two main experts on the report, Dr. Fine oversaw the prioritization of published studies for the kidney and heart sections of the report, provided valuable literature analysis, and developed recommendations for further research.

- *Estella M. Alonso, M.D.*, Associate Professor of Pediatrics, Medical Director of Liver Transplantation, Children’s Memorial Hospital, Chicago, Illinois. One of the two main experts on the report, Dr. Alonso oversaw the prioritization of published studies for the liver and heart sections of the report, provided valuable literature analysis, and developed recommendations for further research.
- *Janet E. Fischel, Ph.D.*, Director, Division of Development & Behavior and Associate Professor of Pediatrics and Psychology, State University of New York at Stony Brook, New York, provided extensive input from the developmentalist’s perspective.
- *John C. Bucuvalas, M.D.*, Associate Professor of Pediatrics and Associate Medical Director of Liver Transplantation, Children’s Hospital Medical Center of Cincinnati, Ohio, provided additional commentary on issues related to pediatric liver transplantation.

Methodological merit of the studies was considered throughout the literature review and recommendation development process. More emphasis was given to studies that were prospective, long-term, controlled, and/or of larger sample size, as opposed to retrospective, short-term, uncontrolled, cross-sectional, and/or of small sample size. Sources of potential confounding or bias were also deliberated.

## **THE LITERATURE REVIEW**

### **Renal**

Growth in children with end-stage renal disease (ESRD) and kidney transplants has improved over the past decade. Treatment advances include ensuring adequate nutrition, minimizing steroid dosage in all recipients, and administering recombinant human growth hormone (rhGH) to the most growth-retarded recipients. Of all clinical interventions, transplantation in children before six years of age has the greatest beneficial effect on subsequent statural growth. Still, a large number of kidney recipients do not go on to reach their ideal adult height.

Two areas of active investigation are addressing this continuing problem in kidney transplantation. The first is “steroid-sparing strategies”, in which immunosuppressive steroids are withdrawn or replaced by alternative drugs with fewer side effects. The second is recombinant human growth hormone (rhGH) therapy to promote growth in growth-retarded children. The effectiveness of rhGH therapy is now reasonably well established. However, more research is needed to determine which long-term drug regimens both preserve functioning of the transplanted organ and allow normal statural growth of the child. Attainment of adult height, not just growth velocity, needs to be followed in these studies.

Historically, children with kidney transplants have scored lower on tests of intelligence than healthy children. Recent findings, however, suggest that today’s children with kidney transplants may be able to achieve a level of cognitive functioning near or at the level of healthy children. This success is in large part due to medical advances that have mitigated the impacts of kidney disease on cognition. Perhaps the single most important clinical

advancement promoting cognitive development is transplantation itself, particularly when performed early on in the course of kidney disease. Indeed, it has been established that one of the major contributors to impaired mental development in children with kidney disease is early onset of disease and longer duration of disease.

In the wake of improvements in the management of kidney transplant patients, well-controlled, long-term studies are now needed to assess the true cognitive status and progress of today's transplanted children. In particular, a need persists for in-school screening for learning disabilities using achievement testing. Studies are also needed to identify the specific types of cognitive domains most vulnerable to the effects of kidney disease, and thus most amenable to correction by transplantation. It is still uncertain whether kidney disease has a global impact on cognitive ability, or whether its effects are specific to definable neurodevelopmental domains. Additionally, the presence of brain lesions in children who were transplanted for nephrotic syndrome is a recent finding warranting future study.

Renal transplantation in children is associated with better psychosocial outcomes and rehabilitation than other modalities of treatment, i.e., continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis (HD). However, substantial evidence in the literature indicates that children with kidney transplants experience delayed social development, maladaptive problems, and increased psychiatric problems. In particular, the physical effects of illness and treatments contribute to low self-esteem, which is a major factor in noncompliance with maintenance medications. Measures of communication, daily living skills, and socialization are also well below healthy norms. Since these deficits occur regardless of graft function, even children with functioning transplants can be expected to continue to show developmental delays.

Because of methodological weaknesses in the current literature, future psychosocial studies of kidney transplant recipients need to include sibling and matched healthy control groups, longitudinal studies, larger and more representative samples, appropriate age groups, and better description of measures and variables. These needs are common themes in this report, and apply equally well to developmental domains for all solid organ transplants. In addition, the role of the family environment in psychosocial adjustment requires clarification due to inconsistencies across studies and diseases.

## **Liver**

Growth failure in end-stage liver disease (ESLD) is also recognized as a significant problem, especially at ages of less than five years. Severe malnutrition is one important contributing factor that may be preventable by liver transplantation, depending on the specific disease. Growth may initially worsen after transplantation, but catch-up growth begins during the second 12 months post-transplantation. Nevertheless, sub-normal height indicated by negative standardized height scores may persist for many years. Several studies suggest there has been an increase in the percentage of liver transplant patients showing catch-up growth. Improvements in growth have been achieved with steroid withdrawal or discontinuation and by supplemental use of rhGH therapy. Liver transplant

patients appear to have greater growth potential than kidney patients, especially after steroid withdrawal.

Further growth-related studies in liver transplant recipients are needed to establish the optimal window for steroid withdrawal. Other studies are needed to address the effects of liver transplant or late loss of kidney function on pubertal growth.

Much of the research relevant to a modern assessment of cognition in pediatric liver recipients centers on three studies only, albeit good studies. Cognitive and developmental delay appear to be common in this population, yet specific risk factors have not been clearly identified. It is still unclear whether cognitive delays are the result of having experienced severe illness in infancy in general, or are attributable to liver disease specifically. Visual-spatial deficits do appear to be a problem in children with liver transplants, with motor abilities generally not a problem. Outside of these findings, specific deficits have yet to be pinpointed. Only one major study has examined academic achievement in these children. This study has suggested that underachievement and learning disabilities are more prevalent in children with liver transplants than in healthy children.

What particularly bears further investigation, however, is the observation that the mental abilities of children with liver transplants tend to improve over time. Whereas studies with only short-term follow-up have noted deterioration in mental ability, studies with longer-term follow-up have found that mental ability improves several years after liver transplantation. Thus, long-term studies are needed to determine the true path of intellectual and scholastic progress in children who have undergone liver transplantation. These studies must use healthy controls to ascertain whether or not problems in the transplanted population are any worse than problems in the normal population. Children with other transplants could also be used as controls to identify organ-specific cognitive problems.

Psychosocial assessments after liver transplantation show that up to 50% of children have adverse psychological reactions. In addition, greater than 50% of children have behavioral or emotional disturbances. Moreover, psychosocial problems tend to be greater for liver than for kidney transplant patients. One possible factor in this difference is a greater concern over body image by adolescents with liver transplants. Liver transplantation is also associated with more depression and anxiety and a lower parent-reported quality of life (QOL) than in other chronic illnesses.<sup>1-3</sup> Although a majority of families of children with liver transplants show normal functioning, they still have significant sibling and marital problems. Recent studies suggest most liver transplant children are attending school and lead a “normal life”.

Additional psychosocial studies in the pediatric liver transplant population are needed to identify risk factors for psychological problems, to study post-traumatic stress disorder (PTSD), and to investigate child and family QOL in long-term studies. Methodological recommendations include the continued use of validated QOL measures (as seen in recent years), further use of longitudinal study designs, and development of multi-center studies.



## Heart

Growth outcomes in pediatric heart transplantation have been encouraging in recent reports. These studies report growth within the normal range and indicate expectations of “normal childhood development”. Favorable growth appears to be the result of eliminating chronic steroid treatment in a large majority of patients, and transplanting at an early age to avoid poor preoperative growth. Some reports have suggested that delayed linear growth may be less of a problem for heart recipients than liver or kidney recipients. However, this may be related to the dichotomy of ages at which children receive heart transplants for congenital and acquired heart disease. Heart recipients transplanted as infants (for congenital heart disease) or as older children (for acquired heart disease) would be expected to largely avoid the growth-retarding effects of disease during their most critical developmental years. Further studies are needed to identify risk factors for delayed growth associated with congenital vs. acquired heart disease.

Too few studies exist on the cognitive functioning of pediatric heart transplant patients for any firm conclusion to be made about their cognitive outcome. It does appear that these children do not demonstrate gross delays in mental or psychomotor development. Despite having normal scores on tests of intelligence and development, however, their scores are still lower than those of healthy children, or children who have had other cardiac surgery.

Heart transplantation has not yet been shown to lead to either improved or worsened cognitive function in children. Studies performed in children with cyanotic heart disease, however, consistently show that chronic cyanosis (low blood oxygen) is associated with progressive cognitive impairment. On the other hand, earlier correction of cyanotic heart disease leads to more favorable cognitive outcome.

Further studies are needed to determine the true course of cognitive development and scholastic progress in pediatric heart transplant patients. It is unknown whether the observed slight delays persist over time, or even worsen as suggested by some findings. Further study is also needed to corroborate findings that younger patients have more developmental delays. With respect to cyanosis, the cognitive impacts of two factors warrant further study. These are cyanosis due to heart disease, and hypoxia (low oxygen in the various body tissues) during heart transplant surgery due to induced profound hypothermic circulatory arrest (PHCA). Studies should use controls and have long-term follow-up, extending from the pre-transplant period into adolescence.

Pediatric heart and heart/lung recipients and their families appear to have significant problems related to psychosocial function. Existing data suggest that psychological distress in pediatric heart transplant recipients is lower than pre-transplant levels after at least 12 months have passed following transplant. Nevertheless, a significant proportion of recipients (20-24%) continue to experience psychological distress and exhibit behavioral problems following transplantation. Global quality of life (QOL) has not been carefully studied in this population.

The emotional well being of children and adolescents proceeding through the pediatric heart transplantation experience demands further study. Outcomes with longer follow-up are

needed to assess compliance over time and to identify potential interventions. Furthermore, family functioning while waiting for an available organ should be optimized to ensure good psychological outcome in the pediatric heart transplant candidate. Research on psychosocial functioning and quality of life in these children must also include as its explicit aim the solutions for identified problems. Determination of the relative amount of distress suffered by these children awaits further longitudinal, long-term studies using healthy controls.

A glossary of technical terms and acronyms appears in Appendix A to this report. Appendices B and C provide, in tabular format, descriptions of the various standardized tests that have been used to measure cognitive and psychosocial functioning in pediatric transplant patients. These tables present the variables measured by the tests, appropriate age ranges, and the frequency and currency of test use.

## RECOMMENDATIONS

### General recommendations for cognitive research

An array of measures across “general” IQ, achievement, neuropsychological processing abilities, and attention are likely to provide the most valuable information to an examination of the cognitive health of transplant recipients. (Note: “Measures” are questionnaires or multi-item, paper- or computer-based tests used in patient evaluation.) Study development in the cognitive arena of transplantation deserves a *three-pronged approach*, defined by three different types of evaluation tools: IQ measures, achievement measures, and neuropsychological measures.

The combination of data from neuropsychological, IQ, and achievement testing of children would paint a much more detailed picture of their strengths, deficits, and age-appropriate skills than the scores from any one type of test alone. For example, IQ testing alone will not uncover scholastic abilities or deficits that achievement testing may be able to detect. Indeed, children with learning disabilities have lower achievement than would be expected based on their IQ.

The three major types of measures are discussed below:

- i. *IQ measures*: IQ tests, which measure global intelligence, should have well-documented standardization, validity, and reliability; standard score results, which allow comparability across a wide age range; and, preferably, subscales for comparisons between different parts of different tests. Examples are the multi-component Stanford-Binet IV test, Wechsler series, and Bayley Scales of Infant Development. (Note: The “validity” of measures is established when their use is deemed applicable in a particular subpopulation, such as chronically ill children.)
- ii. *Achievement measures*: Achievement measures, which measure scholastic/academic aptitude in such subjects as math, reading, and writing, should also have well-documented standardization, validity, and reliability, as well as standard score results for comparability across samples and age or grade levels.

- iii. *Neuropsychological measures:* Neuropsychological measures are usually batteries of tests used to assess a variety of specific psychological, neurological, and cognitive domains. They should have known reliability and validity, and should be able to tap a relatively broad spectrum of abilities, including memory, visual, motor, spatial, language, and attention skills, as well as appropriate cross-modal abilities.

Substantial changes in the medical management of children with renal, liver, and heart problems have rendered the findings of many “earlier” studies less relevant and have resulted in a shifting baseline of cognitive ability. This shifting baseline complicates the analysis of cognitive impact. Further complicating the analysis are the logistical difficulties involved. These difficulties include the repetitive, time-consuming nature of cognitive testing and the tendency of patients to change treatment groups, an important independent variable.

The **identification of key measures** essential to a comprehensive, sensitive evaluation of cognitive impact is clearly not yet a completed task. Given the relatively small sample sizes in transplant research, developing new measures and psychometrically validating them do not seem to be top priorities. It should also be noted that studies should employ standardized tests over screening tests or abbreviated assessments. These latter tests do not provide standardized, quantifiable data that can be compared among children.

Beyond IQ testing, it is not likely that a single test measure can cover such a broad age spectrum as to dismiss the need for transitions from test to test. This problem is addressed by using standard scores, which take into account age, and statistical techniques that determine the relative contributions of various factors to one or more outcomes of interest. In other words, standardized scores and statistical techniques allow investigators to compare the performance of children across different tests and ages.

It is understandable that investigators would want to reduce the number of tests used in studies to a set that is likely to both assess cognitive ability and yield scores comparable across studies. However, since the interactions among cognitive, behavioral, and psychosocial realms are yet far from clear in the existing literature, they deserve continued attention with – necessarily – a variety of instruments.

Moreover, the field is complex. Intellectual and psychosocial aftereffects (called “sequelae”) are not likely to unfold in neat pathways responsive to a small set of measures, especially considering that a good deal of the existing research has included samples that are small from a statistical perspective. The presence of less obvious intellectual problems may indeed necessitate casting a wider net in the area of standardized testing. Use of single measures may not detect certain problems.

Measures should be chosen to allow comparisons of scores across different ages and developmental stages. An optimal way of achieving comparability is to work with instruments that have been adequately standardized, so that standard scores become the measures of interest. For assessments of global intelligence, an essential set of instruments

for across-age and across-study comparisons of IQ scores is found in the Wechsler series of tests (WPPSI, WISC III, WAIS) and the Stanford Binet test (age 2 to adult).

Since cognitive progress tends to change over time, as shown in the literature, ample follow-up time is needed for studies to pick up lasting effects, not simply transient ones. Therefore, measures should be used that can be repeated without the occurrence of test-retest inflation (a phenomenon in which children perform better on a retest because of practice, not because of real cognitive improvement.) Again, to allow effective comparisons, these tests should be normalized with standard score results.

Additionally, **healthy controls** must be used in these long-term studies to prove that intellectual improvement after transplantation does not occur simply as a result of the progression of time and age. Particularly useful are those controls that account for environmental or even genetic characteristics affecting IQ. Children with other solid organ transplants could also be used as controls to identify organ-specific cognitive problems or risk factors.

**Sibling controls** offer an excellent strategy for controlling for environmental and hereditary factors in studies. One should take care, however, to counterbalance siblings older and younger than the child undergoing transplantation. Additionally, larger family size has a negative impact on IQ, with later children having decreases presumably related to parental/adult resources available. The family size-IQ relationship is more remarkable in lower-SES families than in higher-SES families. It also should be noted that even the best IQ heritability research, research using monozygotic twin samples, is still correlational in nature.

In studies evaluating transplanted children for **learning disabilities**, consideration should be given to language receptive and expressive skills. Too few studies have actually examined the connections between emerging language ability in the very young child, and later learning disability in the school-age child. Furthermore, this research must distinguish between different definitions of learning disability. Typically, schools define learning disability as a gap between IQ and tested achievement, while medical practitioners may diagnose learning disability using a neuropsychological test battery. It should also be remembered that school grades and progression through school are not good indicators of intellectual ability or achievement of skills/knowledge. Performance on nationally standardized achievement tests provides a better measure of scholastic progress. Examples of such tests are the California Achievement Test, Stanford Achievement Test, and the Wide Range Achievement Test.

A final, general consideration would be to consider using the three transplantation groups represented in this report as **comparison groups** – kidney, liver, and heart pediatric transplant patients. Armed with the findings accumulated in the report, there might be benefit to using these groups as comparisons for one another. One goal of such comparison would be determining any similarities and differences they may have in their patterns of cognitive developmental delay.

## Specific recommendations for growth, cognitive, and psychosocial research

Organ-specific recommendations resulting from the literature review are provided below. The “Recommendations from the panel of experts” are those that have been formulated by the panel of experts assembled for this literature review. The “Recommendations from expert-selected studies from the literature” are recommendations either made by the actual authors of individual, important studies, or based on their findings.

### Kidney: growth studies

#### *Recommendations from the panel of experts (Kidney – growth)*

- Further investigate the safety and efficacy of **non-steroidal immunosuppressive drugs** in studies with long-term follow-up. Studies on tacrolimus, for example, should follow children longitudinally for up to 10 years post-transplant at least.
- Initiate formal studies with several years’ follow-up to investigate the potential for **alternate-day steroid use** to increase the risk for **graft deterioration**. Investigate the possibility that increased graft rejection under an alternate-day regimen is due to decreased compliance with medications, which in turn may result from the patient’s discouragement at not perceiving immediate beneficial effects. Children initiating this new regimen may start out with unrealistically optimistic hopes for growth enhancement, then stop medications in discouragement when they do not perceive immediate height gains or stoppage of other side effects.
- Perform studies to determine why pediatric **liver and heart** transplant recipients withdraw from steroids **more successfully** than pediatric **kidney** transplant recipients do.
- Further investigate ways to allow **steroid avoidance or withdrawal**, with avoidance the best option for optimizing growth.
- Further investigate the role of steroids in stimulating **erythropoiesis** (red blood cell production), and risk for **anemia** under non-steroidal immunosuppression regimens.
- Investigate the possibility that **recombinant human growth hormone (rhGH)** therapy is needed **during puberty** to improve the pubertal growth spurt.
- Further investigate the **safety of rhGH therapy**.
- Gather more data on **final height attainment under rhGH therapy** (i.e., follow up children under rhGH therapy until they reach their adult height).
- Establish a methodology to **determine genetic target height**. Target height should reflect or be similar to the 50<sup>th</sup> percentile for mid-parental height (i.e., the average of the heights of the two parents). Growth curves, which do not use mid-parental height, do not take into account the child’s genetic height potential.

*For example, if a child attains a final adult height in the 10<sup>th</sup> percentile for height, and the average of his two parents’ heights is in the 10<sup>th</sup> percentile for height, that child would be considered stunted according to the standard*

*growth curves. However, the child would really have attained his/her true, genetic target height. On the other hand, if the average of the parents' combined heights is higher than the 10<sup>th</sup> percentile, then that child would be considered to have achieved sub-optimal final adult height.*

## **Kidney: cognitive studies**

### ***Recommendations from the panel of experts (Kidney – cognitive development)***

Implement studies to identify what cognitive and academic gains are made by children undergoing renal transplantation. Studies should have the following characteristics:

- **Healthy controls. Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. Use of matched, healthy controls in addition to sibling controls would be ideal. *(Note: Please see discussion of sibling controls under “General recommendations for cognitive research”.)*
- **Multi-center with large sample size.**
- **Longitudinal, with long-term follow-up** into at least the late school age years (achievement testing typically does not begin until age 8, or grade 2).
- **Neuropsychological evaluation, school achievement testing, and intellectual assessment.**
- **Numerous, serial measurements** of intelligence and neurodevelopmental capabilities taken well before transplantation as well as after. Measurements should begin at onset of chronic renal insufficiency (CRI) very early in life, then continued through initiation of conservative management, through end-stage renal disease (ESRD), and through to several years post-transplantation.
- **Younger** sample (transplanted < 5 years old), including early infancy.  
*(Note: Younger children are most vulnerable to uremia's deleterious effects on the developing brain. Moreover, their outcomes are more representative {and optimistic} than the outcomes of older children, who have not experienced as many benefits from modern advances in patient management {e.g., tube feeding at early age}.)*
- **Consistent use of instruments** across centers for assessing cognitive performance.
- Use of **instruments permitting comparison among different developmental stages.** The Wechsler series of IQ tests (the WPPSI, WISC III, and WAIS) and the Stanford Binet (age 2 to adult) allow this cross-stage comparison in assessments of global intelligence. Screening tests (e.g., the Denver Developmental Screening Test) and developmental schedules (e.g., the Gesell schedules) are not comparative in standardization.
- Use of **instruments** that can accurately measure **specific neurocognitive deficits** in children with renal disease.

- **Correlation** of clinical/ biomedical findings with cognitive outcomes (e.g., effect of reduced renal function on memory)
- **Multi-factorial analysis** using multiple regression to examine cumulatively and interactively the variety of factors with potential impact on cognitive ability (i.e., both clinical and psychosocial alike). When determinants of outcome are likely to be multi-dimensional, regression designs that ask what variables contribute with what impact, in order to best predict outcomes of interest, are more useful than univariate analytic techniques.
- Examination of effects of **different treatment modalities** on cognitive development. An example of this type of study would be an examination of the effects on cognition of drug therapy that reduces cysteine levels.
- Examination of **disease subtype** as a risk factor.
- Examination of **cyclosporine A and tacrolimus** as risk factors.

*Recommendations from expert-selected studies from the literature (Kidney – cognitive development)*

- Administer **cognitive and achievement testing** to pediatric patients with chronic renal failure on a regular basis, since school grades and progression through school do not reflect real math and language deficits that are otherwise detectable through achievement testing.<sup>4</sup>
- Further investigate the timing of development of **ischemic lesions** in the brain's watershed areas (areas between major vascular territories of brain) pre- and post-transplant.<sup>5</sup> This recommendation may be specific to nephrotic syndrome.
- Look at possible attenuation of beneficial effects by **neurotoxicity of cyclosporine (and tacrolimus)**.<sup>6</sup>
- Investigate the prevalence and etiology of **sensorineural hearing loss (SNHL)** among pediatric renal patients.<sup>5</sup>
- Investigate impact of various treatment modalities on cognitive abilities of children with infantile **nephropathic cystinosis**, and clarify the origin of cognitive deficits in cystinotic children.<sup>7</sup> Determine whether or not they have an isolated problem with spelling.
- Investigate the possible **neurotoxic** effect of the following on IQ and/or the brain of pre- and post-transplant **cystinotic** children:
  - progressive cystine accumulation in the brain
  - cysteamine and phosphocysteamine medication
  - psychosocial difficulties
  - presence of a closely linked gene<sup>7</sup>

*(Note: CTNS, a gene mutated in nephropathic cystinosis, was identified by Town et al in 1998.<sup>8</sup> It is possible, however, that another closely linked gene could be associated with the neurotoxic effects seen in cystinotic patients.)*

- In addition to measures of global intelligence, use **more specific tests for measuring cognitive ability** in pediatric renal patients. Measures of global intelligence are likely not specific enough to differentiate between the cognitive effects of different treatment modalities.<sup>9</sup>

## **Kidney: psychosocial studies**

### ***Recommendations from the panel of experts (Kidney – psychosocial development)***

- Conduct **prospective, longitudinal studies** (from CRI/dialysis through transplantation) to assess the efficacy of **different therapeutic modalities** on transplant outcomes in the psychosocial domain. These studies need to include:
  - **Sibling controls and healthy matched controls.** Failure to include sibling controls in most previous studies has prevented any firm conclusions regarding the relationships between behavior and compliance.
  - **A more precise scale of psychological assessment,** which should be developed and assessed for its ability to measure the individual impact of all factors (e.g., schooling, psychomotor, emotional, social, weight, sex, etc.) on graft survival in a longitudinal study.
- Investigate the relationships among **low self-esteem, medical compliance, and social adjustment:**
  - Investigate the reasons for **low self-esteem** in pediatric kidney transplant patients, and determine why this may lead to **non-compliance**. Collectively, the literature points to close interrelationships between psychological/adaptive behavior problems and medical non-compliance.
  - Develop **interventions to prevent low self-esteem.** Suggestions from the literature include early intervention with multidimensional training/counseling for children and families, incorporating adaptive skills training, anxiety and behavior management training, and counseling to promote family cohesiveness.<sup>10</sup>
  - Prospectively study whether or not **pre-transplant psychological profiles** of children and parents predict **post-transplantation compliance** with maintenance medications.
  - Another suggestion is to study how **low self-esteem** in children with transplants relates to low scores on conventional indicators of **good social adjustment** (e.g., marriage, moving out of parents home) when they grow up.



- Study the effects of different currently available treatment modalities on psychosocial development in children with infantile **nephropathic cystinosis** (e.g., drug therapy to reduce cysteine, white blood cells to reduce impact of disease).

*Recommendations from expert-selected studies from the literature (Kidney – psychosocial development)*

- Provide more complete descriptions of the **reliability and validity of instruments** and of the variables used.
- **Follow up qualitative research** to identify common themes with **quantitative, hypothesis-driven** research. These studies require larger sample sizes within treatment modalities to ensure adequate statistical power. Also, samples must include representative populations in order to provide generalizable results.
- In all studies, distinguish children and adolescents separately, using appropriate age groups, in order to **identify age-appropriate risk factors for psychosocial problems**. Previous use of larger age ranges or combining children, adolescents and adults has limited interpretation of previous studies.<sup>11-16</sup>
- Address the following two questions in additional studies on the role of family structure and environment using a **stress-and-resistance model**:
  - 1) Is the relationship between **family environmental variables and psychosocial/medical outcomes** unidirectional, as previously presumed, or bidirectional (i.e., can the outcomes also influence the environment)?
  - 2) Do **medical indicators** truly reflect illness severity (e.g., they may instead reflect the degree of family organization)?
- Implement studies comparing the effects of **family functioning** on child adjustment for **different disease groups** (kidney vs. other chronic illnesses), with the purpose of helping to resolve inconsistencies reported in the literature. Inherent differences in kidney disease (change in physical appearance, treatment, perception of shortened lifespan) may underlie these discrepancies.<sup>17</sup> However, it is suggested that instruments standardized for healthy populations may not be sufficiently sensitive to detect subtle illness-related differences in these comparisons.
- Investigate family environment and functioning to consider **multiple categories of family structure**, and employ larger, multi-site, longitudinal designs in this investigation.
- Implement larger, multi-center, longitudinal studies that include investigation of **developmental domains and physiological measures** (e.g., blood urea nitrogen – BUN, creatinine, creatinine clearance and physical growth parameters) to elucidate effects of renal disease and transplantation on development.
- **Separate out objective and subjective measures** when assessing quality of life, rather than focusing on objective measures emphasizing delayed social development.

It was suggested that subjective indicators can reveal high quality of life despite maladaptation indicated by conventional objective measures (e.g., marital status).

- Recommendations for **nursing practice** related to psychosocial development include:
  - perform developmental assessments at frequent intervals (social, cognitive, motor development)
  - counsel on the importance of normalizing play activities
  - implement interventions to relieve symptoms (especially fatigue) that interfere with child's desired activities

### **Liver: growth studies**

#### ***Recommendations from the panel of experts (Liver – growth)***

- Conduct randomized, multi-center treatment trials of withdrawal of daily steroids during the first six months post-transplant, coupled with alternative immunosuppression. These trials should help **establish the window for steroid withdrawal** and could ultimately lead to improved growth in this population by inducing changes in physician practice patterns. Patients should be **stratified** by type of graft received (living donor vs. cadaveric), age at transplant, diagnosis, and history of rejection.
- Conduct studies to **better define the cortisol axis** and individual characteristics that lead to slower metabolism of exogenous steroids. These studies would be instrumental in designing monitoring strategies for treatment post-transplant.
- Determine whether **late loss of kidney function** in pediatric **liver** transplant recipients 1) occurs at a significantly high prevalence during puberty and 2) compromises pubertal growth.
- Conduct research to determine if **menarche and the pubertal growth spurt** are delayed in children with liver transplants and children with chronic liver disease. Are they, for example, as delayed as they are in children with chronic renal insufficiency or cystic fibrosis?

#### ***Recommendations from expert-selected studies from the literature (Liver – growth)***

- Evaluate the effects of **decreasing steroid dosage** on growth, **during both induction and maintenance** phases of immunosuppression. Efforts could include the following:
  - prospective, randomized trials to support the validity of steroid withdrawal or avoidance during induction<sup>18,19</sup>
  - broadening studies to include the concept of steroid-sparing immunosuppressive protocols<sup>19</sup>

- adjusting long-term glucocorticoid dose according to the area under the concentration-time curve (AUC) for methylprednisolone to improve growth and minimize need for rhGH treatment<sup>20</sup> (*Note: The relationship between AUC and growth is stronger for liver transplantation than for kidney transplantation.*)
- Conduct randomized trials to determine the **safety of rhGH therapy**.
- Conduct studies to address **long-lasting effects on growth** in children with liver transplants from:
  - corticosteroids
  - chronic cholestasis or other diseases. (Other diseases studied should include renal insufficiency.)
  - various nutritional deficiencies.<sup>21</sup>

### **Liver: cognitive studies**

#### *Recommendations from the panel of experts (Liver – cognitive development)*

**Five areas** emerge as reasonable choices for this more focused research. Two types of studies would be focused on infant recipients, two on older, school-age recipients, and one on neurotoxicity:

1. **Infant recipients – risk factor study from infancy through early school years:**  
Special emphasis should be placed on identifying risk factors for impaired cognition in infant transplant recipients. This **risk factor study** should involve:
  - A large, multi-center, longitudinal study enrolling children who are **less than two years old at time of listing** for liver transplantation.
  - Gathering and updating of specific **epidemiological, demographic, and disease-specific data** at regular intervals both **before and after** liver transplantation. For example, infants could be tested at listing time, followed up at six-month intervals during the waiting period, and then tested at yearly intervals following transplantation.
  - A **more comprehensive survey** of cognitive development of the child **at five years of age, when ready to enter school**.
    - This comprehensive testing at time of school entry should include **intelligence testing** with an instrument such as the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) in 3–7 year-olds and the Wechsler Intelligence Scale for Children, 3<sup>rd</sup> edition (WISC-III) in 6–16-year-olds.
    - The evaluation should include **assessment of language ability** using instruments such as the Clinical Evaluation of Language Fundamentals-Pre-School (CELF-P) test in children younger than six years of age and Clinical Evaluation of Language Fundamentals-Revised (CELF-R) test in children

older than six years of age. The age ranges covered by the two CELF tests parallel those of the WPPSI and WISC. Alternately, the Pre-School Language Scale-III (PLS-III) could be used in pre-school-age children.

2. *Infant recipients – intervention study during late toddler years:* Since the majority of liver recipients are infants, it is also justifiable to design an intervention study for this group. This **intervention study** would require **long-term follow-up**, from randomization at **three years of age**, through achievement testing at **eight years of age or older**. The study would have the following characteristics:

- **Randomization** of children to either a non-intervention group or a intervention group.
  - The intervention group could receive either a focused, **one-on-one language/speech therapy intervention**, or an intervention in a **group setting**, such as a program similar to the federal government’s “Head Start” program.
  - A possible scenario for the intervention study would be randomizing infant liver recipients to a mandatory **Head Start-type program** once they reach three years of age.
  - Most importantly, the interventions should **target mental development** rather than motor development, since clinicians have not observed significant deficits in motor ability in children followed up over the long-term.
- Children in the intervention and non-intervention groups should be tested using the **same instruments as used for the risk factor study**, listed above.
  - Thus, instruments for **assessing intelligence** would include the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) in 3–7 year-olds and the WISC-III in 6–16-year-olds.
  - Instruments for **assessing language ability** would include the CELF-P in children younger than six years of age and the CELF-R in children older than six years of age, or the PLS-III in pre-school-age children. Again, the age ranges covered by the two CELF tests parallel those of the WPPSI and WISC.
- Children in the intervention and non-intervention groups should also be **tested for achievement** once they reach the **age of eight years** (usually during the second grade).
  - Highly recommended **achievement tests** include those contained in the Woodcock-Johnson Psycho-Educational Test Battery-3rd Edition (WJ-III) Achievement Standard Battery.
  - Other recommended tests of achievement include the Gray Oral Reading Test, 3rd edition (GORT-3) and the Test of Written Language, 3rd Edition (TOWL-3).

- Throughout the intervention study, all liver recipient children should be routinely **screened for learning disabilities** and provided standard **remedial instruction** as necessary.
3. ***School-age children – study focusing on school performance and learning disabilities:*** School performance and learning disabilities should be studied in older school-age recipients. Although this second area of study is not advanced enough to support the generation of hypotheses for intervention studies, the current literature still supports widespread clinical screening of liver transplant recipients for learning disability. This study would be **more of a survey study**, followed up by more detailed cognitive assessments, discussed in item 4, below. Investigators could address the issue of school achievement in children with liver transplants in several ways, including data gathering based on teacher and parent report:
- Instruments would be completed by **teachers and parents**.
  - Data should be collected on the child’s **behavior in the classroom and attention ability** using instruments sufficiently sensitive to detect Attention-Deficit/Hyperactivity Disorder (**ADHD**) and validated for use in chronically ill children.
  - **Instruments** highly recommended for use in such a study would be employed. These include:
    - The **Behavior Assessment System for Children (BASC)** (completed by child, teacher, and parents).
    - The **Scales of Independent Behavior-Revised (SIB-R)** (completed by parents) for detecting behavioral problems. The SIB-R comes in two forms, a full-scale form, and an early developmental form. The SIB-R offers an overall developmental assessment and is highly recommended for use in preschool and young school-age children. Although the SIB-R can be used in very young children, its sensitivity is somewhat diminished when used in toddlers. (Dr. Woodcock, one of the creators of the WJ-R, is also one of the creators of the SIB-R).
    - The **Conner’s Continuous Performance Test (CPT)** for evaluating attentional ability. A teacher’s version exists for the Conner’s CPT, which also comes in two scales, one for children ages 4–5 years (the “Kiddie” Version, or CPT-K) and one for children 6 years of age or older (the CPT-III).
    - **Behavior Rating Inventory of Executive Function (BRIEF)**, a quick, teacher-completed survey for screening for learning disabilities or ADHD.
  - Studying functional performance at school from the perspective of teachers would be very important. **Teacher observations** may allow investigators to identify

fundamental differences between two different achievement groups among these children:

- 1) Those liver recipients with **lower IQ** who are nevertheless **able to adapt** and maintain academic achievement that exceeds their expected performance based on IQ, and
- 2) Those liver recipients with lower academic performance than expected based on their IQ (i.e., those who are **learning-disabled**).

*(Caveat: Classroom observation techniques and teacher observations {e.g., questionnaires, surveys, behavioral observations} are labor-intensive and rarely if ever provide “standard” type data. Teacher assessments of achievement are not necessarily consistent from teacher to teacher.*

*It might be preferable to conduct direct child assessment with appropriate IQ tests and academic achievement tests, to ask if there is consistency or discrepancy between tested IQ level and achievement test results.)*

4. **School-age children – domain-specific study focusing on attention ability and higher cognitive (“executive”) functions:** Attention ability and the higher cognitive (“executive”) functions should also be studied in school-age children. Attentional abilities can interact substantially with learning and achievement. This study would involve the following:

- **Much more specific, focused neurocognitive testing**, in contrast to the general testing of school performance described in item 3, above.
- **Instruments** for assessing performance in specific domains, including learning, memory, and concept formation.
- Selection of instruments depending on the **specific research objectives** of the grant applicant.
- Instruments for use in **school-age children and adolescents**. A suggested sample includes:
  - **Tests of attention/executive function** could include the Spatial Span test of the WISC-PI (“WISC as a Process Instrument”), the Conner’s Continuous Performance Test (CPT), the Wisconsin Card Sorting Test (WCST), the Auditory Working Memory scale of the WJ-III Tests of Cognitive Ability, and the Planned Connections, Number Detection tests of the Das-Naglieri Cognitive Assessment System (CAS).
  - **Tests of memory/learning** could include the Picture Recognition test of the WJ-III Tests of Cognitive Ability, the California Verbal Learning Test (Children’s Version; CVLT-C), and the Rey-Osterrieth Complex Figure

(ROCF) test. Neuropsychological evaluations or clinical assessment aids used in support of exploration of ADHD might be considered.

5. **Neurotoxicity study:** The extent of mild neurologic injury in the pediatric transplant population is unknown. Few patients have chronic seizure disorders, but the potential for subtle **mounting neurotoxicity related to drug therapy** has not been explored.
  - Given the growing body of literature suggesting that up to 25% of children receiving **cyclosporine or tacrolimus** will experience a seizure, **a large-scale study** is warranted to screen for **neurologic injury** before and after transplantation.
  - The study's methodology could include MRI or CT scans of the child's brain before and at regular intervals after transplantation. Newer **scanning modalities** such as functional MRI might help evaluate subtle differences in cortical function, which may be a risk factor for abnormal cognitive and psychological function.

Overall, the preliminary published research on cognitive development in pediatric liver transplant patients is adequate for generating hypotheses. Where possible, the next generation of work in the five areas detailed above should:

- Be **hypothesis-driven**.
- Use **longitudinal** designs, to allow investigators to determine if deficits improve or worsen over time.
- Have **larger sample sizes** than previously used. Sample sizes should be adequate for stratifying patients by 1) age at transplant, 2) diagnostic category and acuity of illness at transplant, and 3) level of ongoing medical disability.
- Use of **matched, healthy controls**, which may include sibling controls or “best-friend” controls. **Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. A **best-friend control** would be one of the patient's best friends, brought in by the patient when he/she comes in for cognitive testing. Best-friend controls also have the advantage of having similar SES to the patient. (*Note: Please see discussion of sibling controls under “General recommendations for cognitive research”.*)
- Attempt to clarify whether delays are attributable to early onset of **severe illness in general** or to early onset of **liver disease specifically**. (*Caveat: Achieving this objective would likely require using chronically ill controls, a proposition fraught with difficulty. However, use of chronically ill controls in the form of other, non-liver transplant patients may be feasible and yield important, organ-specific information.*)
- Employ **neuropsychological evaluation, school achievement testing, and intellectual assessment**.

- Relate scores on **IQ** and **neuropsychological** tests to performance on tests of academic **achievement**.
- Relate findings to actual academic achievement as **observed in the classroom**.
- Consider the influence of **environmental factors**.
- Determine the prevalence and etiology of **sensorineural hearing loss (SNHL)**.
- Seek to determine if **IQ distribution** in the pediatric liver transplant population tends to be **normal** (approximating a bell curve), **skewed** (tending to high or low extremes) or **bimodal** (with very low and very high scores predominating).
  - If the distribution is determined to be skewed or bimodal, efforts should be made to determine if **graft function** differs in the low- and/or high-scoring groups. For example, in a bimodal distribution, the children with the higher scores may have better graft function, and the children with the lower scores may have poor graft function.
  - Determining the shape of the IQ distribution specific to children with liver transplants requires a **sufficient sample size**, so that sample statistics can approximate “true” population parameters. (Sample statistics include such characteristics as mean, median, mode{s}, and kurtosis.)

***Recommendations from expert-selected studies from the literature (Liver – cognitive development)***

- Examine the influence of factors **other than illness-related and cognitive factors** on academic performance. These other factors would include family functioning, socialization, and stimulation experiences. Further investigation is needed to determine the relative contribution of **psychosocial and medical factors** to neurodevelopmental status.<sup>22,23</sup>
- Conduct prospective research to determine if any associations exist between cognitive function and the various **biochemical indicators of liver function**, such as bilirubin and ammonia levels.<sup>24</sup>

*(Note: Although mental development was related to serum bilirubin and albumin in a 1987 study<sup>25</sup>, mental delay was not related to these factors in subsequent studies.<sup>22,26</sup> One of the subsequent studies, however, had a high cut-off for bilirubin levels {>1.5 mg/dL} as part of its inclusion criteria, possibly reducing the ability a priori to find a statistically significant association between bilirubin levels and mental ability.<sup>26</sup>*

*In a more recent study, academic outcome was not significantly related to bilirubin, BUN, or creatinine; however, interpretation was limited by small sample sizes that reduced the possibility of finding statistically significant associations, by heterogeneity of age at diagnosis and time since transplantation, and by other confounding factors.<sup>23</sup> Discrepancies between intellectual and academic functioning were also reported in this study.*



*Bilirubin was indeed higher in the mentally deficient group at 3–9 years post-transplantation, although not statistically higher. Specifically, bilirubin was 3.6 mg/dL in the mentally deficient group (n=9), compared with an overall mean of 1.36 mg/dL for all patients (n=47), 0.66 mg/dL for those with learning problems (n=12), and 0.87 mg/dL for those functioning within their expected level (n=26).*

*Putting these post-transplant levels into perspective are 2002 data from the SPLIT database. These show pre-transplant bilirubin levels of 10.86 mg/dL in children < 5 years of age, with levels at three years post-transplant of 0.52 mg/dL.*

- Conduct studies that account for a **wide variety of liver diseases, excluding** those metabolic diseases characterized by neurotoxicity or primary defects in the **central nervous system** (CNS). These defects would affect neurological outcome quite apart from any effect the liver disease itself may have.<sup>22</sup> Diseases with neurotoxicity or primary CNS involvement include citrullinemia and most of the urea cycle deficiencies, but not alpha-1-antitrypsin.
- Investigate the effect of **brain edema** on neurological recovery in children transplanted for **fulminant hepatic failure** (FHF).<sup>27</sup>
- Future investigate the hypothesis that **spatial skills** are slower to recover than other skills after liver transplantation. This investigation should examine the possibility that visual-spatial scores are diminished not due to visual deficits per se, but to **factors underlying visual-spatial testing tasks**, such as timed performance (i.e., examine influence of ability to attend and persist under time pressure on visual-spatial scores). Any impacts<sup>24,28,29</sup> on visual-spatial abilities resulting from transplantation should also be explored.

## **Liver: psychosocial studies**

### *Recommendations from the panel of experts (Liver – psychosocial development)*

#### *Psychosocial function:*

- Perform **longitudinal studies of psychosocial function** prospectively from the time of transplant.<sup>1,24,30,31</sup> The goal of such a longitudinal study would be to **identify risk factors** for psychological problems and identify sub-groups of patients who would benefit from ongoing mental health intervention.
  - It would also be important to study a **large population** that included children from a variety of regional transplant centers and a range of socioeconomic status.
  - Tools used for this assessment must include measures specific for **depression** and **anxiety** as well as assessment of the **family function** and support.
  - **Instruments** measuring depression include the Children’s Depression Inventory (CDI). Instruments measuring family function include the Family Assessment Device (FAD).

- Perform **longitudinal studies of post-traumatic stress disorder (PTSD)** among older children with liver transplants. Since children relate the transplant experience as traumatic, some of their behavior problems may be related to an abnormal stress reaction.
  - Should be a **longitudinal intervention study** that **randomizes older children** to receive ongoing counseling regarding the transplant event.
  - Would help determine if psychosocial function would improve with recognition and treatment of PTSD or PTSD-like symptoms.
- Careful attention should also be given to understanding **family function and stress**. This issue could be addressed through broader quality-of-life studies as detailed below.
- Comparison of the psychosocial outcomes of recipients of livers from **living-related donor versus cadaveric donors** is also recommended. This research should try to determine if more deliberate (i.e., earlier) timing of transplantation through use of living-related donation leads to improved outcome.

*Quality of life (QOL):*

- A **large cross-sectional study** including children from multiple regional centers would be justified to study the **quality of life (QOL)** of pediatric liver transplant recipients. This study should:
  - Have **long-term follow-up**.
  - Describe QOL/functional status using **validated instruments**.
  - Test different **pre-transplant and post-transplant variables** as possible determinants of QOL.
  - Possibly be conducted **by mail** and might use the United Network for Organ Sharing (**UNOS**) as a platform for initial patient identification.
- Evaluate the **functional status** of children who received liver transplantation in the late 1980s, and are now entering adulthood. Their functional status should be measured using tools such as:
  - the Child Health Questionnaire (validated for children aged 5-18)
  - the RAND 36-Item Health Survey-Short Form (SF-36) developed for the Medical Outcomes Study (ages 14 years and older)
  - the Sickness Impact Profile (SIP) (adults)

- Family function and QOL of **parents and siblings** of transplant recipients must likewise be addressed. Longitudinal evaluation of parents and siblings using validated instruments would be appropriate, but this area of focus is less developed and would therefore justify an **individual interview approach**.

*Recommendations from expert-selected studies from the literature (Liver – psychosocial development)*

- Conduct further studies to verify whether changes in **parental attitude** to liver transplantation (as a “family secret”) may help integrate the transplant experience in the child’s personality development.<sup>32</sup> Understanding the psychosocial impact of family reactions to the child’s transplantation experience is important.
- Identify **families** who are at risk of post-transplant complications early, and develop **early intervention strategies** prior to transplant.<sup>33</sup>
- Conduct further studies with larger groups to determine precisely all **growth and development correlates** (including social competence) of improvement versus persistence of deficits.<sup>34</sup> This research is needed because results show that normalization of growth and development may not occur rapidly.
- Provide for a larger longitudinal study (starting before transplantation) to determine whether apparent greater emotional adjustment by children to liver transplantation persists when they reach **adolescence and adulthood**.<sup>1</sup>
- Test interventions allowing young transplanted patients to **discuss the transplantation experience**. It is believed this may assist with difficulties related to anxiety, peer relationships, behavior, and parental expectations.<sup>31</sup>

**Heart: growth studies**

*Recommendations from the panel of experts (Heart – growth)*

- The research on growth in pediatric heart transplant recipients is still at a descriptive level. A **larger study** is required to **identify potential risk factors**.
- A few studies have attempted to look at differences in outcomes of heart transplants for **congenital versus acquired heart disease**. This focus should be extended.
- Larger studies would need to include **patients from multiple centers** and might gather data through a mechanism similar to that used by the Studies of Pediatric Liver Transplantation (SPLIT) Research Group.

*Recommendations from expert-selected studies from the literature (Heart – growth)*

Conduct systematic investigations to determine why many **late (i.e., older) transplant patients** have poor pre-operative growth.<sup>35</sup> Suggested reasons include fluid restriction due to use of diuretics, thereby worsening nutritional intake, and hypercatabolism.

## Heart: cognitive studies

### *Recommendations from the panel of experts (Heart – cognitive development)*

The cognitive research in children with heart transplants is the least developed of all the cognitive research reported here in this report.

- Thus, future studies will have to be **descriptive**.
- Further, investigators should **learn from the methodological imperfections** of previous studies undertaken by their counterparts in the kidney and liver transplant research (e.g., lack of controls, lack of comparable instruments across studies, wide age ranges).

Current findings do suggest that cognitive outcome in children surviving heart and heart/lung transplantation is good. These findings, however, need to be **confirmed in larger, multi-center studies**.

- If these larger studies confirm **good cognitive outcomes**, a risk analysis study looking at multiple factors predicting cognitive ability would not be warranted.
- If these larger studies uncover **cognitive deficits** in children surviving heart transplantation, a risk analysis should be performed, with hypoxemia (low blood oxygen) one of the first determinants investigated.
- These additional larger studies should have the following characteristics:
  - Use of **matched, healthy controls**, which may include sibling controls or “best-friend” controls. **Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. A **best-friend control** would be one of the patient’s best friends, brought in by the patient when he/she comes in for cognitive testing. Best-friend controls also have the advantage of having similar SES to the patient. (*Note: Please see discussion of sibling controls under “General recommendations for cognitive research”.*)
  - **Multi-center with large sample size.**
  - Assessment of cognitive ability in terms of **more specific initial diagnostic categories**, especially in view of the higher proportion of acyanotic lesions in transplant versus the conventional cardiac surgery patients.
  - **Neuropsychological evaluation, school achievement testing, and intellectual assessment.**
  - **Longitudinal design, with long-term follow-up.** Long-term follow-up is especially important in studies of children with heart transplants, since some data suggest that developmental delays identified in young recipients tend to worsen

over time. Research must answer these questions: Do delays intensify over time? And, if so, why?

- **Numerous, serial measurements** of cognitive ability initiated before as well as after transplantation.
- **Consistent use of instruments** across centers for assessing cognitive performance
- **Use of instruments permitting comparison across different developmental stages.** In assessments of global intelligence, the Wechsler series of IQ tests (the WPPSI, WISC III, and WAIS) and the Stanford Binet (age 2 to adult) would allow this cross-stage comparison. Screening tests {e.g., the Denver Developmental Screening Test) and developmental schedules (e.g., the Gesell schedules) are not comparative in standardization.
- Use of instruments that can accurately measure **specific neurocognitive deficits** in children with congenital heart disease and heart transplants.
- Examination of **disease subtype** as a risk factor.
- Examination of **cyclosporine A (CyA) and tacrolimus** as risk factors.

***Recommendations from expert-selected studies from the literature (Heart – cognitive development)***

- Continue to look at the impact of **hypoxia during surgery** on cognition.<sup>36-43</sup> Studies should compare heart transplant recipients to children undergoing other types of surgery requiring periods of hypoxia, e.g. open-heart surgery.
- Look at problems of **medical compliance/adherence**.<sup>44</sup>
- Examine **cognitive and academic functioning** as one of **four broad areas** of functioning in pediatric heart recipients:
  1. developmental progress (cognitive and academic functioning)
  2. emotional and behavioral functioning
  3. medical compliance
  4. quality of life (QOL)<sup>45</sup>
- Investigate the possibility that **more recently transplanted patients**, who experienced **less circulatory arrest** during transplant surgery as a result of more advanced surgery techniques, have better developmental outcomes.<sup>37</sup>
- Determine if developmental improvement is **sustained long-term** after transplant surgery, into the school and adolescent years.<sup>35,46-48</sup>

- If the presence of cognitive abnormalities is confirmed in pediatric heart transplant patients, perform **longitudinal** studies examining **both medical and developmental risk factors** for developmental delay.<sup>48</sup>

### **Heart: psychosocial studies**

#### *Recommendations from the panel of experts (Heart – psychosocial development)*

##### *Intervention study:*

- The current literature would support an **intervention study** aimed at **improving stress levels in families**, thereby improving psychosocial outcomes for young heart transplant patients.
  - To achieve a sample size adequate for determining if the intervention is effective, this study would require **multi-center enrollment**.
  - Since such significant difficulties have been identified in this group, patients should be randomized to receive **two different intervention arms** rather than treatment versus no treatment. The latter scenario would not be ethical.

##### *Quality-of-life study:*

- A **large-scale descriptive quality of life (QOL) study** would also be warranted at this time. This study should:
  - Include specific measures of **family function** and could include directly surveying the patients, since many are adolescents.
  - Examine the effect of **familial stresses during the waiting period** on post-transplant psychosocial functioning and adherence.
  - Look at the **differential treatment bestowed by parents** on the sick child awaiting a donor heart, compared to healthy sibling(s).

##### *Methodological considerations:*

Studies to identify psychosocial factors affecting the emotional well being of pediatric heart transplant recipients and their families should have the following characteristics:

- Use of **matched, healthy controls**, which may include sibling controls or “best-friend” controls. **Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. A **best-friend control** would be one of the patient’s best friends, brought in by the patient when he/she comes in for cognitive testing. Best-friend controls also have the advantage of having similar SES to the patient. (*Note: Please see discussion of sibling controls under “General recommendations for cognitive research”.*)
- **Multi-center with large sample size.**

- **Longitudinal, with long-term follow-up** and **numerous, serial measurements** of psychosocial functioning well before transplantation – and followed through to several years post-transplantation.
- **Consistent use of instruments** across centers for assessing psychosocial functioning.
- Use of **instruments** that can accurately measure **specific psychosocial problems** in children with heart disease.
- Inclusion of **infant recipients**.
- Investigation into how much **psychosocial factors**, particularly self-esteem, predict later **non-compliance** with immunosuppressant medication post-transplant.
- Investigation into **what strategies enhance adherence**. This would involve an intervention study evaluating effectiveness of different family-support models, such as support groups, for improving adherence.

It is important to note here that it is likely infeasible to perform multi-factorial analysis using multiple regression in the pediatric heart transplant transplantation. This is because it would be extremely difficult to recruit an adequate number of patients for such an analysis. Even in a multi-center study, it would be difficult to recruit more than 40 children.

*Recommendations from expert-selected studies from the literature (Heart – psychosocial development)*

- “Further research needs to be done on quality-of-life issues after pediatric cardiac transplantation. Beyond the long-term medical, developmental, and psychological impact of the transplanted child, studies need to address the **emotional, social, and financial impact** of transplantation on the parents and the well siblings.”<sup>49</sup>
- Conduct research comparing psychological functioning of the young heart transplant patient during **three major periods** –
  - the waiting period
  - the first year following transplantation
  - the long-term post-transplant period
- Look at emotional adjustment, parent-child interactions, and child temperament during the **year directly following transplant** (the “transition” year).<sup>50</sup>
- Conduct research to develop **reliable measures of adherence**.<sup>44</sup>
- Investigate the impact that disease- and transplantation-related stressors have in promoting **negative affect, decreased social competence, and disordered behavior** in pediatric transplant recipients.<sup>45</sup> Stressors would include intense medical regimens, delayed physical development, and decreased socialization with peers.

- Investigate the impact of **negative school experiences due to physical appearance** on academic performance and psychosocial well being, and develop the necessary clinical interventions.<sup>51</sup>



## Introduction

The medical strides in solid organ transplantation first investigated for adults in the 1950s began application in the pediatric population in the mid-1960s. The development of more effective immunosuppression, particularly the introduction of cyclosporine in 1983, had the greatest impact on survival, which in turn provided the impetus to expand indications for pediatric transplantation. These new opportunities to treat end-stage renal, liver and cardiac disease in infants and children also presented new challenges to understanding and preventing or treating the short-term and long-term adverse consequences of the life-threatening illness and of the organ transplantation and related treatments. These developmental and growth challenges in the pediatric population are distinct from the medical issues first addressed in the adult population, and are now of major interest in the effective uses of pediatric transplantation.

The adverse effects of organ dysfunction on body growth and the inability of a successful transplantation to fully restore normal growth in infants, children and adolescents were major topics of early studies. Although growth retardation remains a continuing problem, because of improvements in this area the focus has changed over the years toward greater emphasis on the neuropsychological and psychosocial consequences of end organ failure and transplantation, including the impact of required long-term maintenance therapies. Collectively, these studies present a picture of various pre- and post-transplant developmental deficits, the severity, duration, and reversibility of which may depend on a large number of patient-specific and family-specific factors. For example, some of these factors are the organ in failure, the diagnosis, the age at diagnosis and transplantation, and the types of social support received. Deficits in growth and development can have profound effects on the quality of life of pediatric transplant patients. In addition, cognitive and psychosocial problems may impact graft function and graft and patient survival through poor compliance with essential medications.

The objective of this literature review is to examine all relevant publications concerning development and growth issues in pediatric transplantation of the kidney, liver and heart for the period 1966 – 2001, as searchable in the Medline and *Locatorplus* databases at the National Library of Medicine and the National Institutes of Health library. This includes original research and review articles in scientific/medical periodicals, as well as relatively recent book chapters.

The completeness of the literature review, the importance or deficiencies of individual studies and findings, and the expert recommendations were guided by two expert reviewers, Richard N. Fine, M.D., Professor and Chairman in the Department of Pediatrics at Stony Brook Health Sciences Center, State University of New York at Stony Brook, New York; and Estella M. Alonso, M.D., Associate Professor of Pediatrics, Medical Director of Liver Transplantation, Children's Memorial Hospital, Chicago, Illinois.

In addition, critical review of the methodology in the literature as well as recommendations of instruments for future studies was contributed by Janet E. Fischel, Ph.D., Director,

Division of Development & Behavior, and Associate Professor of Pediatrics and Psychology, State University of New York at Stony Brook, New York. Additional commentary on cognitive/neuropsychological, psychosocial, and growth research issues in pediatric liver transplantation was provided by John C. Bucuvalas, M.D., Associate Professor of Pediatrics and Associate Medical Director of Liver Transplantation, Children's Hospital Medical Center of Cincinnati, Ohio.

Several important issues of study quality were considered when developing this review and selecting or developing the recommendations for future research. First, appropriate study design was paramount in determining the weight that was given to findings, conclusions and recommendations made in original research articles. The most important design considerations were prospective vs. retrospective studies, longitudinal vs. cross-sectional studies, use of appropriate control groups (e.g., sibling or matched healthy or chronically ill controls), patient sample size in individual comparisons, and internally acknowledged sources of bias or other study limitations apparent during review. An independent evaluation of the statistical methodology employed in the reviewed literature was not undertaken, although the reported statistical significance of any finding was considered in its inclusion in this review.

In addition, the types of measures and instruments used in patient or family assessments were considered only in as much as standardized instruments and age-appropriate instruments were considered preferable. Since the age ranges of patients was an important factor in many of these studies, small sample sizes for particular age groups or substantial age heterogeneity within a comparison group were considered methodological weaknesses. Any other major aspects of a study that might impact on whether findings could be generalized to a wider population were also considered.

The relevance of older literature to current standards of practice in transplantation and to recommendations for the future was an important factor in deciding what studies or findings should be reported or emphasized. It is evident that changes in the modes of immunosuppression in the pre- and post-cyclosporine eras substantially impacted graft survival rates, complications, and indications, thus potentially influencing post-transplantation growth and development. Other specific changes in patient management, such as the avoidance of aluminum in treatments and the use of tube feeding to improve nutrition, especially in kidney transplantation, have also been considered. Findings or recommendations that would no longer be of value today are either not reported or their limitations indicated.

The body of the report consists of nine major sections on growth, cognitive development and psychosocial development for each of kidney, liver and heart transplantation. Emphasis has been placed on cognitive and psychosocial development, which have not been studied as extensively as growth and for which recent reviews are much more limited. Each section provides a comprehensive assessment of the relevant literature, a summary, recommendations for future research with appropriate methodology provided by the expert consultants (under "Recommendations from the panel of experts"), and additional selected recommendations which appear in studies from the literature (under "Recommendations

from expert-selected studies from the literature”). Clinical recommendations are also given where they were made in the literature (under “Clinical recommendations based on individual studies”).

Appendices include a glossary of technical terms and acronyms (Appendix A) and annotated tables of standardized measures from studies on cognitive development (Appendix B) and psychosocial development (Appendix C). References to literature cited in the report and in these two tables appear at the very end of the report.

## I. Growth literature review and recommendations

### GROWTH: SOME NOTES ON TERMINOLOGY

- The Z score is a widely used measure in the research on height and weight gain in transplanted children. It reflects the number of standard deviations (SD) above or below the mean of the height or weight distribution for the age- and sex-appropriate healthy pediatric population. It is also referred to as “standard deviation score”, “SD score”, or, simply, “SDS”. Mean Z scores for a study population are often reported.
- Currently, height or weight Z scores more than 2 standard deviations (SD) below the healthy mean are generally considered to signify a growth deficit (“< -2 SDS”).
- More realistic final adult height targets, however, would be the 50th percentile of the mid-parental height. For example, Janssen et al. found that whereas only 6 of 17 kidney transplant recipients under growth hormone therapy reached their mid-parental height target, 9 reached the normative Z score target for height within the normal range (> -2 SDS).<sup>52</sup>
- Although final adult target heights are individualized to the pediatric renal patient (i.e., by using mid-parental height as target height), height deficits are still reported based on height distribution curves for the general healthy pediatric population.
- “Catch-up growth”, another term frequently encountered in the pediatric growth literature, usually signifies an increase in height or weight SD score over time.
- “Pre-emptive transplantation” usually indicates transplantation without previous dialysis.
- The North American Pediatric Renal Transplant Cooperative Study, or “NAPRTCS,” is a registry of pediatric renal transplant recipients 0–17 years of age.<sup>53</sup> By January 2001, about 12,000 patients had been registered in NAPRTCS.
- “SPLIT”: The Studies of Pediatric Liver Transplantation (“SPLIT”) Research Group maintains a registry database of pediatric liver transplant patients from Canada and the United States. As of June 2000, about 1,100 patients had been registered in the SPLIT database.

## GROWTH: KIDNEY

Unlike for liver and heart transplantation in children, the growth issues surrounding pediatric kidney transplantation have been fairly well defined, with four recent, outstanding reviews written on the subject. These include:

- Fine (2002) <sup>54</sup>
- Fine (2000) <sup>55</sup>
- Melter and Briscoe (2000) <sup>56</sup>
- Haffner and Schaefer (2001) <sup>57</sup>

The points made in these reviews have been incorporated into this report.

Trends in growth impairment/improvement as well as many of the physiological, clinical, and demographic risk factors for impaired growth have been identified. With advancements in the development of growth-promoting therapies, not to mention patient and graft survival, achievement of normal final adult height has become a realistic goal for children with kidney transplants.

As Melter and Briscoe suggest in their review of growth issues in pediatric renal transplantation, the single most important intervention for improving growth in uremic children is renal transplantation.<sup>56</sup> Haffner and Schaefer add to the chorus, stating that “active transplantation programs are an indispensable part of strategy to improve adult height in patients with childhood-onset chronic renal insufficiency.”<sup>57</sup> Indeed, Hokken-Koelga et al. found that significant decreases in height standard deviation scores (SDS; -0.4 SD/year) that followed initiation of dialysis only halted once children underwent transplantation.<sup>58</sup>

As early as 1981, Ingelfinger et al. observed that “in young children, especially those less than age 7 years, a successful, normal functioning allograft appears to permit striking growth acceleration with the achievement of normal height for age.”<sup>59</sup> At transplantation, however, many children with end-stage renal disease (ESRD) already have a substantial degree of growth retardation not completely correctable by transplantation.<sup>58</sup> Indeed, experts are increasingly broaching the possibility that pre-emptive transplantation in children with chronic renal insufficiency (CRI) may be indicated not simply on the basis of preventing the decline into ESRD, but also to improve growth, among other factors. Pre-emptive renal transplantation has been found to predict height improvement up to three years post-transplant, even in patients transplanted during the pubertal years, typically thought resistant to the beneficial effects of transplantation on growth.<sup>60,61</sup> Other research, however, does not support the proposition that growth improves at better rates with pre-emptive transplantation.<sup>62</sup>

Although statural growth, including final adult height, remains sub-optimal in most transplant recipients, it has improved over the past decade.<sup>53,54,63,64</sup> A number of

advancements account for this improvement in growth. Risk factors for impaired growth have been identified, with consequent modification of pre- and post-transplant clinical management to control these factors. New therapies, such as use of recombinant human growth hormone (rhGH) in growth-retarded children with CRI, have been introduced to stimulate growth directly. On the other hand, alternative therapies are being developed and actively investigated to improve growth indirectly by mitigating or even avoiding altogether the growth-retarding effects of steroid immunosuppressants. Better patient clinical management, such as ensuring adequate nutrition, both prior to and following transplantation, has also contributed to improvements in growth in pediatric renal transplant patients.

### **Pre-transplant risk factors for growth impairment and strategies for growth improvement**

Growth failure in uremic children usually begins well before transplantation. Indeed, most children with ESRD are already growth-retarded at the time of renal transplantation. Investigators still do not understand exactly how primary renal disease leads to growth failure in the pediatric renal patient. What is known is that growth retardation during CRI and subsequent ESRD is the result of many factors. These include young age at onset of chronic renal disease<sup>65</sup>, acidosis<sup>66</sup>, undernutrition<sup>67</sup>, CRI-related renal osteodystrophy (ROD)<sup>68</sup>, including excessive secretion of parathyroid hormone (PTH), and perturbations of the recently elucidated GH/IGF (growth hormone/insulin-like growth factor) axis.<sup>69</sup> The latter four are all related to renal dysfunction.

A plethora of pre-transplant clinical interventions have been implemented in the attempt to improve growth in children with CRI. Most have failed. Improvement in growth velocity rarely accompanies the initiation of either hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) in children with ESRD. Indeed, worsening of growth retardation is observed in young ESRD patients on dialysis.<sup>70</sup> No improvement in growth velocity has resulted from correction of anemia during dialysis with recombinant human erythropoietin (rHuEpo)<sup>71</sup>, remediation of CRI-related anorexia via tube-feeding<sup>72</sup>, or from attempted remediation of ROD with Vitamin D.<sup>73</sup> On the other hand, growth improvement does occur in children following transplantation, particularly in those transplanted by 6 years of age.<sup>53</sup>

Some pre-transplant attempts at improving growth have succeeded, but not to such an extent that growth-retardation at the time of transplant was avoided. Improved growth velocity has been clearly boosted in infants and children whose PTH levels have been kept down through optimal supplemental nutrition.<sup>72</sup> Additionally, a favorable urea reduction ratio promotes growth in pediatric renal patients undergoing hemodialysis.<sup>74</sup> Lastly, the importance of promoting growth through maintaining caloric intake in the young CRI patient should be self-evident.

Thus, optimal clinical management of the pre-transplant patient vis-à-vis improved growth potential would include implementation of PTH monitoring strategies, supplemental nutrition and maintenance of adequate caloric intake (through tube-feeding if necessary),

and reduction in urea ratio through adequate dialysis. Even the combination of these practices, however, is not likely to prevent growth retardation in the child with ESRD by the time that child undergoes transplantation.

Moreover, optimizing height at the time of renal transplantation is crucial to ensuring improved growth in the child post-transplantation. In addition to age at transplantation (discussed in detail below), **height deficit at transplantation** is a risk factor for impaired growth following transplantation.<sup>75</sup> Although greater height deficits are associated with a greater rate of catch-up growth post-transplant and under rhGH therapy, this growth acceleration is not sufficient to bring the child to target height.<sup>57,58,62,76</sup> Thus, optimizing height by the time the child undergoes transplant surgery is crucial to ensuring that final genetic target height is reached post-transplantation.

The latest data (2001) from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), show that height at the time of transplant currently persists near sub-optimal levels (the normative sub-optimal level is -2 SDS). The mean height deficit for all pediatric patients at the time of renal transplantation is -1.91 (1.91 standard deviations {SD} below the appropriate height for age and sex), with deficits for boys greater than those for girls (-1.97 vs. -1.82).<sup>53</sup>

### **Catch-up growth following renal transplantation**

In pediatric renal allograft recipients overall, growth improvement is generally demonstrated only during the first-year post-transplant, with improvement restricted to males. Height deficits reported from the NAPRTCS data have worsened from a baseline of -1.86 to -2.06 at 5 years post-transplant.<sup>77</sup> In their 1994 study of 70 prepubertal children, a portion of whom were on alternate-day steroids, Hokken-Koelega et al. found that 70% did not experience appreciable catch-up growth during the first 2 years after renal transplantation.<sup>58</sup>

These pessimistic findings are yielded when growth data are examined across all age groups. A look at growth in children transplanted at different ages, however, gives reason to anticipate relatively good growth among patients transplanted at earlier ages.

Although “catch-up” growth is not seen in the overall cohort of pediatric recipients over the course of 5 years post-transplant, growth does improve in children transplanted at younger than 6 years of age. This has been a consistent finding across the NAPRTCS reports published over the past decade.<sup>53,59,62,77-85</sup> It is among children above the age of 6, particularly those above 12 years of age, that growth is persistently sub-optimal.

Indeed, data from the most recent NAPRTCS report illustrate how **age at transplantation** is an important risk factor for impaired growth post-transplant. These data show that NAPRTCS-registered children **aged 0-5 years** exhibited catch-up growth during the initial 2 years following transplantation, with this improved growth velocity maintained up until at least 5 years post-transplant.<sup>53</sup> As observed in previous studies,<sup>62,77</sup> growth was best among those transplanted at younger than 2 years of age. These children showed an increase of

0.34 standard deviations from baseline Z score in the first 6 months post-transplant, increasing to 0.75 at 1 year post-transplant.

Older children in the NAPRTCS registry exhibited less improvement in post-transplant growth. Although children **2-5 years of age** at transplant also achieved acceleration of linear growth, they did so more slowly, with an increase in Z score of 0.56 at two years post-transplant and 0.75 at five years.<sup>53,77</sup> Children transplanted between the **ages of 6-12 years**, on the other hand, achieved no acceleration of linear growth to correct for their short stature. Indeed, with their already stunted height, older children with renal transplants have been shown to either grow at the same rate as the normal population, or in fact demonstrate a deceleration in growth velocity. The oldest children with renal transplants – those transplanted between 13-17 years of age – experience loss in relative height.<sup>53,62,84</sup>

Despite the clear association between age at transplantation and post-transplant growth acceleration, the precise mechanism explaining the association between age at transplantation and growth acceleration has not been adequately delineated, as noted by Fine.<sup>55</sup> Unfortunately, it is clear that the very group that achieves the best growth after transplantation – i.e., the youngest children – also runs the highest risk of graft failure, as Melter and Briscoe note in their review.<sup>56</sup>

In view of the striking differences in growth improvement between those transplanted at younger and older ages, it is notable that the percentage of renal transplant operations in children < 6 years has been declining in the past decade: from 30% in 1987 to 21% in 1997.<sup>77</sup> Some investigators have suggested that, if the age distinction in growth is solidly established, national organ procurement and transplantation network allocation policy should give more precedence to children >10 years of age awaiting a kidney in order to optimize their growth potential post-transplant.<sup>62</sup>

New findings are dispelling the pall over the growth prospects of older transplant children. Maxwell et al.'s 1998 combination retrospective/prospective study looking at height gains post-transplant has debunked the conventional wisdom that catch-up growth occurs only rarely in children before puberty.<sup>60</sup> In their retrospective study of 54 patients receiving renal transplants during puberty, they found that significant catch-up growth occurred for up to 5 years post-transplantation during the expected time of puberty. After transplantation, mean height standard deviation score increased significantly for up to 5 years, “by which time nearly all of the children had a height within the normal range.” Z scores rose from -1.8 at baseline (n=54) to -0.6 at 5 years post-transplant (n=13). These positive findings are contrary to the previously published, more pessimistic data,<sup>86,87</sup> and may have been related to consistent and early use of alternate-day steroid by children in this study, as well as to higher than usual rates of pre-emptive transplantation among them.

Maxwell's findings are in bold contrast to those from a much earlier (1987) study by van Diemen-Steenvoorde et al.<sup>87</sup> In their important study on pubertal growth and sexual maturation in renal transplant recipients, van Diemen-Steenvoorde et al. found that “...although poor growth before kidney transplantation has a great influence on adult height, the loss of growth potential during pubertal development seems even more important.”



Differences in steroidal regimens may explain the differences between the findings of Maxwell and van Diemen-Steenvoorde.

The findings of van Diemen-Steenvoorde et al. were not all pessimistic, though; renal allograft recipients with a bone age of > 12 years at transplantation did in fact grow significantly by the time they achieved final adult height, with normal height velocity during puberty in 62.5% of the children. This is in contrast to findings from a much older study by Grushkin and Fine.<sup>86</sup>

Optimal **adult height** is not achieved in a substantial number of pediatric renal transplant recipients, with 25% of NAPRTCS children having a Z score of -2.7 or worse.<sup>53</sup> Ten percent have final Z scores of -3.8 or worse. Final adult height has generally improved over the past fifteen years, however, from a -2.3 standard deviation deficit in the NAPRTCS 1987 cohort to -1.4 and -1.73 in the 1993 and 2001 cohorts, respectively.<sup>53</sup> Even under growth hormone therapy, though, children with renal transplants reaching adulthood are still substantially shorter than their genetic target height. A controlled study of 38 children reaching adult height found that rhGH-treated males were 10.1 cm shorter than genetic target adult height when they attained their final adult height, with rhGH-treated girls 12.2 cm shorter.<sup>88</sup>

The pubertal growth spurt is usually delayed by 2-2.5 years and shortened by 0.5-1.5 years in children with renal allografts.<sup>88,89</sup> This delayed onset of puberty results in later attainment of adult height, at age 20.3 years in boys and age 18.7 years in girls. This finding has important implications for studying the sexual maturation of young renal patients, especially in light of the observation by van Diemen-Steenvoorde et al. that bone age is a more reliable predictor of attained degree of sexual maturation than chronological age.<sup>87</sup> For example, menarche was delayed in female renal patients studied by van Diemen-Steenvoorde as determined by chronologic age (16 years), but not by bone age (12.9 years). In another example of the utility of bone age as a more reliable milestone than chronologic age, IGF-I levels for bone age have been found to be associated with growth velocity during rhGH therapy.<sup>90</sup>

The NAPRTCS data also show that weight scores have rapidly increased for all age groups.<sup>53</sup> Although children below the age of six still have standardized weights below national norms at three years post-transplant, they still achieve relative weight gains into their fifth year post-transplant. Children above the age of 6 years achieve a gain of 0.75 standard deviations within the first 6 months post-transplant, with weight gains comparable to those of the healthy population into the fifth year post-transplant.

### **rhGH therapy and the GH/IGF axis**

Perhaps more than any other advancement in the clinical management of the pediatric renal patient, modification of the GH/IGF system through use of recombinant human growth hormone (rhGH) therapy has consistently improved statural growth in these patients. rhGH therapy increases the activity of IGF-I, which is crucial to the stimulation of cartilage and subsequent bone growth.

### ***The GH/IGF axis***

Various findings over the past decade have clarified some of the intricacies of the GH/IGF (growth hormone/insulin-like growth factor) axis, which is implicated in the growth retardation observed in children with renal disease. It has been found that uremia is associated with combined GH and IGF-I resistance<sup>91</sup>, and that treatment with rhGH increases IGF-I levels. Thus, it has been speculated that GH therapy's beneficial effects on growth may be due to the positive effect on IGF-I levels and IGF-I bioavailability due to rhGH, as well as direct growth-promoting effects on tissues.<sup>90,92</sup> Height SD score was found to be positively correlated with GH levels, which are indeed lower in severely growth-retarded pediatric renal allograft recipients. GH pulsatility patterns do not appear related to growth retardation; they are normal in these patients. Pubertal stage has also been found to be predictive of GH levels, regardless of the type of steroid schedule the child is under (daily or alternate-day).<sup>93</sup> This finding may indicate that pubertal transplant recipients may require a supplemental GH "boost".

According to the current GH/IGF hypothesis, children with CRI have a defective GH/IGF axis in that IGF-I is inadequately stimulated, due to an inadequate number of GH receptors in the liver, and excessively sequestered, due to an excessive level of IGF binding proteins.<sup>55</sup> However, this hypothesis has been contradicted by findings that demonstrate that growth retardation after renal transplantation cannot be attributed to low plasma levels of IGF-I or IGF-II:<sup>93</sup> plasma levels of IGF-I and IGF-II, and serum levels of IGF binding protein-1 have been found to be normal in growth-retarded children with kidney transplants.

Findings also suggest that post-transplant growth retardation may not solely be the result of decreased GH secretion. Instead, as offered by Hokken-Koelega et al., "renal graft impairment together with decreased IGF bioavailability may, in addition to the presumed direct effects of prednisone on cartilage, contribute to the growth retardation after renal transplantation."<sup>93</sup>

The findings from the steroid-withdrawal/sparing literature add mystery to current hypotheses on the GH/IGF axis, including how steroids interfere with its functioning. For example, a study by Hokken-Koelega et al. revealed that daily prednisone does not appear to have a more deleterious effect on endogenous GH secretion in children with kidney transplants than did alternate-day prednisone.<sup>93</sup> Moreover, pubertal stage influenced endogenous GH secretion regardless of what steroid schedule was used. In a study by Ferraris et al., serum IGF-I levels were not observed to change in children treated with deflazacort, a steroid with less pronounced side effects than prednisone.<sup>94</sup> This despite the fact GH secretion and linear growth velocity were indeed enhanced.

### ***Safety and efficacy of rhGH therapy***

Despite confusions regarding the precise functioning of the GH/IGF axis, the efficacy of rhGH therapy in improving growth in children with renal disease has been well established, and is continuing to be intensely investigated.<sup>52,76,79,82,88,90,92,95-112</sup> Indeed, growth is achievable in most patients treated with rhGH either before or after transplantation.<sup>81,90,92,95-98,100,101,107-111,113,114</sup>

Mehls is credited with the breakthrough discovery that use of exogenous growth hormone in uremic rats insensitive to endogenous GH promotes length and weight gain.<sup>115</sup> A decade after this discovery, a seminal, multi-center, randomized controlled trial demonstrated the safety and efficacy of rhGH in humans with CRI<sup>116</sup> Today, findings from a number of recent randomized clinical trials have confirmed the safety and efficacy of rhGH in improving growth in children following renal transplantation.<sup>61,76,92,105</sup>

Although experts advocate the use of rhGH to improve growth in children with renal allografts who remain growth-retarded despite optimal clinical management<sup>75,77,99</sup>, it has not yet been approved by FDA. FDA is withholding approval largely because of fears that rhGH increases the risk of acute graft rejection.<sup>117,118</sup> Indeed, evidence exists that rhGH treatment may increase the risk of immunologic attack of the renal graft.<sup>100,106,119,120</sup>

Findings from the four randomized clinical trials performed on rhGH therapy for pediatric renal patients, however, are building the case for the safety of rhGH as well as its efficacy in children resistant to other growth-promotion strategies.<sup>61,76,92,105</sup> Not only did these studies demonstrate significant improvement in growth velocity with rhGH therapy, they also found no association between rhGH therapy and either incidence of rejection or decline of graft function. Importantly, Guest et al. found that increased risk of rejection in rhGH-treated children was shown only in those patients who had experienced more than one rejection episode *prior* to start of rhGH treatment.<sup>76</sup>

The Hokken-Koelega double-blind controlled trial observed a GH-induced height velocity (HV) increment that exceeded that of the placebo group by 2.9 cm/six months. More impressively, the absolute increment from start of rhGH treatment to final height was a substantial: 10 cm. (19 vs. 9 cm).<sup>90</sup> After two years of rhGH treatment, Hokken-Koelega et al. found differences between rhGH treated and non-treated groups on the order of 15.7 cm vs. 5.8 cm in height increment, and 5.1 vs. 3.4 in height SD, respectively.<sup>92</sup> Other studies also support the case that rhGH therapy is both efficacious in promoting growth in children with CRI and does not lead to increased incidence of acute rejection or significantly reduced glomerular filtration rate (GFR).<sup>82,92,95,99,106,117-119,121-125</sup>

Across all patients, height gain under rhGH therapy is moderate, tending to decrease slightly in subsequent years but nevertheless remaining above baseline.<sup>76,102,103</sup> Its effects are not uniform, with some patients showing remarkable gains, while others do not. It is uncertain what are the factors underlying this variability. Thus, as Guest et al. recommend, “if no adverse effects occur and treatment is efficient, it appears acceptable to continue GH until target height is obtained.”<sup>76</sup>

rhGH markedly stimulates growth during the prepubertal years, resulting in twice the cumulative prepubertal height gain than that seen in the controls. Indeed, while sustained catch-up growth is observed in the treatment group, progressive growth failure occurs in control patients. Haffner et al.’s 2000 study showed a 1.4 gain in SD to a final height deficit of -1.6 SDS, compared to 0.6 loss in SD to a final height deficit of -2.1 SDS in the control group.<sup>88</sup>

Growth velocity subsequently tapers until the start of the pubertal growth spurt.<sup>88</sup> Although data on final adult height were sparse in Fine's retrospective control study of NAPRTCS children, the 13 patients reaching adulthood during study were found to have achieved a height Z score (-1.73) inside the normal growth curve. Moreover, these patients were outside normal at <-2.0 at rhGH initiation.<sup>103</sup>

rhGH therapy is the only known treatment with well-established efficacy in improving growth in the short-term in pediatric renal patients. Moreover, long-term rhGH treatment has been shown not only to induce persistent catch-up growth in children with CRI, but also to improve final adult height. Growth-retarded children on rhGH therapy have achieved adult height within the normative range of > -2 height SDS.<sup>52,90,103</sup> Further studies are needed, however, on rhGH's impact on adult height.

Absolute height gains made under rhGH treatment, from initiation of rhGH treatment to attainment of adult height, were reported to be up to 10 cm or 1.4 SDS by Haffner et al. (2000).<sup>88</sup> Janssen et al. (1997) found absolute gains of 10 cm and 14.2 cm in girls and boys, respectively, even when treatment was initiated at advanced stages of puberty.<sup>52</sup> Overall, Janssen et al. found that height SDS improved from a very sub-optimal -3.6 to a normal final adult height of, respectively, -1.8 and -1.9 in boys and girls treated with rhGH until attainment of final adult height.<sup>52</sup> These numbers actually underestimate the true growth benefit from rhGH, since to these must be added the losses in growth velocity experienced by untreated children.<sup>88</sup> Moreover, children currently on rhGH represent the most growth-retarded children among pediatric kidney transplant recipients. Less growth-retarded children receiving rhGH therapy would likely show even greater gains in height under rhGH treatment.

As noted in the 2001 NAPRTCS report, use of rhGH therapy at least partly explains the consistent improvement observed in recipient height at transplantation over the past decade. Whereas the 1987 NAPRTCS cohort had a height deficit of -2.2 at time of transplantation, the 1998 and 1999 cohorts, a portion of whom received rhGH therapy, had only a -1.5 deficit.<sup>53</sup>

Although weight gain has not been shown to be modified by rhGH treatment, rhGH treatment has been shown to improve muscle bulk and reduce fat mass (BMI), leading to improved body appearance of pediatric renal patients on corticosteroids.<sup>76,90</sup>

Despite these optimistic findings, concerns persist about the safety of rhGH therapy. The discovery of renal cell carcinoma at 9-12 years post-transplantation in two rhGH recipients indicates the need to monitor the use of rhGH in children over the long-term.<sup>126</sup> (rhGH in these two patients was administered over an unusually long period, though – about eight years.) Although fears have been allayed concerning rhGH's association with acute rejection, chronic rejection still remains a concern.<sup>106</sup>

### ***rhGH's effects on catch-down growth, bone age, and pubertal growth***

There have been fears that rhGH, particularly when administered before transplantation, will accelerate **bone age in prepubertal patients** (i.e., accelerate advancement in epiphyseal

maturation and thus diminish growth potential), thereby decreasing growth potential once puberty begins.<sup>127,128</sup> The concern is that this will reduce the growth-stimulating effects of transplantation, and effectively cancel out any statural gains made before transplantation. This phenomenon of “catch-down” growth, as it is termed, has not been observed in rhGH-treated children assessed up to five years post-transplant, however.<sup>88,103,129</sup> Fine’s (2000) controlled study of children enrolled in the NAPRTCS registry, in particular, found that rhGH administered during CRI, before transplantation, did not result in catch-down growth.<sup>103</sup>

In most studies, including in the largest randomized controlled study of rhGH use in children with renal transplants<sup>76</sup>, rhGH did not lead to acceleration in bone aging. Furthermore, bone age at transplantation has not been found to influence post-transplant growth (at two years post-transplant) or response to rhGH therapy.<sup>58,61,90,92</sup>

In the German study by Haffner et al., although rhGH did accelerate skeletal age and thus shorten the pubertal growth spurt by 6 months, it did not lead to catch-down growth.<sup>88</sup> Pubertal height gain was not compromised, nor was the onset of puberty accelerated. Instead, height gain for the rhGH treated group was more pronounced than in the non-treated group, compensating for the abbreviated pubertal growth spurt. Thus, both groups experienced the same gains through puberty, about 65% that of healthy children. (Mean adult height was still 10.1 cm below genetic target height in boys, 12.1 cm in girls.)

There has also been some debate as to the efficacy of rhGH treatment in **pubertal renal disease patients**. Although rhGH treatment is less beneficial during puberty than during the prepubertal years, findings from the German<sup>88</sup>, Dutch<sup>90,130</sup>, Belgian<sup>52</sup>, and British studies<sup>104</sup> reviewed by Haffner and Schaefer support the notion that rhGH therapy during late puberty can still be of growth benefit.<sup>57</sup>

For example, puberty onset was still delayed in children undergoing rhGH therapy in the German study – by 2.5 years.<sup>88</sup> In fact, most of the final height benefit accumulated by rhGH treatment was during the late prepubertal years, with impressive height gains persisting during puberty. No acceleration of growth was observed during puberty, however.

Other studies also give hope that renal patients can benefit from rhGH therapy once they enter the pubertal years. These include the following:

- Maxwell et al. observed significant catch-up growth during puberty in renal allograft recipients, with growth response to rhGH treatment equal in the prepubertal and pubertal treatment groups.<sup>60,61</sup> When age groups were examined, however, maximal response was observed in the very youngest transplant recipients.<sup>61</sup>
- Hokken-Koelega’s double-blind, dose-response trial observed sustained, impressive improvement of height in growth-retarded adolescents with renal allografts treated with rhGH.<sup>92</sup> Although the GH-induced increment was significantly higher in children in early puberty, even patients near the end of puberty had a marked increase in height as a result of GH therapy.

- In a multi-center, prospective study, Guest et al. found that response to rhGH was not related to either age or pubertal state.<sup>76</sup>
- In a study of pre-transplant children (on conservative treatment or dialysis), Mehls et al. found that even though half of their rhGH-treated study sample entered puberty during their first year of treatment, the sample still progressed from sub-optimal height at baseline (< -2.0 SDS) to a final, mid-parental-adjusted adult height of > -2.0 SDS.<sup>131</sup>
- Rees et al. found that growth still continued to improve after discontinuation of rhGH, so that adult height of was -2.2 SDS (still sub-optimal), compared to a baseline of -3.2 SDS.<sup>104</sup>

### ***Factors predicting response to rhGH therapy***

A number of factors have been identified as predictive of a child's growth response to rhGH treatment. These are listed below. Generally speaking, optimal responses to rhGH have been achieved in the youngest children on the lowest steroid dosage with the least time spent on dialysis, highest renal function, and most profound growth retardation at the initiation of rhGH treatment.

#### Seven predictive factors for response to rhGH therapy:

- **GFR at initiation of rhGH therapy**<sup>76</sup>
- **degree of growth retardation at initiation of rhGH therapy**<sup>76,88</sup>
  - Height gain is minimal (<3 cm) in patients with normal growth velocity (>7 cm/year) before rhGH therapy initiation. As Haffner and Schaefer note, "for unknown reasons, the efficacy of GH seems to depend on the biologic 'demand' for catch-up growth."<sup>57</sup>
  - Data from Hokken-Koelega et al.'s small, controlled study, however, found that height velocity tended to increase under GH therapy in children whose pre-GH treatment scores were relatively high.<sup>90</sup>
- **cumulative duration of rhGH therapy**<sup>88</sup>
- **steroid schedule**<sup>61,76</sup>
  - Alternate-day steroid regimen leads to better response than daily.
  - Cumulative steroid dose was the strongest predictor of reduced response to rhGH therapy in Maxwell's study.<sup>61</sup>
- **insulin resistance**<sup>76</sup> – Higher fasting plasma insulin levels at start of rhGH treatment are associated with lower growth velocity after 1 year of rhGH treatment
- **length of time on dialysis**<sup>88</sup> – The longer, the less optimal response.
- **age**<sup>61</sup> – Youngest rhGH recipients benefit most.

rhGH induces improvement in height standard deviation score (SDS) across all treatment modalities, including conservative management and dialysis.<sup>102,123,132</sup> Haffner found that the longer a child spends on dialysis, the more that child's long-term response to rhGH is compromised.<sup>57</sup>

### ***Timing of rhGH treatment***

rhGH treatment has been found to be most efficacious in pre-end-stage children<sup>88</sup>, and is typically administered until attainment of final adult height to children with persistently retarded growth even under optimal clinical management.

Haffner and Schaefer have urged that the best use should be made of the possibility to treat with rhGH before transplantation and before puberty, which appear to be the optimal times for treatment with rhGH.<sup>57</sup> Specifically, they point out that “the relationship between residual renal function and rhGH efficacy supports the concept of starting rhGH early in the course of CRI.”

It has in fact been established that patients treated sooner after transplantation experience better growth than those that go without rhGH treatment for longer periods following transplantation.<sup>76,90</sup> Again, Fine et al. observed no catch-down growth in children beginning treatment on rhGH during CRI, before transplantation.<sup>103</sup> Indeed, they found that rhGH improved growth in these children.

### **Impact of renal function on growth**

In the post-transplant child with renal disease, renal function has a profound impact on post-transplant growth.<sup>60,62,77,78,133,134</sup> This impact has been quantified. Tejani et al. found that a 1 mg/dl increase in serum creatinine level is associated with a 0.15 decrease in Z score.<sup>62</sup> Additionally, Hokken-Koelega et al. found that persistently reduced glomerular filtration rate (GFR) – that is, GFR below 50 mL/min/1.73 m<sup>2</sup> – negatively influenced catch-up growth post-transplantation.<sup>58</sup> They offer the decreased IGF bioavailability resulting from poor renal function as a possible explanation for the association. Similarly, Tejani et al. postulate that the adverse effects on growth from acute rejection are probably due to loss of graft function, and consequent rise in serum creatinine.<sup>62</sup>

Thus, preventing chronic rejection in the pediatric renal allograft recipient will not only increase patient survival rates, but also promote growth. Not only is renal function important to the direct promotion of growth, it is also essential to ensuring optimal response to rhGH therapy.<sup>57</sup>

### **Steroid use and alternative immunosuppression protocols**

Along with reduced renal function, steroid use for immunosuppression is a major risk factor for impaired growth in pediatric renal transplant recipients. Indeed, as Sheldon states, immunosuppression regimens, particularly those using glucocorticosteroids, “may be the most deleterious factor in affecting growth.”<sup>78</sup> Although the growth-retarding effects of

steroids have been noted for more than 40 years, no precise dose has yet been identified to be associated with growth retardation.<sup>55,135</sup>

As noted by Melter and Briscoe, “the mechanisms of growth inhibition by steroids are well-established.”<sup>56,136-140</sup> Pubertal growth failure despite successful transplantation is related to steroid-induced GH hyposecretion. Steroids induce a dose-dependent suppression of GH secretion, leading to a decrease in circulating GH levels. Thus, even while GH pulsatile patterns are normal, GH levels are abnormally low in children post-transplant.<sup>93,141</sup>

Not only do steroids directly inhibit growth, but they also bring about unacceptable cosmetic changes and serious orthopedic abnormalities in the transplanted child. They also cause hypertension and hyperlipidemia, and may predispose children to diabetes.<sup>56</sup>

### *Steroid-sparing strategies*

Treatment with immunosuppressants, usually prednisone, following transplantation is necessary to prevent the immune system of the transplanted child from attacking the new renal graft. Fortunately, immunosuppressive alternatives to steroids exist that do not have the growth-retarding effects of steroids. These include tacrolimus (a calcineurin inhibitor – CNI – as is cyclosporine)<sup>142-144</sup>, deflazacort<sup>94</sup>, interleukin-2 receptor (IL-2R) blockade therapy, which includes use of basilizumab and daclizumab<sup>145-148</sup>, blockade of the CD40 ligand-CD40 (CD40L-CD40) costimulatory pathway<sup>149-151</sup>, and mycophenolate mofetil therapy (MMF)<sup>152-154</sup>. Cyclosporine monotherapy is increasingly being investigated in pediatric renal patients as well.<sup>144,155</sup> Promising growth findings from clinical trials of these novel agents contrast with the more growth-retarding effects of steroids. These are discussed in the ensuing sections.

Various steroid-sparing strategies are being investigated to promote growth in pediatric recipients, while protecting the graft from immunological attack. Most of these strategies involve some measure of steroid use, in either the immunological induction or maintenance phase following transplantation. Pending approval of novel, immunosuppressive alternatives to steroids, investigators are looking into the safety and efficacy of alternative steroid schedules. These include alternate-day steroid therapy (as opposed to daily therapy) and steroid tapering (gradually reducing cumulative steroid dosage).

It is generally understood that optimal catch-up growth can be achieved only through complete steroid avoidance, or steroid withdrawal 6–12 months post-transplant after aggressive induction therapy. Children with renal allografts have been successfully withdrawn from steroids<sup>142,144</sup> and indeed prevented from taking steroids altogether.<sup>152</sup>

Children on alternate-day steroids show better catch-up growth after renal transplantation than those on daily steroids.<sup>58,75</sup> Safety concerns regarding alternate-day therapy, however, have been raised. Furthermore, an alternate-day steroid schedule has been found to lead to better response to rhGH therapy.<sup>61,76</sup> The physiologic mechanism underlying the clinical finding of improved growth in children on alternate-day steroid therapy has yet to be precisely determined.



Well-grounded fears of acute graft rejection in the absence of steroidal renoprotection, however, have prevented the wholesale avoidance of steroids in regular clinical practice. Also fueling fears are studies conducted before the surge in development of novel immunosuppressive agents. These studies show high incidences of rejection upon complete withdrawal of steroids in renal recipients.<sup>155,156</sup>

Even alternate-day steroid schedules may increase a child's risk of acute graft rejection. In one of the most striking findings from Hokken-Kolega's 1994 controlled study, 55% of alternate-day prednisone patients were assessed with a >25% decline in renal function, contrasted with only 14% on daily prednisone. The authors speculate that rhGH stimulated the immune system on the steroid-free day, thus precipitating graft deterioration.<sup>92</sup>

Optimistic investigators, however, have proposed that it may be possible to identify patients who can safely undergo complete steroid withdrawal via use of reliable immune markers.<sup>156</sup> Only then can the idea of complete steroid withdrawal be seriously considered. Markers would also inform clinicians of the need to reintroduce steroid treatment before signs of graft dysfunction become clinically manifest.

Meanwhile, the mechanisms underlying the success of alternate-day regimens are not clear. It has been found that daily steroids do not suppress endogenous GH secretion any more than alternate-day steroids do, regardless of pubertal stage.<sup>93</sup> This finding is in contrast with the general literature on the deleterious effects of steroids on growth, however.

The safety and efficacy of various steroid-sparing regimens currently under investigation are discussed below.

### ***Steroid-withdrawal strategies: tacrolimus-based regimens***

Two major, recent clinical studies have assessed the safety and efficacy of tacrolimus-based steroid withdrawal in pediatric renal transplant recipients. These analyses were conducted by Shapiro and Ellis et al.<sup>142,143</sup>

- **Shapiro:** Reviewing the results from the largest series of children withdrawn from steroids using tacrolimus – the University of Pittsburgh series – **Shapiro** (1998) reports that 66% of successfully transplanted pediatric renal allograft recipients were successfully taken off steroids.<sup>142</sup> These children subsequently demonstrated substantial catch-up growth, with Z scores rising from –2.3 at transplantation to an impressive +0.36 at 4 years post-transplantation. On the other hand, those on steroids only achieved a Z score of –0.6 at 4 years post-transplant.

Again, age at transplant was an important factor in height gain in this study: those transplanted at less than 12 years of age had a Z score of +0.84 at 4 years post-transplant, compared with only –1.6 for those over age 12. Patient and graft survival, moreover, was good (94% and 84%, respectively), as was renal function (mean serum creatinine of 1.1 mg/dl). Not incidentally, 80% were able to stop anti-hypertensive medication, also shown to adversely affect growth. The biggest concern in the children under the tacrolimus-based regimen was a relatively high

incidence of EBV-associated post-transplant lymphoproliferative disorders (PTLD; ranging from 4-17% during different periods studied).

- **Ellis et al.** (2000) also found that steroid withdrawal using a tacrolimus-based immunosuppression impressively stimulated growth without significantly compromising graft function or promoting obesity at three years post-transplant.<sup>143</sup> Indeed, normalization of growth was achieved. At three years post-transplant, they observed that children undergoing transplantation at 0-5 and 13-16 years of age realize the greatest improvements in growth velocity (1.51 SD and 1.57 SD change in Z score at 3 years post-transplant, respectively). Children ages 6-12, however, also demonstrated sustained growth with no diminution of growth velocity (0.37 SD). Rates of failure of steroid withdrawal and graft dysfunction/loss were low: only 13% and 7%, respectively. In contrast to previous reports showing decreased renal function over time post-transplantation, GFR at 3 years was as good in the steroid-free group as at 1 and 2 years. The investigators still caution that tacrolimus-based withdrawal should be further studied for its more long-term effects on GFR and allograft survival.

The Ellis et al. study is particularly important in that it shows that children with an average age of 15.4 years are capable of excellent and sustained growth at 3 years post-transplant. This finding challenges the paradigm that holds that children transplanted between age 13 and 18 grow poorly or not at all even with no or reduced steroid therapy.

### ***Steroid-withdrawal strategies: cyclosporine (CyA) monotherapy***

Two major, recent clinical studies have examined the safety and efficacy of steroid withdrawal using cyclosporine monotherapy in pediatric renal transplant recipients. These were conducted by Klare et al. (1991) and Ghio et al. (1992):<sup>144,155</sup>

- **Klare et al.** (1991) found that remarkable gains in height could be achieved in children under cyclosporine monotherapy, shown in a height SDS improvement from -2.3 at transplant to -0.6 seven years post-transplant. Equally remarkable was the proportion of children able to withdraw successfully from steroids – 70%. Graft function remained acceptable, too, with serum creatinine less than 2.0 mg/dl.<sup>144</sup>
- **Ghio et al.** (1992) found that it was possible to maintain a high percentage of children on cyclosporine A (CyA) alone, with subsequent “resolution of the Cushingoid stigmata”, maintenance in GFR, and reduction in the need for anti-hypertensive medication.<sup>155</sup> It must be noted that about 30% of the original 29 patients in this study who were candidates for withdrawal had to return to steroids; but, steroids were again stopped for about half of them.

### ***Steroid-withdrawal strategies: immunological blockades***

One possible strategy for steroid withdrawal is blockade of the interleukin-2 receptor or CD40L-CD40 costimulatory pathway as induction therapy, followed by a lower dosage of steroids and MMF for maintenance therapy. Multi-center studies on the efficacy of IL-2R

blockade as induction therapy are underway in the U.S., Canada, and Europe.<sup>145,146</sup> Pre-clinical studies have demonstrated the efficacy of CD40L-CD40 “costimulatory blockade” as induction therapy.<sup>149</sup> The CD40L-CD40 blockade, which uses a humanized monoclonal antibody, is unique in that it inhibits alloantibody production (thereby protecting the child from graft rejection) while allowing targeted costimulatory T-cell activation.<sup>151</sup>

Alternatively, after aggressive induction therapy by steroids for 6-12 months post-transplant, MMF could be used for maintenance therapy after withdrawal of the steroids.

### ***Steroid-sparing strategies: deflazacort***

Only one major study in pediatric renal transplant recipients has examined the safety and efficacy of deflazacort, a glucocorticoid with less pronounced side effects than prednisone. This study was conducted by Ferraris et al. (1992):

- **Ferraris et al.** (1992) have observed significant short- and long-term (4 years) growth improvement in prepubertal kidney transplant recipients who switched from methylprednisone to deflazacort therapy.<sup>94</sup> Increased linear growth velocity under deflazacort was accompanied by increases in serum GH concentrations, decreases in weight/height ratio and Cushingoid appearance, and stable renal function. Growth rates in half the patients were at least 2 cm/year.

The findings of Ferraris et al., however, remain to be corroborated by additional studies examining deflazacort’s safety and efficacy. Moreover, deflazacort is currently unavailable in many parts of the world.

### ***Steroid avoidance using daclizumab***

The only study so far examining complete avoidance of steroids in pediatric renal transplant recipients was the controlled study by Sarwal et al. (2001):

- **Sarwal et al.** observed an abundance of positive outcomes in children receiving treatment under a steroid-avoidance immunosuppressive protocol involving extended use of daclizumab, in combination with tacrolimus and mycophenolate mofetil therapy (MMF).<sup>152</sup> Not only was growth superior to that in controls on steroid-based immunosuppression, but there was also no increased incidence of chronic rejection (either clinical or subclinical), hypertension requiring treatment, hypercholesterolemia, proteinuria, or bacterial infection at 6 months post-transplantation.

Moreover, the lack of cosmetic side effects in the steroid-free patients bodes well for compliance, further decreasing the likelihood of graft rejection. The steroid-free group did tend towards anemia and lower white blood cell counts compared to the steroid-based group (remedied by erythropoietin and granulocyte-colony stimulating factor – G-CSF). This finding suggests that steroids may stimulate erythropoiesis, and that anemia may be a risk in steroid avoidance regimens. The findings also suggest that steroid dependency does not develop if a child has not been previously exposed to steroids.

### *Alternate-day steroid therapy*

Several studies support the efficacy of alternate-day therapy in promoting growth in children with renal transplants. Safety concerns are yet to be satisfactorily resolved, however, as to whether or not alternate-day therapy leads to reduced graft function.<sup>92</sup>

Renal function was not found to decrease under alternate-day therapy in the following studies:

- In the **2001 NAPRTCS report**, alternate-day patients demonstrated a height improvement of +0.31 in Z score, compared to a worsening of -0.06 in patients on daily steroid therapy.<sup>53</sup> Furthermore, growth was enhanced without adverse impact on graft function or graft survival.
- **Jabs et al.** (1996) found that alternate-day therapy in NAPRTCS children more than one year post-transplant achieved a +0.5 SD change in height compared to +0.1 for those on daily steroids. Furthermore, graft survival and graft function was not adversely affected.<sup>157</sup>
- **Broyer et al.** (1992), in a randomized, controlled study from 1992, found that both pubertal and prepubertal patients receiving alternate-day steroid therapy experienced improved growth compared to patients on daily therapy (+0.49 SD/year vs. -0.12 SD/year; and 6.2 cm/year vs. 3.8 cm/year).<sup>158</sup> Moreover, growth benefits from alternate-day therapy were not at the expense of renal function, as determined by histologic examination, or blood pressure. Follow-up was only 1-2 years, though.

The Broyer study is important in that it shows statural gains, albeit non catch-up growth, in pubertal patients. Pubertal alternate-day patients achieved an increase of +0.30 SD/year compared to the loss of -0.22 SD/year shown in pubertal daily patients. Prepubertal patients in the alternate-day group did achieve catch-up growth: a +0.61 SD/year gain in height, compared to +0.04 SD/year in the daily group.

Renal function was found to decrease under alternate-day therapy in the following studies:

- **Hokken-Koelega et al.** (1994), in a randomized, controlled study from 1994, found that alternate-day prednisone therapy was associated with a greater than 25% reduction in GFR; 55% of alternate-day prednisone patients had a >25% decline in renal function, compared with only 14% on daily prednisone.<sup>92</sup>
- **Kaiser et al.** (1994) also found that growth was markedly improved among those successfully converted to alternate-day steroid regimen compared with those who failed to convert to this regimen, and instead had to take steroids daily.<sup>159</sup> Patients in the alternate-day steroids group showed catch-up growth, growing at a rate above the normal mean, while those in the daily steroids group did not. Mean growth velocity SD scores based on chronological age for the successful alternate-day group were an

impressive +0.94 , compared to -0.86 for the failed group. (Bone age SD scores were +0.49 for the alternate-day group, compared to -1.24 for the failed group.)

An up to 30% risk of rejection and loss of renal function, however, was found in children converting to alternate-day steroid therapy. Two factors appeared to significantly improve the likelihood of successful conversion to alternate-day steroid therapy (i.e., remaining on it for > 1 year): use of cyclosporine A and a living-related donor source. Graft rejection prior to beginning alternate-day steroids predicted failure of conversion (recalling Guest's similar finding regarding rhGH therapy<sup>76</sup>).

### **Other risk factors for impaired growth following renal transplantation**

Other risk factors for impaired growth following transplantation include the following:

- donor source (cadaveric vs. living)
- avoidance of anti-hypertensive therapy
- azathioprine therapy
- persistent renal osteodystrophy (ROD)
- race

Donor source and avoidance of anti-hypertensives each account for a gain of about 0.3 standard deviations towards the healthy children's average height. The effects of donor source as a risk factor is unclear, though. Although kidney grafts from living donors (LD) are presumed to predict better growth than grafts from cadaveric donors (CAD)<sup>159</sup>, recent NAPRTCS data have indicated otherwise: at 5 years post-transplant, living donor recipients showed no improvement in mean height deficit over baseline.<sup>77</sup>

Analyses comparing growth between living donor and cadaveric donor recipients may be subject to bias or confounding, however, given the differential survival between the two groups. In other words, if more CAD recipients die than LD recipients, then the remaining LD and CAD recipients may be comparable as far as growth potential anyway. Those CAD recipients who died may have had less growth potential than the surviving CAD recipients. Indeed, as Tejani observed in their 1993 study of 300 children enrolled in NAPRTCS, a child with a well-functioning cadaver graft had the same potential for sustained growth for two years post-transplant as a child with a living-related donor graft.<sup>62</sup>

Avoiding anti-hypertensive therapy during the first month following transplantation is associated with growth acceleration in the first two years post-transplant as well as with maintenance of this improved velocity at three years post-transplant.<sup>53</sup> With respect to race, African-American and Hispanic children with renal transplants tend to demonstrate negative changes in Z scores, whereas Caucasians are more likely to demonstrate positive changes.<sup>160</sup> Azathioprine therapy has also been found to have a negative impact on post-transplant growth.<sup>58</sup>

Diagnosis has been correlated with growth insofar that pediatric patients with aplastic or hypoplastic kidneys (congenital lesions) or with obstructive uropathy as the cause of end-stage renal disease (ESRD) have been found to have greater initial height deficit.<sup>62</sup>

### **Pediatric renal transplant recipients compared to pediatric cardiac and hepatic transplant recipients**

Since progressively later age at transplantation has a progressively adverse effect on growth, it is likely that growth deficit in pediatric kidney disease is more pronounced than in pediatric liver or heart disease. Unlike children with liver or heart disease, kidney patients can wait longer before transplantation is absolutely indicated, since they have recourse in the meantime to such alternative renal replacement therapies as dialysis. Likewise, it may be supposed that differences in steroid treatment schedules result in less pronounced growth in renal patients: whereas liver patients can undergo steroid withdrawal over time, renal patients are more prone to require indefinite, daily immunosuppressive maintenance therapy. Findings in the comparative research on growth after kidney vs. liver transplantation in children, however, have not consistently supported the notion that growth is more retarded among kidney patients.

Pasqualini et al. found growth to be more impaired in children with kidney transplants than in children with liver transplants.<sup>161</sup> This finding was reinforced by observations that IGF-I levels and IGF bioavailability were also higher in pediatric liver transplant patients.

On the other hand Sarna et al. found, in two studies, that children with liver transplants were more growth-retarded than children with kidney transplants.<sup>20,162</sup> This despite similar triple immunosuppression used in both groups, and lower cortisol concentration in the hepatic patients.

### **Summary (Kidney – growth)**

Growth in children with end-stage renal disease (ESRD) and kidney transplants has historically been sub-optimal, but has improved over the past decade. Optimizing the growth of pediatric renal transplant recipients begins with good clinical management, starting at the earliest phases of chronic renal insufficiency (CRI). This includes adequate nutrition to maximize height at the time of transplantation. Clinical management continues well after transplantation with the minimization of cumulative steroid dosage (at 6-12 months post-transplant) by either tapering doses or use of alternate-day schedules, and the optimization of graft function. In persistently growth-retarded children resistant to other growth-promoting strategies, therapy with recombinant human growth hormone (rhGH) may be indicated up until the time they achieve final height. Of all clinical interventions, transplantation in children before six years of age has the greatest beneficial effect on subsequent statural growth.

Clear indications for rhGH therapy, however, are still pending results of efficacy studies that follow transplanted children until final height is attained. It is also hoped that further clinical research will also establish the safety, as well as efficacy, of novel immunosuppressive alternatives to steroids. Attainment of adult height, not just growth velocity, needs to be followed in these studies.

## Recommendations from the panel of experts (Kidney – growth)

- Further investigate the safety and efficacy of **non-steroidal immunosuppressive drugs** in studies with long-term follow-up. Studies on tacrolimus, for example, should follow children longitudinally for up to 10 years post-transplant at least.
- Initiate formal studies with several years' follow-up to investigate the potential for **alternate-day steroid use** to increase the risk for **graft deterioration**. Investigate the possibility that increased graft rejection under an alternate-day regimen is due to decreased compliance with medications, which in turn may result from the patient's discouragement at not perceiving immediate beneficial effects. Children initiating this new regimen may start out with unrealistically optimistic hopes for growth enhancement, then stop medications in discouragement when they do not perceive immediate height gains or stoppage of other side effects.
- Perform studies to determine why pediatric **liver and heart** transplant recipients withdraw from steroids **more successfully** than pediatric **kidney** transplant recipients do.
- Further investigate ways to allow **steroid avoidance or withdrawal**, with avoidance the best option for optimizing growth.
- Further investigate the role of steroids in stimulating **erythropoiesis** (red blood cell production), and risk for **anemia** under non-steroidal immunosuppression regimens.
- Investigate the possibility that **recombinant human growth hormone (rhGH)** therapy is needed **during puberty** to improve the pubertal growth spurt.
- Further investigate the **safety of rhGH therapy**.
- Gather more data on **final height attainment under rhGH therapy** (i.e., follow up children under rhGH therapy until they reach their adult height).
- Establish a methodology to **determine genetic target height**. Target height should reflect or be similar to the 50<sup>th</sup> percentile for mid-parental height (i.e., the average of the heights of the two parents). Growth curves, which do not use mid-parental height, do not take into account the child's genetic height potential.

*For example, if a child attains a final adult height in the 10<sup>th</sup> percentile for height, and the average of his two parents' heights is in the 10<sup>th</sup> percentile for height, that child would be considered stunted according to the standard growth curves. However, the child would really have attained his/her true, genetic target height. On the other hand, if the average of the parents' combined heights is higher than the 10<sup>th</sup> percentile, then that child would be considered to have achieved sub-optimal final adult height.*

## Recommendations from expert-selected studies from the literature (Kidney – growth)

- Greater patient entry and longer follow-up are needed to assess sustained beneficial effects of steroid-free regimen on growth potential, longer-term graft function, risk factors such as hypertension and hyperlipidemia.<sup>152</sup>
- Definitive conclusions on improved growth potential due to steroid-free regimen are not possible without larger sample and longer follow-up.<sup>152</sup>
- “Longer follow-up is also needed to gain better insights into improved growth patterns in children with growth potential in a steroid-free versus a steroid-based environment.”<sup>152</sup>
- Investigate role of steroid absence in minimizing interstitial fibrosis.<sup>152</sup>
- Investigate whether it was absence of steroids or absence of cyclosporine A that contributed to absence of hypercholesterolemia in steroid-free group.<sup>152</sup>
- Investigate early role of steroids in erythropoiesis to possibly provide explanation for higher rates of anemia in steroid-free subjects.<sup>152</sup>
- Studies on growth pre- and post-Tx should also focus on obesity.<sup>143</sup>
- Determine if GFR remains stable in children receiving steroid-free tacrolimus-based immunosuppression - particularly given possibility that late ACR decreases allograft survival.<sup>143</sup>
- Further investigate the possibility of converting children with renal Tx to low-dose and/or alternate-day steroid regimen.<sup>60</sup>
- Look into growth benefits of pre-emptive Tx.<sup>60</sup>
- Caveat: It is very difficult to study the effects of rhGH on graft function in isolation because of the relationship between rejection and GFR.<sup>61</sup>
- “Investigate causation of increase in creatinine at start of rhGH treatment: “It is difficult to determine whether rhGH has decreased GFR, if there has been an increase in muscle bulk, or if this is the natural progression of chronic rejection.”<sup>61</sup>
- Conduct studies to see if rhGH benefits final height, particularly if it is not started until puberty. Continue studying the effects of rhGH treatment on duration of the pubertal growth spurt.<sup>61</sup>
- “Further investigations are needed to determine whether pubertal maturation is influenced by GH or interferes with the growth-promoting effect of GH in transplanted children.”<sup>76</sup>
- Further investigate negative correlation between insulin resistance and reduced growth velocity after 1 year of rhGH therapy, esp. in context of glucocorticoid’s effects on different tissues (hepatic, bone cartilage). The same glucocorticoid dose may inhibit growth in one patient and not the other due to individual glucocorticoid pharmacokinetics.<sup>76</sup>



- Further elucidate effect of GH on GFR.<sup>76</sup>
- Determine the long-term effects of hyperinsulinemia in association with GH treatment.<sup>76</sup>
- “Psychological tolerance must also be considered. Some patients did not tolerate daily GH subcutaneous injections.”<sup>76</sup>
- In rhGH studies, continue rhGH treatment in pediatric RTx patients under study until they have attained final height.<sup>90</sup>
- Conduct controlled as opposed to uncontrolled trials to avoid overestimation of growth-promoting effects of GH therapy, since increased professional involvement with patient and family inevitably resulting from their enrollment in study even has growth-promoting effect on placebo patients.<sup>90</sup>
- Perform research to elucidate the biological function of the IGF binding proteins - are elevated concentrations of IGFbPs involved in the growth retardation typically following RTX by inhibiting the bioavailability of the IGFs?<sup>90</sup>
- Perform research to elucidate the effects of prednisone on growth retardation: do steroids directly inhibit cartilage and bone matrix formation or are steroid effects more intermediary, affecting IGF-I production or suppressing endogenous GH secretion? (may be irrelevant in light of new study findings on steroid alternatives?)<sup>90</sup>
- Conduct long-term studies to assess fully any impact of GH therapy on graft function/deterioration.<sup>90</sup>
- Well-controlled, long-term studies are need to verify that the following to do not increase the risk of renal allograft deterioration:
  - alternate-day steroid regimens<sup>58</sup>
  - CyA treatment<sup>58</sup>
- Elucidate mode of action of steroids in inhibiting growth - is there prednisone-induced inhibition of local IGF-I gene expression?<sup>58</sup>
- Further investigate the role of reduced GFR in post-RTx growth retardation - is it mediated by reduced IGF-I bioavailability?<sup>58</sup>
- Investigate correlation between successful conversion to alternate-day steroids and length of time period between conversion and Tx (longer time may lead to more conversion success).<sup>159</sup>
- Conduct studies to determine if remaining on daily steroids results in longer allograft survival compared to alternate-day steroids.<sup>159</sup>
- Conduct studies to determine if final height is truly affected by growth-promoting approaches (e.g., steroid-sparing strategies and rhGH therapy).<sup>159</sup>

- “Effects of GH are more difficult to evaluate during puberty... a placebo-controlled study would only provide valuable data if patients were matched and paired before the start of the study on the basis of several variables, including pubertal stage, which is unlikely to be feasible.” (authors did do placebo-controlled study subsequently, but I don’t think with this level of matching described here)<sup>92</sup>
- Perform further studies on relative merits of alternate-day vs. daily use of steroids.<sup>92</sup>
- “...it seems worthwhile to investigate the optimal prednisone regimen for the duration of GH therapy.” (again, perhaps becoming moot in light of development of new drug alternatives to steroids?)<sup>92</sup>
- Conduct a controlled trial of recombinant growth hormone post-RTx, with proper stratification for immunosuppressive dosage, serum creatinine level, and other risk factors.<sup>62</sup>
- Further studies are needed to elucidate the mechanisms whereby growth is 1) retarded in pediatric renal disease and 2) promoted by GH treatment. For example, determine whether PDN’s inhibitory effect on bone matrix formation is direct or mediated by modulating local IGF-I effects. Perhaps PDN’s induction of increased IGFBP-3 levels causes a decrease in IGF-I bioactivity.<sup>93</sup>
- Longer follow-up periods are necessary to exclude significant worsening of renal function/GFR and an increased incidence of chronic rejection after stopping steroids.<sup>155</sup>
- Although substituting deflazacort for maintenance MP therapy leads to an improvement in the growth and metabolic prognosis of children with successful RTx, additional and larger studies are needed to justify widespread use of deflazacort post-RTx.<sup>94</sup>
- Conduct studies to further elucidate the mechanisms whereby:
  - glucocorticoids inhibit growth, particularly in light of finding here that growth velocity improved in absence of an increase in IGF-I.<sup>94</sup>
  - deflazacort inhibits growth less than other steroids: does it not reach the hypothalamic or pituitary circulation?<sup>94</sup>
- More studies are needed on the association of circulating GH levels and growth velocity in puberty, and between pubertal stages (both in normal and pediatric renal patients).<sup>141</sup>
- Longitudinal data are needed before firm conclusions can be made about relationship between GH characteristics and growth in CRF.<sup>141</sup>
- “Appropriate prospective studies should be performed to identify which factors affect pubertal growth in {pediatric post-RTx} patients.”<sup>87</sup>
- “Evaluation of the development of hormonal changes is especially important” in studies of sexual maturation after transplantation.<sup>87</sup>

- Caveat: Predicting growth post-RTx based on delay of bone maturation relative to chronologic age is too optimistic.<sup>87</sup>

### **Clinical recommendations based on individual studies (Kidney – growth)**

- “We believe that a completely steroid-free immunosuppressive milieu from the beginning should, by exclusion, not give rise to a steroid-dependant suppression of the immune response, which makes either steroid withdrawal or alternate dosing hazardous for rebound acute rejection.”<sup>152</sup>
- Combination and balance of immunosuppressive drugs in a steroid-free regimen may be efficacious in preventing subclinical acute and chronic rejections, with “subsequent better preservation of graft function”.<sup>152</sup>
- Close monitoring of patients for PTLD, especially those EBV seronegative.<sup>163</sup>
- It is recommended to get a baseline set of IgG and IgM antibodies to antigen prior to Tx and EBV titer in presence of viral symptoms post-Tx in previously seronegative patients.<sup>163</sup>
- Early surgical intervention and reduction in tacrolimus dose once PTLD occurs.<sup>163</sup>
- “Future strategies for transplant immunosuppression may focus on a steroid-free milieu...however, for a large number of children with a functioning transplant and growth retardation, the use of rhGh is the only solution.”<sup>77</sup>
- Ensure that children at risk for Epstein-Barr virus-related post-Tx lymphoproliferative disease are diagnosed and treated prior to selecting them for tacrolimus monotherapy.<sup>143</sup>
- Carefully consider risks of continuing GH after a first rejection during GH treatment: an episode during treatment was associated here with a high risk of further episodes and eventual graft loss.<sup>76</sup>
- With respect to predicting individual sensitivity to glucocorticoid treatment by relating adrenal suppression to growth: Adjust long-term glucocorticoid dose according to the AUC for methylprednisolone to improve growth and minimize need for rhGH treatment; in this study the upper limit for MP, above which adrenal suppression and growth inhibition occur, was 650 µg/L. Relationship between AUC and growth is strongest for liver Tx.<sup>20</sup>
- CyA and methylprednisolone should be administered on an individual and age-dependent basis.<sup>162</sup>
- “Optimization of pretransplant height appears very important,” for optimizing growth outcome.<sup>58</sup>
- After RTx, administer alternate-day prednisone, minimal cumulative dose of prednisone, and CyA instead of Aza treatment, and maintain a GFR above 50

mL/min/1.73 m<sup>2</sup> to optimize post-Tx growth. “Immunosuppressive treatment with cyclosporine therapy in combination with a minimal dose of alternate-day prednisone would then result in optimal post-transplant growth, particularly if the GFR remains above 50 mL/min/1.73 m<sup>2</sup>.”<sup>58</sup>

- “Each pediatric nephrologist must decide whether the risk associated with conversion {to alternate-day steroids} is worth the potential for improved growth in a given patient.”<sup>159</sup>
- Biosynthetic GH treatment followed by alternate-day prednisone treatment is recommended for optimizing height.<sup>75</sup>
- Preemptive Tx for remediating severe growth retardation does not appear to be recommended.<sup>75</sup>
- Investigate role of reduced GFR in retarding growth - does it occur via increased serum IGFBP levels together with reduced IGF bioavailability?<sup>75</sup>
- Well-controlled, long-term studies are needed (as of 1994) to verify an alternate-day steroid regimen does not increase risk of graft deterioration.<sup>75</sup>
- “If other studies confirm that children who undergo Tx > age of 13 years do not grow, and may as a group lose height, a modification of the national organ procurement and transplantation network {UNOS} organ-sharing criteria might be necessary, because children > 10 years of age do not currently receive additional points for a preferential allotment of a cadaver kidney.” (i.e., UNOS should give more precedence to children >10 years of age awaiting a kidney since they could realize greater growth potential post-Tx if transplanted before age 13.)<sup>62</sup>
- The study data do not support the proposition that growth would be better with preemptive RTx (i.e., without previous dialysis).<sup>62</sup>
- Pediatric Tx physicians must face dilemma that whereas there is greater mortality in children < 2 years of age undergoing Tx, there is also maximal growth benefit when Tx occurs at this age.<sup>62</sup>
- Stopping corticosteroids should be considered when graft survival is good, in order to promote maximal linear growth of the post-RTx child.<sup>155</sup>
- CyA’s efficacy suggests that “...other treatments, such as {growth} hormonal therapy, should be reserved for patients who have not stopped taking steroids.”<sup>155</sup>
- “We believe that this work provides additional evidence for switching children with renal transplants to an alternate-day corticosteroid regimen.”<sup>158</sup>
- Recombinant GH therapy should be considered in children with CRF with poor pubertal growth, particularly those with growth failure and insufficient endogenous GH secretion.<sup>141</sup>

## GROWTH: LIVER

Points made in the following reviews have been incorporated in the following section on growth in pediatric liver transplant patients:

- Fine (2002) <sup>54</sup>
- Reding (2000) <sup>19</sup>
- McDiarmid (2000) <sup>18</sup>
- Kelly (1997) <sup>164</sup>

Additional reviews consulted include the following:

- Everson et al. (1999) <sup>165</sup>
- Maes et al. (1997) <sup>166</sup>
- Balistreri et al. (1995) <sup>21</sup>

### **Pre-transplant risk factors and strategies for growth improvement**

Growth failure in patients with chronic liver disease occurs in 56-80% of patients (two studies cited by Kelly, 1997).<sup>164</sup> Moreover, numerous studies show that overall 60% of patients demonstrate severe malnutrition (defined as height or weight 2 standard deviations {SD} below the mean) at the time of transplant assessment (see review by Kelly, 1997)<sup>164</sup>.

Malnutrition in the pre-transplant period is recognized as one of the few preventable variables affecting both pre- and post-transplant mortality (McDiarmid, 2000).<sup>18</sup> It was also noted that anthropometric measurements rather than weight would provide more reliable indicators of malnutrition because of treatment effects on fluid retention following transplantation. Because of behavioral feeding problems in 60% of children, supplemental enteral feeding may be necessary (reviewed by Kelly, 1997).<sup>164</sup>

In children with end-stage liver disease (ESLD), the greatest retardation occurs at less than 5 years of age (SPLIT Research Group, 2001).<sup>167</sup> Reports of standardized height in the pre-transplant period vary from -1.2 to -1.7; the standardized height reported in the most recent annual report from the Studies of Pediatric Liver Transplantation (SPLIT) research group is -1.3 (SPLIT Research Group, 2001).<sup>167</sup>

Other pre-transplant factors that are believed to affect growth after transplantation are age at the time of transplantation and the specific diagnosis of liver disease (*discussed further below*).

## Catch-up growth following liver transplantation

There have been several important studies cataloging growth in liver transplant recipients over the past ten years. The largest single center study was done by McDiarmid et al. (1999).<sup>168</sup> The recent SPLIT report (2001) shows similar findings.<sup>167</sup> Most children approaching liver transplantation have growth failure, that may actually get worse during the first 6 months post-transplant. Growth in weight occurs during the first year post-transplant. Children then appear to begin “catch-up” linear growth during the second 12 months after liver transplantation. Still many have negative standardized (SDS) scores for height even many years after liver transplantation.

There are suggestions from the literature that the incidence of catch-up growth after liver transplantation has been increasing. Andrews et al. (1989)<sup>169</sup> reported 59% catch-up growth, while Beath et al. (1993)<sup>170</sup> and Codoner-Franch et al. (1994)<sup>171</sup> reported 80% (discussed in Kelly, 1997).<sup>164</sup>

However, a number of studies have shown that normal linear growth is not restored following liver transplantation, despite excellent graft function (see McDiarmid, 2000).<sup>18</sup> Thirty-one percent of patients were found to be at less than the 5<sup>th</sup> percentile both before and after transplantation (Moukarzal, 1990).<sup>172</sup>

Several studies provide longer-term height outcomes after liver transplantation. McDiarmid et al. (1999) reported that standardized height improved from -1.7 to -1.4 at 5 years, but the actual height deficit was increased.<sup>168</sup> Similarly, Viner et al. (1999) found the Z score to improve from -1.2 to -0.84 at 7 years, with the mean final height being -0.55.<sup>173</sup> Asonuma et al. (1998) also reported significant improvement in height/weight Z scores between the pre-operative period and the last follow-up.<sup>174</sup> There is currently insufficient data on adult final height (Fine, 2002).<sup>54</sup> (*see additional data under rhGH therapy*)

Greatest catch-up growth following liver transplantation is associated with age of less than 2 years (SPLIT Research Group, 2001).<sup>167</sup> At ages up to 2 years, standardized height (Z score) is reported to improve from -1.8 to -1.3 at 18 months (SPLIT Research Group, 2001)<sup>167</sup>, while one study reported poor growth velocity (Condoner-Franch et al., 1994).<sup>171</sup> These results suggest possible growth benefits of pre-emptive transplantation. Similarly, McDiarmid (2000) recommended that delays should be “assiduously” avoided in listing children who meet the medical criteria for liver transplantation, since better growth generally occurs when transplantation is performed earlier.<sup>18</sup>

Improved growth after transplantation does not invariably occur, however. It is in large measure dependent on type of liver disease. In some cases, for example in children with biliary atresia/failed Kasai procedure, growth failure may be a manifestation of severe liver disease that is associated with malnutrition and amenable to correction by liver transplantation. In these cases, growth is likely to improve upon transplantation. (Most liver transplant patients under 2 years of age have biliary atresia.) In other cases, as in Alagille Syndrome, the child suffers from a multi-system problem not necessarily correctable by transplantation. In these cases, transplantation is not likely to lead to catch-

up growth. Finally, along with considerations of disease type, post-transplant survival must be considered

The impact of initial diagnosis on catch-up growth is at present inconclusive (discussed in Kelly, 1997).<sup>164</sup> McDiarmid et al. (1999) recently reported the following changes in standardized height (delta Z scores) for three distinct diagnoses: biliary atresia (+0.70), liver tumor (-0.92), and hepatic failure (-1.02).<sup>168</sup> However, the better growth rate in patients with biliary atresia might be attributable to 1) an earlier age at transplantation, 2) magnitude of the growth failure in the pre-transplant period, and, importantly, 3) the lack of irreversible, multisystem disease associated with this condition. Catch-up growth is initially greater in patients with greater initial growth deficit, but subsequent normalization of growth is less likely to occur. In contrast with other diagnoses, patients with Alagille Syndrome and Familial Cirrhosis did not show catch-up growth (Viner et al., 1999).<sup>173</sup> As one possible explanation, it was suggested that patients with Alagille Syndrome may be resistant to nutritional supplementation (see Kelly, 1997).<sup>164</sup>

Bivariate and multivariate models have been used to identify the significant predictive factors for standardized height after liver transplantation (McDiarmid et al., 1999).<sup>168</sup> These factors are: baseline height Z score, follow-up time, age at transplantation, diagnosis of tumor, diagnosis of fulminant liver failure, retransplantation, graft dysfunction, post-transplantation lymphoproliferative disorders (PTLD), and stoppage of prednisone.

### **rhGH therapy**

Supplemental treatment with recombinant human growth hormone following liver transplantation is reported by Sarna et al (1996) to improve growth velocity from 3.2 to 7.1 cm/year, with a resulting change in Z score of -3.9 to -3.1.<sup>175</sup>

### **Steroid-sparing strategies**

Several studies have suggested that daily steroids are a risk factor for delayed or sub-optimal “catch-up” growth. It has also been suggested by Sarna (1995, 1997) that steroids may not be metabolized equally in all liver transplant recipients and that higher levels of exogenous cortisol activity may be a risk factor for poor growth in individual patients.<sup>162,176</sup> Several authors have advocated early steroid withdrawal. However, the window for safe steroid withdrawal has never been adequately established.

Studies demonstrating the negative impact of chronic steroid administration on growth retardation at periods between 6 months and 4 years post-transplantation have been reviewed by Reding (2000).<sup>19</sup> As further evidence of the impact, discontinuation of steroid results in significant increases in linear growth in 66% of children (Dunn et al., 1994).<sup>177</sup> Mediators of these steroid effects are uncertain. While growth velocity following transplantation correlates with basal or stimulated cortisol levels, it does not correlate with growth hormone (GH) secretion or concentrations of IGF-I (insulin-like growth factor-1) or IGFBP-3 (insulin-like growth factor binding protein) (see review by Kelly, 1997).<sup>164</sup>

Several studies have documented the effects of withdrawal of maintenance steroid therapy, with the objective of maximizing linear growth while minimizing organ rejection. Optimal

timing of steroid withdrawal has not yet been determined, but initiation of withdrawal in the first year after liver transplantation is now common practice (S. McDiarmid, personal communication to R. Fine).

Five studies, albeit without controls, have shown up to 13% graft loss or patient death following steroid withdrawal at less than 18 months (see Reding, 2000 and Fine, 2002.<sup>19,54</sup> In the only randomized study of steroid withdrawal, McDiarmid et al. (1995) reported a low incidence (6%) of acute rejection after steroid withdrawal (mean time of 3.5 years), but without significant effect on linear growth in the pediatric subgroup.<sup>178</sup> Reding (2000) reported a 14-29% acute rejection when tacrolimus immunosuppression was combined with steroid withdrawal.<sup>19</sup> In this same study, comparisons of linear growth for three different immunosuppressive agents during steroid withdrawal were inconclusive.

Furthermore, there is evidence that kidney function in many liver transplant patients on calcineurin inhibitors (tacrolimus is a CNI) deteriorates in the long-term. In a study of adult liver transplant patients treated with CNIs for a minimum of five years post-transplant, Gonwa et al. found that kidney function deteriorated at more than 10 years post-transplant.<sup>179</sup> Specifically, 13 years after transplantation, 8.6% of patients had chronic renal failure (CRF), and 9.5% had end-stage renal disease (ESRD). Moreover, during the follow-up time, 25.3% of the controls had a serum creatinine of > 2 mg/dl, approaching CRF levels. The implication for pediatric liver transplantation is that children receiving liver transplants may go on to experience this late loss of kidney function during their adolescent growth spurt. Significant loss of kidney function during this crucial time of growth would likely compromise growth.

Sarna (1995) reported that transplantation patients on triple immunosuppression were more growth retarded for liver transplants than for kidney transplants, suggesting differences in growth potential for liver and kidney patients.<sup>162</sup> Pasqualini et al. (2000) found that steroid withdrawal was more successful in liver transplant patients (i.e., steroid could be withdrawn and discontinued) compared with renal recipients (receiving corticoid maintenance of 0.18 – 0.16 mg/kg/day), thus allowing catch-up growth in liver patients but not in kidney patients.<sup>161</sup>

In an earlier study, Sarna et al. (1987) correlated growth and prednisone concentration, as area under the curve (AUC), and was able to predict effects on both adrenal function and growth.<sup>20</sup> A concentration above 650 µg/L was associated with growth deceleration. These results still need confirmation.

### ***Steroid-sparing strategies: tacrolimus/ cyclosporine A (CyA) monotherapy***

McDiarmid (2000) stated that there is “universal agreement” that a calcineurin inhibitor (i.e., cyclosporine A or tacrolimus) should be the basis for immunosuppression induction for liver transplantation, with steroids used at least some of the time.<sup>18</sup> Nonrandomized studies suggest that primary immunosuppression with tacrolimus instead of cyclosporine A (CyA) can allow earlier steroid withdrawal and with lower incidence of rejection (reviewed by McDiarmid, 2000).<sup>18</sup> A retrospective study from Brussels of 78 children undergoing steroid withdrawal (1984-98) showed a relative lack of risks or benefits to using CyA or



Neoral-formulation, with the suggestion of improved linear growth in the tacrolimus group.<sup>19</sup>

McDiarmid (2000) also noted that dual and triple therapy for induction had not been adequately studied in prospective, randomized, trials.<sup>18</sup>

### **Summary (Liver – growth)**

Growth failure in end-stage liver disease (ESLD) is recognized as a significant problem, especially at ages less than 5 years. Severe malnutrition is one important contributing factor that may be preventable by liver transplantation, depending on the specific disease. Growth may initially worsen after transplantation, but catch-up growth begins during the second 12 months post-transplantation. Nevertheless, sub-normal height indicated by negative Z scores may persist for many years. Various factors predictive of standardized height include age at transplant, initial diagnosis, and baseline Z score (i.e., SDS score).

Several studies suggest there has been improvement in the percentage of liver transplant patients showing catch-up growth. Improvements in growth have been achieved with steroid withdrawal or discontinuation and by supplemental use of rhGH. Liver transplant patients appear to have greater growth potential than kidney patients, especially after steroid withdrawal.

Further growth-related studies in liver transplant recipients are needed to establish the optimal window for steroid withdrawal. Other studies are needed to address the effects on pubertal growth of liver transplant or of late loss of kidney function in liver transplant recipients.

### **Recommendations from the panel of experts (Liver – growth)**

- Conduct randomized, multi-center treatment trials of withdrawal of daily steroids during the first six months post-transplant, coupled with alternative immunosuppression. These trials should help **establish the window for steroid withdrawal** and could ultimately lead to improved growth in this population by inducing changes in physician practice patterns. Patients should be **stratified** by type of graft received (living donor vs. cadaveric), age at transplant, diagnosis, and history of rejection.
- Conduct studies to **better define the cortisol axis** and individual characteristics that lead to slower metabolism of exogenous steroids. These studies would be instrumental in designing monitoring strategies for treatment post-transplant.
- Determine whether **late loss of kidney function** in pediatric **liver** transplant recipients 1) occurs at a significantly high prevalence during puberty and 2) compromises pubertal growth.
- Conduct research to determine if **menarche and the pubertal growth spurt** are delayed in children with liver transplants and children with chronic liver disease. Are they, for example, as delayed as they are in children with chronic renal insufficiency or cystic fibrosis?

### **Recommendations from expert-selected studies from the literature (Liver – growth)**

- Evaluate the effects of **decreasing steroid dosage** on growth, **during both induction and maintenance** phases of immunosuppression. Efforts could include the following:
  - prospective, randomized trials to support the validity of steroid withdrawal or avoidance during induction<sup>18,19</sup>
  - broadening studies to include the concept of steroid-sparing immunosuppressive protocols<sup>19</sup>
  - adjusting long-term glucocorticoid dose according to the area under the concentration-time curve (AUC) for methylprednisolone to improve growth and minimize need for rhGH treatment<sup>20</sup> (*Note: The relationship between AUC and growth is stronger for liver transplantation than for kidney transplantation.*)
- Conduct randomized trials to determine the **safety of rhGH therapy**.
- Conduct studies to address **long-lasting effects on growth** in children with liver transplants from:
  - corticosteroids
  - chronic cholestasis or other diseases. (Other diseases studied should include renal insufficiency.)
  - various nutritional deficiencies.<sup>21</sup>

### **Clinical recommendations based on individual studies (Liver – growth)**

- Provisional guidelines for **steroid withdrawal** are given by Reding (2000).<sup>19</sup>
- A **nutritional strategy** is suggested, including intensive preoperative nutritional support, peritransplant management of patients with significant vomiting/gastrointestinal reflux, postoperative nutritional management, and possible role for GH (Kelly, 1997).<sup>164</sup>

## **GROWTH: HEART**

Information from the following reviews have been incorporated into this section on growth in pediatric heart transplant patients:

- Baum, Freier & Chinnock (2000)<sup>48</sup>
- Fortuna et al. (1999)<sup>37</sup>

### **Catch-up growth following heart transplantation**

Data on growth after heart transplantation has been limited to smaller, single-center experiences.

Baum et al. (2000) have recently reviewed somatic growth in infant and pediatric transplant patients. Two themes were deduced: 1) interference of steroids with growth in heart transplant patients, as reported in various studies (*see section below on steroid sparing*), and 2) relatively normal growth (mean height percentile still below age norm means), especially as seen in studies without use of steroid and with transplantation at an early age.<sup>48</sup>

Baum et al. (1991) reported that 79% of heart recipients (< 14 years old) had growth improvements despite the continued use of daily prednisone for more than 1 year.<sup>180</sup> However, growth deceleration was noted within 6 months of starting steroid treatment and growth impairment occurred during puberty. In a subsequent study, Baum et al. (1993) compared transplantation at ages of < 30 days vs. > 30 days, but found no growth differences in follow-up to age 7; use of steroids in this study may be a factor in the outcomes.<sup>35</sup>

de Broux et al. (2000) reported that children and adolescents grow normally after cardiac transplantation for congenital heart and cyanotic heart disease, and attain their target height, but do not show long-term catch-up growth.<sup>63</sup> The severity of growth defect at the time of transplantation was indicated as having a major impact on adult height.

Two recent studies by de Broux (2001 and 2000) suggest that delayed linear growth may be less of a problem for heart recipients than liver or kidney recipients.<sup>63,181</sup> This may in part be secondary to the dichotomy of ages at which children receive heart transplant. Some are very young infants with congenital heart disease who have not had much opportunity to grow. They receive transplant early in infancy and then re-establish a fairly normal growth pattern (Baum, 1993).<sup>35</sup> An older group of children with acquired cardiac disease may have had an extended period of normal growth before they became ill, and then may be transplanted quickly before growth failure is a prominent problem.

### **Steroid-sparing strategies**

The most optimistic growth results have been seen with low dose steroid or steroid discontinuation.

Au et al. (1992) found heart transplant recipients not receiving prednisone had an improvement in standardized height from -2.15 to -1.15 at a follow-up of greater than 1 year.<sup>182</sup> Chinnock & Baum (1998) reported catch-up growth during the first year following transplantation in infants not receiving steroid; only 12% were below the 5<sup>th</sup> percentile for height at 5 years.<sup>183</sup> Similarly, in a study where only 14% of patients received chronic steroid, Ferrazzi et al. (1993) reported no impairment of growth (height or weight) in liver transplant patients in comparison with a control group.<sup>184</sup> Based on these results and a cumulative 88% 5-year survival, they suggested the feasibility of the dual drug immunosuppression regimen (cyclosporine A + azathioprine).

Although Hirsh et al. (1996) found that low-dose prednisone maintenance in comparison with steroid withdrawal was not different in terms of Z scores for height, overall growth was poor.<sup>185</sup>

Chinnock & Baum (1998) reported good catch-up growth after transplantation of infants (all < 1 year old and some < 1 month) and without the use of steroids.<sup>183</sup> Growth velocities for length were significantly improved in the first 3 months following transplantation (i.e., 35 cm/year). Assessment of growth beyond 5 years post-transplantation showed 88% of patients to have height and weight within the normal range (Z scores of -0.48 and -0.55, respectively). Factors significantly affecting growth were age at transplant, complications of surgery (i.e., hospitalization), mid-parental height, and isotopic glomerular filtration rate (GFR). In a recent follow-up review of these studies (at Loma Linda University), Fortuna et al. (1999) concludes “the majority of recipients have normal childhood development” with remaining obstacles being graft loss due to acute rejection and post-transplant coronary artery disease (PTCAD).<sup>37</sup>

### ***Steroid-sparing strategies: tacrolimus/ cyclosporine (CyA) monotherapy***

A very small study by Chand et al. (2001) of heart and kidney transplant patients showed good growth when patients were converted to tacrolimus for various reasons, suggesting use of tacrolimus for patients unresponsive to steroids.<sup>163</sup>

### **Summary (Heart – growth)**

Growth outcomes in pediatric heart transplantation have been encouraging in recent reports. This appears to be the result of eliminating chronic steroid treatment in a large majority of patients, and transplanting at an early age to avoid poor preoperative growth. Recent studies report growth within the normal range (with mean Z scores about 0.5 below norms) and indicate expectations of “normal childhood development”. Favorable growth appears to be the result of eliminating chronic steroid treatment in a large majority of patients, and transplanting at an early age to avoid poor preoperative growth. Clinical concerns in recent studies primarily relate to occurrence of acute rejection, post-transplant coronary artery disease (PTCAD) and post-transplant lymphoproliferative disorder (PTLD) with existing immunosuppressive regimens.

There have been suggestions that delayed linear growth may be less of a problem for heart recipients than liver or kidney recipients. However, this may be related to the dichotomy of ages at which children receive heart transplants for congenital and acquired heart disease. Heart recipients transplanted as infants (for congenital heart disease) or as older children (for acquired heart disease) would be expected to largely avoid the growth-retarding effects of disease during their most critical developmental years. Further studies are needed to identify risk factors for delayed growth associated with congenital vs. acquired heart disease.

### **Recommendations from the panel of experts (Heart – growth)**

- The research on growth in pediatric heart transplant recipients is still at a descriptive level. **A larger study** is required to **identify potential risk factors**.
- A few studies have attempted to look at differences in outcomes of heart transplants for **congenital versus acquired heart disease**. This focus should be extended.

- Larger studies would need to include **patients from multiple centers** and might gather data through a mechanism similar to that used by the Studies of Pediatric Liver Transplantation (SPLIT) Research Group.

### **Recommendations from expert-selected studies from the literature (Heart – growth)**

Conduct systematic investigations to determine why many **late (i.e., older) transplant patients** have poor pre-operative growth.<sup>35</sup> Suggested reasons include fluid restriction due to use of diuretics, thereby worsening nutritional intake, and hypercatabolism.

### **Clinical recommendations based on individual studies (Heart – growth)**

- The recent literature on pediatric heart transplantation supports the **early withdrawal or elimination of steroids** in favor of other immunosuppressive agents. Benefits of **early transplantation** are also indicated.
- **Early inclusion on heart transplant waiting list** to reduce mortality rate; **do not exclude** extremely ill patients, those with systemic disease or complex congenital disease despite expectations of less encouraging outcomes (Parisi et al., 1999).<sup>186</sup>
- Close **monitoring** of patients receiving **tacrolimus** for **PTLD**, and early surgical intervention and reduction in tacrolimus dose once PTLT occurs (Chand et al., 2001).<sup>163</sup>

## II. Cognitive development literature review and recommendations

### GENERAL RECOMMENDATIONS ON METHODOLOGY

There has been substantial change in medical, surgical and pharmacological management of children with renal, liver, and heart problems, such that cognitive outcomes from “earlier” work deserve now less weight than cognitive outcomes identified by more recent work. These outcomes include accompanying comorbid considerations such as risk factors and illness duration and severity. Improvements in treatment strategies have resulted in a shifting baseline of cognitive ability that complicates the analysis of cognitive impacts in transplanted children. Further complicating the analysis are the logistical difficulties involved. These difficulties include the repetitive, time-consuming nature of cognitive testing and the tendency of patients to change treatment groups, an important independent variable.

Changes in cognitive outcomes over time are a key issue in the transplantation literature. This phenomenon is especially impressive in data comparing cognitive outcomes in early age of onset of disease with later age of onset of disease, and in liver transplantation studies in which improvement several years post-transplant is well above scores just post-transplant.

Such data lend strong support to the need for ample follow-up time to pick up lasting effects, not simply transient ones. Healthy controls must be used in these long-term studies to prove that intellectual improvement after transplantation does not simply occur because of the progression of time and age. Pre- post- longitudinal designs alone cannot refute the alternative explanation of improvement simply as a function of time and age. Controls composed of siblings, balanced for older versus younger than the target children, address both heritability factors as well as environmental and socioeconomic aspects of IQ comparisons. Children with other solid organ transplants could also be used as controls to identify organ-specific cognitive problems or risk factors.

There are a few basic principles of psychometric testing that deserve note: 1) a single assessment is less reliable than multiple assessments, 2) the earlier (younger) we evaluate, the less reliable the outcome, and 3) the larger the aggregate of items used in assessment, the more reliable the outcome.

#### **Three-pronged approach**

An array of measures across “general” IQ, achievement, neuropsychological processing abilities, and attention are likely to provide the most valuable information to an examination of the cognitive health of transplant recipients. Study development in the cognitive arena of transplantation deserves a *three-pronged approach*, defined by three different types of evaluation tools: IQ measures, achievement measures, and neuropsychological measures.

- i. *IQ measures:* IQ tests, which measure global intelligence, should have well-documented standardization, validity, and reliability; standard score results, which allow comparability across a wide age range; and, preferably, subscales for comparisons between different parts of different tests. Examples are the multi-component Stanford-Binet IV test, Wechsler series, and Bayley Scales of Infant Development.
- ii. *Achievement measures:* Achievement measures, which measure scholastic/academic aptitude in such subjects as math, reading, and writing, should also have well-documented standardization, validity, and reliability, as well as standard score results for comparability across samples and age or grade levels.
- iii. *Neuropsychological measures:* Neuropsychological measures are usually batteries of tests used to assess a variety of specific psychological, neurological, and cognitive domains. They should have known reliability and validity, and should be able to tap a relatively broad spectrum of abilities, including memory, visual, motor, spatial, language, and attention skills, as well as appropriate cross-modal abilities.

The combination of data from neuropsychological, IQ, and achievement testing of children would paint a much more detailed picture of their strengths, deficits, and age-appropriate skills than the scores from any one type of test alone. The importance of using the different tests in conjunction is underscored by such findings as those of Lawry et al., discussed later. Lawry et al. found that a “disconnect” existed between cognitive ability and actual school achievement in children with kidney transplants (it must be noted that sample size in that study is extremely small).<sup>4</sup> In other words, IQ testing alone will not uncover scholastic abilities or deficits that achievement testing may be able to detect. Thus, although neuropsychological testing of transplanted children has yielded suggestive, concrete, and curious data, these data must be viewed alongside data from tests of achievement and global intelligence for a true profile of cognitive status.

### **Choosing measures**

*Note: Please see Appendices B and C for descriptions of the various standardized tests that have been used to measure cognitive and psychosocial functioning in pediatric transplant patients. These tables present the variables measured by the tests, appropriate age ranges, and the frequency and currency of test use.*

The identification of key measures essential to a comprehensive, sensitive evaluation of cognitive impact is clearly not yet a completed task. Given the relatively small sample sizes in transplant research, developing new measures and validating them psychometrically do not seem to be top priorities.

Many of the tests used in the literature reviewed are standardized, with documented validity and reliability in their technical histories and ample samples of children in their norming. These are preferable to screening tests or abbreviated assessments (e.g., Denver

Developmental Screening Test, the Gesell Schedules) which do not provide standardized scores or reliability data with a track record of use for tapping the cognitive or achievement or neuropsychological abilities of interest.

When impact on intellectual status is somewhat subtle (that does not imply unimportant, but simply less easily grasped) a fishing expedition tends to emerge in the research. A wide net is cast using a variety of measures to pick up deficits that might not be revealed in single measures, or in a narrowly focused psychometric approach. This is not necessarily a bad thing. The field is complex and intellectual/psychosocial sequelae are not likely to unfold in neat pathways responsive to a small set of measures, especially when a good deal of the existing research has included samples that are small from a statistical perspective.

Beyond IQ testing, it is not likely that a single test measure can cover such a broad age spectrum as to dismiss the need for transitions from test to test. This is a problem that plagues longitudinal research in cognitive, achievement, and academic curriculum research. This problem is addressed by using standard scores, which take age into account, and multivariate techniques to assess the relative contributions of various factors to one or more outcomes of interest. In other words, standardized scores and statistical techniques allow investigators to compare the performance of children across different tests and ages.

It is understandable that investigators would want to reduce the number of tests used in studies to a set that is likely to both assess cognitive ability and yield scores comparable across studies. This “pay off” is an important goal. However, at this point, no one set of measures exists in the research that conclusively and clearly taps cognitive impact. There is reason to cast a wide net.

Moreover, since the interactions among cognitive, behavioral, and psychosocial realms are yet far from clear in the existing literature, they deserve continued attention with a variety of instruments. Evaluations of attentional deficit characteristics (e.g., impulsivity, distractability) known to impact on test performance, and child comorbidity/behavior features such as those tapped on the Achenbach Child Behavior Checklist, for example, might be valuable additions to a core intellectual battery of evaluations. Similarly, family functioning summarized perhaps in parental completion of surveys reflected in the literature review here, or data from sources such as a life stress events scale might be useful to round out a picture of intellectual and achievement impact.

Measures should be chosen to allow comparisons of scores across different ages and developmental stages. An optimal way of achieving comparability is to work with instruments that have been adequately standardized, so that standard scores become the measures of interest. Standardized scores allow for comparisons regardless of chronological age. Many excellent tools, psychometrically, have limited utility in terms of age span. For example, the Bayley Scales do not extend into the pre-school years, or much before. On the other hand, the Wechsler series of IQ tests has versions that fit different age spans.

It would seem that an essential set of instruments for across-age and across-study comparisons of global intelligence scores is found in the Wechsler series (WPPSI, WISC



III, WAIS) or the Stanford Binet (age 2 to adult). Screening (e.g., the Denver Developmental Screening Test) or developmental schedules are less directly linkable to “harder” intellectual data, are not comparative in standardization, and do not yield an IQ or IQ-equivalent.

Additionally, long-term follow-up will require choosing measures that can be repeated without test-retest inflation (a phenomenon in which children perform better on a retest because of practice, not because of real cognitive improvement), and that can be appropriately normalized with standard score results. Again, tests normalized with standard score results are essential in allowing effective comparisons, for example, from time 1 to time 2 to time 3, even when the test content must change for age-appropriate challenges to knowledge and skills.

### **Learning Disabilities**

Learning disabilities (LD) are predominantly language-based but are not necessarily a homogenous category of disorders. There appears to be significant interest in the childhood risk of developing a learning disability as a function of disease or of treatment type, but little emphasis on the early evaluation of expressive and receptive language skills, and developing pragmatics and language processing or types of language impairment.

While some language and memory skills are tested mostly in the context of IQ testing, more attention appears to have been paid to date to motor and visual-spatial skills as outcome measures of interest. Consideration should be given to including language receptive and expressive skills, such as the Peabody Picture Vocabulary Test (PPVT-II) or the Expressive One-Word Picture Vocabulary Test (EOWPVT), as well as evaluation of emergent literacy and eventually reading achievement if there is indeed risk or reason for concern about emerging learning disabilities. (Interestingly, the liver literature review on disease/transplantation does include expressive and receptive language evaluation data.)

Further, school definitions of learning disability (usually in the form of a substantial gap between tested IQ and tested achievement) and school guidelines for remedial assistance while in normal classrooms, are not necessarily the same as criteria for medical/neuropsychological diagnosis of learning disability. Therefore, findings of no significant difference in neuropsychological battery outcomes of children getting remedial help and children not getting remedial help in school are not proof of no difference. For example a study by Qvist et al. (2001), discussed later, suggests that children in regular classes with remedial assistance had “no significant difference” in cognitive or neuropsychological scores from children in full-time, regular classes.<sup>5</sup>

It should also be remembered that school grades and progression through school are not robust or comparative cross-population indices of intellectual ability or achievement of skills/knowledge. Nationally standardized achievement tests are more fully acceptable tools for measuring true scholastic progress. Examples of such tests are the California Achievement Test, Stanford Achievement Test, and the Wide Range Achievement Test.

### **Use of sibling controls – some caveats**

Using sibling controls is an excellent methodological strategy for controlling for environmental and hereditary factors. One should take care, however, to counterbalance siblings older and younger than the child undergoing transplantation. Additionally, larger family size has a negative impact on IQ, with later children having decreases presumably related to parental/adult resources available. The family size-IQ relationship is more remarkable in lower-SES families than in higher-SES families. It also should be noted that even the best IQ heritability research, research using monozygotic twin samples, is still correlational in nature.

### **Comparisons across kidney, liver, and heart transplant patients**

This final point is an exploratory question. Is it reasonable to entertain between-group as well as within-group comparisons among the three illness groups represented in this report? With the known findings accumulated in the report, there might be benefit to using the groups here as comparisons for one another. Feasibility may be an issue in doing so, as the same institution conducting transplantation in one sphere may not do all three, but multi-center collaboration with an agreed upon core set of shared measures might make such an option viable. Despite having different organs transplanted, transplanted children still experience many common co-morbidities. This commonality could help distinguish which organ-specific risk factors are contributing to any observed impairment in cognition.

One goal of such comparison might be the ability to describe similarities and differences in the patterns of cognitive developmental delay or atypicalities pre- and post-transplantation. Further, one might ask whether differences in those patterns across kidney, liver, and heart patient populations are correlated with such factors as the predominant age of transplantation (early vs. late chronologically, early vs. late in the course of disease), severity of disease, sites of predominant impact, or the physiologic compromises suffered or the medications used in management.

Use of other chronically ill controls is a difficult proposition. It is not only difficult to do, but difficult to publish. Firstly, it is still not clear just which other diseases are sufficiently comparable for use as control diseases. Secondly, chronically ill children without transplants tend to have diseases that deteriorate over time, unlike transplant patients, whose health states generally improve after transplantation. Thus, if other chronically ill children are to be used as controls, it is suggested they should be transplant patients who have undergone other, non-liver transplant surgery.

## COGNITIVE DEVELOPMENT: KIDNEY

### **A note on acronyms, technical terms, and standardized measures**

A glossary of technical terms and acronyms found in the following sections are provided in Appendix A for easy reference.

Additionally, please refer to Appendix B for a listing of standardized measures of intelligence, neuropsychological development, and achievement used in studies of pediatric end-stage renal disease (ESRD) and transplant patients. This list also provides variables measured, age ranges, and frequency and currency of use.

### **Introduction**

Three good literature reviews on the subject of cognitive development in pediatric renal transplant recipients were published in the early-mid 1990s<sup>187-189</sup>. Many of the studies cited in these reviews, however, were conducted before the introduction in the mid-1980s of two major advancements in patient management that have significantly enhanced the neurodevelopmental outcome of pediatric kidney transplant recipients. These advancements were:

- 1) The elimination of aluminum-containing phosphate binders in the treatment of uremia.
- 2) The introduction of aggressive nutritional regimens via tube-feeding during chronic renal insufficiency (CRI), before transplantation, to maintain caloric intake.

Therefore, many of the early studies cited in these otherwise excellent reviews are of limited relevance to a modern assessment of cognitive development in pediatric renal transplant recipients. Findings of these earlier studies are much more pessimistic than those of recent studies, whose outcomes are more representative of what may be expected with today's clinical management practices. Indeed, recent findings give reason to believe that children with end-stage renal disease (ESRD) who undergo renal transplantation today stand a good chance of demonstrating favorable cognitive outcome.

In infants developing ESRD in early infancy, four factors appear to optimize developmental outcome. These are:

- 1) aggressive nutrition
- 2) elimination of treatment with neurotoxic aluminum-containing phosphate binders
- 3) provision of adequate peritoneal dialysis in early infancy
- 4) subsequent transplantation<sup>190-192</sup>

Favorable developmental outcomes in children treated with the combination of these modalities include full-time school attendance in age-appropriate classes and at least average scores on developmental tests.<sup>190</sup>

The review by Hobbs and Sexson (1993) concludes that the association between pre-transplant renal disease and cognition is unclear, thus making it difficult to assess the effects of kidney transplantation on cognition and learning.<sup>187</sup> Stewart et al. (1994), on the other hand, conclude that too few longitudinal studies exist to provide a basis for assessing the differential effects of ESRD treatment alternatives (e.g., CAPD vs. transplantation) on cognitive ability.<sup>188</sup>

### **Factors in ESRD affecting cognitive development**

It has been fairly well-established that sustained uremia leads to cognitive impairment in children with CRI. Indeed, duration of ESRD prior to corrective medical intervention appears to be a key factor in cognitive impairment among children with chronic renal disease. Children enduring ESRD for longer periods or having earlier onset have lower IQ, poorer school achievement, and slower rates of developmental gain when compared to children who have had ESRD for shorter periods or had later onset.<sup>4,193-197</sup> In other words, younger children with ESRD are at increased risk of cognitive impairment due to uremia, arguably because their central nervous systems, still in a crucial period of development, are more sensitive to the deleterious effects of the uremic insult. Conversely, children with later onset are less adversely affected cognitively. These observations, which have been replicated over many studies, support the conclusion that earlier transplantation will cut short the deleterious effects of renal disease on cognition.

Although the underlying causes of impaired cognition in uremic children are likely multi-factorial, multi-factorial analyses of cognitive ability in these children have been few. In a sibling-controlled study examining multiple factors, Williams et al. (1994) found that the lower IQ of cystinotic children relative to their siblings' IQ did not appear to be related to the psychosocial effects of chronic illness, school absence, creatinine clearance, or duration/age at initiation of cysteamine and/or phosphocysteamine treatment.<sup>7</sup> In a much earlier, uncontrolled study of 20 children with very limited follow-up, Fennell et al. (1984) found that blood urea nitrogen (BUN) and serum creatinine levels and blood pressure did not consistently correlate with cognitive or academic achievement measures in children tested around the time of transplant.<sup>194</sup> Findings on the correlation of blood pressure to cognitive ability have been conflicting.<sup>194,198</sup>

### **Does renal transplantation lead to improved cognitive development?**

Most studies on cognitive ability, both before and after pediatric renal transplantation, tend to support the conclusion that renal transplantation contributes to greater mental efficiency than would be seen had children remained under conservative management or dialysis.<sup>4,6,9,196,199,200</sup> Furthermore, several studies support the conclusion that infants show improved gross and fine motor development, cognitive ability, and head circumference after renal transplantation.<sup>190,200-203</sup>

More studies, however, are needed to corroborate these encouraging findings. Past investigations have suffered from methodological limitations of one kind or another that have seriously precluded the formation of any definitive conclusion on transplantation's effects on cognition. Sample sizes have been too small; assessment instruments used for

different age groups too disparate to permit comparisons over time; follow-up much too brief; assessments lacking of any pre-transplantation measurements; and sample populations too old, failing to represent the outcomes of younger patients most vulnerable to uremia's effects on intelligence. {Studies with younger patients are preferable for two reasons: 1) the developing brains of younger children are more vulnerable to the onslaughts of uremia on cognitive development, and 2) their progress before and after renal transplantation is more representative of the progress anticipated under modern renal patient management.} Lastly, and perhaps most importantly, samples have lacked a comparison group made up of sibling controls to account for socioeconomic status (SES) and genetic differences. Investigators themselves have acknowledged all of these methodological limitations.

Only two studies in the literature on pediatric cognitive development post-renal-transplant have used sibling controls. These studies were performed by Williams et al. (1994) and Brouhard et al. (2000).<sup>7,193</sup> Both found that children with renal disease have cognitive abilities that are inferior to those of healthy siblings. Comparisons cannot be made between the cognitive capabilities of transplanted children and dialyzed children in these studies, however, since both studies suffer from very low sample sizes of transplanted children. The findings of Williams et al. emphasize the importance of sibling controls, insofar that they contrast with findings from a similar study on cystinotic children by Wolff et al. from the early 1980s that did not use any controls.<sup>204</sup> Whereas the sibling-controlled study by Williams et al. found that children with cystinosis had a significantly lower mean IQ than their siblings and their parents, the Wolff study found that they demonstrated normal intellectual performance when compared to normative data. Use of different instruments also may have contributed to the contrast in the findings. (Williams et al. used the Stanford-Binet Intelligence Scale; Wolff et al. used the Wechsler intelligence tests)

Moreover, findings from existing studies have not been conclusive as to whether children make cognitive gains after transplantation that would not otherwise be seen during uremia correction by dialysis. Whereas some studies show that cognitive gains are indeed achieved from pre- to post-transplantation,<sup>6,9,196,199</sup> recent, methodologically rigorous research using sibling controls has found no difference in IQ between dialysis and transplant patients.<sup>193</sup> Similarly, the much older research of Crittenden et al. (1985) found that although the IQ of children improved from conservative management to transplantation, it did not improve in transplanted children who had undergone dialysis prior to transplantation.<sup>196</sup> On the other hand, Lawry et al. (1994) found that transplant patients scored much higher on IQ tests than dialysis patients (103 vs. 92 on verbal IQ, 103 vs. 96 on performance IQ, and 103 vs. 92 on full-scale IQ). The high amount of variability in the score differences between the two groups, however, did not allow the difference to be statistically significant.<sup>4</sup> Again, methodological improvements – in the form of increased sample size in this study – may have permitted the determination of significantly higher scores in transplant patients than those found in dialysis patients.

Studies do seem to support the conclusion that both ESRD patients on dialysis and those with transplants score lower on tests of IQ and academic achievement than healthy children.<sup>193,198,205</sup> More recent research with longer follow-up, however, indicates that post-transplant children today can expect to achieve a level of cognitive functioning near or at the

level of healthy children.<sup>5</sup> This finding may be attributable to advancements made in pediatric renal patient management that have had a beneficial impact on child neurodevelopment.

Despite apparent cognitive enhancement in children following renal transplantation, children with transplants still require additional intervention to help them achieve their cognitive and academic potentials. Compared with healthy controls, ESRD children with transplants and those on dialysis both perform less well on tests of neurodevelopment and cognitive ability and in school achievement.<sup>193,198,205</sup> Despite finding that transplant recipients had better visuomotor skills related to attentional and visuoanalytic function than dialysis patients, Fennell et al. (1986) found that these children nevertheless demonstrated a deficit in these skills.<sup>9</sup> Thus, some sustainment of visuomotor deficits appears to persist post-transplant. In the sibling-controlled Williams et al. (1994) study, even though cystinotic children were found to have an IQ within the average range (94.4 +/- 10), they apparently still demonstrated a previously undetected, mild global intellectual deficit relative to their *expected* IQ.<sup>7</sup>

The series of cognitive studies performed by Fennell and Rasbury in the mid-1980s, frequently referenced above, compellingly suggest that cognitive improvement does in fact occur after transplantation. Their studies document improvements in visuomotor skills, non-verbal intelligence, and performance and full-scale IQ following renal transplantation in children.<sup>9,194,195,197-199,206</sup> Methodological limitations, however, prevent definitive conclusions from being drawn from these studies. These limitations include lack of long-term follow-up, lack of pre-transplantation assessments during CRI that were then carried through well after transplantation, small numbers of transplanted children, and mixed samples of transplanted and dialyzed children, preventing comparisons of those two treatments. Since many of the studies conducted by Fennell and Rasbury pre-date the elimination of aluminum-containing phosphate binder treatment of children with ESRD, the outcomes documented by the studies likely underestimate the outcomes that today's children with renal transplants can hope to enjoy. Again, these older studies have diminished relevance to this literature review, in wake of the development of neurologically-sparing disease management techniques since the late 1980s.

The mixed findings of the Fennell and Rasbury studies also warrant further investigation to identify clearly the true cognitive gains made by children post-transplant when they are compared with healthy (preferably sibling) controls and dialysis patients. The methodological strengths of these studies – e.g. use of comparison groups in the form of dialysis patients and healthy controls – do seem to underscore the possibility that long-term uremia will result in cognitive impairment. From a cognitive standpoint, this possibility would argue for early corrective action, namely transplantation, to rectify the uremia.

In one of the few studies in the literature of its kind, Qvist et al. (2001) prospectively assessed the long-term neurodevelopmental outcomes of young children who received transplants when they were younger than 5 years old.<sup>5</sup> Despite lacking a healthy comparison group and having a small sample size, the Qvist study is significant because it looked at children who had very early onset of ESRD and follows them through well after

transplantation – for an average of six years post-transplant. It also employed a combination of performance testing (cognitive and neuropsychological) and medical examination/imaging (e.g., MRI, EEG) to assess the neurodevelopmental health of the children studied. The study, however, did not take cognitive measurements prior to transplantation, during CRI. It is important to note here that positive outcomes in the American pediatric renal transplant population may in fact be underestimated by outcomes noted in this Finnish study, which primarily looked at children with nephrotic syndrome. This disease is fraught with more medical complications than the conditions usually indicating renal transplantation here in the United States. Thus, the children in this study likely demonstrated worse outcomes than would be expected among American children with ESRD, who are likely to undergo fewer medical rigors due to lower prevalence of nephrotic syndrome.

Moreover, the study by Qvist et al. (2001) is a very recent study whose patient sample has neurologically benefited from advancements made in the management of pediatric renal patients. Therefore, outcomes noted in the study are still likely more representative of the outcomes we can anticipate in today's pediatric transplanted population than those outcomes documented in older studies. For example, only 15% of patients in the study had brain atrophy either before or after transplantation, compared to past estimates of 60% and 23% – an improvement attributable to avoiding treatment with aluminum-containing phosphate binders and improved nutrition around the time of transplantation. *(However, it must be noted here that Qvist et al. also found that all children in the sample who had higher than normal aluminum levels still attended normal school, consistent with the finding by Wolff et al. that brain atrophy apparently did not alter mental or neurological function.<sup>204</sup>)* The neurologic benefit of anti-coagulation treatment for hypercoagulable states, such as congenital nephrotic syndrome, was supported by the study as well. All patients found to have major neurological sequelae were patients who had had cerebral infarcts before transplantation, most likely the result of not having received treatment with anticoagulant prior to being transplanted.

Qvist et al. (2001) found that two dialysis-related factors seemed to predict attendance of post-transplant children at a special school. These factors were a higher number of hypertensive crises and seizures, mainly during dialysis, and a higher incidence of graft failure, which lengthened overall time on dialysis. The authors point out that further minimizing risk factors prior to transplantation, particularly hypertensive crises and seizures during dialysis, is of “crucial importance” to improving neurodevelopmental outcome of young children with CRI. Special attention should also be given to patients with CNS complications.

Qvist et al. (2001) suggest that “renal transplantation {before 5 years of age in this study} seems to be the treatment of choice to ensure a good long-term neurodevelopmental outcome in children who have suffered from renal insufficiency since infancy.” They also state that they expect neurodevelopmental outcomes of transplanted CRI children to continue to improve in the future. This pronouncement is bolstered by the fact that many of the children showing neurological deficits either had in fact received aluminum therapy or had not received anti-coagulation therapy.

Neurodevelopmental outcomes of the post-renal-transplant children studied by Qvist et al. (2001) were quite good after six years of follow-up: the majority of these high-risk patients have normal or near normal cognitive performance at school age. Most children attend normal school (79%), with those in normal school demonstrating IQ in the normal range (>90 IQ) and normal motor performance. Overall, across both normal and special schools, transplanted children scored a bit lower than the normal range of 90-110 on tests of full-scale, verbal, and non-verbal IQ (all were 87.5), with more than 40% in the average range (90-110 IQ) and more than 40% in the borderline-below average (70-90 IQ). Although more than 20% were found to have had reduced attention spans, visuospatial deficits, and low memory scores, these negative findings are difficult to interpret without rates of these deficits in healthy children. Only 6% had low verbal scores.

Again, the IQ scores in the high 80s found by Qvist et al. (2001) likely underestimate the IQ of the typical American child with a renal transplant: many of the children studied by Qvist et al. had nephrotic syndrome, a condition with a more complex, problematic course than the kidney conditions typically indicating transplantation in the United States. A glance at the IQ scores of (slightly older) children with kidney transplants from the study by Lawry et al. (1994) will attest to this: 103 on verbal IQ, 103 on performance IQ, and 103 on full-scale IQ.<sup>4</sup> Both Lawry and Qvist used the Wechsler tests of intelligence.

### **Specific cognitive abilities affected by uremia**

Findings are mixed regarding the types of cognitive domains most vulnerable to the effects of uremia, and thus potentially amenable to the uremia correction afforded by transplantation. Indeed, there is uncertainty as to whether or not uremia's cognitive impact is global or specific to certain neurodevelopmental capabilities. Some findings support the global impact theory in that they directly suggest that uremia's impact is global,<sup>7</sup> or find that neuropsychological improvements following transplantation are not modality-specific (i.e., visual, auditory).<sup>6</sup> Discussing their results from a study conducted in the early 1980s (again, before the elimination of treatment with neurotoxic aluminum-containing phosphate binders), Fennell et al. (1984) venture that "acquisition of new information and problem-solving processes are more likely to be disrupted by ESRD than is the recall of previously learned material such as factual information or vocabulary."<sup>194</sup>

In the methodologically very strong study by Brouhard et al. (2000), which used healthy sibling controls, ESRD dialysis and transplant patients scored lower on tests of non-verbal intelligence, with those having ESRD for longer duration scoring lower in mathematics in particular.<sup>193</sup> This finding is consistent with those of other studies of children with ESRD, which have found that they have similar verbal learning abilities to healthy children<sup>5,194,197,199</sup>. In their large longitudinal study, however, Fennell et al. (1990) did find that increased duration of renal dysfunction leads to decreased verbal performance.<sup>198</sup>

Specific neuropsychological abilities such as visuomotor skills, memory, and attention, have been assessed by a few studies.<sup>5-7,9,198</sup> The varied methodology and timeliness of these studies, coupled with the use of both transplanted and non-transplanted children in the sample of patients studied, however, limits the conclusions that can be made concerning



differential neurodevelopmental status in transplanted vs. non-transplanted children with ESRD. Some studies use healthy controls but are old studies, conducted on children who received treatment with aluminum-containing phosphate binders. Some use sibling controls but have low sample size. Some are uncontrolled but recent. Further confusing interpretation is the use, seen in many studies, of a sample combining transplanted and non-transplanted ESRD patients, thereby obscuring any gains made by those children with transplants.

For example, one could tentatively infer that renal transplantation results in improved verbal ability by comparing the findings from the Qvist study, which used a sample consisting entirely of post-transplant children, and the Fennell et al. (1990) study, whose sample contained a high proportion of children who were not transplanted.<sup>5,195</sup> Whereas the Qvist study found no verbal deficits, the study by Fennell et al. found decreased verbal ability with increased duration of renal disease. Both studies were longitudinal, and studied similarly-aged samples.

On the same token, the Qvist study found impairment of neither verbal or non-verbal intelligence in its cohort of transplanted children. This finding is likely attributable to sample make-up and recentness of the study. First, the sample consisted entirely of transplanted children, with no measurements from non-transplanted children, and thus represented cognitive capabilities of transplanted children, not ESRD children undergoing various treatment modalities. Second, the sample in this newly published study had no doubt benefited from neurologically-sparing medical advancements in renal patient management unknown to previous study samples.<sup>5</sup>

Mendley et al. (1999) found that whereas “motor-free” decision speed improved, actual motor response or combined motor and mental processing did not. No improvement was found in verbal learning, focal attention, visuospatial ability, motor dexterity and speed, and visual motor speed following transplantation. They did, however, find significant improvements following transplantation in mental processing speed, reaction time and discrimination sensitivity, and working memory.<sup>6</sup> The findings of Mendley et al. are hard to interpret, however, because of brief follow-up (1 year post-transplant), small sample size (9), older age range (10-18 years of age), and lack of controls. The uncontrolled nature of the study makes it difficult to assert that a finding of no gains represented a negative finding, since baseline abilities prior to transplantation may have been normal anyway.

Studies have been fairly consistent in the observation that children with ESRD have deficits in visuospatial capabilities and non-verbal intelligence. Whether or not these abilities improve upon transplantation, particularly in the long-term, has not been determined.

In a controlled study of children with ESRD (only a small portion of which were transplanted), Fennell et al. (1990) have found that renal disease exerts a consistent, adverse effect on abstracting ability and visual perceptual reasoning.<sup>198</sup> This visual perceptual deficit was also found in the newly published study by Qvist et al., in which more than one-fifth of transplanted patients had visuospatial deficits.<sup>5</sup> *(The lack of comparison group in the Qvist study makes these particular results difficult to interpret. Without a control group,*

*we cannot determine whether or not healthy children would exhibit the same rates of visuospatial deficits as those of transplanted children.*) More importantly, though, the sibling-controlled study by Williams et al. (1994) determined that the lower IQ found in cystinotic children was not solely due to the visual processing deficits typically observed among children with cystinosis, but rather to a more global intellectual impairment in these children<sup>7</sup>

Findings on memory in children with ESRD, either before or after transplant, are not conclusive. Not only the findings, but also the methodological rigor varies across studies. Collectively, though, the findings do suggest memory impairment due to uremia, at least partially correctable through transplantation. Mendley et al.'s (1999) small study of 9 children found significant improvement in working memory after transplantation, despite the older age of the children studied<sup>6</sup>. Again, this study used normative data, not controls. In a controlled study of children undergoing a mix of treatment modalities – both dialysis and transplantation – Rasbury et al. (1986) found no differences in memory between children with ESRD and controls.<sup>197</sup> In a recent, prospective, uncontrolled study with longer-than-usual follow-up, Qvist et al. found that 20% of transplanted children had low memory scores during a follow-up of up to six years.<sup>5</sup> Again, the cognitive outcomes identified in the Qvist study are likely more reflective of modern medical advances than those of other studies. In an uncontrolled study of decent sample size, Fennell et al. (1990) found that reduced renal function has a negative impact on short-term memory.<sup>195</sup> In an earlier study from the mid-1980s, they found that transplanted and patients on continuous ambulatory peritoneal dialysis (CAPD) performed better on both vigilance and memory tasks than hemodialysis patients, and suggested that memory dysfunction in uremia partially related to an attentional deficit,<sup>9</sup> possibly partially correctable with renal transplantation.<sup>6</sup>

Yet untested, but suggested by research findings, is a hypothesis tentatively advanced by Fennell et al. (1990) that renal disease exerts two different types of harmful effects on the developing brain. One is a “**trait-like**” effect that prevents the acquisition of new skills as uremia persists, and is not very amenable to correction by transplantation. The other is a “**state-like**” effect that affects attention, speed of mental processing, and modulation of responses. This state-like effect is dependent on changes in physiology and is thus modifiable through transplantation.<sup>198</sup> If determined to exist, both types of effects would support the case for early transplantation with the objective of improving cognitive development. Moreover, the non-modifiability of the “trait-like” effect over time would argue for preemptive transplantation.

### **Neurological sequelae of uremia/transplantation**

As stated before, medical advances have significantly improved the neurological prognosis of children with renal disease. If modern, standard practices are followed in the management of pediatric renal patients, many of the dire neurological sequelae noted in older studies can be avoided. Standard practices include aggressive nutritional therapy and adequate CAPD prior to transplantation, anti-coagulation treatment where indicated, which has prevented the formation of brain infarcts in ESRD children, and non-use of aluminum-containing phosphate binders.

Recent neurological assessments of children with ESRD, however, still indicate the presence of neurological sequelae post-transplant. Brain imaging of children assessed for up to six years post-transplantation in the Qvist et al. study revealed the presence of ischemic lesions in the brain's watershed areas (areas between major vascular territories of brain), a potentially important finding. Although neuroradiological testing is usually done only when clinically indicated, 54% of patients – many with normal school and motor performance and all with stable clinical condition – were found to have these lesions. Furthermore, only 2% of patients had these lesions pre-transplant. Most of those with watershed-area ischemic lesions, as well as most of those with major neurological sequelae had a history of hypertensive crises or seizures during dialysis. This last finding underscores the importance of the study's main observation that neurodevelopmental deficits are in large part attributable to complications that occur *before transplantation*, during chronic renal failure (CRF) and dialysis. Thus, determining the timing of development of watershed-area ischemic lesions areas pre- and post-transplant is important. The study's finding of 20% prevalence of sensorineural hearing loss (SNHL) also warrants further investigation.

### **School achievement among pediatric renal transplant recipients**

In addition to improvements in cognitive ability, examination must also be made into the extent to which pediatric renal transplant recipients realize their intellectual performance in the area of school achievement. Findings on school achievement in ESRD children, like those on IQ, are also mixed. Whereas Lawry et al. (1994) found that children with renal transplants performed better academically than children on dialysis,<sup>4</sup> Fukunishi and Honda (1995) found the opposite to be true.<sup>205</sup> Neither of these cross-sectional studies, however, followed the children longitudinally to assess sufficiently the children's academic progression over time, from well before to well after transplantation. It does appear evident that children with transplants perform less well academically when compared to healthy children, with lower achievement in spelling, arithmetic, and reading.<sup>193,205</sup> The sibling-controlled study by Williams et al. (1994), however, found that children with cystinosis did indeed score lower in spelling, but did not find deficits in the areas of reading and arithmetic (it must be noted that only 2 of 14 children in this study had transplants).<sup>7</sup> They also found that cystinotic children had average to above average school performance.

Pediatric transplant patients do appear to attend full-time school at higher rates than pediatric dialysis patients. A large European study of 617 children under various renal replacement therapy (RRT) modalities found that about 90% of transplant patients attended full-time school, compared to about 50% of dialysis patients.<sup>207</sup> Progression through school appears to be satisfactory among children with ESRD, but there are no strong studies on grade retention rates among American transplant vs. dialysis patients.<sup>208-211</sup>

As far as school absenteeism, the two sibling-controlled studies in our review have contrasting findings: whereas Brouhard et al. (2000) found that both transplanted and dialysis patients are more likely to miss school than their healthy siblings,<sup>193</sup> Williams et. al. (1994) found that children with cystinosis did not miss more school than their healthy siblings did.<sup>7</sup>

Lawry's study did reveal an interesting disconnect between cognitive ability and actual school achievement: although dialysis and transplant patients demonstrated similar intellectual ability, the transplant children achieved at a much higher level at school, in math, reading, and writing. This finding suggests that children on dialysis are more at risk of developing a learning disability than those who have undergone renal transplantation. Conversely, the findings show that despite acceptable grades and normal progression through school, children with chronic renal failure still have deficits in language and mathematics detectable through achievement testing. This finding recalls the observation by Qvist et al. (2001) that those post-transplant children receiving remedial instruction while in normal school had similar cognitive or neuropsychological capabilities to post-transplant children not receiving remedial instruction.<sup>5</sup>

The findings of both Lawry and Qvist underscore the importance of distinguishing between different definitions of learning disability. For example, school professionals tend to view learning disability as a discrepancy between IQ and actual achievement. Medical practitioners, on the other hand, may deem a child learning-disabled if that child performs poorly on tests of learning when subjected to a neuropsychological test battery.

### **Summary (Kidney – cognitive development)**

Although numerous studies in the literature have determined that children with renal disease demonstrate some level of cognitive and academic difficulty, no specific etiology of these difficulties has been identified. To a much lesser extent have interventions been proposed to remediate them. The mixed findings of earlier studies need clarification, since newer data are much more optimistic and reflective of outcomes to be expected under modern patient management. A number of risk factors for impaired cognitive development in pediatric renal patients have been identified, however. Foremost among these are early onset of renal disease and longer duration of end-stage renal disease (ESRD).

Overall, findings are optimistic for an improvement in cognitive ability as a result of kidney transplantation performed early on in the course of chronic renal insufficiency (CRI). Although scores on tests of intelligence and achievement are still lower for children with renal transplants than their healthy siblings,<sup>193</sup> improvements in cognition have been observed from before to after successful renal transplantation.<sup>4,6,9,196,199,200</sup>

Historically, children with kidney transplants have scored lower on tests of intelligence than healthy children. Recent findings from studies with long-term follow-up, however, suggest that today's children with kidney transplants may be able to achieve a level of cognitive functioning near or at the level of healthy children. This success is in large part due to advances in the management of renal patients that have mitigated the impacts of kidney disease on cognition. These advances include the elimination of treatment with aluminum-containing phosphate binders, adequate peritoneal dialysis during infancy, adequate nutritional regimens administered via tube-feeding, use of anticoagulant therapy where indicated, and subsequent transplantation. Perhaps the single most important clinical advancement promoting cognitive development is transplantation itself, particularly early on in the course of kidney disease.

Thus, it is anticipated that cognitive outcomes of pediatric kidney transplant recipients today will be superior to those assessed in previous studies of children not benefiting from these advances. In the wake of improvements in the management of kidney transplant patients, well-controlled studies are now needed to assess the true cognitive status and progress of today's transplanted children. In particular, a need persists for in-school screening for learning disabilities using achievement testing. Studies are also needed to identify the specific types of cognitive domains most vulnerable to the effects of kidney disease, and thus most amenable to transplantation. It is still uncertain whether kidney disease has a global impact on cognitive ability, or whether its effects are specific to definable neurodevelopmental domains.

Additionally, the presence of brain lesions in children who were transplanted for nephrotic syndrome is a recent finding warranting future study. The presence of ischemic lesions in the brain's watershed areas (areas between major vascular territories of brain) of pediatric renal recipients is a recent finding of potential importance. More than half of pediatric kidney recipients in one study were found to harbor these lesions, which were present only in a small minority of the patients before transplantation.<sup>5</sup> Most children with lesions, however, were without serious intellectual or clinical manifestations.

### **Recommendations from the panel of experts (Kidney – cognitive development)**

Implement studies to identify what cognitive and academic gains are made by children undergoing renal transplantation. Studies should have the following characteristics:

- **Healthy controls. Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. Use of matched, healthy controls in addition to sibling controls would be ideal. (*Note: Please see “Use of sibling controls – some caveats” under “General recommendations on methodology”.*)
- **Multi-center with large sample size.**
- **Longitudinal, with long-term follow-up** into at least the late school age years (achievement testing typically does not begin until age 8, or grade 2).
- **Neuropsychological evaluation, school achievement testing, and intellectual assessment.**
- **Numerous, serial measurements** of intelligence and neurodevelopmental capabilities taken well before transplantation as well as after. Measurements should begin at onset of chronic renal insufficiency (CRI) very early in life, then continued through initiation of conservative management, through end-stage renal disease (ESRD), and through to several years post-transplantation.
- **Younger** sample (transplanted < 5 years old), including early infancy.

*(Note: Younger children are most vulnerable to uremia's deleterious effects on the developing brain. Moreover, their outcomes are more representative {and optimistic} than the outcomes of older children, who have not experienced as*

*many benefits from modern advances in patient management {e.g., tube feeding at early age}.)*

- **Consistent use of instruments** across centers for assessing cognitive performance.
- Use of **instruments permitting comparison among different developmental stages**. The Wechsler series of IQ tests (the WPPSI, WISC III, and WAIS) and the Stanford Binet (age 2 to adult) allow this cross-stage comparison in assessments of global intelligence. Screening tests (e.g., the Denver Developmental Screening Test) and developmental schedules (e.g., the Gesell schedules) are not comparative in standardization.
- Use of **instruments** that can accurately measure **specific neurocognitive deficits** in children with renal disease.
- **Correlation** of clinical/ biomedical findings with cognitive outcomes (e.g., effect of reduced renal function on memory)
- **Multi-factorial analysis** using multiple regression to examine cumulatively and interactively the variety of factors with potential impact on cognitive ability (i.e., both clinical and psychosocial alike). When determinants of outcome are likely to be multi-dimensional, regression designs that ask what variables contribute with what impact, in order to best predict outcomes of interest, are more useful than univariate analytic techniques.
- Examination of effects of **different treatment modalities** on cognitive development. An example of this type of study would be an examination of the effects on cognition of drug therapy that reduces cysteine levels.
- Examination of **disease subtype** as a risk factor.
- Examination of **cyclosporine A and tacrolimus** as risk factors.

#### **Recommendations from expert-selected studies from the literature (Kidney–cognitive development)**

- Administer **cognitive and achievement testing** to pediatric patients with chronic renal failure on a regular basis, since school grades and progression through school do not reflect real math and language deficits that are otherwise detectable through achievement testing.<sup>4</sup>
- Further investigate the timing of development of **ischemic lesions** in the brain's watershed areas (areas between major vascular territories of brain) pre- and post-transplant.<sup>5</sup> This recommendation may be specific to nephrotic syndrome.
- Look at possible attenuation of beneficial effects by **neurotoxicity of cyclosporine (and tacrolimus)**.<sup>6</sup>
- Investigate the prevalence and etiology of **sensorineural hearing loss (SNHL)** among pediatric renal patients.<sup>5</sup>

- Investigate impact of various treatment modalities on cognitive abilities of children with infantile **nephropathic cystinosis**, and clarify the origin of cognitive deficits in cystinotic children.<sup>7</sup> Determine whether or not they have an isolated problem with spelling.
- Investigate the possible **neurotoxic** effect of the following on IQ and/or the brain of pre- and post-transplant **cystinotic** children:
  - progressive cystine accumulation in the brain
  - cysteamine and phosphocysteamine medication
  - psychosocial difficulties
  - presence of a closely linked gene<sup>7</sup>

*(Note: CTNS, a gene mutated in nephropathic cystinosis, was identified by Town et al in 1998.<sup>8</sup> It is possible, however, that another closely linked gene could be associated with the neurotoxic effects seen in cystinotic patients.)*

- In addition to measures of global intelligence, use **more specific tests for measuring cognitive ability** in pediatric renal patients. Measures of global intelligence are likely not specific enough to differentiate between the cognitive effects of different treatment modalities.<sup>9</sup>

### **Clinical recommendations based on individual studies (Kidney – cognitive development)**

Further minimize risk factors prior to transplantation, particularly hypertensive crises and seizures during dialysis, in order to improve neurodevelopmental outcome.<sup>5</sup>

Renal transplantation appears to be the treatment of choice to ensure a favorable long-term neurodevelopmental outcome in young children with CRI.<sup>5</sup>

Administer cognitive and achievement testing to pediatric patients with chronic renal failure on a regular basis, since school grades and progression through school do not reflect real math and language deficits that are otherwise detectable through achievement testing.<sup>4</sup>

## COGNITIVE DEVELOPMENT: LIVER

### **A note on acronyms, technical terms, and standardized measures**

A glossary of technical terms and acronyms found in the following sections are provided in Appendix A for easy reference.

Additionally, please refer to Appendix B for a listing of standardized measures of intelligence, neuropsychological development, and achievement used studies of pediatric end-stage liver disease (ESLD) and transplant patients. This list also provides variables measured, age ranges, and frequency and currency of use.

### **Pre-transplant cognition**

Children with liver disease are vulnerable to developmental delays related to their disease. Because their dysfunctional livers have a reduced metabolism, these children cannot efficiently clear their blood of potentially cerebrototoxic substances. This potential cerebrototoxicity is all the more deleterious to pediatric liver patients, whose disease usually develops at a very young age. Indeed, most children undergoing transplantation have liver diseases – biliary atresia and neonatal hepatitis – with onset during infancy, when the developing brain is most vulnerable to insult from toxins.

It has been observed that children with liver disease show global intellectual deficits that persist after transplantation, at least in the short term. This is contrary to what is observed in adult-onset liver disease.<sup>212</sup> It is probable that the unique metabolic abnormalities brought about by chronic liver disease are more damaging to the infant's central nervous system than to the more mature brains of older patients with liver disease. As Wayman (1997) suggests, "since infancy is a time of critical brain growth with glial proliferation and rapid myelination, severe liver disease requiring transplantation has the potential to significantly interfere with the developing brain and future neurodevelopmental function."<sup>213</sup>

Deficits in visual-spatial skills have been identified in children with end-stage liver disease (ESLD) awaiting liver transplantation, with IQ scores averaging as low as 76.<sup>25</sup> These findings largely stem from the body of research conducted in the late 1980s and early 1990s by Stewart et al. at the Children's Medical Center in Dallas, TX. Their findings also indicate that the longer children endure liver disease before the onset of ESLD, the more compromised their intellectual function.<sup>26</sup> Most importantly, the research of Stewart et al. has suggested that brain insult from early-onset liver (during first year of life) disease leads to more profound adverse cognitive effects than those found in later-onset disease (after 1 year of age). Two of their studies in particular support this hypothesis.<sup>24,26</sup> Both used a group of children with cystic fibrosis as a control group.

Their 1992 study of 43 children with early and late onset of liver disease found that children with early onset had poorer scores than the control group on all cognitive domains tested.<sup>24</sup> The late onset group, on the other hand, differed significantly from the controls only on measures of acquired knowledge, and from normative data on verbal IQ. Moreover, the



children with early onset had significantly lower scores than the children with late onset on tests of performance IQ and spatial and sequential abilities. Higher arterial ammonia levels were found to predict worse scores on acquired knowledge tests. Duration of disease predicted worse scores on tests of spatial and sequential abilities. Diagnostic factors seemed to predict specific cognitive deficits as well, with biliary atresia associated with deficits in performance IQ, full scale IQ, and spatial and sequential abilities; and alpha-1 antitrypsin deficiency was associated with deficits in verbal IQ and acquired knowledge.

Similarly, their 1988 study of 36 children with early and late onset liver disease<sup>26</sup> observed lower ranges of intelligence on verbal, performance, and full-scale IQ scores alike in the early onset group (85-86) compared to the late-onset group (96-103). Measurements of head circumference were also significantly lower in the early onset than in the late-onset group (98 vs. 101 cm). As in their subsequent 1992 study, Stewart et al. found that longer duration of disease was associated with more profound intellectual impairment. Eighty-two percent of the early-onset patients showed intellectual impairment. A subsequent study of 3-month- to 15-year-old children also corroborated the observation that mental and motor delays are associated with early onset of liver disease symptoms.<sup>34</sup>

Such findings have prompted the investigation of early onset liver disease as a potential risk factor for impaired cognitive development. Findings from these more recent investigations have been mixed. Whereas a recent study by Kennard et al. (1999) did not find that poor cognitive outcome was associated with early onset,<sup>23</sup> an earlier, cross-sectional study by Hopkins et al. found that infants and toddlers with biliary atresia were at increased risk of developmental delay.<sup>214</sup> This latter study did not compare the developmental health of these young children, however, with that of children with later onset of liver disease. It must be kept in mind that it is yet unclear whether cognitive delays are the result of having experienced severe illness in infancy in general, or are attributable to liver disease specifically.

The infants and toddlers (<30 months of age) in the study by Hopkins et al. had significantly decreased functioning in both mental and motor skills. Their average scores on the Bayley Mental Development Index (MDI) and Psychomotor Developmental Index (PDI) were 89.78 and 81.54, significantly below the standard normal range (typically set at 85-115.) Low test scores were also supported by parental report, in which the children's mothers rated them as significantly less responsive on the Infant Characteristics Questionnaire.

Unlike in post-transplant children, inferior scores among these pre-transplant children were more pronounced in the psychomotor than in the mental developmental areas. Whereas 40% demonstrated significant delays in motor development, 20% demonstrated significant delays in mental development. Moreover, these findings signify that motor delays were four times more prevalent, and mental delays twice as prevalent as in the healthy population of young children. Normally, only 10% of children would be expected to show delays (formally defined as Bayley scores that are 1.5 standard deviations or more below the normative mean). Only 50% had PDI scores in the normal range, whereas 78% had MDI scores in the normal range. Again, this observation of lower psychomotor scores relative to mental scores in pre-transplant children is in contrast to findings in post-transplant children.

## **Neurological sequelae**

There is a growing body of literature that suggests that approximately 25% of pediatric liver transplant patients receiving cyclosporine or tacrolimus treatment for immunosuppression will experience a seizure. The risk of seizure or other neurologic complication is higher in children who experience multiple organ failure.

Autopsy review of children who expired after transplant has revealed that the majority have central nervous system (CNS) injury, with vascular lesions prominent.<sup>215</sup> Cognitive delay is much more prevalent in children who have seizure disorders and or neurologic injury, independent of other comorbidities. The extent of mild neurologic injury in the pediatric transplant population is unknown. Few have chronic seizure disorders, but the potential for subtle, mounting neurotoxicity related to drug therapy has not been explored.

A small amount of research has looked at the intellectual impact of cyclosporine A use and encephalopathy. In their 1999 study of 47 pediatric liver recipients, Kennard et al. (1999) examined the association between average cyclosporine A (CyA) levels on academic outcome.<sup>23</sup> Although they found no association, they perceived a need for more comprehensive assessment of CyA's effects on intellectual and academic function. They also noted that they examined CyA levels only during the six months prior to academic assessment. A study looking at total dosage since transplantation, they offer, would yield more useful information on cognitive impacts due to CyA.

In a small study of eight children undergoing transplant for fulminant hepatic failure, Hattori et al. (1998) looked at the effect of degree of disease-related encephalopathy on neurodevelopment. They observed that children with grade III or less severe hepatic encephalopathy were left with no intellectual deficit. In fact, their IQ or DQ (development quotient) was well within normal range of 86-110.<sup>27</sup> Even children with grade IV hepatic encephalopathy who survived showed no long-term intellectual deficit. Those showing evidence of brain edema on CT (n=2), however, had severe neurological sequelae, and died not long after transplantation (one of aplastic anemia, the other from sepsis). As noted by Kennard et al. (1999), though, it may be the timing of encephalopathy relative to brain growth that influences cognitive development.<sup>23</sup> Moreover, the children in the Hattori study did not have long-term liver disease before transplantation, possibly rendering them less vulnerable to the more chronic effects of liver disease on cognition.

## **Overall cognitive functioning after liver transplantation**

Observing the reversal of some of the cognitive delays afforded by transplantation, some investigators have been provoked to advocate early liver transplantation “to prevent ongoing cerebral insult associated with” uncorrected liver disease.<sup>216</sup> The specific nature of neurodevelopmental improvements in children after transplantation, however, has not been clarified.<sup>24,28,212</sup>

Also yet to be described adequately is the distribution of IQ scores in the pediatric liver transplant population. Studies are needed to determine if this distribution is normal (approximating a bell curve), skewed (tending to high or low extremes) or bimodal (with

very low and very high scores predominating). It is quite possible that as time goes by, the pediatric liver transplant population will divide into two groups whose differing cognitive abilities will result in a skewed or bimodal curve. These two groups would be those with good graft function and minimal organ dysfunction, and those with complications due to post-transplant immunosuppression or graft dysfunction.

Clinical investigators have not observed significant deficits in motor ability in children with liver transplants followed up over the long term. Deficits in mental development, particularly in visual-spatial skills, however, have been noted.<sup>24,28,212</sup>

Much of the older literature on cognitive development in pediatric liver transplant recipients originates from the studies performed by Stewart et al. during the late 1980s and early 1990s.<sup>28,34,188,212</sup> This seminal work used a variety of standardized, appropriate tools and yielded findings that stimulated the formulation of a number of hypotheses. For the most part, however, the samples used were small and heterogeneous (esp. wide age ranges) and follow-up brief. Moreover, these studies were performed at a time when clinicians managing pediatric liver transplant recipients were on a steep learning curve. Access to liver transplantation and the medical management of these children after transplantation has changed substantially over the past ten years. Therefore, it may not be appropriate to generalize the findings of Stewart et al. to contemporary pediatric transplant recipients.

The foundation set by Stewart et al.'s research, however, has identified pediatric liver transplant recipients as "at risk" for cognitive delays and learning disabilities. Collectively, their findings indicate that gross indicators of cognitive functioning, such as IQ scores, are frequently in the low-average range in school-age recipients. Hypotheses explored – and supported – by their research include the potential adverse impact of early onset liver disease on cognitive function (discussed above). Stewart et al. were also some of the first investigators to observe that developmental deficits tended to persist more in children with ESLD than in adults with ESLD.

The recent literature in the area of cognitive development in children with liver transplants is very limited. Only three major, recent studies, by Wayman et al. (1997), Kennard et al. (1999), and van Mourik et al. (2000), have examined the issue.<sup>22,23,217</sup> All of these studies were longitudinal and well designed.

Wayman et al. (1997) prospectively studied a relatively large (n=42), homogenous group of very young children transplanted < 2 years of age to determine developmental progress from 3 months before to 12 months after liver transplantation.<sup>22</sup> The study was unique in that it exclusively looked at children with biliary atresia, a disease with no known primary CNS defect. Thus, controlling for disease-specific CNS involvement allowed the cognitive effects of liver failure and transplantation to be evaluated independent of effects from specific diagnosis. Additionally, the study was unique in that it divided the sample into three different developmental classifications: normal, suspect, and delayed (normal: MDI and PDI >90, suspect: MDI or PDI <90, delayed: MDI and PDI <90).

Consistent with findings by Stewart et al. (1991),<sup>212</sup> Wayman et al. (1997) found that 35% of the children were still delayed in both mental and psychomotor areas at one year post-transplant, as determined by the Bayley Scales. Furthermore, there was no significant change in developmental classification from pre- to post-transplant. One year after transplant, neurodevelopmental functioning in the children had returned to levels assessed at three months post-transplant. The study's lack of control group, however, limits interpretations as to the relative prevalence of delays in the transplanted children compared to healthy children or children with other chronic disease.

In general, Wayman et al. found that cognitive delays progressed from mild (low-average) at three months pre-transplant, to moderate at three months post-transplant, and back to pre-transplant levels at one-year post-transplant. Motor delays progressed from moderate at three months pre-transplant, to severe at three months post-transplant, and back to pre-transplant levels at one-year post-transplant. As Wayman notes, however, "this pattern of interrupted development resulted in the delayed emergence of expressive language and independent walking in over 50% of the children."<sup>213</sup> Indeed, at one year post-transplant, 70% demonstrated delays in independent walking, and 48% in expressive language ability.

Specific findings from the Wayman et al. study are provided below. Again, the normal range of scores for the Bayley Mental Development Index (MDI) and Psychomotor Developmental Index (PDI) is typically set at 85-115.

#### Findings from Wayman et al. (1997)<sup>22</sup>

##### *Mental Development Index scores (Bayley scales)*

3 months pre-transplant: 92.0 (low-average)  
3 months post-transplant: 80.1 (1 standard deviation below normal = moderate delay)  
1 year post-transplant: 92.7 (pre-transplant level = low-average)

##### *Psychomotor Development Index scores (Bayley scales)*

3 months pre-transplant: 82.5 (1 standard deviation below normal)  
3 months post-transplant: 69 (2 standard deviation drops below normal)  
1 year post-transplant: 80.9 (pre-transplant level = 1 standard deviation below normal)

The study's findings may have been more optimistic had the children been followed up for longer than one year following transplant. Infants and toddlers probably do not achieve full rehabilitation at one year post-transplant. Thus, the deficits identified in the Wayman et al. study may not be permanent. Long-term improvement would be more important in view of the observed deterioration in cognitive and motor abilities at three months post-transplant. Interpretation of studies with only a few months' follow-up post-transplant, therefore, should be guarded. The first, "transition" year following transplantation is filled with emotional and medical uncertainties for the transplanted child. Therefore, it may not be unusual that some developmental delays, particularly in psychomotor domains, are observed during this time.

Moreover, long-term follow-up of transplanted children into the school-age years is advisable since Bayley are generally believed not to predict later IQ. Lastly, a larger sample size would have permitted a more detailed description of age-related neurodevelopmental patterns post-transplant.

The recent, more optimistic study by van Mourik et al. (2000) illustrates the importance of long-term follow-up of infant recipients in obtaining a true picture of post-transplant developmental progress.<sup>217</sup> In this study, 17 children receiving liver transplants as infants (<12 months of age) were prospectively followed up from before transplant to one and four years after transplant. The investigators used the Griffiths developmental scales (normal range=80-120) They found that although language skills and eye-hand coordination had deteriorated by six months and one year post-transplant, respectively, by four years they had significantly improved above those levels. Indeed, the mean score for language ability was higher than the pre-transplant score (110.8 vs. 101.3). At four years post-transplant, eye-hand coordination scores (mean of 105) approached pre-transplant scores (mean of 112.5).

Overall performance scores on the Griffiths developmental test in the children were normal throughout the four-year follow-up period (pre-transplant=103.5, 6 mos. post-transplant=104.1, 1 year post-transplant=108.8). Mean motor scores increased gradually, from a pre-transplant score of 90.6 on the Griffiths Scale, to 93.8 at one year post-transplant, to 97.3 at four years post-transplant (normal range is 80-120). Overall performance increased significantly not only from pre-transplant to four years post-transplant (from 103.5 to 108.8), but also from one year to four years post-transplant (from 104.1 to 108.8). This finding further underscores the possibility that over time, children with liver transplants do make developmental gains not detectable in the short term.

It is important to note here, however, that the children studied by Wayman et al. may have been clinically more representative than those used by van Mourik et al. The latter could not assess the development of eight infants who qualified for their study because they were too sick to participate. Therefore, good clinical condition may have been a confounding factor explaining the largely positive cognitive outcomes of the children able to participate in van Mourik et al.'s study. Had the "missing data" from the very ill eight been included, less positive outcomes may have been assessed. Indeed, the children from Wayman's study were overall more developmentally delayed at pre-transplant than the children in van Mourik et al.'s study. (Children from both studies underwent transplant at < 2 years of age).

A recent study by Kennard et al. (1999) had quite a long follow-up – up to nine years.<sup>23</sup> This study also included some of the children from the earlier Stewart studies.<sup>24-26,28,34,188,212</sup> Children were aged 6-23 years at assessment, and had survived at least three years post-transplantation. This study was the first to look systematically at the school functioning of pediatric liver transplant recipients. Moreover, it is strong methodologically in that it included assessments made prior to transplantation (i.e., pre-/post- testing).

Intelligence in the children studied by Kennard et al. did not increase as a result of liver transplantation and subsequent medical treatment. No significant differences in intelligence

scores were found in pre- vs. post-transplantation scores: 86.4 vs. 86.3., both of which are in the low-average range. Thus, the study corroborated previous findings that pediatric liver transplant recipients as a group demonstrate cognitive deficits, shown by lower IQ scores. The study, however, did not corroborate the previously observed impact of early onset liver disease on cognitive ability.

Use of healthy controls would have more definitively identified relative cognitive deficits among the transplanted children. Simply put, healthy children may have also demonstrated IQ scores in the low-average range had they been tested alongside the transplanted children.

A study using age- and gender-matched controls has been performed on cognitive functioning in children following liver transplantation.<sup>32</sup> In their 2001 study eighteen 4-10-year-old transplant recipients, Gritti et al.<sup>32</sup> found that IQ scores were indeed significantly lower in transplanted children compared to controls at > 1 year post-transplant. Delays were not prevalent, however. Only one of the 18 transplant recipients, however, was actually intellectually delayed. The delay, due to perinatal asphyxia, had been present since before transplantation. Thus, IQ scores of the children post-transplant were in the normal range (mean of 91.6 with a range of 70-117), albeit lower than control children (mean of 118 with a range of 94-135).

It could be argued, though, that the IQ score from the child who had undergone perinatal asphyxia (IQ=70) was unusually low even for an outlier, and thus “dragged down” the average IQ score of the transplanted group. The study would have been even stronger had it included a larger sample size and pre-transplant IQ assessments. The latter would have allowed detection of IQ changes from pre- to post-transplant. Lack of specified follow-up makes the findings difficult to interpret as well. Given that mean age at assessment was 6.8 years and mean age at transplantation was 3.4 years, it is unlikely follow-up was long enough to detect such developmental gains as those observed by van Mourik et al. in their longer-term study.<sup>217</sup>

A small, long-term study of neurodevelopmental outcome was performed by Hattori et al. (1998) in eight children transplanted for fulminant hepatic failure (FHF).<sup>27</sup> They found that none of these children were left with long-term neurological deficit. At the end of a six-year follow-up, IQ or DQ was well within the normal range (97 in a normal range of 86-110). Again, it is important to keep in mind that the children in this study did not have long-term, antecedent liver disease before FHF onset. Thus, they may have been less vulnerable to the long-term, disease-related effects of liver disease on cognitive ability than other children with liver disease.

### **Risk factors**

Although some neurodevelopmental deficits appear to be attributable to the “general interference exerted by chronic illness on development”, as expressed by Wayman et al., some appear appear to be associated with specific disease processes.<sup>23,213</sup> A number of risk factors have been found to predict lower cognitive functioning in children with ESLD, both with and without transplants. These include both temporal factors (e.g., duration of illness) and physiological/anthropometric factors.

It is fairly clear that early age at onset of liver disease predicts more profound cognitive impairment.<sup>22,24,26,34</sup> Again, it is important to remember that the research has not distinguished whether delays result from severe illness experienced during infancy, independent of the biochemical idiosyncracies of liver disease, or from liver disease specifically. True etiology can only be established by carefully controlled studies using controls who have experienced other chronic illness during infancy will establish the true etiology. (*Note: Please see “Overview of Methodology and Instruments” for discussion on using chronically ill controls.*)

The recent findings of Kennard et al., however, did not find that early onset liver disease had an impact on academic performance.<sup>23</sup> In fact, academic performance in school-age liver recipients in that study did not differ based on a variety of temporal factors – including age of onset, duration of illness, time between diagnosis and transplantation, and age at time of transplantation. Academic outcome, as demonstrated by school grades, however, is a different manifestation of mental efficiency than cognitive ability, as demonstrated by IQ scores. This assertion is especially true in children with learning disabilities, whose academic achievement falls short of what is expected based on their native IQ.

Whereas Kennard found no association between academic outcome and age at transplant, Wayman et al. did find that younger age at transplantation predicted less favorable cognitive development.<sup>22</sup> Specifically, they found that mental and psychomotor scores were significantly lower for children transplanted in the first six months of life than in children transplanted later in the first year and during the second year of life. This finding may be *confounding*, however; children transplanted at an earlier age are those very children with earlier onset of liver disease, an important risk factor for impaired cognitive ability.

As studies are published with increasingly longer follow-up, time since transplantation will likely emerge as an important predictor of improved cognitive ability. Whereas studies with short follow-up (less than four years) observe adverse mental and psychomotor outcomes,<sup>22,28,212</sup> recent studies with longer follow-up (4-6 years) have found more favorable outcomes after several years post-transplant.<sup>27,217</sup> In fact, the findings from these studies suggest that cognitive ability worsens during the first year directly following transplant, then eventually recovers and in some domains improves.<sup>217</sup>

Additionally, a number of anthropometric, physiological, and clinical risk factors for impaired cognition have been identified in children with liver disease. Wayman et al. (1997) found that low albumin along with decreased weight (< 5<sup>th</sup> percentile) predicted delayed development in transplant recipients at one year post-transplant.<sup>22</sup> Low albumin reflects both nutritional status and poor liver synthetic function, while decreased weight is a reflection of malnutrition. Malnutrition, in fact, may partly explain the finding by Stewart et al. (1989) that lower IQ scores were associated with impaired growth, particularly height and head circumference.<sup>34</sup> Galactose elimination rate has been significantly correlated with intelligence scores.<sup>214</sup> Longer hospital stays have also been implicated as a risk factor;<sup>22</sup> but this factor is rife with confounding potential.

With respect to risk factors for academic underachievement, Kennard et al. (1999) found that academic outcome was *not* affected by type of liver disease, average cyclosporine A levels, number of hospitalizations and rejection episodes, bilirubin levels, blood urea nitrogen levels, or creatinine levels.<sup>23</sup> Nevertheless, in the Kennard study, bilirubin tended to be higher in the mentally deficient group; bilirubin in this group (n=9) was 3.6 mg/dL compared with an overall mean for all patients of 1.36 mg/dL.

With respect to bilirubin, the earlier findings of Stewart et al. (1987, 1988) are conflicting. Their 1987 study suggests that mental development was related to serum bilirubin and serum albumin levels – both measures of liver function.<sup>25</sup> On the other hand, Stewart et al. (1988) found no relationship between presence of mental delay and levels of bilirubin, albumin, or ammonia or prothrombin time.<sup>26</sup> A decade later, univariate analyses by Wayman et al. (1997; n=42) did not find mental delay to be significantly associated with bilirubin, ammonia, prothrombin time, or potassium one year after transplantation.<sup>22</sup> (Again, they did find that mental delay was significantly associated with low albumin.) This latter finding supports the statistical conclusions of Kennard et al. (1999).<sup>23</sup>

Although the preponderance of evidence suggests that cognitive ability is not related to bilirubin levels, this non-association is by no means conclusive. The studies examining the bilirubin-cognitive association have used various methodologies yielding inevitably mixed findings. Indeed, sample characteristics may have precluded the observation of a statistically significant association in the 1999 Kennard and 1988 Stewart studies.<sup>23,26</sup> Small sample size and wide age range limits the interpretation of Kennard's results on bilirubin. Again, although no statistically significant bilirubin-cognitive associations were found in the 1999 Kennard study, a trend did exist for higher bilirubin levels to be associated with mental deficiency. And, again, Kennard's emphasis was an academic performance, a different measure from pure cognitive ability. In the 1988 Stewart et al. study, which also found no bilirubin-cognitive association, only those patients were included whose bilirubin levels were already above 1.5 mg/dL (the study considered the normal bilirubin range to be 0–1.5 mg/dL is the considered the normal range for total bilirubin). This upper cut-off may have reduced their ability *a priori* to find statistically significant differences in bilirubin levels between mentally delayed and non-delayed groups.

Other indicators of liver dysfunction have also been implicated in reduced mental efficiency and neurologic function. These include deficiencies in  $\gamma$ -glutamyl transpeptidase and Vitamin E<sup>25,26,218-220</sup>, and excessive levels of ammonia (hyperammonemia).<sup>221,222</sup> The latter findings are in contrast to those of Wayman et al. (1997) and Stewart et al. (1988).<sup>22,26</sup>

### **Specific cognitive abilities**

As discussed above, the research on cognitive development in pediatric liver disease patients indicates that **visual-spatial skills** in these children are delayed, and are slower to recover after transplantation than other skills.<sup>24,25,28,212</sup> This delay results in a pattern of relative deficit in spatial function.



Importantly, it is fairly well-established that the **mental** development of pediatric liver transplant patients is more vulnerable to inhibition than motor development. Clinical investigators have not observed significant long-term deficits in motor ability in children with liver transplants.

The findings on language ability do suggest that this domain is delayed in transplant recipients in the short term. Wayman et al. (1997) found that, whereas receptive language was not delayed, expressive language was delayed in 48% of 42 infant and toddler recipients studied at one year post-transplant. This finding suggests that language ability during the first year following transplantation is more vulnerable in growing liver transplant children than other emerging developmental skills. Independent walking was delayed in the study group as well, with 70% of the patients experiencing delays.<sup>22</sup>

Again, the findings of Wayman et al. at one year follow-up post-transplant must be viewed alongside findings from studies with longer-term follow-up. In their study of 25 children also transplanted as infants, van Mourik et al. (2000) also found language and motor deficits significantly declined within the first year following transplantation.<sup>217</sup> At four years post-transplant, however, both abilities had significantly recovered. This was especially true for language ability, which was more enhanced than before transplant (110.8 vs. 101.3 on the Griffiths scale).

### **Hearing loss**

In a retrospective study of 77 children, Buschle et al. (2001) found hearing impairment to be a significant complication in children after liver transplantation.<sup>223</sup> Ten of the 77 children (13%) had sensorineural hearing loss (SNHL), with five experiencing severe to profound hearing loss. SNHL was associated with longer treatment with aminoglycosides, longer hospital stay, short gut syndrome (treated by antibiotics), and hepatoblastoma (treated by chemotherapy). It was not associated with age at transplantation, UNOS status, and duration of loop diuretics treatment.

This finding is of particular importance to considerations of cognitive ability in post-transplant children. Transplantation usually occurs during a critical period for language acquisition (median age of 1 to 1.5 years). Any increased prevalence of hearing problems would likely have an impact on cognitive performance in this group of children. Buschle et al. speculate that chemotherapy for treatment of hepatoblastoma or use of ototoxic antibiotics for treatment of short gut syndrome may predispose some transplanted children to hearing loss.

### **School achievement**

It appears that while some children with liver transplants with lower IQ are able to adapt and maintain academic achievement that exceeds their expected performance based on IQ, others perform lower than expected. In the first (and only) study to systematically look at school functioning of liver transplant recipients, Kennard et al. (1999) found that half of their sample of 47 school-age recipients had a history of repeating a grade. Forty-four percent had academic problems as a result of either learning disabilities or mental deficiency.<sup>23</sup> Even for those recipients who were not mentally deficient, school grades

remained in the low-average range for each academic area tested (reading, math, and writing). The most frequent academic deficits occurred in mathematics and writing, detected through achievement testing.

Surprisingly, underachievement was apparently not related to age of disease onset, duration of illness, time between diagnosis and transplantation, or age at time of transplantation. Additionally, it was not related to number of hospitalizations, either. This latter finding is surprising, since high frequency of hospitalization would be expected to result in high rates of absenteeism. (Absenteeism was not examined.)

It must be noted, though, that two-thirds of the recipients were functioning at least at the low-average level academically. Seventeen of these 28 children actually performed *above* average in at least one of the academic areas tested.

Kennard et al. identified a subset of their study group who were functioning below their cognitive ability, suggesting that learning disabilities may be common among children with liver transplants. Specifically, three groups emerged from the study:

- 56% functioning academically within their own cognitive capabilities, with more than half of this group functioning above their capabilities
- 26% functioning below their own cognitive capabilities (i.e., had learning disabilities)
- 18% deemed mentally deficient, with IQ <70

The study also uncovered a need to identify and provide remedial instruction to liver recipients with learning disabilities. Although half of all the subjects had received special education services at one point, only 38% of the learning-disabled children had received such services. Stewart et al. (1991) perceived this gap in service delivery as early as 1991.<sup>212</sup> In one of their studies, they observed that fewer than one third of liver transplant patients were receiving the special education services they needed, given their academic deficits.

### **Summary (Liver – cognitive development)**

The existing literature on cognitive development in pediatric liver transplant patients supports further research. Much of the research relevant to a modern assessment of cognition in these children centers on three studies only, albeit good studies.<sup>22,23,217</sup> Older studies have been small, with highly heterogeneous samples. Thus, many gaps still exist.

Cognitive and developmental delay appear to be common in this population, yet specific risk factors have not been clearly identified. Early age at onset appears to be an important risk factor for cognitive impairment in children after liver transplantation. Recent research, however, has contradicted this assumption.<sup>23</sup> Indeed, it is still unclear whether cognitive delays are the result of having experienced severe illness in infancy in general, or are attributable to liver disease specifically.

Visual-spatial deficits do appear to be a problem in children with end-stage liver disease (ESLD) and in children with liver transplants. Motor deficits, meanwhile, have not generally been observed to be significantly prevalent. Outside of these findings, specific deficits have yet to be pinpointed.

Also yet to be described adequately is the distribution of IQ scores in the pediatric liver transplant population. Studies are needed to determine if this distribution is normal (approximating a bell curve), skewed (tending to high or low extremes) or bimodal (with very low and very high scores predominating). It is quite possible that as time goes by, the pediatric liver transplant population will divide into two groups whose differing cognitive abilities will result in a skewed or bimodal curve. These two groups would be those with good graft function and minimal organ dysfunction, and those with complications due to post-transplant immunosuppression or graft dysfunction.

The research on academic outcomes, however, is very sparse. Only one major study has examined academic achievement in these children. This study has suggested that underachievement and learning disabilities are more prevalent in children with liver transplants than in healthy children.<sup>23</sup>

It is important to keep in mind that deficits identified in the short term may in fact disappear over the long term. This trend was confirmed by van Mourik et al.'s 2000 study of long-term neurodevelopmental outcome in pediatric liver recipients.<sup>217</sup> Consistent with previous studies, their study found that developmental measures did indeed deteriorate during the first year following transplantation. Unlike previous studies, however, they continued to follow up the children for several years past transplant ation, finding that deficits eventually recovered. Some deficits, namely those in language ability, actually improved over pre-transplant levels.

Long-term studies are needed to determine the true path of intellectual and scholastic progress in children who have undergone liver transplantation. These studies must use healthy controls to ascertain whether or not problems in the transplanted population are any worse than problems in the normal population. Children with other solid organ transplants could also be used as controls to identify cognitive problems or risk factors specific to liver disease.

### **Recommendations from the panel of experts (Liver – cognitive development)**

**Five areas** emerge as reasonable choices for this more focused research. Two types of studies would be focused on infant recipients, two on older, school-age recipients, and one on neurotoxicity:

4. ***Infant recipients – risk factor study from infancy through early school years:***  
Special emphasis should be placed on identifying risk factors for impaired cognition in infant transplant recipients. This **risk factor study** should involve:
  - A large, multi-center, longitudinal study enrolling children who are **less than two years old at time of listing** for liver transplantation.

- Gathering and updating of specific **epidemiological, demographic, and disease-specific data** at regular intervals both **before and after** liver transplantation. For example, infants could be tested at listing time, followed up at six-month intervals during the waiting period, and then tested at yearly intervals following transplantation.
  - A **more comprehensive survey** of cognitive development of the child **at five years of age, when ready to enter school**.
    - This comprehensive testing at time of school entry should include **intelligence testing** with an instrument such as the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) in 3–7 year-olds and the Wechsler Intelligence Scale for Children, 3<sup>rd</sup> edition (WISC-III) in 6–16-year-olds.
    - The evaluation should include **assessment of language ability** using instruments such as the Clinical Evaluation of Language Fundamentals-Pre-School (CELF-P) test in children younger than six years of age and Clinical Evaluation of Language Fundamentals-Revised (CELF-R) test in children older than six years of age. The age ranges covered by the two CELF tests parallel those of the WPPSI and WISC. Alternately, the Pre-School Language Scale-III (PLS-III) could be used in pre-school-age children.
5. *Infant recipients – intervention study during late toddler years:* Since the majority of liver recipients are infants, it is also justifiable to design an intervention study for this group. This **intervention study** would require **long-term follow-up**, from randomization at **three years of age**, through achievement testing at **eight years of age or older**. The study would have the following characteristics:
- **Randomization** of children to either a non-intervention group or a intervention group.
    - The intervention group could receive either a focused, **one-on-one language/speech therapy** intervention, or an intervention in a **group setting**, such as a program similar to the federal government’s “Head Start” program.
    - A possible scenario for the intervention study would be randomizing infant liver recipients to a mandatory **Head Start-type program** once they reach three years of age.
    - Most importantly, the interventions should **target mental development** rather than motor development, since clinicians have not observed significant deficits in motor ability in children followed up over the long-term.
  - Children in the intervention and non-intervention groups should be tested using the **same instruments as used for the risk factor study**, listed above.
    - Thus, instruments for **assessing intelligence** would include the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) in 3–7 year-olds and the WISC-III in 6–16-year-olds.

- Instruments for **assessing language ability** would include the CELF-P in children younger than six years of age and the CELF-R in children older than six years of age, or the PLS-III in pre-school-age children. Again, the age ranges covered by the two CELF tests parallel those of the WPPSI and WISC.
  - Children in the intervention and non-intervention groups should also be **tested for achievement** once they reach the **age of eight years** (usually during the second grade).
    - Highly recommended **achievement tests** include those contained in the Woodcock-Johnson Psycho-Educational Test Battery-3rd Edition (WJ-III) Achievement Standard Battery.
    - Other recommended tests of achievement include the Gray Oral Reading Test, 3rd edition (GORT-3) and the Test of Written Language, 3rd Edition (TOWL-3).
  - Throughout the intervention study, all liver recipient children should be routinely **screened for learning disabilities** and provided standard **remedial instruction** as necessary.
6. *School-age children – study focusing on school performance and learning disabilities:* School performance and learning disabilities should be studied in older school-age recipients. Although this second area of study is not advanced enough to support the generation of hypotheses for intervention studies, the current literature still supports widespread clinical screening of liver transplant recipients for learning disability. This study would be **more of a survey study**, followed up by more detailed cognitive assessments, discussed in item 4, below. Investigators could address the issue of school achievement in children with liver transplants in several ways, including data gathering based on teacher and parent report:
- Instruments would be completed by **teachers and parents**.
  - Data should be collected on the child’s **behavior in the classroom and attention ability** using instruments sufficiently sensitive to detect Attention-Deficit/Hyperactivity Disorder (**ADHD**) and validated for use in chronically ill children.
  - **Instruments** highly recommended for use in such a study would be employed. These include:
    - The **Behavior Assessment System for Children (BASC)** (completed by child, teacher, and parents).
    - The **Scales of Independent Behavior-Revised (SIB-R)** (completed by parents) for detecting behavioral problems. The SIB-R comes in two forms, a full-scale form, and an early developmental form. The SIB-R offers an

overall developmental assessment and is highly recommended for use in preschool and young school-age children. Although the SIB-R can be used in very young children, its sensitivity is somewhat diminished when used in toddlers. (Dr. Woodcock, one of the creators of the WJ-R, is also one of the creators of the SIB-R).

- The **Conner's Continuous Performance Test (CPT)** for evaluating attentional ability. A teacher's version exists for the Conner's CPT, which also comes in two scales, one for children ages 4–5 years (the "Kiddie" Version, or CPT-K) and one for children 6 years of age or older (the CPT-III).
  - **Behavior Rating Inventory of Executive Function (BRIEF)**, a quick, teacher-completed survey for screening for learning disabilities or ADHD.
- Studying functional performance at school from the perspective of teachers would be very important. **Teacher observations** may allow investigators to identify fundamental differences between two different achievement groups among these children:
    - 3) Those liver recipients with **lower IQ** who are nevertheless **able to adapt** and maintain academic achievement that exceeds their expected performance based on IQ, and
    - 4) Those liver recipients with lower academic performance than expected based on their IQ (i.e., those who are **learning-disabled**).

*(Caveat: Classroom observation techniques and teacher observations {e.g., questionnaires, surveys, behavioral observations} are labor-intensive and rarely if ever provide "standard" type data. Teacher assessments of achievement are not necessarily consistent from teacher to teacher.*

*It might be preferable to conduct direct child assessment with appropriate IQ tests and academic achievement tests, to ask if there is consistency or discrepancy between tested IQ level and achievement test results.)*

5. **School-age children – domain-specific study focusing on attention ability and higher cognitive ("executive") functions:** Attention ability and the higher cognitive ("executive") functions should also be studied in school-age children. Attentional abilities can interact substantially with learning and achievement. This study would involve the following:

- **Much more specific, focused neurocognitive testing**, in contrast to the general testing of school performance described in item 3, above.

- **Instruments** for assessing performance in specific domains, including learning, memory, and concept formation.
  - Selection of instruments depending on the **specific research objectives** of the grant applicant.
  - Instruments for use in **school-age children and adolescents**. A suggested sample includes:
    - **Tests of attention/executive function** could include the Spatial Span test of the WISC-PI (“WISC as a Process Instrument”), the Conner’s Continuous Performance Test (CPT), the Wisconsin Card Sorting Test (WCST), the Auditory Working Memory scale of the WJ-III Tests of Cognitive Ability, and the Planned Connections, Number Detection tests of the Das-Naglieri Cognitive Assessment System (CAS).
    - **Tests of memory/learning** could include the Picture Recognition test of the WJ-III Tests of Cognitive Ability, the California Verbal Learning Test (Children’s Version; CVLT-C), and the Rey-Osterrieth Complex Figure (ROCF) test. Neuropsychological evaluations or clinical assessment aids used in support of exploration of ADHD might be considered.
6. **Neurotoxicity study:** The extent of mild neurologic injury in the pediatric transplant population is unknown. Few patients have chronic seizure disorders, but the potential for subtle **mounting neurotoxicity related to drug therapy** has not been explored.
- Given the growing body of literature suggesting that up to 25% of children receiving **cyclosporine or tacrolimus** will experience a seizure, **a large-scale study** is warranted to screen for **neurologic injury** before and after transplantation.
  - The study’s methodology could include MRI or CT scans of the child’s brain before and at regular intervals after transplantation. Newer **scanning modalities** such as functional MRI might help evaluate subtle differences in cortical function, which may be a risk factor for abnormal cognitive and psychological function.

Overall, the preliminary published research on cognitive development in pediatric liver transplant patients is adequate for generating hypotheses. Where possible, the next generation of work in the five areas detailed above should:

- Be **hypothesis-driven**.
- Use **longitudinal** designs, to allow investigators to determine if deficits improve or worsen over time.
- Have **larger sample sizes** than previously used. Sample sizes should be adequate for stratifying patients by 1) age at transplant, 2) diagnostic category and acuity of illness at transplant, and 3) level of ongoing medical disability.

- Use of **matched, healthy controls**, which may include sibling controls or “best-friend” controls. **Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. A **best-friend control** would be one of the patient’s best friends, brought in by the patient when he/she comes in for cognitive testing. Best-friend controls also have the advantage of having similar SES to the patient. (*Note: Please see “Use of sibling controls – some caveats” under “General recommendations on methodology”.*)
- Attempt to clarify whether delays are attributable to early onset of **severe illness in general** or to early onset of **liver disease specifically**. (*Caveat: Achieving this objective would likely require using chronically ill controls, a proposition fraught with difficulty. However, use of chronically ill controls in the form of other, non-liver transplant patients may be feasible and yield important, organ-specific information.*)
- Employ **neuropsychological evaluation, school achievement testing, and intellectual assessment**.
- Relate scores on **IQ** and **neuropsychological** tests to performance on tests of academic **achievement**.
- Relate findings to actual academic achievement as **observed in the classroom**.
- Consider the influence of **environmental factors**.
- Determine the prevalence and etiology of **sensorineural hearing loss (SNHL)**.
- Seek to determine if **IQ distribution** in the pediatric liver transplant population tends to be **normal** (approximating a bell curve), **skewed** (tending to high or low extremes) or **bimodal** (with very low and very high scores predominating).
  - If the distribution is determined to be skewed or bimodal, efforts should be made to determine if **graft function** differs in the low- and/or high-scoring groups. For example, in a bimodal distribution, the children with the higher scores may have better graft function, and the children with the lower scores may have poor graft function.
  - Determining the shape of the IQ distribution specific to children with liver transplants requires a **sufficient sample size**, so that sample statistics can approximate “true” population parameters. (Sample statistics include such characteristics as mean, median, mode{s}, and kurtosis.)

### **Recommendations from expert-selected studies from the literature (Liver – cognitive development)**

- Examine the influence of factors **other than illness-related and cognitive factors** on academic performance. These other factors would include family functioning, socialization, and stimulation experiences. Further investigation is needed to



determine the relative contribution of **psychosocial and medical factors** to neurodevelopmental status.”<sup>22,23</sup>

- Conduct prospective research to determine if any associations exist between cognitive function and the various **biochemical indicators of liver function**, such as bilirubin and ammonia levels.<sup>24</sup>

*(Note: Although mental development was related to serum bilirubin and albumin in a 1987 study<sup>25</sup>, mental delay was not related to these factors in subsequent studies.<sup>22,26</sup> One of the subsequent studies, however, had a high cut-off for bilirubin levels {>1.5 mg/dL} as part of its inclusion criteria, possibly reducing the ability a priori to find a statistically significant association between bilirubin levels and mental ability.<sup>26</sup>*

*In a more recent study, academic outcome was not significantly related to bilirubin, BUN, or creatine; however, interpretation was limited by small sample sizes that reduced the possibility of finding statistically significant associations, by heterogeneity of age at diagnosis and time since transplantation, and by other confounding factors.<sup>23</sup> Discrepancies between intellectual and academic functioning were also reported in this study.*

*Bilirubin was indeed higher in the mentally deficient group at 3–9 years post-transplantation, although not statistically higher. Specifically, bilirubin was 3.6 mg/dL in the mentally deficient group (n=9), compared with an overall mean of 1.36 mg/dL for all patients (n=47), 0.66 mg/dL for those with learning problems (n=12), and 0.87 mg/dL for those functioning within their expected level (n=26).*

*Putting these post-transplant levels into perspective are 2002 data from the SPLIT database. These show pre-transplant bilirubin levels of 10.86 mg/dL in children < 5 years of age, with levels at three years post-transplant of 0.52 mg/dL.*

- Conduct studies that account for a **wide variety of liver diseases, excluding** those metabolic diseases characterized by neurotoxicity or primary defects in the **central nervous system** (CNS). These defects would affect neurological outcome quite apart from any effect the liver disease itself may have.<sup>22</sup> Diseases with neurotoxicity or primary CNS involvement include citrullinemia and most of the urea cycle deficiencies, but not alpha-1-antitrypsin.
- Investigate the effect of **brain edema** on neurological recovery in children transplanted for **fulminant hepatic failure** (FHF).<sup>27</sup>
- Future investigate the hypothesis that **spatial skills** are slower to recover than other skills after liver transplantation. This investigation should examine the possibility that visual-spatial scores are diminished not due to visual deficits per se, but to **factors underlying visual-spatial testing tasks**, such as timed performance (i.e., examine influence of ability to attend and persist under time pressure on visual-spatial scores). Any impacts on visual-spatial abilities resulting from transplantation should also be explored.<sup>24,28,29</sup>

### **Clinical recommendations based on individual studies (Liver – cognitive development)**

- Routinely assess school-age liver transplant recipients for **learning disabilities**.<sup>24</sup>
- Need **comprehensive educational evaluations** on routine basis and heightened delivery of special education services to liver transplant children.<sup>23</sup>
- “**Careful nutritional support** during infancy and **aggressive management of liver disease** prior to transplantation may be important in optimizing the development of children with biliary atresia who subsequently undergo liver transplantation.”<sup>22,25,26,217</sup>
- “**Ongoing monitoring** would allow for the early detection of developmental delays and referral for early intervention.”<sup>214</sup>

## COGNITIVE DEVELOPMENT: HEART

### **A note on acronyms, technical terms, and standardized measures**

A glossary of technical terms and acronyms found in the following sections are provided in Appendix A for easy reference.

Additionally, please refer to Appendix B for a listing of standardized measures of intelligence, neuropsychological development, and achievement used studies of pediatric patients who are eligible for or have undergone heart transplant or open-heart surgery. This list also provides variables measured, age ranges, and frequency and currency of use.

### **Introduction**

The research on cognitive development is less developed in heart transplant recipients than in liver and kidney recipients. Indeed, the three reviews written on cognitive development related to heart transplantation in children all conclude that data on the subject are scarce.<sup>45,48,188</sup> Furthermore, Baum et al. (2000) note that the marked diversity of methodologies, age ranges, and testing measures used in existing studies preclude the formation of any conclusions as to the children's cognitive development.<sup>48</sup> Much less, they continue, can we conclude anything about distinct developmental or cognitive outcomes achieved by recipients within specific age ranges.

### **Do pediatric heart transplant recipients have normal neuro/cognitive development?**

All three reviews do agree that infants and children who have undergone heart transplantation do *not* show gross delays in development when compared to healthy children or children who have undergone other cardiac surgery. They are quick to point out, however, that although the developmental/cognitive functioning of these children falls within the normal range on standardized tests, it is still lower than that of the general pediatric population. In other words, although children with heart transplants perform normally on standardized developmental tests, a high proportion of them still score lower than healthy children.

Indeed, the few studies on development in pediatric heart transplant recipients consistently observe this trend.<sup>35,37,46,47,224-226</sup> Lower scores despite normal cognitive functioning have been observed in studies employing serial assessments post-transplantation as well, a noteworthy observation since data gleaned from serial assessments are more conclusive than those from single, cross-sectional observations.<sup>35,47</sup> These studies have included children receiving transplants later in childhood<sup>47</sup> as well as during infancy.<sup>35</sup>

### ***Infants***

Findings suggest that infants receiving heart transplants today may be expected to have higher cognitive ability than infants who underwent heart transplant surgery several years ago. In a fairly recent report (from 1999), Loma Linda University Children's Hospital looked at cognitive functioning in children receiving heart transplants as infants over the

course of the hospital's entire 15-year experience with infant cardiac transplantation.<sup>37</sup> The study looked at both infants/toddlers and older children (43 children over age 5 and 22 infants/toddlers 4-8-months). Whereas the infants/toddlers showed normal cognitive development, the older children showed low-average intelligence.

Specifically, normal cognitive development in the Loma Linda infants was demonstrated by a mean Bayley Mental Developmental Index (MDI) score of 93, and mild developmental delays, shown by a mean Bayley Psychomotor Developmental Index (PDI) score of 80. (The normal range on the Bayley MDI and PDI is typically set at 85-115.) The older Loma Linda infant recipients had low-average mean verbal IQ (IQ=82), performance IQ (IQ=82), and full-scale IQ (IQ=80) when tested using the Wechsler tests of intelligence. Results from this study, however, would be more interpretable had the test data been compared to test data from healthy controls, preferably sibling controls.

This finding of lower cognitive ability in older children has at least two possible explanations. First, improvements in patient management and surgical techniques over time may have led to the better cognitive outcome in the more recently transplanted patients (i.e., the infants). Or, as has been corroborated by formal studies, slight developmental delays identified early on after transplantation may worsen over time.<sup>36,47</sup> The cross-sectional perspective of the study (the study did not follow the same children as they reached different ages but instead used children of different ages) does not allow the determination of which explanation is stronger. As far as surgical improvements, all children in the study had been subjected to variable lengths of hypothermic circulatory arrest during their transplant surgery.

The 1999 Loma Linda findings of normal infant development are consistent with those from earlier studies by Loma Linda on infant heart transplant recipients. In a 1993 study of 57 infants transplanted at Loma Linda, more than half of whom were transplanted due to hypoplastic left heart syndrome (HLHS), Baum et al. found normal neurodevelopment in infants receiving heart transplants before the age of 6 months.<sup>35</sup> Normal development was shown in 67% of the 48 infants, with a mean Bayley MDI of 87 and PDI of 90. Follow-up in this study was brief, however; only 4 months following transplantation. Nineteen percent of the infants demonstrated abnormal neurologic development at 4 months after transplantation, with generalized hypotonia (deficient muscle tone) being the most common finding. These recent Loma Linda findings are hopeful in that scores on the Bayley's infant tests, normal in this study, generally correlate with IQ later in childhood, as pointed out by Stewart et al. in their review article.<sup>188</sup>

In an earlier (1991) review of a study by Trimm, Baum et al. also concluded that infants with heart transplants have a favorable neurodevelopmental outcome as measured by standardized tests of hearing ability and motor and mental development<sup>227</sup>. The study found normal language, audiologic, psychomotor, and mental functioning in 54 infants ranging in age from 1 week to 4 months. Adding strength to the conclusion was the serial nature of the psychomotor and mental assessments, which were performed at 4, 8, 12, 18, and 30 months. Mental development did appear stronger than psychomotor development, however: whereas only 4 of the 54 infants scoring below 84 on the Bayley's MDI during the

30 months of follow-up, 12 scored lower than 84 on the PDI. (Eighty-four is typically the cut-off score at the low end of the normal range.) In their review article, Stewart et al. (1994) point out that the use of mean scores for the multiple assessments performed in the study by Trimm et al. makes it difficult to identify directional trends in developmental status.<sup>188</sup> Ninety percent of the infants in the Trimm study had normal hearing; abnormal hearing consisted of prolonged latencies not associated with clinical dysfunction.

Normal development was reported by Backer et al. (1991) in a study of 16 infant recipients, most of whom had HLHS.<sup>228</sup> The study did not use an actual developmental assessment, but rather a screening tool (e.g., the Denver Developmental Screening Test), for assessing infant development.

### *Children (including toddlers)*

In a 2001 study of 18 school-age children who received heart transplants at a mean age of 10.2 years, Wray et al. found that these pre-teen children tested quite well on IQ tests.<sup>47</sup> Mean IQ scores were 102, 104, and 102 at 0.5, 1, and 3 years post-transplantation, respectively. Similarly, no developmental delays were found by Dunn et al. (1987) in their clinical examination of six 6-19-year-olds transplanted due to cardiomyopathy.<sup>229</sup>

Findings from studies comparing the cognitive abilities of younger and older recipients suggest that younger recipients are more prone to scoring lower on IQ tests than their healthy peers. In a retrospective cross-sectional study of 41 heart and 24 heart/lung transplant recipients assessed 3-25 months after transplant, Wray et al. found that children under 4 1/2 years of age in particular had significantly lower scores than healthy children and pediatric conventional cardiac surgery patients on all developmental parameters tested (locomotor, personal-social, speech and hearing, eye-hand coordination, performance IQ, and overall IQ).<sup>224</sup> This despite the fact that their performance on all tests was within the normal range. Compared to the performance IQ score of 96.4 obtained by these younger transplant patients, performance IQ scores for the other cardiac patients and healthy children were 107.9 and 119.4, respectively. Scores among the < 4.5-year-olds were particularly low on tests of short-term memory, indicating problems in concentration. The study found that older children (aged 4.5-16 years), on the other hand, scored relatively well, with a mean IQ of 99 (94.8 for arithmetic, 98.2 for reading, and 86.5 for spelling). Again, their scores were still lower than both those obtained by healthy children (111.2) and the other cardiac patients (109.9). (No differences were found between transplant and open-heart surgery patients.)

Baum et al.'s 1997 data on Loma Linda heart transplant recipients also support the hypothesis that younger pediatric recipients score lower on IQ tests than older pediatric recipients.<sup>225</sup> All children in their sample were transplanted in the first year of life, predominantly for HLHS. Whereas 5-6-year-olds had a mean overall IQ in the low average range (mean IQ=76), 7-10-year-olds scored within the average IQ range (mean IQ=87). Scores of verbal IQ and performance IQ also bear out this difference: verbal IQ scores were 78 vs. 87 and performance IQ scores were 77 vs. 89 in the younger vs. older children.

An earlier, preliminary study by Wray and Yacoub of 149 children, however, noted that developmental scores for recipients above the age of 5 years were significantly lower than those of both healthy children and children undergoing alternative open-heart surgeries at 1 year post-transplant, despite falling within the normal range.<sup>226</sup> Scores for recipients below 5 years of age were also significantly lower when compared to healthy children (and, again, also within normal range), but not when compared to the other cardiac patients.

It may be of interest to note here a 1983 study by O'Dougherty et al. of 34 school-age children who had undergone open-heart surgery for transposition of the great arteries.<sup>230</sup> The IQ distribution that emerged in the analysis was not the standard bell curve, but a bimodal distribution with more children with lower IQ scores than those of the general population, but also more children with IQ scores superior to those in the general population.

### ***Infants and children undergoing non-transplant heart surgery***

In their review, Baum et al. (2000) also looked at past studies of cognitive outcomes in infants and children undergoing open-heart surgery or cardiac repair.<sup>48</sup> Regarding infants, they note that the observed normal neurodevelopmental status of infant heart transplant recipients reflects data gathered in the mid-late 1990s on outcomes of infants undergoing cardiac repair.<sup>41,231,232</sup>

Regarding children, they cite several studies showing that children undergoing open-heart surgery tend to have average intelligence,<sup>38,40,233-235</sup> Mean overall, verbal, and performance IQ scores in the studies discussed in their review tend to fall within the 80s,<sup>236,237</sup> although one older study noted significant neurodevelopmental delays in 82% of 11 children with heart transplants.<sup>238</sup> Paralleling findings for transplant recipients, a recent study by Mahle et al. (2000) found that although a majority of school-aged children with HLHS who have undergone staged palliation had IQ scores within the normal range, their mean IQ score was lower than that of the general population.<sup>239</sup>

### **Specific cognitive abilities in pediatric heart transplant recipients**

It has yet to be determined that deficits in specific cognitive domains account for these lower scores among pediatric heart transplant recipients. In their review of studies on cognition in pediatric heart transplant recipients, Stewart et al. (1994) note that instruments used in previous studies generally have not been ones able to detect subtle deficits in neurodevelopmental status. Their measurements are too global. They point out that many widely-used, standardized tests of cognitive function, such as the Stanford-Binet test, provide only global scores of function. A current review of the literature does reveal possible deficits in short-term memory, non-verbal reasoning, and loco-motor skills when compared to healthy controls, despite normal overall mean scores on developmental tests, as detailed below:

In an earlier, controlled study, published in 1992, Wray et al. did find that although transplant children (ages <1-16 years) had pre-transplant cognitive ability within the normal range, they still performed at a lower level on tasks involving short-term memory, non-verbal reasoning, and speed of information processing.<sup>46</sup> They also found that pre-

transplant, the transplant group had significantly lower locomotor and eye-hand coordination compared with normal children. These subtest scores did not significantly change post-transplant. Although this study was methodologically strong in that it was controlled and prospective, the extreme brevity of its follow-up – three months – does not permit conclusions regarding any long-term, sustained deficits in these children.

In their 1994 retrospective cross-sectional study, Wray et al. found that short-term memory and concentration emerged as problematic areas for school-age heart transplant recipients.<sup>224</sup> Younger children in this study (under 4.5 years of age) scored lower than healthy children or other pediatric cardiac patients on tests of locomotor, personal-social, speech and hearing, eye-hand coordination skills, as well as on performance and overall IQ tests. Children above the age of 4.5 years scored lower than healthy children on short-term memory, non-verbal reasoning, and speed of information subtests, and lower than cardiac patients on short-term memory subtests.

Consistent with their 1994 findings for children below the age of 4.5 years, Wray and Yacoub (1991) found that locomotor deficits in pediatric transplant and conventional open-heart surgery patients were more pronounced than those found in healthy controls.<sup>226</sup> Findings from an early study by Silbert et al. (1969) suggest that cyanosis may be a factor in motor deficits observed in pediatric heart transplant patients.<sup>240</sup> They found that cyanotic children with congenital heart disease did not perform as well as acyanotic children with congenital heart disease on tests of perceptual motor and gross motor coordination skills.

The 1991 study by Trimm on neurodevelopmental outcome in infant recipients of heart transplants found that although these infants achieved normal language, audiologic, psychomotor, and mental functioning, more of them had delays in psychomotor development than in mental development<sup>227</sup>. Follow-up in this study consisted of serial assessments using a standardized developmental test (the Ruth Griffiths Developmental Scales) over the course of 30 months post-transplant.

### **Does pediatric heart transplantation lead to improved cognitive capability?**

As Baum et al. (2000) note in their review,<sup>48</sup> further research is needed to establish the potential for improved cognitive functioning following pediatric heart transplantation. Findings on cognitive development pre- and post- pediatric heart transplantation are mixed. Whereas Haneda et al. (1996) and Blackwood et al. (1986) have reported improved cognitive functioning following cardiac transplantation in children,<sup>232,241</sup> Wray et al. (1992) report that cognitive ability did not significantly change post-transplant.<sup>46</sup> Specifically, they found that deficits existing prior to transplantation in locomotor and eye-hand coordination did not significantly change post-transplant.

For a discussion on developmental improvements observed subsequent to non-transplant surgical correction of cyanotic heart disease, please see “Disease-related variables: cyanosis secondary to congenital heart disease”, discussed later.

## School achievement

School achievement among pediatric heart transplant recipients generally falls within normal limits, with mixed findings existing on specific achievement areas.

In their 1999 study, Fortuna et al. observed highly favorable school outcomes in 43 children over age 5 who received heart transplants at Loma Linda as infants, before 6 months of age.<sup>37</sup> These children were able to perform in the classroom at the level of their peers and had average mean achievement scores for reading (95), language (96), and total score (91), as tested via the Wechsler measure. They did, however, have a lower mean mathematics score (85) relative to their reading and language scores.

In contrast, Wray et al. (1994) observed relatively good performance in arithmetic and reading, and poorer performance in spelling in their 1994 study of 4.5-16-year-old children with heart transplants.<sup>224</sup> Moreover, transplant patients did not significantly differ on any attainment score besides spelling when compared to healthy children, who had a mean spelling score of 100.3. (Attainment scores on the British Ability Scales for the transplant patients were, 95, 98.2, and 86.5 for arithmetic, reading, and spelling, respectively.) It is notable that school attainment of the transplant patients was in fact lower across all achievement areas compared to that of both healthy children and children receiving conventional heart surgery, even though this difference was only statistically significant for spelling. A later study by Wray et al. (2001), confirmed there were no deficits in arithmetic, but deficits in spelling, in a sample described as unusually “bright”.<sup>47</sup>

Baum et al.’s 1997 data on Loma Linda heart transplant recipients found that 5-10-year-olds who received heart transplants as infants had normal overall achievement scores.<sup>225</sup> Their overall achievement score was 92, with a reading composite score of 94, language composite score of 97, and a math composite score of 86. Earlier, in their small, controlled 1987 study of seven 6-15-year-olds surviving 3 months to 3 years post-transplantation, Lawrence and Fricker (1987) found that these children maintained their pre-transplant academic performance.<sup>242</sup>

In the first major study focusing on school issues faced by children aged 5-14 with heart and heart-lung transplants, Wray et al. (2001) also observed that parental reporting of academic problems peaked at 3 years at 53%.<sup>47</sup> Actual measurements of achievement, however, found that underachievement – defined as scoring at least 1 standard deviation below IQ score on the achievement test – did not peak at 3 years: underachievement was found in 39%, 53%, and 33% at 0.5, 1, and 3 years, respectively. A look at mean achievement scores reveals that the transplanted children performed strongly in arithmetic and reading, with potential underachievement in spelling. Compared to IQ scores of 102, 104, and 102, at 0.5, 1, and 3 years post-transplantation, respectively, transplanted children obtained the following scores in arithmetic, reading, and spelling:

Arithmetic scores were 93, 93, and 86  
Reading scores were 100, 101, and 95  
Spelling scores were 87, 88, and 85



### ***School absenteeism and special schooling***

Wray et al. (2001) found that children who took longer to return to school after transplant had lower academic achievement.<sup>47</sup> They also found that an average of 6 months passing before pediatric heart recipients returned to school, with no difference between heart and heart-lung recipients in length of absence from school. In an earlier study, however, they did observe that transplant recipients missed “substantially more schooling” than healthy children and conventional cardiac surgery patients.<sup>224</sup> They also noted that cognitive/academic parameters did not differ between those attending and those not attending school,<sup>224</sup> with, as they observe in a later study, 84% of the transplant recipients returning to normal school, 11% to special school, and 5% not returning to school.<sup>47</sup> In a yet earlier study, Wray and Yacoub reported both lower grades and higher absenteeism among children with heart transplants compared to healthy children, noting that the absenteeism likely contributed to the lower grades.<sup>226</sup>

In their 1994 cross-sectional study of 41 recipients, however, Wray et al. observed that only 30% of children eligible to return to school after surgery did so within the mean follow-up time period of 10 months post-transplant. Thirteen of these 15 children attended normal school upon return.<sup>224</sup> In contrast, Serrano-Ikkos et al. (1999) found that school attendance improved, reaching levels attained by open-heart surgery patients prior to surgery, among 44 heart and heart-lung transplant recipients aged 5-17 years studied longitudinally for one year post-transplant.<sup>51</sup>

Importantly, in their review of psychosocial aspects in pediatric heart transplantation, Hangard-Patton and Lawrence note that children undergoing heart transplantation may face a lack of encouragement from teachers who do not expect and therefore do not encourage optimal academic achievement from them.<sup>243</sup> This disincentive to perform academically has yet to be confirmed, however.

### **Factors in pediatric heart disease and transplantation affecting cognitive development**

#### ***Disease-related variables: initial diagnosis***

In their study of cognitive functioning in heart transplant recipients compared to healthy children and conventional cardiac surgical patients, Wray et al. (1994) observed that initial diagnosis, rather than surgical technique, appeared to be an outstanding factor contributing to cognitive differences between the two groups of patients, with heart transplant recipients scoring lower on IQ tests.<sup>224</sup> Levels of gross medical disability were similar in the two groups. Whereas the conventional group primarily had acyanotic lesions, a higher percentage of the transplant recipients had cyanotic heart disease. Although this observation points to cyanosis as the underlying cause of the lower cognitive scores among the heart transplant patients, the heart transplant patient sample also contained children with cardiomyopathy and cystic fibrosis, conditions not known to have deleterious effects on the developing brain. Thus, as Wray et al. conclude, “we must look at cognitive ability in terms of more specific diagnostic categories.”

### ***Complexity of disease and treatment course***

A more complex disease and treatment course has also been found to predict poorer neurologic outcome in pediatric heart transplant recipients. Freier et al. (1999) have observed lower scores on psychomotor tests among infant recipients less than one year of age who have experienced serious medical setbacks such as infections and rejection episodes.<sup>36</sup> Data from the study by Trimm et al., reported by Baum et al. (1991), suggest that delayed psychomotor development within the first 30 months following heart transplantation in infants may be associated with rejection episodes requiring steroid use; however, this hypothesis has yet to be tested or corroborated by other findings.<sup>227</sup>

Although statistically insignificant, differences in poorer academic performance were consistently found by Wray et al. (2001) in children with the initial diagnosis of congenital heart disease (CHD), compared with healthy children or children with other diagnoses.<sup>47</sup> This particular study is notable for analyzing cognitive ability among the different original diagnoses represented in its sample of transplanted patients.

### ***Disease-related variables: cyanosis secondary to congenital heart disease, including early correction thereof***

Inextricable from the consideration of initial diagnosis as a risk factor is the presence of cyanosis secondary to the initially diagnosed disease. Indeed, it is fairly well-established that cyanotic heart disease in children is associated with impaired cognitive functioning.<sup>218,230,244-248</sup>

In 1983, O'Dougherty et al. observed that chronic hypoxia secondary to cyanotic heart disease had particularly adverse impacts on perceptual-motor functioning in school-age children (n=31).<sup>230</sup> Moreover, they noted that the longer a child was hypoxic, the more negative the impact on subsequent intellectual functioning and academic achievement. Children receiving earlier surgical correction of their cyanosis-inducing heart disease showed better cognitive outcome. Similarly, in 1984, Newburger et al. observed that longer duration of hypoxia led to progressive impairment of cognitive function in children (n=38).<sup>218</sup> Specifically, they found that although cyanotic children who had undergone corrective cardiac surgery had normal IQ scores (mean of 102), those who underwent corrective surgery earlier had higher scores on IQ and psycholinguistic tests. The study had the methodological strengths of comparing a range of ages-at-transplant (6 months to > 4 years) and using acyanotic pediatric cardiac patients as controls.

Linde et al.'s longitudinal study from 1970 also supports the case for early surgical correction of the cyanosis-inducing heart disease: in their controlled study of 98 cyanotic pediatric cardiac patients and 100 acyanotic controls, they found that only those cyanotic patients receiving corrective surgery showed improvement on various developmental tests administered over the course of 5 years.<sup>248</sup> An earlier, sibling-controlled study by Linde et al. of 98 cyanotic children (mean age of 3.5 years) found that cyanotic children scored significantly lower on IQ tests than acyanotic children (96 vs. 104), and that healthy children and siblings scored higher than both cardiac groups.<sup>247</sup> Although these studies are more than thirty years old, they boast the methodological strengths of prospective and serial assessment, use of both sibling controls and healthy controls, and large sample size.

A 1985 controlled study by O'Dougherty et al. found that chronic hypoxia in children with transposition of the great arteries was associated with attention difficulties and impaired motor function (n=47).<sup>246</sup> Their finding of low academic achievement in these children is difficult to interpret, since they did not control for school absence. That same year, Aram et al. (1985) would find that cyanotic pediatric cardiac patients had lower IQ scores than acyanotic children, although both scored within the normal range – 103.5 for cyanotic, 113 for acyanotic (n=82). The study is important in that it attempted to account for a variety of confounding variables. For example, the investigators found that lower IQ scores persisted even when disease severity (e.g., only the “well” cyanotic patients were compared with acyanotic patients), neurologic abnormalities, definitive surgery, and child's age at testing were accounted for in the analysis.<sup>245</sup>

A study by Silbert et al., from 1969, found that cyanotic children with congenital heart disease had lower IQ scores and performed less well than acyanotic children with congenital heart disease on perceptual motor and gross motor coordination tasks.<sup>240</sup> IQ among the cyanotic children was quite good, though, with a mean of 105.

More recent studies have also corroborated this association between cyanosis and impaired cognition. Wray et al.'s 2001 study on back-to-school issues faced by pediatric heart transplant recipients found that an original diagnosis of cyanotic heart disease consistently predicted lower IQ scores than those obtained by children with an initial diagnosis of cardiomyopathy or cystic fibrosis.<sup>47</sup> In their preliminary 1991 study, Wray and Yacoub observed that children with previous cyanotic heart disease of congenital origin had lower scores than children with acquired heart disease or parenchymal lung disease, regardless of whether they had undergone transplant or conventional open-heart surgery.<sup>226</sup>

***Treatment-related variables: hypoxia during surgery and other peri-operative factors***

Deficient oxygenation during transplant surgery also impairs development in very young heart transplant recipients. During heart transplant surgery, children must be put into a state of profound hypothermic circulatory arrest (PHCA). PHCA is necessary to maintaining the viability of vital organs during surgery, which it achieves by compensating for the drastically reduced delivery of oxygen to these organs during surgery. In a 1999 study, Freier et al. found that infants who underwent more than 30 minutes of profound hypothermic circulatory arrest (PHCA) during transplant surgery had worse mental *and* psychomotor functioning than infants undergoing less than 30 minutes of PHCA.<sup>36</sup> The recent 15-year retrospective study by Loma Linda University Children's Hospital, found that infant recipients, once reaching school-age, had average school achievement and low-average intelligence, despite being subjected to variable lengths of hypothermic circulatory arrest (CA). The study's authors state that it is unknown whether or not more recently transplanted children, subjected to no or minimal CA, have better cognitive outcomes.<sup>37</sup>

Findings from studies of children undergoing non-transplant cardiac surgery also shed light on hypoxia's effects on neurodevelopment. Similar to the findings of Freier et al (1999), Miller et al. (1996) found that deep hypothermia for longer than 45 minutes was associated with an IQ less than 85 in children undergoing open-heart surgery.<sup>38</sup> They also found that

neonates (under 1 month of age) were particularly vulnerable to the effects on neurodevelopment of duration of hypothermia.

In an earlier study, from 1994, Miller et al. looked at the effects that prolonged hypothermic circulatory arrest during open-heart surgery had on neurologic functioning of 23 children with congenital heart disease.<sup>39</sup> All children underwent the surgery at less than 6 months of age. They found that diffuse brain abnormality on MRI as well as adverse neurologic sequelae were common in children who had undergone prolonged hypothermic circulatory arrest. All six patients with normal MRI also had normal IQ and neurologic examination results. Those without diffuse brain abnormality but signs of focal cortical infarction also had a normal neurologic examination; they were also more likely to have not undergone hypothermic circulatory arrest and to be older than 6 months at surgery.

The series of studies by Bellinger et al. on the use of total circulatory arrest (CA) during pediatric open-heart surgery has yielded useful findings on the association of CA with impaired neurodevelopment. Interestingly, in their 1991 and 1999 studies, Bellinger et al. found that duration of CA did not have an impact on either IQ scores or overall neurological status.<sup>40</sup>

Findings from both of their randomized trials on CA use in infants undergoing D-transposition of the great arteries (arterial-switch operation) support the conclusion that CA is to some degree associated with impaired development. In their 1999 randomized trial of 158 infants, they found that although use of total CA during surgery was associated with worse motor coordination and planning when these infants reached the age of 4 years, it was not associated with lower IQ or worse overall neurological status.<sup>40</sup> Compared to children who had undergone low-flow cardiopulmonary bypass instead of total CA, the CA group did score lower on tests of gross and fine motor function and had more severe speech abnormalities (oromotor apraxia). All children, both those who underwent CA and low-flow, performed below expectations in IQ, expressive language, visual-motor integration, motor function, and oromotor control.<sup>40</sup>

Likewise, in their trial randomizing 171 infants, published in 1997, Bellinger et al. found that infants who underwent CA scored lower on tests of development at 1 year of age than those who underwent low-flow bypass.<sup>41</sup> They found that CA was particularly associated with developmental difficulties in the domains of motor and language function.

Findings from 1991 and 1999 by Bellinger et al. found two specific, potentially important risk factors associated with poorer neurodevelopmental status: seizures and too-brief core cooling periods. In their 1999 study, they found that, once core cooling periods dropped to less than 20 minutes' duration, shorter cooling periods were associated with lower developmental scores.<sup>42</sup> Therefore, to avoid central nervous system injury, they postulate, patients undergoing long periods of deep hypothermic CA may require some minimum time of cardiopulmonary bypass cooling. Their 1999 study found that seizures during the perioperative period were associated with lower mean IQ, whether they were clinically apparent or only detectable by EEG.<sup>40</sup> Their recent, 2001 study comparing neurodevelopmental outcomes in children undergoing the alpha-stat versus the pH-stat acid-

base management strategy during deep hypothermic cardiopulmonary bypass found no difference in outcomes.<sup>43</sup>

Hesz and Clark (1988) found that children experiencing profound hypothermic circulatory arrest during cardiac repair for transposition of the great arteries had lower scores on intelligence subtests and more aggressive behaviour when compared both to healthy siblings and children with acyanotic disease.<sup>249</sup> (10 cyanotic, 7 acyanotic, 12 healthy siblings)

In a multi-center study of possible neurologic sequelae following pediatric open-heart surgery, Ferry (1990) found that all six major pediatric cardiac surgery units canvassed reported seeing a small but unmistakable incidence of postoperative neurologic symptoms.<sup>250</sup> These included alterations of consciousness, seizures, and hemiparesis or delayed choreoathetoid syndromes. Ferry noted a “disturbing” incidence of hypoxic-ischemic encephalopathy, unsuspected cerebral atrophy, and subdural hematomas revealed by neuroimaging following surgery. They urge the development of techniques to minimize the occurrence of these sequelae, in order to prevent or mitigate resultant neurologic disability.

#### ***Treatment-related variables: time since transplantation***

When considering the optimistic findings of previously-mentioned studies with brief follow-up, it is important to keep in mind that studies with longer follow-up have revealed an intensification of developmental delays over time. Thus, it appears that slight developmental delays identified early on after transplantation tend to worsen over time.<sup>36,47</sup> In a small 1999 study on Loma Linda infants Freier et al. found that although early cognitive functioning fell within normal limits, mild to moderate decline became more prominent in children more than one year of age. Mental Developmental Index scores fell from the low 90s at 4-8 months of age to the mid 70s at 28-37 months of age. Similarly, a larger Loma Linda study found that cognitive scores were lower in older children who underwent heart transplant surgery as infants than in younger infant recipients. In view of the cross-sectional design of the study (i.e., children of different ages were examined, instead of following the same children as they reached different ages), this finding may be explained by the fact that improved patient management and surgical techniques over time have led to improved patient cognitive outcome.

Contrasting with the findings of Freier et al. are those of Wray et al. from studies published in 1994 and 2001. In their 1994 study of cognitive functioning in heart transplant recipients compared to healthy children and conventional cardiac surgical patients, they found no correlation between overall IQ and time since transplantation; however, their study sample was followed up an average of only 10 months post-transplantation.<sup>224</sup> Similarly, in their 2001 study, they found that IQ scores did not change as a function of time from transplant. No significant change in either overall IQ or achievement were observed in 18 pediatric heart transplant recipients assessed 6 months, 12 months, and 3 years post-transplantation.<sup>47</sup> They did find, however, that parental reporting of academic (39%) and adjustment (28%) problems in transplanted children peaked at 3 years post-transplantation.<sup>47</sup>

### ***Other factors***

Stewart et al.'s 1994 review discusses the possibility that IQ differences among cyanotic patients, acyanotic patients, and cyanotic patients who have undergone corrective surgery may partially stem from differences in physical activity among the groups.<sup>188</sup> This hypothesis has never been tested with strong, well-controlled studies, however.

O'Dougherty et al.'s 1983 study examined possible associations between several medical and psychosocial risk factors and intelligence in children undergoing open-heart surgery to repair transposition of the great arteries. They found that age at correction (the younger, the better outcome), height deficit, congestive heart failure, associated heart defects, need for further palliative surgery, CNS infection, and stroke were all significant risk factors for negative cognitive outcome.<sup>230</sup> Silbert et al.'s 1969 study of cyanotic vs. acyanotic children with congenital heart disease also found congestive heart failure to be a risk factor for slightly lower IQ; IQ scores for acyanotic children with a history of congestive heart failure fell between those for cyanotic children and acyanotic children without a history of congestive heart failure (cyanotic = 105, acyanotic with CHF = 115, acyanotic without CHF = 118.5).<sup>240</sup>

### **Summary (Heart – cognitive development)**

Too few studies exist on the cognitive functioning of pediatric heart transplant patients for any firm conclusion to be made about their cognitive outcome. It does appear that these children do not demonstrate gross delays in mental or psychomotor development. Despite having scores within the normal range on tests of intelligence and development, however, their scores are still lower than those of healthy children, or children who have had other cardiac surgery. Thus, although slight delays are reported in pediatric heart recipients, impact on cognitive function remains equivocal.

Various risk factors have been identified as predictive of adverse cognitive outcome in pediatric heart disease and transplant recipients. Apparent risk factors include both treatment- and disease-related hypoxia – specifically, persistence of cyanosis secondary to congenital heart disease and hypoxia experienced during heart transplant surgery due to induced profound hypothermic circulatory arrest. Some study data suggest that delays identified early in development may intensify over time after transplantation. Other data suggest that different initial diagnoses and disease/treatment courses are associated with different cognitive prognoses. Younger age also seems to place children with transplants at risk of developmental delay, although further study is needed to corroborate this observation.

Heart transplantation has not yet been shown to lead to either improved or worsened cognitive function in children. Studies performed in children with cyanotic heart disease, however, consistently show that chronic cyanosis (low blood oxygen) is associated with progressive cognitive impairment. On the other hand, earlier correction of cyanotic heart disease leads to more favorable cognitive outcome.

Further studies are needed to determine the true course of cognitive development and scholastic progress in pediatric heart transplant patients. It is unknown whether the observed slight delays persist over time or worsen, as has been suggested by some findings. Some study data suggest that delays identified early in development may intensify over time after transplantation. Other data suggest that different initial diagnoses and disease/treatment courses are associated with different cognitive prognoses. Younger age also seems to place children with transplants at risk of developmental delay, although further study is needed to corroborate this observation. With respect to cyanosis, the cognitive impacts of two factors warrant further study. These are cyanosis due to heart disease, and hypoxia (low oxygen in the various body tissues) during heart transplant surgery. Studies should use controls and have long-term follow-up, extending from the pre-transplant period into adolescence.

### **Recommendations from the panel of experts (Heart – cognitive development)**

The cognitive research in children with heart transplants is the least developed of all the cognitive research reported here in this report.

- Thus, future studies will have to be **descriptive**.
- Further, investigators should **learn from the methodological imperfections** of previous studies undertaken by their counterparts in the kidney and liver transplant research (e.g., lack of controls, lack of comparable instruments across studies, wide age ranges).

Current findings do suggest that cognitive outcome in children surviving heart and heart/lung transplantation is good. These findings, however, need to be **confirmed in larger, multi-center studies**.

- If these larger studies confirm **good cognitive outcomes**, a risk analysis study looking at multiple factors predicting cognitive ability would not be warranted.
- If these larger studies uncover **cognitive deficits** in children surviving heart transplantation, a risk analysis should be performed, with hypoxemia (low blood oxygen) one of the first determinants investigated.
- These additional larger studies should have the following characteristics:
  - Use of **matched, healthy controls**, which may include sibling controls or “best-friend” controls. **Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. A **best-friend control** would be one of the patient’s best friends, brought in by the patient when he/she comes in for cognitive testing. Best-friend controls also have the advantage of having similar SES to the patient. (*Note: Please see “Use of sibling controls – some caveats” under “General recommendations on methodology”.*)
  - **Multi-center with large sample size.**

- Assessment of cognitive ability in terms of **more specific initial diagnostic categories**, especially in view of the higher proportion of acyanotic lesions in transplant versus the conventional cardiac surgery patients.
- **Neuropsychological evaluation, school achievement testing, and intellectual assessment.**
- **Longitudinal design, with long-term follow-up.** Long-term follow-up is especially important in studies of children with heart transplants, since some data suggest that developmental delays identified in young recipients tend to worsen over time. Research must answer these questions: Do delays intensify over time? And, if so, why?
- **Numerous, serial measurements** of cognitive ability initiated before as well as after transplantation.
- **Consistent use of instruments** across centers for assessing cognitive performance
- **Use of instruments permitting comparison across different developmental stages.** In assessments of global intelligence, the Wechsler series of IQ tests (the WPPSI, WISC III, and WAIS) and the Stanford Binet (age 2 to adult) would allow this cross-stage comparison. Screening tests {e.g., the Denver Developmental Screening Test) and developmental schedules (e.g., the Gesell schedules) are not comparative in standardization.
- Use of instruments that can accurately measure **specific neurocognitive deficits** in children with congenital heart disease and heart transplants.
- Examination of **disease subtype** as a risk factor.
- Examination of **cyclosporine A (CyA) and tacrolimus** as risk factors.

### **Recommendations from expert-selected studies from the literature (Heart – cognitive development)**

- Continue to look at the impact of **hypoxia during surgery** on cognition.<sup>36-43</sup> Studies should compare heart transplant recipients to children undergoing other types of surgery requiring periods of hypoxia, e.g. open-heart surgery.
- Look at problems of **medical compliance/adherence**.<sup>44</sup>
- Examine **cognitive and academic functioning** as one of **four broad areas** of functioning in pediatric heart recipients:
  1. developmental progress (cognitive and academic functioning)
  2. emotional and behavioral functioning
  3. medical compliance
  4. quality of life (QOL)<sup>45</sup>



- Investigate the possibility that **more recently transplanted patients**, who experienced **less circulatory arrest** during transplant surgery as a result of more advanced surgery techniques, have better developmental outcomes.<sup>37</sup>
- Determine if developmental improvement is **sustained long-term** after transplant surgery, into the school and adolescent years.<sup>35,46-48</sup>
- If the presence of cognitive abnormalities is confirmed in pediatric heart transplant patients, perform **longitudinal** studies examining **both medical and developmental risk factors** for developmental delay.<sup>48</sup>

#### **Clinical recommendations based on individual studies (Heart – cognitive development)**

- Focus on **reintegrating** the pediatric heart transplant recipient **into the school system**. This task will include encouraging schools to develop tailored educational strategies.<sup>47</sup>
- Provide **ongoing education support to** minimize impact of lost schooling. Educational interventions should be planned early on in the transplant process.<sup>47</sup>

### III. Psychosocial development literature review and recommendations

#### PSYCHOSOCIAL DEVELOPMENT: INTRODUCTION

Children receiving organ transplants, as in other chronic illnesses, have a higher risk of negative psychosocial outcomes. Psychosocial adjustment in transplantation is concerned with how the child and family behaviorally, emotionally, and socially adjust to the changing circumstances and stresses of the child first being chronically ill, requiring and waiting for a transplant, and then living with the limitations and uncertainties after transplantation. Psychological and emotional disturbances often include anxiety, feelings of helplessness, dependency on parents and depression. Physical retardation or functional impairment attributable to the disease, and continuing into the post-transplant period, are often important factors affecting a child's self concept and self-esteem. Social rejection and isolation by peers may add to the emotional burden.

Child behavioral problems are often manifestations of psychosocial maladjustment. Changing family interactions also come into play as the emotional and financial stresses of coping with the disease and transplant may influence parental behavior and interactions between the child and the parents or siblings, and may contribute to parental psychiatric disorders or marital breakdown. It has been suggested that these changes in family environment may in turn influence a child's psychosocial functioning.

Many of the problems associated with psychosocial adjustment in pediatric transplantation are similar for kidney, liver and heart, although there are also important differences between these three types of transplantation in the duration of illness prior to transplant and in the consequences of a lengthy wait or graft rejection. Because of the options for dialysis during renal failure or after a failed transplant, the stresses of renal transplantation may be mitigated compared with more immediate life or death situations occurring with liver and heart transplantation.

Better psychosocial adjustment may not only influence the quality of life in the pediatric transplant patient through greater self-esteem and greater peer interaction, but may have an immediate impact on their health and life-span as a result of higher compliance with critical medications and reduced medical needs.

The following literature review has included these review articles on psychosocial issues:

- in renal transplantation, Shaben (1993),<sup>251</sup> Frauman and Myers (1994),<sup>189</sup> and Davis (1999)<sup>252</sup>
- in liver transplantation, Bradford (1991)<sup>253</sup> and Burdelski et al. (1999)<sup>254</sup>
- in heart transplantation, Todaro et al. (2000),<sup>45</sup> Hangard Patton and Lawrence (2000),<sup>243</sup> and Hanton (1998)<sup>255</sup>

## PSYCHOSOCIAL DEVELOPMENT: KIDNEY

### A note on acronyms, technical terms, and standardized measures

A glossary of technical terms and acronyms found in the following sections are provided in Appendix A for easy reference.

Additionally, please refer to Appendix C for a listing of standardized measures psychosocial functioning used in studies of pediatric end-stage renal disease or transplant patients. This list also provides variables measured, age ranges, and frequency and currency of use.

### Introduction

According to Shaben's review of the literature,<sup>251</sup> the first concerns regarding physical and psychological trauma of transplantation in children with end-stage renal disease (ESRD) were expressed by Riley in 1964.<sup>256</sup> A focus on multidisciplinary team care developed and led to separate statistics for kidney transplant children beginning in 1968, but psychosocial issues only began to be studied in the 1970s.<sup>12</sup>

### Psychosocial adjustment

Various studies found marked emotional and social adjustments necessary following renal transplantation, with the majority of children experiencing problems related to social isolation, dependency on parents, depression, and peer and sibling relationships.<sup>12,257-261</sup>

Tisza, Dorsett & Morse (1976) described the combination of adolescence and chronic illness as one of the greatest challenges.<sup>262</sup> They also reported that constant uncertainty of kidney rejection was associated with fostering an integrated identity, which if not successful was believed to lead to psychological and emotional problems of adaptation. Kidney transplantation in children and adolescents was later described by Levi (1982) as a chronic illness.<sup>263</sup>

Early studies by Korsch et al. (1973) and Simmons, Klein & Simmons (1977) reported psychosocial adjustment in children with kidney transplantation to be mostly comparable to that of healthy children.<sup>264,265</sup> Nevertheless, in these studies psychological problems were identified in children with renal transplants, including dissatisfaction with body image (related to steroid effects) and lower self-esteem. Adolescents, particularly girls, were found to be at greater risk.

In one small study by Wolff (1988), children with infantile nephropathic cystinosis were reported to have normal intellectual capacity/performance and adequate emotional and social functioning, despite their severe illness.<sup>204</sup>

A controlled study by Reynolds et al. (1993), which had relatively long follow-up, confirmed earlier findings of delayed social development in young adult survivors of ESRD

despite good overall social adjustment.<sup>266</sup> Poorer social outcome was associated with an early start of illness and with being on dialysis as an adult. Suboptimal or delayed social functioning was manifested by conventional indicators: living with parents, few intimate relationships, unemployment, unmarried, not having children, and drawing social security benefits. Males were more likely to be living with parents and much less likely to be married. In contrast with other studies, physical appearance did not emerge as a psychosocial problem area in this investigation. Use of sibling controls would have strengthened these results.

In 1994, Frauman and Myers reviewed the psychosocial literature concerning adjustment and habilitation in renal transplantation and concluded few problems were found in psychosocial adjustment or with completion of normal developmental tasks.<sup>189</sup> A number of earlier studies were cited in support of this conclusion.<sup>208-211,267-269</sup> Long-term problems identified were growth failure and difficulties in the social domain, particularly maintenance of intimate relationships.

Frauman, Gilman and Carlson (1996) identified fatigue and short stature as major factors interfering with activity in children and adolescents, respectively.<sup>270</sup> They found measures of communication, daily living skills, and socialization in kidney transplant recipients to be substantially below norms for healthy children; percentiles were 19%, 21% and 23%. Furthermore, scores on these measures did not differ between patients with functioning grafts and those on dialysis with non-functioning grafts. Similarly, the degree of rehabilitation based on work or school age-specific activities, did not differ with graft function; overall, only 48% of children engaged in extracurricular school activities. This absence of beneficial effect of a functioning graft led to the conclusion that even after transplantation there may be delays in social and adaptive behavior over time, and either slow or nil improvements. Fukunishi and Kudo (1995) found that 29.6% of transplant patients continued to have poor peer relationships, suggesting that factors other than graft function are also important and should be addressed.<sup>271</sup>

The benefits to psychosocial well being of kidney transplantation compared with alternative treatments for children with ESRD has been reported by Brem et al. (1988), Brownbridge & Fielding (1991), and Reynolds et al. (1993).<sup>266,272,273</sup> Alternative treatments included continuous ambulatory peritoneal dialysis (CAPD), home hemodialysis (HD), and in-center HD. In these studies, children having in-center dialysis had worse psychosocial adjustment, higher depression scores, and more behavioral disturbances than with other modes of dialysis or with transplantation.

School maladjustment seen in both transplant and non-transplant renal patients was related to poor academic achievement and many psychological factors according to a study by Fukunishi & Honda (1995).<sup>205</sup> Children on CAPD had more psychological problems, including greater absenteeism and less social interaction, than either transplant or healthy children. However, interpretation of these findings is limited by the cross-sectional approach and lack of a sibling control group to neutralize socioeconomic status (SES), psychosocial and genetic differences, especially in view of the small sample sizes.

Davis (1999) reviewed various factors affecting optimization of school reentry after transplantation, including physical effects, social and emotional difficulties, academic difficulties, caregiver attitudes and school resources.<sup>252</sup> Attitudes of caregivers were considered extremely important to school adjustment. Intervention with an individualized education plan (IEP) was previously reported by Brouhard et al. (1997) to significantly improve coping with stress, socialization, reduction in somatic complaints, and positive parental perception of overall medical condition.<sup>274</sup>

Psychosocial adjustment in parents of transplanted children has been suggested as a problem in various earlier reports. A recent Swedish study by Karrfelt, Berg & Lindblad (2000) using semi-structured interviews with parents, many of whom were living donors, identified significant psychological distress in the parents.<sup>275</sup> Unemployment related to the care of the child was often a factor. Quality of life of parents was affected by continual worries about medication, organ rejection, and general prognosis. Parents had feelings of isolation, uncertainty for the future, and insecurity. Despite their own distress, most parents reported improved psychological functioning of the family after transplantation. Before firm conclusions can be drawn, corroboration of these findings is needed by correlating findings from parental reporting with objective measurements of the children.

Psychosocial adjustment is considered further below in terms of psychiatric adjustment/behavior, self-esteem/non-compliance, quality of life and rehabilitation. It is recognized that these topics have considerable overlap.

### **Psychiatric adjustment and behavior**

Children with ESRD were found to have more psychiatric symptoms (e.g., depression, conduct disorders) than those with less severe kidney disease in reports by Eisenhauer, Arnold & Livingston (1988) and Garralda et al. (1988).<sup>276,277</sup>

Morton et al. (1994) conducted a rigorous study on renal transplant patients of lifetime psychiatric adjustment and self-esteem that has provided validation to past findings.<sup>278</sup> Although psychological problems are greater in childhood, and self-esteem lower in adulthood, adult lifetime psychiatric morbidity was comparable between transplant recipients and a healthy, matched, comparison group. Nevertheless, depressive disorders were greater in the transplant group (9% vs. 4%). Reduced self-esteem was suggested as a possible vulnerability factor for later psychiatric morbidity.

In a subsequent study, Davis, Tucker & Fennell (1996) reported significant levels of maladaptive behavior in both kidney transplant patients (82%) and renal failure patients prior to dialysis or transplantation (96%).<sup>10</sup>

In a recent paper by Soliday, Kool and Lande (2000), psychosocial adjustment of children with a kidney transplant was compared with age-, sex-, and demographically-matched healthy controls, as well as with groups having other related illnesses (steroid sensitive nephrotic syndrome – SSNS, or chronic renal insufficiency – CRI).<sup>17</sup> This study reported elevated scores (although still within normal range) for behavioral problems in pediatric kidney transplant patients, thus validating earlier studies by Rasbury, Fennell and

colleagues. This study further demonstrates the impact of elevated psychological symptoms (internalizing and externalizing behavior, clinically significant distress, parenting stress) on long-term developmental outcome of children, regardless of whether they are healthy or have kidney disease. Study limitations include smaller sample sizes and lack of sibling controls.

Medical intervention by tube-feeding, while an important factor in improved outcomes in kidney transplantation, may also negatively impact psychosocial and behavioral adjustment. Previous studies in this area are of limited value because of their focus on older children and adults. A study by Douglas, Hulslen and Trompeter (1998) is important in that it addressed tube-feeding during the first two years of life in children who received kidney transplants at less than 6 years of age.<sup>279</sup> While they conclude that early tube-feeding does not adversely effect behavior or impair the development of normal feeding patterns, they less optimistically state that 28% of mothers reported continued problems in their child's eating behavior. Offering tube feeding in early pre-transplant years, and avoidance of forced oral feeding, was suggested as crucial in the transition to oral feeding after transplant. Overall, this study reported no marked negative impact of renal transplantation at pre-school age on the children's emotional or behavioral state, which is consistent with earlier reports.

### **Body image, self-esteem and non-compliance**

The adverse physical effects of immunosuppressive steroid use on body image, particularly in adolescent girls, were first recognized by Kahn et al. (1971), and proposed to be a factor in non-compliance with medications.<sup>259</sup>

The first use of a chronically ill control group with cystic fibrosis, and of additional control groups from a database that controlled for extraneous variables by matching of children for age, sex, ethnicity and SES, was an important methodological development described by Korsch et al. (1973).<sup>264</sup> This study showed no increase in psychological disturbance of the transplant group compared with control groups, although anxieties related to the fear of rejection and steroid-induced body changes were described. While additional data from this study showed personality tests for a majority of transplanted children to be within normal limits, lowest scores were associated with non-compliance.

A subsequent study on non-compliance by Korsch, Fine & Negrete (1978) demonstrated that 9.2% of patients had some non-compliance over a 10 year period.<sup>280</sup> Non-compliance was associated with extreme scores in measures of personality, anxiety and especially low self-esteem, as well as with differences in some family function test items. Family factors associated with non-compliance included lower income, fatherless household, and communication difficulties. In this study, non-compliance in adolescents was hypothesized to be related to development stage more than to other factors.

In another study, Fine et al. (1978) found quite favorable personality outcomes at one year post-transplant, but still a high proportion of patients with low self-esteem.<sup>208</sup> Reasons given by patients for non-compliance included physical side-effects, adolescent rebellion, depression and denial. Another study, by Bock et al. (1980) related non-compliance in renal transplant patients to the factors of adolescence, female sex, and family instability; in

this study, introduction of extensive counseling reduced the non-compliance rate from 43% to 19%.<sup>281</sup>

Davis, Tucker & Fennell (1996) suggested poor socialization and communication skills to be most associated with poor medical adherence, while family behavior was unrelated; in this study family functioning had a greater influence on adaptive behavior in renal failure patients than in transplant patients.<sup>10</sup> Fine (1985) previously suggested that the incidence of non-compliance leading to allograft loss was probably underestimated.<sup>282</sup>

Low self-esteem is considered a very important factor in non-compliance (Fine et al, 1978).<sup>208</sup> Low growth rates and short stature in ESRD were considered for their adverse effects on body image and self-esteem by Fine et al. (1987) and Fine & Tejani (1987), and in relation to the psychosocial causes of non-compliance by Fine & Tejani (1987) and Offner et al. (1988).<sup>283-285</sup> Morton et al. (1994) reported reduced educational achievement to be the strongest mediator between illness and lower self-esteem; other factors involved were social dysfunction and early onset of renal disease.<sup>278</sup>

Changes in facial appearance likely to increase risk of non-compliance in adolescents have also been identified Reznik et al. (1987), but follow-up studies were not developed.<sup>286</sup>

In contrast with other studies suggesting an important effect of physical appearance on psychosocial adjustment, Reynolds et al. (1991) found that concerns regarding appearance and growth in children with kidney transplants were reported by less than 7% of pairs of parents.<sup>287</sup> However, parental reporting used in this study may not represent the true views of the children.

Non-compliance rates for anti-rejection medications have been reported by Ettenger et al. (1991) at about 64% of adolescents with kidney transplants, compared with 25-35% non-compliance for other health problems in the general population.<sup>288-290</sup> Nekolaichuk (1990) stated that focusing on the dire consequences of non-compliance has not helped provide a better understanding of its causal factors.<sup>291</sup>

Psychological functioning, which could potentially influence compliance, has been studied in relation to graft survival. In a study by Mongeau et al. (1997) a combination of psychosocial and cognitive factors assessed prior to transplantation, specifically the psychological/cognitive score, was highly predictive of renal graft survival within the first year after transplantation.<sup>292</sup> Social scores alone did not predict graft survival. Usefulness of this result is limited by the knowledge that multiple other factors are important to graft survival (e.g., sex and weight) but were not reported.

### **Social interaction**

Henning et al. (1988) found the effects on social life of Cushingoid appearance and short stature in children with kidney transplants was more prevalent than in a comparison group with juvenile diabetes.<sup>293</sup> Sexual problems were also more prevalent in the transplant group. However, low participation rate in the diabetic comparison group and uncertainty about the quality of matching between the two groups limits any conclusions.

The relationship between ESRD as a chronic illness and development of a social network was studied by Melzer et al. (1989) in adolescents matched to a healthy control group.<sup>294</sup> Results suggested that the transplant group had smaller support networks of peers, particularly of members of the opposite sex. The small sample size is a limitation of this study. Recommendations were for an intervention to develop peer relationships and to further study the issue by comparison to an adolescent group on dialysis.

### **Quality of life**

A small study by Pozanski et al. (1978) on “quality of life” in renal transplanted children and adolescents employed semi-structured interviews, with measures based on objective or functional properties.<sup>295</sup> Greatest effects were seen in adolescents, with problems of low self-esteem, depression and social isolation. Positive benefits of successful transplantation on social contacts were suggested, but the small sample size prevents generalizations.

### **Rehabilitation**

Rehabilitation has often been measured in terms of full-time employment or school attendance, which may depend on various factors, not only those in the psychosocial domain. On the basis of employment and school attendance, ESRD treatment programs were considered quite successful in reports by Potter et al. (1986), So et al. (1986), and Offner et al. (1988).<sup>285,296,297</sup> A team approach to rehabilitation has been recommended.

A study by Broyer et al. (1993) using data from the European Dialysis and Transplant (EDTA) registry reports substantially greater full-time school attendance in children with renal transplants compared with dialysis patients (approximately 90% vs. 50% attendance); however, for all modalities of renal replacement therapy, 20-50% of children still had school-related problems.<sup>207</sup> Higher unemployment was also reported for the dialysis group.

This same study also addressed several social integration issues in transplantation patients. Adolescents were continuing to use specialized pediatric centers to receive care in the European setting. Rates of marriage for 25–29 year olds were 27% for females and 12% for males. Pregnancy in transplant recipients did not affect graft outcome when creatine levels were <160 µmo/l prior to conception. In mothers with renal transplants 56% of babies were born at < 37 weeks gestation.

### **Family structure and environment**

A stress and coping (i.e., resistance) framework described by Wallander & Varni (1998), in which family structure and family quality are resistance factors, has been used as a predictor of psychosocial and physical adjustment.<sup>298</sup> (*The stress and coping theoretical framework is discussed in a separate section below with respect to pediatric chronic illness.*) Within this framework, traditional families (two-parent, intact) are considered to typically have greater psychological, financial and other caregiving resources available for coping with the chronically ill child, than would be found in one-parent or blended families.



The major limitation of this theoretical model, as a means of understanding the role of family functioning in transplantation outcomes, is that results have been inconsistent across studies and diseases. Family structure and environment were predictive of child behavior or adjustment problems in diabetes in one study but not another, and family environment but not family structure were predictive of behavior problems in pediatric cancer.<sup>299-301</sup> Furthermore, “inflexibility”, which is considered a negative family attribute, was associated with improved outcomes in diabetes.<sup>300</sup> Based on these and other studies, Soliday, Kool & Lande (2001) stated that the relationship between family environment and psychosocial/physical adjustment are equivocal; however, their own studies reported in this paper went on to support the stress and resistance model (*see below*).<sup>302</sup>

Few studies have provided data on relationships between family environment and objective measures of physical health.

In children with CRI, family stress correlated with lower growth velocity (Crittenden & Holaday, 1986).<sup>303</sup> In another study, family functioning (cohesiveness and expressiveness) correlated with school adjustment in children with ESRD (Fukunishi & Kudo, 1995).<sup>271</sup> In the study by Soliday, Kool & Lande (2001) using objective medical indicators in a stress and resistance framework, family conflict predicted greater externalizing symptoms and higher number of prescribed medications, while lower family cohesion predicted greater hospitalizations.<sup>302</sup> Nontraditional family structure was also predictive of higher prescriptions. However, questions about lack of consistency across studies using the stress and coping framework remain.

Quality of the family environment theoretically has an impact on the effects of stressors in transplantation. In the recent study by Soliday, Kool & Lande (2001), positive family environments have been attributed to the following features: high cohesion (i.e., support), “expressiveness” of emotions, and low levels of conflict.<sup>302</sup> However, because this study is questionnaire-based it is of limited value.

### **Theoretical models**

As described above, the “Stress and Coping” model or framework of Wallander & Varni (1998) has been used to help understand the impact of pediatric chronic illnesses, including transplantation, on children and families.<sup>298</sup>

In this model, the pediatric chronic illness is conceptualized as the principal stressor, which may be balanced by various resistance factors, including the family environment. The model proposes that stress and resistance factors, the interactions of which may be complex, predict both psychosocial and physical adjustment.

Another unique model has been used to analyze the psychosocial adjustment of pediatric renal transplant patients. Davis, Tucker & Fennell (1996) used the “Difference” model to Compare the psychosocial health of transplant and renal failure patients.<sup>10</sup> The “Difference” model does not simply compare the transplant and renal failure patients on the variables being investigated, as is typically done, using the “Deficit” model. Rather, the Difference

model individually looks at groups that differ on variables closely related to the variables being investigated. The “Deficit” model only considers the variables being investigated.

### **Incorporation of foreign organ**

Studies on the reaction of children to incorporating a foreign organ into their bodies are few and primarily descriptive.<sup>12,304,305</sup>

### **Summary (Kidney – psychosocial development)**

Although overall psychosocial adjustment of pediatric kidney transplant patients has been reported to be mostly comparable to healthy children, there is substantial evidence in the literature of delayed social development, maladaptive problems, and increased psychiatric problems in these children. In particular, problems with low self-esteem – related to physical effects of illness and treatments – and development of social networks have often been cited. Low self-esteem, most prevalent in adolescent girls, is associated with non-compliance with maintenance medications and remains a major problem. Measures of communication, daily living skills, and socialization are also well below healthy norms. Since these deficits occur regardless of graft function, even children with functioning transplants can be expected to continue to show developmental delays. Despite these continuing psychosocial adjustment problems, renal transplantation is still associated with better psychosocial outcomes and rehabilitation than other modalities of treatment, i.e., continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD).

Because of methodological weaknesses in the current literature, future psychosocial studies of kidney transplant recipients need to include sibling and matched healthy control groups, longitudinal studies, larger and more representative samples, appropriate age groups, and better description of measures and variables. In addition, the role of the family environment in psychosocial adjustment requires clarification due to inconsistencies across studies and diseases.

### **Recommendations from the panel of experts (Kidney – psychosocial development)**

- Conduct **prospective, longitudinal studies** (from CRI/dialysis through transplantation) to assess the efficacy of **different therapeutic modalities** on transplant outcomes in the psychosocial domain. These studies need to include:
  - **Sibling controls and healthy matched controls.** Failure to include sibling controls in most previous studies has prevented any firm conclusions regarding the relationships between behavior and compliance.
  - **A more precise scale of psychological assessment,** which should be developed and assessed for its ability to measure the individual impact of all factors (e.g., schooling, psychomotor, emotional, social, weight, sex, etc.) on graft survival in a longitudinal study.
  
- Investigate the relationships among **low self-esteem, medical compliance, and social adjustment:**

- Investigate the reasons for **low self-esteem** in pediatric kidney transplant patients, and determine why this may lead to **non-compliance**. Collectively, the literature points to close interrelationships between psychological/adaptive behavior problems and medical non-compliance.
  - Develop **interventions to prevent low self-esteem**. Suggestions from the literature include early intervention with multidimensional training/counseling for children and families, incorporating adaptive skills training, anxiety and behavior management training, and counseling to promote family cohesiveness.<sup>10</sup>
  - Prospectively study whether or not **pre-transplant psychological profiles** of children and parents predict **post-transplantation compliance** with maintenance medications.
  - Another suggestion is to study how **low self-esteem** in children with transplants relates to low scores on conventional indicators of **good social adjustment** (e.g., marriage, moving out of parents home) when they grow up.
- Study the effects of different currently available treatment modalities on psychosocial development in children with infantile **nephropathic cystinosis** (e.g., drug therapy to reduce cysteine, white blood cells to reduce impact of disease).

#### **Recommendations from expert-selected studies from the literature (Kidney – psychosocial development)**

- Provide more complete descriptions of the **reliability and validity of instruments** and of the variables used.
- **Follow up qualitative research** to identify common themes with **quantitative, hypothesis-driven** research. These studies require larger sample sizes within treatment modalities to ensure adequate statistical power. Also, samples must include representative populations in order to provide generalizable results.
- In all studies, distinguish children and adolescents separately, using appropriate age groups, in order to **identify age-appropriate risk factors for psychosocial problems**. Previous use of larger age ranges or combining children, adolescents and adults has limited interpretation of previous studies.<sup>11-16</sup>
- Address the following two questions in additional studies on the role of family structure and environment using a **stress-and-resistance model**:
  - 3) Is the relationship between **family environmental variables and psychosocial/medical outcomes** unidirectional, as previously presumed, or bidirectional (i.e., can the outcomes also influence the environment)?
  - 4) Do **medical indicators** truly reflect illness severity (e.g., they may instead reflect the degree of family organization)?

- Implement studies comparing the effects of **family functioning** on child adjustment for **different disease groups** (kidney vs. other chronic illnesses), with the purpose of helping to resolve inconsistencies reported in the literature. Inherent differences in kidney disease (change in physical appearance, treatment, perception of shortened lifespan) may underlie these discrepancies.<sup>17</sup> However, it is suggested that instruments standardized for healthy populations may not be sufficiently sensitive to detect subtle illness-related differences in these comparisons.
- Investigate family environment and functioning to consider **multiple categories of family structure**, and employ larger, multi-site, longitudinal designs in this investigation.
- Implement larger, multi-center, longitudinal studies that include investigation of **developmental domains and physiological measures** (e.g., blood urea nitrogen – BUN, creatinine, creatinine clearance and physical growth parameters) to elucidate effects of renal disease and transplantation on development.
- **Separate out objective and subjective measures** when assessing quality of life, rather than focusing on objective measures emphasizing delayed social development. It was suggested that subjective indicators can reveal high quality of life despite maladaptation indicated by conventional objective measures (e.g., marital status).
- Recommendations for **nursing practice** related to psychosocial development include:
  - perform developmental assessments at frequent intervals (social, cognitive, motor development)
  - counsel on the importance of normalizing play activities
  - implement interventions to relieve symptoms (especially fatigue) that interfere with child's desired activities

## PSYCHOSOCIAL DEVELOPMENT: LIVER

### A note on acronyms, technical terms, and standardized measures

A glossary of technical terms and acronyms found in the following sections are provided in Appendix A for easy reference.

Additionally, please refer to Appendix C for a listing of standardized measures psychosocial functioning used in studies of pediatric end-stage liver disease or transplant patients. This list also provides variables measured, age ranges, and frequency and currency of use.

### Introduction

Children with chronic liver diseases have general developmental delays<sup>26,306,307</sup> that have been related to a number of growth variables<sup>25,34</sup>. Patients with liver disease associated with Alagille syndrome, a dominantly inherited disorder, also frequently show growth failure, which has been attributed to congenital anomalies, cholestasis, and malabsorption/malnutrition.<sup>308</sup> Mental retardation is considered a less frequent characteristic of this syndrome.<sup>309</sup>

Several authors have attempted to evaluate psychological status and social adjustment and to relate psychosocial development to intellectual function in pediatric liver transplantation. These studies are considered in the following sections.

### Psychosocial adjustment

Several papers report on functional adjustments after liver transplantation. Both DeBolt et al. (1995) and Tornquist et al. (1999) noted gender specific differences in scholastic and athletic function; specifically, boys had lower school and activity/athletic scores than healthy children, while girls had lower scholastic competence but better psychological adjustment than a normative population.<sup>30,310</sup> van Mourik et al. (2000) suggested that patients receiving transplants as infants experience motor and language delay after transplant that may require years to improve.<sup>217</sup>

Tornquist et al. (1999) suggested that children may view their level of social competence differently as they get older.<sup>310</sup>

### Psychological/Psychiatric adjustment and behavior

Early studies by House, Dubovsky & Penn (1983) suggested that up to 50% of pediatric liver transplant recipients have adverse psychological reactions.<sup>2</sup> Problems reported were organic brain syndrome, regression, belligerence, apprehension/fear, difficulty forming relationships, feelings of helplessness and rejection, worries about finding a donor in time, and thoughts of suicide. Greater psychopathology was reported in liver transplant patients compared to renal transplant patients, less than 20% of whom had adverse psychological reactions. Moreover, only 2% of the renal patients had organic brain syndrome, a likely contributor to psychological distress. The greater adverse psychological effects in liver

versus kidney transplant recipients may have been related to the severity of liver disease, effects of the illness on the brain, lack of alternatives, exclusive use of cadaveric donors, and greater effects on physical appearance. The authors suggested that greater parental anxiety due to the lack of alternatives in liver transplant was an additional factor.

Psychological problems in liver transplant children are not unexpected. Comparison data suggests that the liver transplant recipients have psychosocial function that is similar to children with other forms of chronic disease. Depression, fear of death and anxiety are prevalent.

Windsorova et al. (1991) found that when liver transplant recipients are matched to children with diabetes they have similar emotional adjustment, but have more depressive experiences and anxiety than norms.<sup>1</sup>

Schwering et al. (1997) also related greater behavioral and adaptation problems and lower competence to liver transplant in infancy.<sup>311</sup>

Gritti et al. (2001) recently confirmed that over 50% of recipients had behavioral and/or emotional disturbances that extended beyond the first post-transplant year. Children in this study described the transplant event as a traumatic experience and had more fear of death and depressive feelings than age- and gender-matched controls.<sup>32</sup>

### **Body image, self-esteem and non-compliance**

House, Dubovsky & Penn (1983) reported that body image concerns for liver disease were more common in the preoperative period and less common after transplantation than for kidney transplant patients.<sup>2</sup> A recent study by Apjasalo et al. (1997) involving liver, kidney and heart transplants confirms that adolescents with liver transplants were least satisfied with their appearance, while those with kidney transplants were most satisfied.<sup>312</sup>

### **Social interaction**

Stewart et al. (1989) reported significantly improved social function following transplantation in children greater than 4 years of age.<sup>34</sup>

### **Quality of life**

Quality of life (QOL) assessment in this population is especially important. The existing literature reveals that many children do have functional deficits. To date published reports have been too small to allow analysis of factors that affect QOL. Furthermore, Burdelski et al. (1999) concluded that “quality of life as a measure of transplant results has not been sufficiently studied”.<sup>254</sup>

There has been a steady increase in QOL studies in this population over the past five years. Many of the earlier studies were based on the subjective opinion of the treating physicians or the descriptive report of parents. Recent studies have been based on validated instruments that measure physical and mental health, social and role function. In general,

results of psychosocial QOL have been difficult to compare in longitudinal studies since methods are validated for different age groups.<sup>254</sup>

More recently, investigators have begun to concentrate on measuring the health-related QOL (HRQOL) in children. This process has been complicated by the need to account for changes in expected role functioning as children mature (i.e., children of different ages require different instruments). Moreover, although the median age at transplantation is 12–18 months, few instruments have been designed to measure HRQOL in infants and toddlers. Thus, it is particularly important to use age-appropriate instruments that incorporate developmentally sensitive measures for the evaluation of pediatric liver transplant recipients. Those who develop instruments must also take into consideration the frequent need to use a parent as a proxy for the child.

Midgley (2000) found that the majority of children with liver transplants had mild functional deficits. Utility scores in this group were significantly lower than a reference population, but similar to children with other health conditions.<sup>313</sup> In a retrospective study of 50 families by Schulz (2001), parents described their children's QOL lower than children with asthma or healthy controls; however, child and parent QOL assessments strongly diverged in this study.<sup>3</sup>

Zamberlan (1992) employed individual interviews with QOL tools to assess 20 children. Many of the children were identified as having distress related to physical appearance although they were similar to a normative sample with regard to self-assessment for popularity, happiness and satisfaction.<sup>31</sup>

## **Rehabilitation**

Earlier studies of rehabilitation after liver transplantation report that 51% of children with liver transplants are in age-appropriate education and there are fewer medical admissions than before transplant.<sup>314,315</sup> These studies also suggested improvements in motor and social skills post-transplant, but other reports are inconsistent regarding improvements in these areas.<sup>34,316</sup>

More recently, Stone et al. (1997) reported on a small study showing all children with liver transplants attended school, with 70% having no special education needs.<sup>317</sup> Similarly, Asonuma et al. (1998) found 86% of child/adolescent liver transplant recipients to be leading a normal life (i.e., schooling and recreation) over the last six months assessed.<sup>174</sup>

Burdelski et al. (1999) recently reported an improvement in rehabilitation after liver transplantation in a European study using United Network for Organ Sharing (UNOS) criteria.<sup>254</sup> In comparison with pre-transplant status, patients with UNOS 1 status (*normal growth with no extra medical care*) doubled to 42% and UNOS 2 status (*no growth*) increased from about 20 to 25%, while UNOS criteria for repeated outpatient visits and hospital care decreased.

## **Family structure and environment**

Family function may play an important role in determining a patient's psychosocial and intellectual function. Parental overprotection and child dependency are common themes in families waiting for a transplant for a chronically ill child with end-stage liver disease (ESLD), and are associated with family discord and with child emotional and behavioral problems.<sup>2,306,315</sup> Major stressors to the families include achieving a target weight for the child and realizing that those most ill will be the first transplanted. Following transplantation, family psychological adjustment was described as closely following the course of the medical condition.<sup>253</sup> Long-term problems with family adjustment have also been reported.<sup>318-320</sup>

Kennard et al. (1990) employed a stepwise discriminant analysis to classify families of children with liver transplants as "successful" or "at risk" based on cognitive and psychosocial factors.<sup>33</sup> "Successful" family characteristics included fewer developmental difficulties, intact marriages and less financial stress. Social competence did not differ in this classification.

In a small, prospective study with relatively long follow-up, Stone et al. (1997) reported that 70% of families functioned within the normal range in a family QOL measure, and all families maintained or achieved financial integrity.<sup>317</sup> Less optimistically, a larger, retrospective study by Schulz et al. (2001) reported 90% of families reporting problems with siblings and 40% having experienced a marital crisis.<sup>3</sup>

## **Incorporation of foreign organ**

In general, suggestions that there are psychological problems associated with accepting and integrating a foreign organ have had little supporting evidence.<sup>306,321,322</sup>

Schulz et al. (2001) found that 20% of children with liver transplants were distressed by feelings of thankfulness for the donor.<sup>3</sup>

## **Summary (Liver – psychosocial development)**

Psychosocial assessments after liver transplantation show that up to 50% of children have adverse psychological reactions. In addition, greater than 50% of children have behavioral or emotional disturbances. Moreover, psychosocial problems tend to be greater for liver than for kidney transplants. One possible factor in this difference is a greater concern over body image by adolescents with liver transplants. Liver transplantation is also associated with more depression and anxiety and lower parent-reported quality of life (QOL) than in other chronic illnesses. The family environment appears to have an important role in child development after liver transplantation; the characteristics of a "successful" family were identified above. Results on family functioning suggest that a majority of families function normally, but with significant sibling and marital problems. Recent studies suggest most liver transplant children are attending school and lead a "normal life".

Additional psychosocial studies in the pediatric liver transplant population are needed to identify risk factors for psychological problems, to study post-traumatic stress disorder



(PTSD), and to investigate child and family QOL in long-term studies. Methodological recommendations include the continued use of validated QOL measures (as seen in recent years), further use of longitudinal study designs, and development of multi-center studies.

### **Recommendations from the panel of experts (Liver – psychosocial development)**

#### ***Psychosocial function:***

- Perform **longitudinal studies of psychosocial function** prospectively from the time of transplant.<sup>1,24,30,31</sup> The goal of such a longitudinal study would be to **identify risk factors** for psychological problems and identify sub-groups of patients who would benefit from ongoing mental health intervention.
  - It would also be important to study a **large population** that included children from a variety of regional transplant centers and a range of socioeconomic status.
  - Tools used for this assessment must include measures specific for **depression** and **anxiety** as well as assessment of the **family function** and support.
  - **Instruments** measuring depression include the Children’s Depression Inventory (CDI). Instruments measuring family function include the Family Assessment Device (FAD).
- Perform **longitudinal studies of post-traumatic stress disorder (PTSD)** among older children with liver transplants. Since children relate the transplant experience as traumatic, some of their behavior problems may be related to an abnormal stress reaction.
  - Should be a **longitudinal intervention study** that **randomizes older children** to receive ongoing counseling regarding the transplant event.
  - Would help determine if psychosocial function would improve with recognition and treatment of PTSD or PTSD-like symptoms.
- Careful attention should also be given to understanding **family function and stress**. This issue could be addressed through broader quality-of-life studies as detailed below.
- Comparison of the psychosocial outcomes of recipients of livers from **living-related donor versus cadaveric donors** is also recommended. This research should try to determine if more deliberate (i.e., earlier) timing of transplantation through use of living-related donation leads to improved outcome.

#### ***Quality of life (QOL):***

- A **large cross-sectional study** including children from multiple regional centers would be justified to study the **quality of life (QOL)** of pediatric liver transplant recipients. This study should:

- Have **long-term follow-up**.
  - Describe QOL/functional status using **validated instruments**.
  - Test different **pre-transplant and post-transplant variables** as possible determinants of QOL.
  - Possibly be conducted **by mail** and might use the United Network for Organ Sharing (UNOS) as a platform for initial patient identification.
- Evaluate the **functional status** of children who received liver transplantation in the late 1980s, and are now entering adulthood. Their functional status should be measured using tools such as:
    - the Child Health Questionnaire (validated for children aged 5-18)
    - the RAND 36-Item Health Survey-Short Form (SF-36) developed for the Medical Outcomes Study (ages 14 years and older)
    - the Sickness Impact Profile (SIP) (adults)
  - Family function and QOL of **parents and siblings** of transplant recipients must likewise be addressed. Longitudinal evaluation of parents and siblings using validated instruments would be appropriate, but this area of focus is less developed and would therefore justify an **individual interview approach**.

### **Recommendations from expert-selected studies from the literature (Liver – psychosocial development)**

- Conduct further studies to verify whether changes in **parental attitude** to liver transplantation (as a “family secret”) may help integrate the transplant experience in the child’s personality development.<sup>32</sup> Understanding the psychosocial impact of family reactions to the child’s transplantation experience is important.
- Identify **families** who are at risk of post-transplant complications early, and develop **early intervention strategies** prior to transplant.<sup>33</sup>
- Conduct further studies with larger groups to determine precisely all **growth and development correlates** (including social competence) of improvement versus persistence of deficits.<sup>34</sup> This research is needed because results show that normalization of growth and development may not occur rapidly.
- Provide for a larger longitudinal study (starting before transplantation) to determine whether apparent greater emotional adjustment by children to liver transplantation persists when they reach **adolescence and adulthood**.<sup>1</sup>

- Test interventions allowing young transplanted patients to **discuss the transplantation experience**. It is believed this may assist with difficulties related to anxiety, peer relationships, behavior, and parental expectations.<sup>31</sup>

## PSYCHOSOCIAL DEVELOPMENT: HEART

### **A note on acronyms, technical terms, and standardized measures**

A glossary of technical terms and acronyms found in the following sections are provided in Appendix A for easy reference.

Additionally, please refer to Appendix C for a listing of standardized measures of psychosocial functioning used in studies of pediatric patients who are eligible for or have undergone heart transplant or open-heart surgery. This list also provides variables measured, age ranges, and frequency and currency of use.

### **Introduction**

The first study to examine psychosocial adjustment issues in pediatric heart transplantation was published in 1987 and performed by Lawrence and Fricker.<sup>242</sup> After this study, a handful of case studies followed in the late 1980s and early 1990s.<sup>227,242,323</sup> It was not until the mid-1990s that large, formal studies of psychosocial issues in pediatric heart transplantation were first published. These studies included prospective assessments of patient and family psychological functioning before and after heart transplantation.

In view of the dearth of such studies, note Hangard-Patton (2000) and Lawrence (1987), clinical observations are still critical to identifying potential areas of problematic psychosocial outcome in heart transplant patients.<sup>242,243</sup> For example, the child may encounter changing stresses as they proceed through the transplantation process. These range from increased worrying about graft rejection and their own death as cognitive ability matures, to a compulsion to ritualize the date of the donor's death, to chronic stresses from peer pressure due to steroid-induced changes in physical appearance.

The sections below begin with the good news from the literature on psychosocial research in pediatric heart transplantation. The discussion then moves on to less positive findings, then focuses on the return to school and on issues of particular relevance to heart transplantation in children – namely, non-compliance with medication, family functioning, and the intense, stress-filled period of waiting for an available donor heart.

### **Psychosocial adjustment**

#### ***Positive findings***

One of the first studies to examine psychosocial outcome in pediatric heart transplant recipients was Lawrence and Fricker's small, controlled 1987 study of seven 6-15-year-olds surviving 3 months to 3 years post-transplantation.<sup>242</sup> Looking at activity levels both pre- and post-transplantation, Lawrence and Fricker found that these children returned to normal activities and appeared to adjust well to the stress of transplantation. Moreover, social adjustment improved remarkably following heart transplantation. Before transplantation, the children were home-bound, showed no interest in play or interaction, had few age-appropriate friends, and experienced frequent hospitalization. After heart transplantation,

however, all children became ambulatory, competent in self-care, attended school regularly, and most had age-appropriate friends.

One developmentally delayed child showed substantial developmental gains post-transplantation. Furthermore, post-transplant, these heart transplant recipients maintained their pre-transplant academic performance. Among the three younger children, two were normal on the personality inventory, except for somatic concern, and all had activity levels similar to those of their peers. Adolescents scored high on questionnaires assessing adjustment (i.e., ego/coping abilities), impulse control, and social relationships.

Subsequent, larger studies have corroborated the optimistic findings of the Lawrence and Fricker case studies. In their 1992 multi-center study of 49 children < 16 years old surviving at least 3 months post-transplant (mean post-transplant follow-up = 21 months), Uzark et al. found that self-concept, anxiety, and overall coping among transplant recipients were similar to those found in the normative population.<sup>324</sup> Moreover, transplant recipients were more likely to cope by ventilating their feelings rather than avoiding their perceived problems. This coping mechanism was associated with better adaptation. The study's correlational and cross-sectional design, however, did not allow direction of relationships to be determined. Additionally, bias may have been introduced in that participating families may be more or less adaptive than families who chose not to participate in the study.

In their controlled, prospective 1992 study of 28 pediatric heart transplant recipients (0-16 years of age), Wray et al. found that behavior problems significantly decreased following transplantation.<sup>46</sup> This was especially true for neurotic symptoms. They report that physical activity, self-esteem, and independent behavior also increased after transplantation, which may have contributed in the diminishment of behavioral disorders observed after transplantation. Long-term outcome was not determined by the study; follow-up spanned a meager three months following transplantation. The study, however, had the advantage of pre- and post-assessments, allowing changes in emotional state to be detected from before to after transplantation, not simply emotional state after transplantation.

A later study with longer follow-up also found that psychological functioning improved from before to after transplantation. In their 1995 uncontrolled study of 23 heart transplant recipients 3-20 years of age and surviving at least 1 year post- follow-up, DeMaso et al. (1995) found that psychologic adjustment among recipients improved at an average of 2.1 years after transplantation.<sup>50</sup> They found that the number of children demonstrating pathological psychological functioning (a score of 70 or lower on the Children's Global Assessment Scale, which uses a range of 0-100) dropped from 43.5% pre-transplant to 22% at one year post-transplant. Thus, 78% of transplant recipients were assessed as having good psychological functioning at the end of a mean follow-up period of 2.1 years post-transplant. Likewise, on evaluation using DSM-IV criteria, 35% and 13% of children before transplant evinced "Psychological Symptoms Affecting the Medical Condition" and "Mood Disorders Due to the Medical Condition," respectively; after transplant, these percentages dropped to 4% and 0%. That 22% of recipients still had pathological psychological functioning post-transplant raises a concern; but the extent to which this pathology is related to transplantation cannot be determined without healthy controls.

Still more recently, among 44 heart and heart-lung transplant recipients aged 5-17 years studied longitudinally by Serrano-Ikkos in their controlled 1999 study, average psychosocial functioning was significantly improved in transplant recipients at one year post-transplantation<sup>51</sup>; however, half of them still showed psychological problems, and prevalence of psychiatric disorders as defined by DSM-III-R did not decrease significantly. This latter finding is in contrast to DeMaso et al.'s 1995 findings.<sup>50</sup>

Research with longer-term follow-up has also observed positive psychosocial outcomes in children following heart transplantation. In a 2000 study of 3 years' follow-up post-transplant, Higgins reported that quality of life/functional status of pediatric heart transplant recipients was excellent at three years post-transplant. This positive outcome, however, was dependent on the child's having an intact, supportive family.<sup>49</sup>

### *Negative findings*

Despite the optimistic findings detailed above, up to one-quarter of children may have impaired psychosocial functioning following heart transplantation. Although transplantation brings about improvements in social activity and emotional functioning, the absolute percentage of children in distress during the post-transplantation period appears to remain quite high. Again, however, determinations as to the relative amount of distress suffered by these children cannot be made in the absence of studies using healthy controls. Moreover, sufficient research has not been conducted on the differences in psychosocial functioning during the three major periods defining the psychosocial journey of the young heart transplant patient – the waiting period, the first year following transplantation (a “transition” period), and the more distant follow-up period of several years post-transplantation.

Some signs of post-transplant maladjustment were detected in Lawrence and Fricker's small, controlled 1987 study of post-transplant social outcomes at 3-34 months post-transplantation, which by and large yielded positive findings.<sup>242</sup> Only 1 of the 4 adolescents studied obtained a normal score on the self-image questionnaire; and others obtained one or more abnormal scores on vocational and/or educational goals and morals. Although 3 of the 4 demonstrated duration of exercise within the normal range, all four discontinued exercise because of muscle fatigue and sub-optimal heart rates. Half of the parents believed their children had more than an average number of behavior problems.

Likewise, despite a more than 20% drop from pre-transplant to an average of 2.1 years post-transplant in the number of children with scores on the Children's Global Assessment Scale (CGAS) scores indicating pathological psychological functioning, 22% of children in DeMaso's 1995 study still scored at the pathological level post-transplant (a score below 70 on the CGAS).<sup>50</sup> Moreover, 35% still had psychological symptoms after transplant that may have been affecting their medical condition. This finding would be easier to interpret had the study used controls. Use of healthy controls would have allowed the investigators to verify whether or not the percentage of pathological functioning differed between transplant recipients and healthy children. For example, 20% of healthy children may also demonstrate pathological psychological functioning on examination. If true, such a finding

would indicate that psychological maladjustment was likely due to factors not related to transplantation. Nevertheless, the absolute percentage of children in this study still showing distress following transplantation is clinically significant, and not to be ignored.

In their small 1989 study, Shapiro and Kornfeld found that 5 out of 9 pediatric heart transplant recipients studied experienced anxiety, low self-concept, and depression, and/or exhibited behavior problems.<sup>325</sup> Anxiety, depression, and anger were also reported among family members of the recipients. The study did not specify the length of its follow-up period, but did use solid criteria for characterizing mood and behavior disturbance (the DSM-III-R criteria). Later findings from a larger study (n=49) by Uzark et al., however, did not find any differences between pediatric heart transplant recipients and healthy children on questions of self-concept and anxiety (this study represented both young children and adolescents).<sup>324</sup>

Self-reports from children (< 16 years of age) with heart transplants recipients in Uzark et al.'s 1992 multi-center study revealed significantly less social competence and more behavior problems among recipients than in the normative population.<sup>324</sup> Family members also reported significantly greater stress and fewer resources than families without chronically ill children. Mean follow-up was 21 months.

In their 1994 study of 65 heart and heart/lung transplant recipients, Wray et al. found that one-quarter (24%) of transplant recipients had clinically significant behavioral problems in the home, compared to only 6% of healthy children and 17% of the open-heart surgery reference group.<sup>224</sup> Although these prevalence differences were not statistically significant, they are still telling, and difficult to discount. Problems noted included neurotic behavior, difficulty accepting his/her own need for transplant, and personality change in the form of withdrawal, introversion, and loneliness. The intensity of these problems did not vary depending on much time had elapsed since transplantation. These findings are in contrast to those of Wray et al. (1992) reporting generally good psychological functioning in children following heart transplantation.<sup>46</sup>

In contrast to DeMaso et al.'s 1995 study, which found that pathological psychological functioning decreased in a sample of 23 children at one year post-transplantation, Serrano-Ikkos et al. found that prevalence of actual psychiatric disorders did not change significantly at one year post-transplant.<sup>51</sup> This despite significant improvement in psychological functioning. Whereas the prevalence of psychiatric disorders among recipients only dropped from 27% pre-transplant to 18.5% post-transplant, prevalence in a control group undergoing conventional cardiac surgery dropped significantly, from 26% to 6.5%. Similarly, whereas 52.2% and 47.6% of heart and heart-lung recipients, respectively, were assessed with psychosocial problems post-transplant, only 6–10% of conventional cardiac surgery patients had psychosocial problems post-surgery. It should be noted that half of recipients still had impairment in their psychological functioning. Differences in the trends identified in the DeMaso and Serrano-Ikkos studies may be attributable to any number of factors, including instruments used. Whereas the DeMaso study used the Children's Global Assessment and DSM-IV criteria,<sup>50</sup> the Serrano-Ikkos study used the Global Assessment of Functioning Scale and DSM-III-R criteria.

Any study of children's adjustment following heart transplantation cannot ignore those children whose negative outcomes are severe enough to stand out amid the generally positive findings. These "outliers" require special attention from clinicians and others in the child's support network. Outliers include, for example, the one child of the seven studied by Lawrence and Fricker who showed a high degree of maladjustment when drawing a person<sup>242</sup>; and the two children of the 65 studied by Wray et al. in their 1994 study whose severe adjustment problems kept them from returning to school following transplantation, despite their good medical condition.<sup>224</sup>

### ***Returning to school***

Findings on children's success in returning to school following heart transplantation have been mixed. In Uzark et al.'s 1992 multi-center study of 49 children < 16 years old surviving at least 3 months post-transplant (mean post-transplant follow-up = 21 months), 93% of the children over 8 years of age attended school and participated in recreational activities after transplantation.<sup>324</sup> Similarly, in Serrano-Ikkos et al.'s controlled study of 44 heart and heart-lung recipients from 1999, school attendance was observed to improve at one year post-transplant, reaching levels attained by open-heart surgery patients prior to surgery.<sup>51</sup>

In contrast to these positive findings, a later, larger study by Wray et al., published in 1994, found that only 30% of children eligible to return to school after surgery among the 65 pediatric heart and heart/lung transplant recipients studied (aged <17 years) did so within the mean follow-up time period of 10 months post-transplant.<sup>224</sup> The authors do note, however, that most of the children not returning to school were still in the first six months following transplantation. No behavior problems at school were noted among any of the returning children. In fact, the prevalence of behavior problems was lower in the transplant group returning to school than in the two reference groups used by the investigators – healthy children and pediatric open-heart surgery (non-transplant) patients.

Selection bias may account for the superior behavioral outcome among the transplant children returning to school, however. The 30% of school-age recipients returning to school during the post-transplant follow-up period were likely the healthiest of the recipients, their positive health status likely having a positive impact on their behavioral outcome. This supposition is not universally true, of course; indeed, two transplant recipients with good medical outcome in this study had adjustment problems of such severity they could not return to school. Besides larger than usual sample size, this study also benefited from the methodological strengths of using two reference groups (52 open-heart surgery and 45 healthy children); similarity of characteristics between the cardiac groups (duration of illness, physical limitations, sex, and socioeconomic status – SES); and good response rates (92–96% in all three groups). The study had two major limitations related to follow-up however; mean follow-up was less than one year, and varying follow-up periods among the sample probably led to the assessment of varying behavioral outcomes (i.e., behavioral outcome measures are probably dependent on how much time has elapsed since transplantation).



Time since transplantation may be a risk factor for progressive social maladjustment at school. This is also consistent with the observation that children with heart transplants perform more poorly on cognitive tests with increasing time post-transplant.<sup>36,47</sup> Wray et al.'s controlled study from 2001, which followed children and adolescents for longer periods post-transplant than in their 1994 study, had less positive findings about recipients' school adjustment.<sup>47</sup> They found that school adjustment among pediatric heart transplant recipients returning to school tended to deteriorate over time. Specifically, post-transplant school behavior problems in the 18 patients assessed serially for 3 years increased from 8% at 6 months post-transplant to 29% and 27% at 3 and 5 years post-transplant. Likewise, parental reporting of adjustment problems peaked at 3 years (28%).

Wray et al.'s 2001 study on the return to school is unique in that it attempted to determine behavioral (and cognitive) differences among recipients with different initial diagnoses. In an interesting finding, behavioral problems at school were most frequently seen in children with a diagnosis of congenital heart disease (CHD), thus suggesting that initial diagnosis may be another predictor of school behavioral outcome.

Most children returning to school after heart transplantation attend a normal school. Wray et al. found that 13 of the 15 children returning to school during the first year following transplantation attended normal school upon return.<sup>224</sup> Similarly, their later study of 81 pediatric heart transplant recipients, which also followed the children for a longer period post-transplantation, found that 84% returned to a normal school during a five-year follow-up post-transplant, with the remaining 11% returning to a special school and 5% not returning to school.<sup>47</sup>

### **Body image, self-esteem and non-compliance**

One of the most important psychosocial issues surrounding pediatric heart transplantation is the issue of children and adolescents' non-compliance in taking their life-saving immunosuppressant medications. Non-compliance is a serious problem with psychosocial motivations yet to be clarified. Stoppage of an immunosuppressant regimen by the pediatric heart transplant patient can lead to graft failure and, within weeks, patient death. As Hangard-Patton and Lawrence note in their review article, "in some centers, death due to non-compliance with medications remains the commonest cause of late mortality after transplantation."<sup>243</sup>

It is of crucial importance to patient survival to elucidate the factors underlying patient non-adherence and address them. Although motivation in the non-adherent patient is likely complex, some factors stand out. In an emphatic example, Hangard-Patton and Lawrence recall an alarming case study by Lawrence et al. from 1992 that describes the panoply of post-transplant stresses experienced by a teenage girl, who ultimately commits suicide by deliberate non-adherence. Foremost among this unfortunate girl's stresses were discrimination at school and work because of her transplant, and her perception of the financial burden she placed on her family because of her medical expenses.

Adolescents are more at risk of non-compliance than younger heart transplant recipients.<sup>44,208</sup> Important factors underlying adolescents' tendency to not comply include

the changes in body image and actual physical appearance brought about by steroid immunosuppressants, coupled with increasing self-care in the administration of their own medications. Body image and physical appearance are particularly salient factors among adolescent girls<sup>208</sup>, who may stop their immunosuppressant steroid medications due to loathing for the Cushingoid features caused by these drugs. These features include an aesthetically displeasing “moon face” and “buffalo hump” that can be shattering to a girl’s body image and self-esteem, especially given her craving of acceptance among her peers at school. Obesity across all age groups has been noted in post-transplant patients as well, suspected to be aggravated by steroid use.<sup>243</sup> Adolescence and non-adherence have been previously shown to be correlated in pediatric cancer and renal transplant patients.<sup>280,326,327</sup> Better adherence in heart transplant recipients has been shown to be predicted by two factors: families including both biological parents, and mothers who showed warmth and an absence of hostility towards their recipient children.<sup>44</sup>

Indeed, in their 1998 study of non-adherence among pediatric heart and heart/lung transplant recipients Serrano-Ikkos et al. reported that one of the main reasons adolescents gave for stopping their medications was the side effects they caused.<sup>44</sup> In that prospective study, which attempted to clarify psychosocial factors related to non-compliance, Serrano-Ikkos found that non-compliance among 53 recipients was disturbingly high, particularly in adolescents.<sup>44</sup> Almost *one-third* showed unsatisfactory compliance during the follow-up period, which was at least one year. This finding raises particular concern for patients in the crucial first year following transplantation, when the immune system must be prevented, through immunosuppressant medication, from attacking the “foreign” heart. All patients showing poor adherence in this sample, which ranged in age from < 5 years to > 10 years old, were from the adolescent group of > 10-year-olds.

The Serrano-Ikkos study from 1998 was also important in that it found no strong evidence of factors to guide transplantation teams in their prioritization of pediatric patients for heart transplantation. Interestingly, adherence was not associated with mental illness, level of psychosocial functioning, parental psychiatric illness, family or marital adjustment, or poverty. It is important to note that compliance was found to be related to intact family, albeit not patient or family psychological functioning. Adherence problems were greater in heart-lung than heart transplant patients, but this may have been attributable to higher proportion of adolescents in this study group. With these observations in mind, the authors warn that the failure of psychosocial factors to emerge as strong risk factors for non-compliance in this study would indicate that use of adverse psychosocial factors as a contraindication to heart transplantation would be ill-advised.

There have been differences of opinion on this matter, though, with other experts urging that psychological profiling may be necessary in assessing candidacy for transplant surgery if psychological factors really can predict non-adherence. The debate does beg the question: If, for example, low self-esteem is found to strongly predict unsatisfactory compliance, does this mean that patients with exceedingly low self-esteem should be denied potentially life-sparing heart transplantation? Needless to say, this debate is a highly controversial one.

Results from existing studies do indicate that clinicians and family members should be vigilant in monitoring adherence as patients mature. Compliance tends to decrease as more time elapses since transplantation, as patients enter adolescence and confront the combined challenges of dealing with peer pressure and body image problems, and their own increasing responsibility for self-administering their steroid medications.

## **Family structure and environment**

### ***The waiting period***

Looming as large as non-compliance as one of the major psychosocial issues in pediatric heart transplantation is that of the waiting period. For waiting families, the waiting period in heart transplantation is a stretch of time filled with feelings of anxiety and impotence about the child's life and possible death. About one-third (one quarter to one-half) of children awaiting donor hearts die before a donor heart becomes available. This time of waiting for a donor heart to potentially save the life of a child with end-stage heart disease is rife with stresses and uncertainties for the child and the child's family – even more so than experienced in liver or kidney transplantation. Whereas the child with end-stage kidney disease can turn to the alternative renal replacement therapy of dialysis, the child with end-stage heart disease has no such recourse. Likewise, children awaiting either kidney or liver transplants do not require cadaveric donations – they can receive transplants from living donors, unlike in heart transplantation. Finally, the totality of the donor's sacrifice in heart transplantation is underscored by the fact that the entire organ must be given up, unlike in kidney or liver transplantation, where the living donors retain one kidney, or only donate part of their liver. Heart transplantation, in other words, represents an all-or-nothing contingency.

Indeed, one of the worst stressors for waiting families is the fear that the sick child will die before a suitable heart is found.<sup>328</sup> As Hanton notes in what is possibly the only literature review on the stresses encountered in the pediatric heart transplantation waiting period, the length of the waiting period is highly variable among patients.<sup>255</sup> Whereas average waiting time for the “Status 1” patient is 40 days, for the “Status 2” patient, it is a very long 563 days.

In addition to life-or-death prospects faced by the child awaiting a donor heart, the child experiences a number of other daily stressors. Hanton reviews numerous stressors observed by several studies to be commonly experienced in children and their families while waiting for a suitable organ.<sup>318,329,330</sup> These include feelings of isolation, boredom, hopelessness and feelings of loss of control as waiting becomes prolonged, exhaustion, lack of privacy, financial strain, and social disruption. Among family members, she notes that role strain, marital/family discord, exhaustion, inability to keep up home tasks, child care, and social commitments have all been reported by parents as problems. Parents also feel guilty that another child must die to save their own. Family members' coping strategies have included reframing events to make them more manageable, seeking social support, and creating a sense of family strength to solve problems.

Nursing staff, too experience stress in their multiple roles as health care provider, educator, patient advocate, confidant, and coordinator for other services.<sup>255</sup> They must struggle with moral dilemmas over transplant surgery and care. Hanton suggests that the Stress and Coping Model<sup>331</sup> can be used to provide a conceptual framework for addressing psychosocial stressors of pediatric transplant patients and their families.

Putting into relief the influence of the waiting period on the emotional well being of the waiting family are findings by DeMaso et al. and Wray et al. from their 1992 and 1995 studies, respectively.<sup>46,50</sup> Wray et al. reported more pre-transplant behavior problems in heart transplant candidates than in healthy children. DeMaso's analysis found that pre-transplant emotional and family functioning had more influence on the child's post-transplant psychologic functioning after transplantation than even illness/side effect severity. Consistent with these findings was DeMaso et al.'s 1991 finding that severity of illness was less critical to successful adaptation in 99 children with congenital heart disease than the quality of the mother-child relationship.<sup>332</sup> In this study sample, maternal perceptions were potent predictors of emotional adjustment in children with congenital heart disease, with one-third of variability in adjustment accounted for by maternal perceptions. In contrast, medical severity accounted for less than 3% of the variability.

Few studies have longitudinally examined stress and coping of families with children on the waiting list for a donor heart. Suddaby et al.'s 1997 study of parents of heart transplant patients found that although the moderate levels of stress found in 26 parents of waiting children remained constant during the study period of three months (77%), coping ability diminished over this time.<sup>333</sup> Stress levels were similar for mothers and fathers and were not directly related to the parent's perception of how sick their child was.

Coping mechanisms in the waiting parents were not found to be different from those used by the normative population. Whereas these parents scored higher on seeking social support, they scored lower on seeking spiritual support, and they tended to passively appraise problems. Parents of girls tended to view the transplantation experience more negatively with the more negative perceptions found among the more stressed parents. Firm conclusions cannot be drawn from these findings, however, due to the study's methodological limitations. The sample was small and non-random, and follow-up was poor (only one-third of families). Moreover, three months may not be sufficient to assess the impact of waiting on family stress levels, and the timing of questionnaire administration may not have reflected peak moments of stress.

Consistent with Suddaby's findings, Serrano-Ikkos et al. found that psychological functioning did not change in children on the waiting list over the course of six months.<sup>334</sup> This sibling-controlled, prospective study involved administering a large battery of validated instruments in addition to standardized psychiatric interviews to 51 children (ages 5-16 years) on the waiting list for heart or heart/lung transplantation. Twenty-five of the children had psychiatric diagnosis and 58% had mild impairment in psychosocial function. None, however, showed major impairment such as suicidal preoccupation, defiance, academic failure or aggression (determined by score < 40 on Global Assessment of Functioning Scale). The sick children, however, did not significantly differ from healthy

siblings in terms of depression, poor self-concept or behavioral/emotional problems. Moreover, most measures fell within the normal range, except for depression in the severely ill.

Moderate to poor adjustment was found in 57% of families, with higher anxiety found in mothers and social dysfunction found in both mothers and fathers. Negative patterns of parent-child interaction were noted in distressed or depressed parents, which in turn were associated with more psychopathology in the children.

In addition to the more static emotional stressors placed on the waiting family, parents also experience considerable stress due to the logistical welter in which they find themselves as they adjust to their child's illness state. As Rodrique observed, a family's stability is challenged during the pre-transplant period by such logistical hardships as relocating to the transplant center community, consequently maintaining two separate households, and all the while attending to the needs of the child's healthy siblings.<sup>335</sup> Mothers typically assume more of the burden of undertaking all of these responsibilities, which frequently entails leaving their job.

### ***Post-transplant***

As Hangard-Patton and Lawrence assert in their comments on the study, the array of post-transplant stresses identified in this study likely originated well before transplantation, when they were given the initial diagnosis of their child's heart disease. Family functioning has been observed to be a key factor in the emotional health of the child following heart transplantation. Indeed, reassuring discoveries have been made regarding the salutary effects of good family functioning a child's emotional health post-transplant. In a study published in 2000, Higgins found high quality of life/functional status of pediatric heart transplant recipients to be dependent on the presence of an intact, supportive family.<sup>49</sup> Compliance is also predicted by an intact family: Serrano-Ikkos et al. found that compliance was related to having an intact family, independent of child or family psychological functioning.<sup>44</sup>

Conversely, in Uzark et al's 1992 multi-center study of 49 children and adolescents with heart transplants, the prevalence of behavioral problems was also correlated with family stress.<sup>324</sup> Likewise, behavior problems and decreased social competence in recipients were also associated fewer family resources for dealing with stress. Interestingly, however, amount of family resources was not found to be correlated with parental coping ability.

Consistent with these findings, De Maso et al. found that pre-transplant emotional and family functioning have more influence on the post-transplant psychologic functioning of pediatric heart transplant recipients than even illness/side effect severity.<sup>50</sup> The study's findings would have been easier to interpret had a narrower age range been represented in its sample of 23 heart recipients. Instead, the study's age range of 3-20 years may obscure differences due to different developmental stages represented among the children.

It is conceivable that family-focused clinical interventions should be targeted especially to more "high risk" families, including those with non-adherent children, low socioeconomic

status (SES), and high stress levels. Uzark et al.'s small 1989 cross-sectional study of 10 children 3-24 months post-transplant supports the need for prioritizing the allocation of interventional resources to families based on their SES and identified stress levels.<sup>336</sup> Up to 90% of parents reported concerns about inadequate insurance and community support. Parents indicated informational needs and help needed concerning physical care of child, play/recreational activities, and physical, social, and emotional development. Moreover, in their later, much larger study of 49 pediatric heart transplant recipients, Uzark et al. found that higher socioeconomic status and parental education predicted greater social competence in the child post-transplant.

Uzark's small 1989 study also revealed that parents experienced social isolation and marital strain after their child's heart transplantation, and found little time to "get away" to relieve their stress. Financial strain was reported as well, with financial troubles due to the child's medical condition often conveyed to the child, causing feelings of guilt in the child. While a majority of parents were also concerned about the uncertainty of their child's future, they felt they had little control over it. Additionally, while they were extremely concerned about their child's happiness and their ability to provide optimal care (role strain), they also worried about the extra demands on their own time/energy, time alone and sexual relationships with their spouse, and time for relaxation/recreation.

## **Other risk factors**

### ***Setting***

Although selection bias may explain the finding, setting has also been found to be a possible risk factor for behavioral outcome, in that recipients exhibit fewer behavioral problems at school than at home. In their 1994 controlled, retrospective cross-sectional study of 41 heart and 24 heart/lung transplant recipients below the age of 17 years, Wray et al. found that whereas recipients had behavioral problems in the home, none of those returning to school showed these problems at school.<sup>224</sup> It is important to note here, however, that selection of "better behaved" children may have occurred here: only 30% of the children eligible to return to school did so during the study's mean follow-up period of 10 months. The remaining 70% who stayed at home may well have demonstrated behavioral problems at school as well, had the investigators been able to assess them at school. Indeed, two of the 35 recipients eligible for school who stayed at home did so because of severe adjustment problems.

### ***Time since transplantation***

Time since transplantation may be a risk factor for worsening behavior problems and school adjustment. Although Wray et al. (1994) did not find the prevalence of behavioral problems in pediatric heart transplant patients to be related to time since transplantation or age at time of assessment, their subsequent findings indicate otherwise.<sup>224</sup> Whereas their 1994 study found no behavioral problems at school at an average of 10 months' follow-up, they did find that school behavior problems in patients assessed serially for three years following transplantation increased from 8% at 6 months post-transplant to 29% at 3 years post-transplant. Parental reporting of adjustment problems also peaked at 3 years (28%). Indeed, it is possible that only those children with the best adjustment during the first, emotionally

intense year following transplant surgery return to school that year. Later on, as the less well-adjusted recipients return to school, the prevalence of behavioral problems seen in the transplant cohort may effectively increase.

### ***Age, sex, and SES***

Age, sex, and SES may influence psychological functioning of pediatric heart transplant patients. Serrano-Ikkos observed that post-transplant improvements in psychological functioning were less pronounced in older children.<sup>51</sup> In their 1995 study, DeMaso et al. found no differences in psychological functioning between male and female recipients.<sup>50</sup>

Adolescence has been discussed in this report as a risk factor for potentially deadly non-compliance with immunosuppression regimens. In their review, Hangard-Patton et al. discuss related difficulties likely faced by adolescents undergoing heart transplantation.<sup>243</sup> These include forced reliance on parents despite the adolescent struggle for independence; mood changes precipitated by steroid use; and discrimination at school by peers, and by teachers who do not expect and therefore do not encourage optimal academic achievement.

Uzark et al.'s 1992 findings underscore the observation that lower socioeconomic status is associated with worse familial psychosocial adjustment post-transplantation.<sup>324</sup> They suggest a need for pediatric heart transplant recipients and families to be systematically assessed for psychosocial maladaptation, in order to equitably allocate social support to families.

### ***Clinical and physiological factors***

More concrete, clinical factors may also have an impact on the rehabilitation progress of the pediatric heart transplant recipient. In their 2001 controlled study covering three years post-transplant Wray et al. found that behavioral problems were most frequently seen in recipients who had an initial diagnosis of CHD: half of 8 patients with CHD had significant problems with behavior at school.<sup>47</sup> With respect to congenital vs. acquired heart disease, DeMaso et al. found no differences in psychological functioning between recipients with congenital and acquired heart disease in their 1995 study of 23 recipients followed for one year post-transplantation.<sup>50</sup>

Hypoxia due either to profound hypothermia during surgery or cyanotic heart disease may also be a risk factor for adverse behavioral outcome.<sup>249</sup> In their 1988 study of 10 children who underwent profound hypothermic circulatory arrest during open-heart surgery to correct transposition of the great arteries, Hesz and Clark found that these children exhibited more aggressive behavior than either healthy siblings or children with acyanotic disease.

Serrano-Ikkos et al. found that psychological functioning improved with improvements in physical ability.<sup>51</sup> This finding is consistent with the 1992 findings of Wray et al., in which post-transplant improvements in physical condition were mirrored by improvements in self-esteem.<sup>46</sup> Decreases in disordered behavior following transplantation in that study were also accompanied by increased independence. The study's follow-up was brief, however – only three months.

DeMaso et al. observed that a lower number of hospitalizations correlated with higher emotional functioning. This relationship may not be direct and there may be a number of potential confounding variables that explain the link.<sup>50</sup>

### **Summary (Heart – psychosocial development)**

Heart and heart/lung recipients and their families appear to have significant problems related to psychosocial function. Function does not appear to improve greatly after transplant and some studies suggest that patients' function as measured by behavior problems, may actually decrease over time. Existing data suggest that psychological distress in pediatric heart transplant recipients is lower than pre-transplant levels after at least 12 months have passed following transplant. Nevertheless, a significant proportion of recipients (20-24%) still continue to experience psychological distress and exhibit behavioral problems following transplantation. Global quality of life (QOL) has not been carefully studied in this population and the major focus in this area has been on psychological outcomes.

The emotional well being of children and adolescents proceeding through the pediatric heart transplantation experience demands further study. Research on psychosocial functioning and quality of life in these children will require the development of reliable, valid tools, and must have as its explicit aim solutions for identified problems. Outcomes with longer follow-up are needed to assess compliance over time and to identify potential interventions. Furthermore, family functioning while waiting for an available organ should be optimized to ensure good psychological outcome in the pediatric heart transplant candidate.

Determination of the relative amount of distress suffered by these children awaits further longitudinal, long-term studies using healthy controls. Finally, researchers should turn a comparative eye to the examination of the three major periods in the life of a young heart transplant patient – the waiting period, the first year following transplantation, and the long-term experience of the growing child, many years after the transplantation surgery.

### **Recommendations from the panel of experts (Heart – psychosocial development)**

#### ***Intervention study:***

- The current literature would support an **intervention study** aimed at **improving stress levels in families**, thereby improving psychosocial outcomes for young heart transplant patients.
  - To achieve a sample size adequate for determining if the intervention is effective, this study would require **multi-center enrollment**.
  - Since such significant difficulties have been identified in this group, patients should be randomized to receive **two different intervention arms** rather than treatment versus no treatment. The latter scenario would not be ethical.

#### ***Quality-of-life study:***



- A **large-scale descriptive quality of life (QOL) study** would also be warranted at this time. This study should:
  - Include specific measures of **family function** and could include directly surveying the patients, since many are adolescents.
  - Examine the effect of **familial stresses during the waiting period** on post-transplant psychosocial functioning and adherence.
  - Look at the **differential treatment bestowed by parents** on the sick child awaiting a donor heart, compared to healthy sibling(s).

***Methodological considerations:***

Studies to identify psychosocial factors affecting the emotional well being of pediatric heart transplant recipients and their families should have the following characteristics:

- Use of **matched, healthy controls**, which may include sibling controls or “best-friend” controls. **Sibling controls** would neutralize confounding factors due to socioeconomic status (SES), psychosocial/familial, and genetic differences. A **best-friend control** would be one of the patient’s best friends, brought in by the patient when he/she comes in for cognitive testing. Best-friend controls also have the advantage of having similar SES to the patient. (*Note: Please see “Use of sibling controls – some caveats” under “General recommendations on methodology”.*)
- **Multi-center with large sample size.**
- **Longitudinal, with long-term follow-up** and **numerous, serial measurements** of psychosocial functioning well before transplantation – and followed through to several years post-transplantation.
- **Consistent use of instruments** across centers for assessing psychosocial functioning.
- Use of **instruments** that can accurately measure **specific psychosocial problems** in children with heart disease.
- Inclusion of **infant recipients.**
- Investigation into how much **psychosocial factors**, particularly self-esteem, predict later **non-compliance** with immunosuppressant medication post-transplant.
- Investigation into **what strategies enhance adherence.** This would involve an intervention study evaluating effectiveness of different family-support models, such as support groups, for improving adherence.

It is important to note here that it is likely infeasible to perform multi-factorial analysis using multiple regression in the pediatric heart transplant transplantation. This is because it would be extremely difficult to recruit an adequate number of patients for such an analysis. Even in a multi-center study, it would be difficult to recruit more than 40 children.

### **Recommendations from expert-selected studies from the literature (Heart – psychosocial development)**

- “Further research needs to be done on quality-of-life issues after pediatric cardiac transplantation. Beyond the long-term medical, developmental, and psychological impact of the transplanted child, studies need to address the **emotional, social, and financial impact** of transplantation on the parents and the well siblings.”<sup>49</sup>
- Conduct research comparing psychological functioning of the young heart transplant patient during **three major periods** –
  - the waiting period
  - the first year following transplantation
  - the long-term post-transplant period
- Look at emotional adjustment, parent-child interactions, and child temperament during the **year directly following transplant** (the “transition” year).<sup>50</sup>
- Conduct research to develop **reliable measures of adherence**.<sup>44</sup>
- Investigate the impact that disease- and transplantation-related stressors have in promoting **negative affect, decreased social competence, and disordered behavior** in pediatric transplant recipients.<sup>45</sup> Stressors would include intense medical regimens, delayed physical development, and decreased socialization with peers.
- Investigate the impact of **negative school experiences due to physical appearance** on academic performance and psychosocial well being, and develop the necessary clinical interventions.<sup>51</sup>

### **Clinical recommendations based on individual studies (Heart – psychosocial development)**

- Emphasize importance of **reintegration into school system** and for the school to develop **tailored educational strategies**. Suggests ongoing education support to minimize impact of lost schooling. Educational interventions should be planned early on in the transplant process.<sup>47</sup>
- Provide opportunities for **family members to communicate their feelings**. Provide anticipatory guidance to parents regarding child’s physical care and socio-emotional needs, and assess family stress and coping before and after transplantation.<sup>336</sup>
- Commence **preparations for changes in body shape and appearance** while awaiting transplantation/donor heart.<sup>44</sup>
- Implement effective preventive and support **programs for single parents** before transplantation (e.g., clinician guidance/support, nurse home visits).<sup>44</sup>

- Provide support, guidance or intervention to **adolescents**, closely **monitoring adherence**.<sup>44,243</sup>
- “**Parents** of pediatric heart transplant recipients should be educated on how to **monitor their children’s psychological status**. Early detection of poor psychological adjustment should be brought to the attention of mental health providers.”<sup>45</sup>
- Consider allocating relatively **more resources to low-SES families** of pediatric heart transplant patients, or to institutions caring for them, for emotionally dealing with transplantation issues.

## Appendix A – Glossary of acronyms and technical terms

**ADD: Attention-Deficit Disorder.** Now typically referred to as “Attention-Deficit/Hyperactivity Disorder”, or “ADHD”.

**ADHD: Attention-Deficit/Hyperactivity Disorder.** A behavioral disorder characterized by excessive impulsivity, inattention, and often hyperactivity.

**AUC: area under the curve.** A measurement from calculus with various applications, including pharmaceutical dosing based on the area under the concentration-time curve.

**BEHL: better ear hearing level.** One of the standard levels of hearing ability set forth by the European Union (EU) Working Group on Genetics of Hearing Impairment.

**BUN: blood urea nitrogen.** BUN levels are a measure of kidney or liver function. Urea is formed in the liver as a waste product that is secreted into the blood and ultimately excreted in the urine by the kidneys. BUN levels are especially elevated in patients with poor renal (kidney) function.

**CA: circulatory arrest.** See “PHCA”.

**CAPD: continuous ambulatory peritoneal dialysis.** CAPD is a type of dialysis done in the home that uses the natural lining of the abdomen (called the “peritoneum”) as the dialysis membrane. The patient undergoing CAPD can be ambulatory (walking around) as the dialysis works through bags placed in the abdomen..

**CAD: cadaveric donor.** Donor who is brain dead at the time of organ donation.

**CD40L-CD40: CD40 ligand-CD40** “CD40” denotes immunologic cells containing “CD40” receptors on their surface. “CD40 ligand” denotes molecules that bind to this receptor.

**CGAS: Children’s Global Assessment Scale.** A test used to measure children’s overall psychosocial functioning.

**CHD: congenital heart disease.** Heart disease present from the time of birth, as opposed to acquired during lifetime.

**CNI: calcineurin inhibitor.** Cyclosporine and tacrolimus are the most widely used CNIs in pediatric solid organ transplantation. CNIs are used to prevent the immune system from attacking a transplanted organ. Also referred to as CIs.

**CNS: central nervous system.** The CNS encompasses the brain and spinal nerves.

**CRF: chronic renal failure.** A gradual decline in kidney function over time.

**CRI: chronic renal insufficiency.** Condition in which the ability of the kidney to function is reduced. CRI is frequently accompanied by anemia.

**CT: computed tomography** (also referred to as “CAT”) Diagnostic imaging procedure in which x-rays are used to visualize “slices” of the body.

**CyA: cyclosporine A.** Widely used drug used in transplanted patients to prevent the immune system from attacking the transplanted organ. Part of the calcineurin inhibitor family of drugs. Its introduction in the early 1980s revolutionized pediatric transplantation, greatly increasing survival of transplant recipients.

**DQ: developmental quotient.** Score yielded by some development tests of very young children. Provides a general measure of developmental health. Distinct from an IQ.

**DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition – Revised,** published by the American Psychiatric Association, 1987. The primary diagnostic reference used by U.S. mental health professionals.

**DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,** published by the American Psychiatric Association, 1994. The primary diagnostic reference used by U.S. mental health professionals.

**EEG: electroencephalogram.** Diagnostic exam in which the brain's electricity is measured.

**ESLD: end-stage liver disease.** Condition, caused by a variety of diseases, in which liver function is inadequate to support life.

**ESRD: end-stage renal disease.** Condition, caused by a variety of diseases, in which kidney function is inadequate to support life. ESRD patients must rely on dialysis to survive.

**FHF: fulminant hepatic failure.** Medical emergency characterized by massive destruction of epithelial liver cells. Usually brought on by a virus or toxin.

**GFR: glomerular filtration rate.** Measure of efficiency of kidney to filter and remove wastes.

**GH: growth hormone.** Hormone produced by the pituitary gland that is necessary for stimulation of normal growth.

**HD: hemodialysis.** Dialysis technique in which the patient's blood is circulated through a filtering machine. Performed in the hospital.

**HLHS: hypoplastic left heart syndrome.** Condition in which the left side of the heart is underdeveloped.

**HNTBC: Halstead-Neuropsychological Test Battery for Children.** A group of tests used to evaluate a variety of neuropsychological domains in children. See Appendix B.

**HRQOL: health-related quality of life.** Day-to-day quality of life as affected by health status.

**IEP: Individualized Education Plan.** A written statement of learning goals for a particular child. An IEP prioritizes areas of concern and sets annual achievement goals.

**IGF-I/ IGF-II: insulin-like growth factor-I/ insulin-like growth factor-II.** Also known as somatomedins. Polypeptides structurally resembling insulin that play important roles in stimulating bone and muscle growth.

**IGFBP-3: insulin-like growth factor binding protein-3.** One of six types of similar proteins able to bind IGF-I and IGF-II (see above). High levels of IGFBP usually mean lower levels of IGF, due to IGF sequestration by IGFBP.

**IQ: Intelligence Quotient.** The average IQ range is generally considered 91-110, with intellectual impairment generally indicated by a score below 70.

**IL-2R: interleukin-2 receptor.** A cell-surface receptor that binds IL-2. IL-2 is a substance similar to a hormone that stimulates cells of the immune system even in the absence of antigen. IL-2 is itself produced by immunologic cells.

**LD: living donor.** An organ donor who is living, as opposed to cadaveric donors, who are brain dead at the time of organ donation.

**LRD: living-related donor.** An organ donor who is living and related to the child needing a transplant.

**MDI: Mental Development Index.** The MDI, which measures mental development, is half of the Bayley Scales of Infant Development, an instrument for measuring developmental health in infants. The other half of the Bayley test is the Psychomotor Developmental Index (PDI).

**MMF: mycophenolate mofetil.** MMF is a drug used in immunosuppression regimens in which steroid use is withdrawn.

**MRI: magnetic resonance imaging.** MRI images can be used to detect lesions of the central nervous system that are not clinically manifest.

**NAPRTCS: North American Pediatric Renal Transplant Cooperative Study.** NAPRTCS is a registry of pediatric renal transplant recipients 0–17 years of age. By January 2001, about 12,000 patients had been registered in NAPRTCS.

**PDI: Psychomotor Developmental Index.** The PDI, which measures behavioral and motor development, is half of the Bayley Scales of Infant Development, an instrument for measuring developmental health in infants. The other half of the Bayley test is the Mental Development Index (MDI).

**PHCA: profound hypothermic circulatory arrest.** Patients undergoing heart transplant surgery must be put into a state of PHCA. PHCA is necessary to maintaining the viability of vital organs during surgery, which it achieves by compensating for the drastically reduced delivery of oxygen to these organs during surgery.

**PTCAD: post-transplant coronary artery disease.**

**PTH: parathyroid hormone (also known as “parathormone”).** A hormone that regulates calcium and phosphate metabolism in the body. PTH stimulates cells responsible for bone absorption and removal (osteoclasts) and promotes intestinal absorption and renal recovery of calcium in order to increase blood calcium levels.

**PTLD: post-transplant lymphoproliferative disorder.** Disorder in immunosuppressed, post-transplant patients characterized by proliferation of immunologic cells infected by the Epstein-Barr virus (EBV).

**PTSD: post-traumatic stress disorder.** Psychiatric disorder that can occur after experiencing life-threatening events. PTSD sufferers may have flashbacks, difficulty sleeping, and feelings of detachment from life.

**QOL: quality of life.** See “HRQOL”

**rhGH: recombinant human growth hormone.** Growth hormone (see “GH”) of human origin produced in the laboratory by cells genetically engineered to produce this hormone.

**rHuEpo: recombinant human erythropoietin.** Erythropoietin of human origin produced in the laboratory by cells genetically engineered to produce this hormone. Erythropoietin prevents programmed cell death of pro-erythroblasts, thereby increasing circulating red blood cells. It is used to treat anemia (e.g., in chronic renal failure).

**RINTBC: Reitan-Indiana Neuropsychological Test Battery for Children.** A group of tests used to evaluate a variety of neuropsychological domains in children. See Appendix B.

**ROD: renal osteodystrophy.** A bone disease resulting from improper maintenance of blood levels of calcium and phosphorus due to kidney failure. Consequences in children include deformity in the legs (rickets) and short stature.

**RRT: renal replacement therapy.** A general term referring to the different treatment modalities used to artificially compensate for (“replace”) lost kidney function. These modalities include the various types of dialysis and transplantation.

**SD: standard deviation.** A statistical unit of measurement that denotes how far, on average, measured values in a population are from the population’s average.

**SDS: standard deviation score.** A statistical unit of measurement that denotes how far a specific, measured value is from the population’s average.

**SES: socioeconomic status.** A general term referring to social and financial status of an individual or group of people.

**SNHL: sensorineural hearing loss.** Hearing loss due to poor conduction along the nerves. In SNHL, air conduction is greater than bone conduction. This is in contrast to conductive hearing loss, in which bone conduction is greater than air conduction.

**SPLIT: Studies of Pediatric Liver Transplantation.** A patient registry. The SPLIT Research Group maintains a registry database of pediatric liver transplant patients from Canada and the United States. As of June 2000, about 1,100 patients had been registered in the SPLIT database.

**SSNS: steroid sensitive nephrotic syndrome.** Nephrotic syndrome that is responsive to steroids. Nephrotic syndrome is characterized by protein leaking into the urine.

**UNOS: United Network for Organ Sharing.** A nonprofit organization that maintains the organ transplant waiting list of the United States under contract with the Health Resources and Services Administration. It is responsible for matching donors with recipients.

**Z score:** same as “SDS”.





## Appendix B – Standardized measures for assessment of cognitive ability and achievement

### Standardized measures used in studies of COGNITIVE ability in pediatric renal, liver, and heart patients

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>GLOBAL INTELLIGENCE</b>						
British Ability Scales (BAS) short form IQ estimate  <i>Note – 2nd edition is the current test.</i>	Measures general intellectual functioning. Specific measures include short-term memory, verbal/nonverbal reasoning, retrieval of knowledge, and speed of information processing.  <i>Caveat: Has been validated for use only in British populations.</i>	2.5 years– 17.5 years	3  2001			3 studies 2001, 1994, 1992  46,47,224
Cattell Infant Intelligence Scale (CIIS)	Measures mental ability, yielding scores for mental age and IQ. Focus is on mental development. Includes items from Stanford-Binet test to ensure continuity of testing using Cattell during infancy and Stanford Binet during toddler years and maturity.	2-30 months	3  1985	1 study 1985  196		2 studies 1970, 1967  247,248

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Cognitive Abilities Test (CAT or CogAT®)	Evaluates reasoning and problem-solving skill across verbal, quantitative, and nonverbal abilities. End points include mental processing speed, reaction time, stimulus discrimination, and learning. Used especially by teachers in planning and tailoring instructional interventions.	grades K-12	1  1999	1 study 1999  6		
Leiter International Scale	Nonverbal test of intelligence test for use in children unable to communicate in a verbal way. These include children who too young to talk, of different ethnic backgrounds, deaf children, and very shy children. Scores from this scale correlate well with Wechsler IQ scores.	Pre-language children	1  1984			1 study 1984  218
Raven's Standard Progressive Matrices (SPM) or the easier "Raven's Coloured Progressive Matrices"	Non-verbal measure of general intelligence ("g"), including problem-solving ability. Tests ability to perceive and think clearly and identify solutions in a visual-perceptual context.	5 years–adult	2  1990	2 studies 1990, 1986  9,198		

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<p>Stanford-Binet Intelligence Scales</p> <p><i>Notes: The latest revision of this test is the Stanford-Binet IV (4<sup>th</sup> edition, revised in 1986). The Tanaka-Binet Scale is the Japanese version of the Stanford-Binet. A Wechsler test – see below – is usually administered before the Stanford-Binet.</i></p>	<p>Widely used measure of intelligence across three broad factors and across three specific factors, yielding an IQ score. The three broad factors are crystallized abilities (academic/scholastic), fluid-analytical abilities (non-language), and short-term memory). The three specific factors are verbal reasoning, quantitative reasoning, and abstract/visual reasoning.</p> <p>Especially good for assessing gifted children. Commonly used as a tool for school placement and detecting learning disabilities or neurological impairments.</p>	2 years–adult	12  1999	4 studies 1994, 1990, 1987, 1985  7,196,200,201	3 studies 1999, 1989, 1987  23,25,34	5 studies 1996, 1980, 1970, 1969, 1967  (3 used older version of scales)  232,233,240,247,248
<p>Test of Non-Verbal Intelligence (TONI-2)</p> <p><i>Note: There now exists a TONI-3 with age range 6 years +.</i></p>	<p>A language-free measure of intelligence and reasoning especially useful in children of different ethnicities.</p>	5 years +	1  2000	1 study 2000  193		

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Wechsler Adult Intelligence Scale-Revised (WAIS-R)	Widely used measure of performance IQ and verbal IQ; yields a composite full IQ score.	16–74 years	6  2001	5 studies 2001, 1999, 1994, 1990, 1985  4-6,196,198	1 study 1999  23	
Wechsler Intelligence Scale for Children (WISC)  <i>Note: the 3rd edition of the test, the WISC-III, is the current version of the test, and supersedes the older WISC-R for use in culturally heterogeneous samples.</i>	Widely used measure of performance IQ and verbal IQ; yields a composite full IQ score.  Includes tests of memory, non-verbal and verbal intelligence/learning, and visual-motor speed. (at least 10 years)  <i>Note: Banatyne's four-factor classification system can be used in conjunction with the WISC. It is used to derive composite Spatial, Sequential, Conceptual, and Acquired Knowledge measures based on WISC scores.</i>	6–16 years	18  2001	6 studies ( <i>all except one of which used the WISC-III</i> ) 1999, 1994, 1990, 1985, 1983, 1982  4,6,196,198,199,204	8 studies ( <i>all of which used the WISC-R</i> ) 2001, 1999, 1999, 1998, 1992, 1991, 1991, 1989  23,24,27,28,32,34,21 2,216	4 studies ( <i>latest of which used the WISC-III</i> ) 1999, 1994, 1985, 1985  37,244-246

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<p>Wechsler Preschool and Primary Scale of Intelligence (WPPSI)</p> <p>or</p> <p>Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)</p> <p><i>Note: WPPSI is outdated. WPPSI-R is the current test.</i></p>	<p>Widely used measure of performance IQ and verbal IQ; yields a composite full IQ score.</p>	<p>3–7 years</p>	<p>6</p> <p>2001</p>		<p>3 studies 2001, 1999, 1991</p> <p>23,28,32</p>	<p>3 studies 1999, 1985, 1984</p> <p>37,218,245</p>
<p>Woodcock-Johnson-III Tests of Cognitive Ability</p> <p><i>Notes: Recommended by expert. Part of WJ-III Complete Battery, which also measures scholastic aptitude.</i></p>	<p>Measure of both general intellectual ability and specific cognitive abilities. Tests include Comprehension-Knowledge, LongTerm Retrieval, Visual-SpatialThinking, Auditory Processing, Fluid Reasoning, Processing Speed, and Short-Term Memory.</p>	<p>2 years–adult</p>	<p>0</p> <p>but recommended by expert</p>			

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>YOUNG DEVELOPMENT – COMPREHENSIVE</b>						
Bayley Scales of Infant Development (BSID or BSID -II)	Widely used measure of mental, motor and behavioral development in infants. Consists of two major scales, the Mental Development Index (MDI) and the Psychomotor Developmental Index (PDI).	BSID: 0 –2.5 years  BSID-II: 1 month–3.5 years	16  2001	3 studies 1990, 1987, 1985  196,200,201	4 studies 1999, 1997, 1995, 1989  22,23,34,214	9 studies 2001, 1999, 1999, 1998, 1997, 1993, 1991, 1991, 1985  35-37,41-43,227,231,245
Griffiths Mental Development Scales  <i>Also known as the Ruth Griffiths Developmental Scales (RGDS).</i>	Measure of locomotor ability, personal–social interaction, hearing and speech, eye–hand coordination, and performance infants and young children. The scale for children includes a practical reasoning component.	0–8 years  <i>Scale 1 covers 0–2 years.</i>  <i>Scale 2 covers 2–8 years.</i>	4  2000		1 study 2000  217	3 studies 1994, 1992, 1991  46,224,226

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
McCarthy Scales of Children's Abilities	Not an IQ test, it provides an overall measure of cognitive and fine and gross motor development.	2.5 yrs-8.5 yrs	4  1999		1 study 1999  216	3 studies 1991, 1985, 1983  42,235,245
Minnesota Child Development Inventory (MCDI)	Developmental test for infants and young children measuring gross and fine motor, expressive language, comprehension-conceptual, situation comprehension, self-help, and personal-social skills.	3 months–6 years	2  1989		2 studies 1989, 1987  25,34	
Revised Yale Developmental Schedule	Comprehensive assessment of cognitive and motor skills, including language, personal/social, gross motor, and fine motor skills.	1–3 years	1  1985	1 study 1985  202		
Tsumori-Inage Developmental Scale/ Kyoto Scale of Psychological Development ( <i>Japanese</i> )	Yields a development quotient (DQ) score for very young children.	younger than school age	1  1998		1 study 1998  27	

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>NEURODEVELOPMENTAL TEST BATTERIES</b>						
NEPSY – neuropsychological test battery	<p>Test battery used in assessing underlying neurological deficiencies. NEPSY is used to detect attention deficits, learning problems, brain injury, and other neurological deficits. Tests can be chosen from among five elements:</p> <ul style="list-style-type: none"> <li>◦ <b>Attention and Executive Functions</b> (the latter are “high-order” cognitive processes): inhibition, self-regulation, monitoring, vigilance, selective and sustained attention, maintenance of response set, planning, flexibility in thinking, figural fluency</li> <li>◦ <b>Language:</b> phonological processing abilities, receptive language comprehension, expressive naming under confrontation and speeded naming conditions, verbal fluency, ability to produce rhythmic oral motor sequences</li> <li>◦ <b>Sensorimotor Functions:</b> tactile sensory input, fine motor speed, hand position imitation, rhythmic and sequential movements, visuomotor precision in handwriting</li> <li>◦ <b>Visuospatial Processing:</b> ability to determine position/directionality, ability to copy 2-D and 3-D reconstructions</li> <li>◦ <b>Memory and Learning:</b> assesses memory for words, sentences, and faces, including immediate recall and narrative memory, both free and cued.</li> </ul>	3–12 years	1  2001	1 study 2001  5		



Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<p><b>Halstead-Reitan Neuropsychological Battery (HRNB):</b></p> <p>Comprised of tests from the following batteries:</p> <p>Halstead-Neuropsychological Test Battery for Children (HNTBC)</p> <p>Reitan-Indiana Neuropsychological Test Battery for Children (RINTBC)</p> <p>(numerous tests, many of which are described below)</p>	<p>Widely used neuropsychological test battery for assessing brain function/dysfunction. Tests a variety of skills involving visual-motor, visual perception, motor speed, auditory discrimination sensitivity, tactile perception, and problem-solving abilities. Includes aphasia screening, tests for lateral dominance, and hand dynamometer testing.</p> <p>Specific tests include the following:</p> <ul style="list-style-type: none"> <li>◦ The <b>HNTBC</b> consists of the Trail-Making, Category Test, Tactile/Tactual Performance, Finger Oscillation, Sensory-Perceptual Measures, Aphasia Screening, Grip Strength, Lateral Dominance Examination, Seashore Rhythm, Speech Sounds Perception, and Finger-Tip Number Writing Perception Tests.</li> <li>◦ The <b>RINTBC</b> contains the Category Test, Tactile/Tactual Performance, Finger Oscillation, Sensory-Perceptual Measures, Aphasia Screening, Grip Strength, Lateral Dominance Examination, Color Form, Progressive Figures, Matching Pictures, Target, Individual Performance, and Marching Tests. Specific Halstead-Reitan tests actually used in studies included in this literature review are described in the ensuing rows.</li> </ul>	<p>4 years–14 years</p>	<p>5  1999</p>	<p>3 studies 1999, 1984, 1983  6,194,199</p>	<p>2 studies 1991, 1991 28,212</p>	

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Neuropsychological Deficit Scale (NDS) for interpreting HNTBC and RINTBC scores	Used to compare right-brain/left-brain strength differences, the NDS is one of many strategies for interpreting the results of the HRNB/HNTBC and RINTBC.		1  1991		1 study 1991  28	
<b>ATTENTION, LEARNING, WORKING MEMORY &amp; EXECUTIVE FUNCTION</b>						
	<i>Note: Measures of memory are also provided by the Selective Response test of the NEPSY.</i>					
Achenbach Behavior Checklists and behavior profiles  <i>Note: Recommended by expert.</i>	Not a measure of intellectual functioning per se, but a measure of key factors affecting learning ability, namely, attention deficit characteristics (e.g., impulsivity, distractability).	completed by children, parents, and teachers	1  1994	1 study 1994  4		
Auditory Consonant Trigrams with the Peterson-Brown distraction task	A measure of attention, working/short-term memory, and memory decay from distraction. Assesses levels of alternating and divided attention and verbal learning ability. Subjects try to recall spoken sets of three consonants (e.g., B Q X) while performing another task. Good for assessing learning ability in face of suboptimal conditions.	6–18 years	2  1990	2 studies 1990, 1986  9,198		

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Auditory Working Memory scale of the WJ-III Tests of Cognitive Ability (see above for description of WJ-III)  <i>Note: Recommended by expert.</i>	Measure of attention/executive function.	2 years–adult	0 but recommended by expert			
Behavior Rating Inventory of Executive Function (BRIEF)  <i>Note: Recommended by expert.</i>	Used to assess impairment of executive function in the home and school environments. Applications include detection of learning disabilities or attention deficit disorder.	parents and teachers of 5–18-year-old children	0 but recommended by expert			
Buschke Restricted Reminding Memory Procedure/ Selective Reminding Task (BSRT)	Measures verbal memory/verbal learning using word lists. Used as a supplemental measure. A subject learns word lists and tries to recognize omission errors when modified lists are repeated.	6–18 years	3  1999	3 studies 1999, 1990, 1986  6,9,198		

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
California Verbal Learning Test (Children's Verision; CVLT-C)  <i>Note: Recommended by expert.</i>	Measure of memory/learning. Quick test during which the child must recall a list despite performing an interference task.	5–17 years	0  but recommended by expert			
Children's Paced Auditory Serial Addition Test (CHIPASAT)	A measure of attention and working/short-term memory, the CHIPASAT evaluates a the ability to hold discrete numbers in working memory and add them quickly.	< 16 years	1  1999	1 study 1999  6		
Conner's Continuous Performance Test (CPT)  <i>Notes: Recommended by expert. Also comes in a teacher's version. "Conner's" is spelled a variety of ways in the literature (Conner's, Connors, Connors, etc.)</i>	Provides measures of attention and vigilance, i.e., how the child responds and attends to situational stimuli. Specifically, it measures ability to control and modulate responses, ability to focus and maintain attention, fine motor regulation, auditory and visual balance, and readiness. Included in the measurements are mental processing speed, reaction time, and discrimination sensitivity.	two scales:  4–5 years ("Kiddie" Version, or CPT-K)  6 years + (CPT-III)	2  1999	2 studies 1999, 1990  6,198		1 study 1985 <sup>246</sup>

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Distraction Paradigm	Test of selective attention and memory decay. Measures ability of subject to maintain attention on central stimulus despite introduction of peripheral, distracting stimuli.	Infants–adolescent	1  1990	1 study 1990  198		
HNTBC and RINTBC's Tactual Performance Task (TPT)	Measure of memory, as well as hypothesis-testing and problem-solving ability. Blindfolded subject places block shapes into formboard, then, unblinded, draws them from memory. Common to both the HRB/HNTC and RINTC.	5 years +	1  1991		1 study 1991  212	
Das-Naglieri Cognitive Assessment System (CAS) Test battery  <i>Note: Recommended by expert.</i>	Provides measures of planning and attention abilities. Aids the diagnosis of attention-deficit/hyperactivity disorders, learning disabilities (ability-achievement discrepancy), mental retardation, and giftedness. The Planned Connections and Number Detection tests are particularly useful for measuring attention/executive function.	5–17 years	0  but recommended by expert			
Paced Auditory Serial Addition Test (PASAT)	A measure of attention and working/short-term memory, the PASAT evaluates a the ability to hold discrete numbers in working memory and add them quickly.	16 years +	1  1999	1 study 1999  6		

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Picture Recognition test of the WJ-III Tests of Cognitive Ability (see above for description of WJ-III)  <i>Note: Recommended by expert.</i>	Measure of memory/learning.	2 years–adult	0  but recommended by expert			
Rey-Osterrieth Complex Figure (ROCF) test  <i>Note: Recommended by expert.</i>	Measure of memory/learning. Child is assessed on how accurately he/she reproduces a complex figure drawing and on the ways he/she approaches the task.	5-14 years	0  but recommended by expert			
RINTBC's Target Test	Measure of learning and memory. Can be used in detection of non-verbal learning disabilities. One of the RINTBC tests.	4–14 years	1  1991		1 study 1991  212	

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Spatial Span Board test of the WISC-PI (“WISC as a Process Instrument”, a supplement to the WISC-III) <i>Note: Recommended by expert.</i>	Measure of attention/executive function.	6–16 years	0 but recommended by expert			
Stroop Color-Word Naming Test	Primarily a test of focal attention and concentration, this measure can be used to detect the presence of brain damage and psychiatric disorders. Well-known test wherein subject is presented with names of colors printed in colors not the same as the named color. The subject must tell tester the ink color, without being distracted by word itself.	7 years +	1 1999	1 study 1999 6		
Wechsler tests’ Digit Span test (part of WISC)	Auditory-perceptual test of alertness, arousal, attention, and immediate recall. Subject must repeat sequences of increasingly long, spoken strings of numbers.	5–15 years	1 1990	1 study 1990 198		
Wechsler tests’ memory scales, including coding subtests	Provide measures of immediate recall.	16+ years	1 1990	1 study 1990 198		

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Wisconsin Card Sorting Test (WCST)  <i>Note: Recommended by expert.</i>	Allows quick assessment of executive functioning Widely used.	6 years +				
<b>MOTOR</b>						
Grooved Pegboard Test	This test of motor and psychomotor ability assesses localized brain damage through measuring manual dexterity, including speed and Static Steadiness.	5 years–adult	1  1999	1 study 1999  6		
HNTBC and RINTBC's Finger Oscillation (tapping) Test	Measure of manual dexterity and speed. Common to both the HRB/HNTC and RINTC.	4–14 years	1  1991		1 study 1991  212	



Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>VISUAL-MOTOR</b>						
	<p><i>Note: Visual-motor ability is also measured by:</i></p> <ul style="list-style-type: none"> <li>◦ <i>Halstead- Reitan test batteries (HNTBC and RINTBC)</i></li> <li>◦ <i>NEPSY</i></li> </ul>					
Beery-Buktenica Development Test of Visual-Motor Integration (VMI)	<p>Pencil and paper test of visual-perception and fine motor coordination. Looks at handwriting and pattern-copying skills in particular. Low scores indicate need for further evaluation to determine if problems are of visuoperceptual or motor nature, or both.</p> <p><i>Note: Two scales exist – one for age 3–7 years, one for older children.</i></p>	3 years +	3  1991	2 studies 1990, 1986  9,198	1 study 1991  212	
Bender Visual-Motor Gestalt Test	<p>A classic, non-verbal measure of visual-motor and visual-perceptual development. Subject copies geometric patterns. May be used to assess role of brain dysfunction in learning disability.</p> <p><i>Caveats: Test yields high false negative and false positive rates, though, and validation tests may have had biased subject selection.</i></p>	4 years–adult	1  1985			1 study 1985  246

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
HNTBC's Trail-Making Test	Measure of visual-motor speed and tracking and executive functions. Especially evaluates attention. Younger subjects connect numbers in ascending order while timed. Older subjects alternate connecting numbers and letters in ascending order while timed.	Part A: 4 years–adult  Part B: 4–14 years	2  1999	1 study 1999  6	1 study 1991  212	
RINTBC's Marching Test	Test of perceptual-motor ability using dominant hand, non-dominant hand, and both hands. One of the RINTBC tests.	4–14 years	1  1991		1 study 1991  212	
<b>VISUAL SPATIAL/ VISUAL PERCEPTUAL</b>						
	<p><i>Note: Visual-spatial ability is also measured by:</i></p> <ul style="list-style-type: none"> <li>◦ <i>WISC's Object Assembly test</i></li> <li>◦ <i>WISC's Block Design test</i></li> <li>◦ <i>Halstead- Reitan test batteries</i></li> <li>◦ <i>NEPSY</i></li> </ul>					

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Frostig Developmental Test of Visual Perception (DTVP)	Measure of visual perception ability.  <i>Caveats: Although well-validated for assessing overall visual-perceptual ability, it is not as well-validated for use in identifying specific visual-perceptual deficits.</i>	4–8 years	1  1969			1 study 1969  240
Meier Visual Discrimination Test	Measure of visual spatial and verbal learning ability.	not available	1  1999	1 study 1999  6		
RINTBC's Individual Performance Test	Measure of visual-spatial ability (matching figures, matching V's, concentric square, star tests). One of the RINTBC tests.	4–14 years	1  1991		1 study 1991  212	

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>PROBLEM-SOLVING, HYPOTHESIS-TESTING &amp; ABSTRACT THINKING</b>						
HNTBC and RINTBC's Categories Test	Measure of problem-solving ability. Common to both the HRB/HNTC and RINTC.	15 years +	3  1991	2 studies 1984, 1983  194,199	1 study 1991 212	
RINTBC's Progressive Figures Test	Commonly used to measure executive function ("higher-order" cognitive processes). One of the RINTBC tests.	4-14 years	1  1991		1 study 1991 212	
RINTBC's Color Form Test	Measure of abstract thinking/concept formation. One of the RINTBC tests.	4-14 years	1  1991		1 study 1991 212	
RINTBC's Matching Pictures Test	Evaluates hypothesis-testing and problem-solving abilities in visual-perceptual context. One of the RINTBC tests.	5-8 years	1  1991		1 study 1991  212	

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>HEARING LOSS</b>						
Auditory Brainstem Response (ABR)	Diagnostic test of hearing ability.  Used when more conventional hearing tests cannot be used. Indirectly measures hearing level in middle and inner ear by measuring brain wave activity in brain's auditory centers.	Newborns and up	1  2001		1 study 2001  223	
Behavioral testing including soundfield localizations, localizations under headphones, play audiometry and conventional audiometry	Hearing ability		1  2001		1 study 2001  223	
Brainstem Auditory-Evoked Responses (BAER)	Diagnostic test of hearing ability. Determines hearing threshold.		1  1991			1 study 1991  227
Distortion Product Otoacoustic Emissions (DPOAE)	Diagnostic test of hearing ability.  Applications include neonatal screening, determining ototoxic effects on cochlear function, detecting sensory hearing loss and/or early signs of noise exposure, and distinguishing cochlear- versus retrocochlear-based hearing loss.		1  2001		1 study 2001  223	

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
European Union (EU) Working Group on Genetics of Hearing Impairment hearing ability standards	Standards of hearing ability. Categories of hearing level include the following: <ul style="list-style-type: none"> <li>◦ better ear hearing level (BEHL)</li> <li>◦ conductive hearing loss</li> <li>◦ mixed hearing loss</li> <li>◦ sensorineural hearing loss (SNHL)</li> </ul>		1  2001	1 study 2001  5		
<b>LANGUAGE ABILITY</b>	<i>Notes: Tests of language ability should be administered where there is concern about incipient learning disability. Testing should begin with assessments of early language expressive and receptive skills in the very young, including basic vocabulary, then continue on to evaluation of emergent literacy and full-fledged reading achievement.</i>					
<i>Note: The WISC also contains tests of language ability, including vocabulary.</i>						

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Clinical Evaluation of Language Fundamentals (CELF-R {revised}, CELF-3 {3 <sup>rd</sup> edition}, CELF-4{4 <sup>th</sup> edition})  <i>Note: Recommended by expert.</i>	Clinical diagnostic tool for identifying language deficits in preschool older children, adolescents, and adults. Assesses ability in receptive and expressive language.  Specific tests include Sentence Structure, Word Structure, Concepts and Directions, Formulated Sentences, Word Classes, Recalling Sentences, Sentence Assembly, Semantic Relationships, Word Associations, Listening to Paragraphs, Rapid Automatic Naming.	6–21 years	0  but recommended by expert			
Clinical Evaluation of Language Fundamentals, Pre-School (CELF-P)  <i>Note: Recommended by expert.</i>	Clinical diagnostic tool for identifying language deficits in preschool children. Used to assess expressive and receptive language, including linguistic concepts, sentence structure, recalling sentences in context, and label formulation.	3–7 years	0  but recommended by expert			
Expressive One-Word Picture Vocabulary Tests (EOWPVT)  Receptive One-Word Picture Vocabulary Tests (ROWPVT)  <i>Note: Recommended by expert.</i>	Measures of expressive and receptive vocabulary.	2–18 years	0  but recommended by expert			

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Gray Oral Reading Test, 3rd edition (GORT-3)  <i>Note: Recommended by expert.</i>	Measure of oral reading ability. Rates speed and error commission in reading aloud.	7–19 years	0  but recommended by expert			
Illinois Test of Psycholinguistic Abilities (ITPA)	Measures oral and written language ability. Measures include writing, reading, and spelling as well as auditory reception, memory, closure, and expression.	2–10 years	1  1984			1 study 1984  218
Peabody Picture Vocabulary Test (PPVT)  <i>Note: Recommended by expert. Current version is the PPVT-III.</i>	Measure of receptive vocabulary. Child points to one of four pictures corresponding to a spoken word, with word sequences increasing in complexity. Since no verbal response is required, it can be used in very young children and children from for whom English is not their first language.	Very young children with emerging language ability	0  but recommended by expert			
Pre-School Language Scale-III (PLS-III) pre-school age children.  <i>Note: Recommended by expert.</i>	Measure of receptive and expressive language, attention, social communication, and vocal development.	2 weeks –7 years	0  but recommended by expert			



Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Sequenced Inventory of Communication Development (SICD)	<p>Developmental test of language and communication. Tests both expressive and receptive language skills.</p> <p><i>Note: The SICD has also been adapted for use in assessing speech pathology in severely handicapped adolescents and adults.</i></p>	4 months–4 years	1  1991			1 study 1991  227
<p>Test of Written Language, 3<sup>rd</sup> Edition (TOWL-3)</p> <p><i>Note: Recommended by expert.</i></p>	<p>Measure of writing competence. Subtests include Vocabulary, Spelling, Style, Story Construction, Logical Sequence, Sentence Combining, Contextual Conventions, and Contextual Language.</p>	7–17 years	0  but recommended by expert			

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>ACHIEVEMENT</b>	<i>Notes: School grades and progression through school are not robust or comparative cross-population indices of intellectual ability or achievement of skills/knowledge. Nationally standardized achievement testing such as the California Achievement Test, Stanford Achievement Test, and Wide Range Achievement Test are more fully acceptable tools to measure progress and relative standing with standardized scores.</i>					
British Ability Scales (BAS) achievement tests (includes Schonell graded spelling test)  <i>Note: BAS-II is the newer, 2nd edition.</i>	Provides measures of achievement in mathematics and spelling.		3  2001			3 studies 2001, 1994, 1992  46,47,224
California Achievement Test  <i>Note: Recommended by expert.</i>	Nationally standardized achievement tests in subjects normally taught in school: reading, language, spelling, mathematics, science, and social studies.	grades K–12  (test for every grade)	0  but recommended by expert			

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Peabody Individual Achievement Test (PIAT)  <i>Note: Has been revised. Current version is the PIAT-R. ("R" for revised).</i>	Provides an overview of academic achievement/scholastic attainment.	5–18 years	2  1985	1 study 1984  194		1 study 1985  246
Stanford Achievement Test (Stanford-9)  <i>Note: Recommended by expert.</i>	Nationally standardized, widely used achievement tests in reading comprehension, written language, science, social studies, and mathematics. One of the tests administered under the California Standardized Testing And Reporting (STAR) Program.	grades 2–11  (test for every grade)	0  but recommended by expert			
Wechsler Individual Achievement Test (WIAT)  <i>Note: There also exists a screening version.</i>	Provides measures of achievement in reading, language, mathematics.	5–19 years	1  1999			1 study 1999  37
Wide Range Achievement Test-Revised (WRAT-R)  <i>Note: There now exists a 3rd edition, called WRAT-III.</i>	Widely used, well-validated measure of academic achievement in reading, spelling, and arithmetic.	5 years +	4  2000	2 studies 2000, 1994  7,193	1 study 1991  212	1 study 1994  244

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Woodcock-Johnson Psycho-Educational Test Battery-Revised (WJ-R) Achievement Standard Battery  <i>Note: There now exists a 3<sup>rd</sup> edition, called. WJ-III.</i>	Contains an achievement portion and a cognitive portion. Evaluates scholastic aptitude; achievement in mathematics, reading, and oral and written language; Subtracting WJ-R scores from IQ scores can determine the presence of a learning disability.	8 years +	2  1999	1 study 1994  4	1 study 1999  23	
<b>SCREENING ONLY/ ABBREVIATED ASSESSMENTS</b>	<i>Notes: The DDST and Gesell schedules should not be used to actually measure cognitive or neuropsychological functioning. They do not provide standardized scores, are less directly linkable to “harder” intellectual data, are not comparative in standardization, and do not yield an IQ or IQ-equivalent. Their application is in detecting potential deficits/problem areas.</i>					
Denver Developmental Screening Test (DDST)	A screening tool, not a measure. Used to screen apparently normal children for potential, suspected problems. Looks at gross motor, fine motor/adaptive, personal-social, and language skills.	2 weeks–6 years	3  2000	1 study 1987  201	1 study 2000  313	1 study 1991  228
Gesell Developmental Schedules	Assesses physical, emotional, and behavioral development of infants and toddlers. Evaluates ability to adapt, motor functioning, attention, social interaction, and language ability. Yields a developmental quotient (DQ) score.	4 weeks–3 years	3  1996			3 studies 1996, 1970, 1967  232,247,248

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>OUTDATED/ SUPERSEDED TESTS</b>						
Merrill-Palmer Scale of Mental Tests	Measures motor and verbal abilities. Includes the little pink tower test, nested cubes, buttoning test, manikin test, color-matching test, pyramid test, Decroly matching game, Wallin pegboard, formboard, association test, copying test, and language test.	21–63 months	1  1988		1 study 1988  315	
Peabody Individual Achievement Test (PIAT)  <i>PIAT-R is the current version.</i>	Provides an overview of academic achievement/scholastic attainment.  Superseded by the PIAT-R (see above).	5–18 years	2  1985	1 study 1984  194		1 study 1985  246
Wechsler Intelligence Scale for Children-Revised (WISC-R)  <i>WISC-III is the current test.</i>	Measures performance IQ and verbal IQ, and yields a composite full IQ score.  Superseded by the WISC-III (see above).  <i>Note: This test is inappropriate for use in culturally heterogeneous populations, but may still be in use today in studies with homogenous samples.</i>	6–16 years	12  2001	1 study  4	8 studies 2001, 1999, 1999, 1998, 1992, 1991, 1991, 1989  23,24,27,28,32,34 ,212,216	3 studies 1994, 1985, 1985  244-246

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Wechsler Preschool and Primary Scale of Intelligence (WPPSI)  <i>WPPSI-R is the current test.</i>	Measures performance IQ and verbal IQ, and yields a composite full IQ score.  Superseded by the WPPSI-R (see above).	3–7 years	6  2001		3 studies 2001, 1999, 1991  23,28,32	3 studies 1999, 1985, 1984  37,218,245
Wide Range Achievement Test-Revised (WRAT-R)  <i>WRAT-III is the current version.</i>	Widely used, well-validated measure of academic achievement in reading, spelling, and arithmetic.  Superseded by the WRAT-III (3 <sup>rd</sup> edition).	5 years +	4  2000	2 studies 2000, 1994  7,193	1 study 1991  212	1 study 1994  244
Woodcock-Johnson Psycho-Educational Test Battery-Revised (WJ-R) Achievement Standard Battery  <i>WJ-III is the current version.</i>	Contains an achievement portion and a cognitive portion. Evaluates scholastic aptitude; achievement in mathematics, reading, and oral and written language; Subtracting WJ-R scores from IQ scores can determine the presence of a learning disability.  Superseded by the WJ-III (3 <sup>rd</sup> edition).	8 years +	2  1999	1 study 1994  4	1 study 1999  23	

Instrument name	Variables measured	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
-----------------	--------------------	-----------	--	---	--	--

The following tests are also considered outdated or superseded:

- Cube Test (Goldstein-Scheerer): Measure of visual-motor ability in children, adolescents, and adults.
- General Aptitude Test Battery (GATB): Measures of intelligence, verbal ability, visual perception, and motor ability for grades 9–12.
- Motor-Free Visual Perception Test (MVPT): Superseded by the revised edition, MVPT-R. Quick measure of visual-perceptual ability useful for screening.
- Otis Higher Test: Measure of intellectual ability across various domains for use in children 12 years of age +.
- Otis Intermediate Test: Measure of intellectual ability across various domains for use in children 9–14 years of age.
- Peabody Picture Vocabulary Test-Revised (PPVT): Superseded by the Peabody Picture Vocabulary Test-3<sup>rd</sup> Edition (PPVT-III). Measure of receptive (hearing) vocabulary for 2 years–adult.
- Stick Test (Goldstein-Scheerer): Measure of visual-motor ability in children, adolescents, and adults.

## Appendix C – Standardized measures for assessment of psychosocial functioning

### Standardized measures used in studies of PSYCHOSOCIAL functioning in pediatric renal, liver, and heart patients

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>PSYCHOLOGICAL DISTRESS/ PSYCHIATRIC DISORDERS/ MOOD</b>						
Birleson Depression Scale	A clinical assessment of degree of depressive feelings.	7 years–adolescent	1  1997			1 study 1997  334
Children’s Depression Inventory (CDI)	Screening tool for depression, the CDI is used to identify need for further evaluation on depressive symptoms. Specific measures include negative mood, hopelessness, interpersonal problems, ineffectiveness, anhedonia (loss of pleasure in once pleasurable activities), and low self-esteem. The cognitive aspects of depression are also examined by this 27-item instrument.	6–17 years	2  1991	1 study 1991  272	1 study 1991  1	



Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Diagnostic Interviews for Children and Adolescents (DICA)	Interview for diagnosing psychiatric disturbance based on the 3 <sup>rd</sup> or 4 <sup>th</sup> editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R, DSM-IV). Can be used for structured or semi-structured formats.	separate interviews for children (6–12 years)  & adolescents (13–18 years)	3  1997	3 studies 1997, 1995, 1995  80,205,271		
General Health Questionnaire (GHQ)	Used to detect psychiatric disorders. Evaluates intensity of somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression. The GHQ-28 is the 28-item version of the questionnaire. The GHQ-12 is the quick, 12-item version.	adolescent–adult  <i>Has been used in transplanted children and their parents.</i>	3  1998	1 study 1998  279		2 studies 1998, 1997  44,334
International Classification of Diseases, 9th Revision (ICD-9)	Can be used to define psychiatric disorders.	all ages	2  1999			2 studies 1999, 1998  44,51

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Personal Adjustment and Role Skills Scale III (PARS III)	<p>Measure of the psychological adjustment and behavioral and emotional function of chronically ill school-age children. Areas of maladjustment measured include dependency, hostility, withdrawal, anxiety-depression, poor productivity, and peer relations. Allows comparison with other chronically ill children.</p> <p>Although not widely used, its use is particularly appropriate in the chronically ill pediatric population, unlike the Children’s Behavioral Checklist (CBCL).</p>	5–18 years	1  1995		1 study 1995  30	
Rutter and Graham semistructured psychiatric interview ( <i>European</i> )	Used to gather information on psychiatric state.	children	1  1999			1 study 1999  51
Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L)	Widely used measure of psychiatric morbidity focusing on 11 areas of psychiatric disturbance. These areas include anxiety, depression, obsession, alcohol abuse, panic phobic, manic, and parasuicidal. It can be used to develop a structured interview. Has been updated for use with DSM-IV. Also available in “Kiddie SADS-Present and Lifetime Version” (K-SADS-PL).	All ages	1  1994	1 study 1994  278		

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
State-Trait Anxiety Inventory for Children (STAIC)	Measures both “state” and “trait” anxiety severity. State anxiety is a temporary emotional response to a stressful situation. Trait anxiety is an innate predisposition to anxiety. Specific measures include apprehension, tension, and intensified autonomic response.	8–14 years old	3  1992	1 study  272	1 study 1991  1	1 study 1992  324
<b>BEHAVIOR/ SOCIAL ADJUSTMENT</b>	<i>Note: Behavioral assessments, at home and in the classroom, should also be used in conjunction with studies of cognitive ability and achievement.</i>					
Achenbach Behavior Checklists and behavior profiles	Measure of child behavior, including measures of depression, social competence, and externalizing versus internalizing.	completed by children, parents, and teachers	1  1994	1 study 1994  4		
Achenbach Teacher’s Report Form	Measures many of the same potential problem areas as in the Child Behavior Checklist (see below). Yields a multi-dimensional profile of behavioral problems, including adaptive behavior and school performance.	completed by teachers for students ages 6–11 years and 12–16 years of age  sex-specific	1  1994	1 study 1994  4		

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Behavior Assessment System for Children (BASC) <i>Note: Recommended by expert.</i>	Measure of behavioral and emotional status in children. Consists of parent, teacher, and child reports, allowing comparison to be made among the different perspectives. Especially applicable when trying to distinguish between behavior at school and in the home.	parents and teachers of children 4–18 years old	0 but recommended by expert			
Child Behavior Checklist (CBCL or CBC)	Measure of child’s behavior problems and competencies by parental report. Includes social history, interests and activities, school performance, and internalizing versus externalizing tendencies. Allows comparison with healthy children.  <i>Caveat: Although widely used, the CBCL may not be optimal for use in chronically ill children.</i>	Parents of children aged 2-18 years	11  2001	3 studies 2001, 2000, 1998  17,279,302 4	6 studies 1999, 1997, 1995, 1991, 1990, 1989  1,30,33,34,310,311	2 studies 1992, 1991  324,332
Children’s Behavior Questionnaire Scale A	Measure of child’s behavior at home, by parental report.	parents	1  1999			1 study 1999  51
Children’s Behavior Questionnaire Scale B	Measure of child’s behavior at school, by teacher report.	teachers	1  1999			1 study 1999  51

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Eyberg Child Behavior Inventory (ECBI)	Screening test assessing common behavior problems across three factors – conduct, aggression, and attention. Used to help determine whether or not child requires referral for behavioral intervention.	2–4 years	1  1987			1 study 1987  242
Griffiths Mental Development Scales  <i>Also known as the Ruth Griffiths Developmental Scales (RGDS).</i>	Primarily a cognitive/neurological measure, these scales also include a measures of social-personal interaction.	0–8 years  <i>Scale 1 covers 0–2 years.</i>  <i>Scale 2 covers 2–8 years.</i>	4  2000		1 study 2000  217	3 studies 1994, 1992, 1991  46,224,226
Personal Adjustment and Role Skills Scale III (PARS III)	Measure of the psychological adjustment and behavioral and emotional function of chronically ill school-age children. Areas of maladjustment measured include dependency, hostility, withdrawal, anxiety-depression, poor productivity, and peer relations. Allows comparison with other chronically ill children.  Although not widely used, its use is particularly appropriate in the chronically ill pediatric population, unlike the Children’s Behavioral Checklist (CBCL).	5–18 years	1  1995		1 study 1995  30	

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Richman behaviour checklist (Richman BCL) <i>(British)</i>	A checklist used to assess behavior at home. Application is to detect any emotional or behavioral difficulties of preschool children in the home. Quick administration.	2–5 years	2  1994			2 studies 1994, 1992  46,224
Rutter Child Scale A <i>(British)</i>	A checklist used to assess behavior at home.	5–17 years	5  1998	1 study  272		4 studies 1998, 1997, 1994, 1992  44,46,224,334
Rutter Child Scale B <i>(British)</i>	A checklist used to assess behavior at school.	7–13 years	4  2001			3 studies 1997, 1994, 1992  46,47,224,334
The Scales of Independent Behavior-Revised (SIB-R)  <i>Note: Recommended by expert.</i>	An overall developmental assessment highly recommended for use in preschool and young school-age children. Also can be used in very young children, although its sensitivity is somewhat diminished when used in toddlers.	completed by parents of preschool children, young school-age children, and toddlers	0  but recommended by expert			

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Vineland Adaptive Behavior Scales (VABS)	A measure of personal and social adjustment, including measures of quality of life (QOL), communication, socialization and social maturity, and daily living functioning.  There also exists a classroom edition.	Interview edition: 0–18 years  Expanded Form: 3–12 years	3  1996	2 studies 1996, 1996  10,270	1 study 1988  315	
Youth Self-Report	Self-administered measure of behavioral problems, competencies, and internalizing and externalizing behaviors.	children and adolescents	1  1994	1 study 1994  4		
<b>PERSONALITY</b>						
Children’s Apperception Test (CAT), includes Human Figure test	A measure of personality, including relationships with family and peers and personal drives.	3-10 years	1  2001		1 study 2001  32	
California Test of Personality (CTP)	Evaluates general personality and social adjustment across several important factors.	2 years–adult	1  1978	1 study 1978  208		

<b>Instrument name</b>	<b>Variables measured in cited studies</b>	<b>Age range</b>	<b>Number of times used (all organs) &amp; latest year used</b>	<b>KIDNEY Number of times used, dates of studies reference numbers</b>	<b>LIVER Number of times used, dates of studies reference numbers</b>	<b>HEART Number of times used, dates of studies reference numbers</b>
Draw-A-Person test	Projective drawings by child of figures, interpreted by clinician. Used to detect signs of mental disturbance.	children and adolescents	1  1987			1 study  242
Infant Characteristics Questionnaire	A measure of temperament in infants (e.g., fussy, difficult, responsive).	parents of infants	1  1995		1 study 1995  214	
Loney Draw-A-Car test	Projective drawings by child, interpreted by clinician using battery of questions. Used to detect signs of mental disturbance.	children and adolescents	1  1987			1 study  242
Personality Inventory for Children (PIC)	Highly regarded screening tool for aiding diagnosis of psychological problems. Provides measures of overall adjustment, cognitive functioning, emotional functioning/affect, energy level/hyperactivity, delinquency, physical problems/ psychosomatic problems, and interpersonal/family functioning.	3–16 years	1  1987			1 study 1987  242
Pigem's test	Projective personality test in which children assign symbols to themselves. The meaning of the symbols are highly interpretive, and may indicate drives and desires.	school age	1  1992		1 study 1992  31	



Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Rorschach inkblot test with Revised Depression Index and Rorschach Egocentricity Index	One of the most widely used projective personality measures. Based on child's interpretations of inkblots, it is used to assess motivations, impulses, and other aspects of personality.	3 years +	1  1991		1 study 1991  1	
<b>SELF-ESTEEM</b>						
Self-Perception Profiles for Children	Self-report instruments measuring self-perceived competence. Measures global self worth as well as competence in scholastic/cognitive, athletic, social, physical appearance, and behavioral conduct.  <i>Note: This instrument is part of a battery of self-perception profiles covering the life span.</i>	school-age–13 years	1  1999		1 study 1999  310	
Self-Perception Profiles for Adolescents  (created by Dr. Harter)	Self-report instruments measuring self-perceived competence in the following domains:  global self worth as well as competence in scholastic/cognitive, athletic, social, physical appearance, and behavioral conduct, romantic appeal, and job competence.  <i>Note: This instrument is part of a battery of self-perception profiles covering the life span.</i>	14–18 years	1  1999		1 study 1999  310	

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Offer Self-Image Questionnaire (OSIQ)  <i>Caveat: Has been revised. Current version is the OSIQ-R.</i>	Self-report measure of adolescent self-image. Provides measures of self-perceived impulse, control, family functioning, emotional tone, self confidence, body image, vocational attitudes, social functioning, ethical values, self reliance, mental health, sexuality, and idealism.  Applications include use in normal teens, those at risk for depression or suicide, delinquent youths, and teens with eating disorders.	12–19 years	1  1987			1 study 1987: 242
Pictorial Scale of Perceived Competence and Social Acceptance for Young Children	Measure of self-perceived cognitive competence, physical competence, maternal acceptance, and peer acceptance.	4–7 years  Preschool/kinder garten & grades 1–2 versions	1  1999		1 study 1999  310	
Piers-Harris Children’s Self-Concept Scale	Measures perceptions of own self-esteem across several factors, including physical appearance and attributes, anxiety, intellectual and school status, behavior, happiness and satisfaction, and popularity.	7–18 years	7  1999	1 study 1978  208	2 studies 1992, 1991  1,31	4 studies 1999, 1998, 1997, 1992  44,51,324,334

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Rosenberg Self-Esteem Scales	One of the most widely used measures of self-esteem. Examines self-esteem as part of global self-concept.	young adults, adolescents	1  1994	1 study 1994  278		
<b>QUALITY OF LIFE &amp; PHYSICAL/ FUNCTIONAL WELLNESS</b>						
15-dimensional, 16-dimensional, and 17-dimensional measures of health-related quality of life (15D-, 16D-, 17D-HR QOL measures)	Multi-dimensional, age-appropriate measures of health-related quality of life (HR QOL) for three age groups (see right), either self-administered or by structured interview. Subjects rate how problematic or successful each QOL dimension is for them because of their health status (e.g., the “friends” dimension rates the difficulty of making friends due to health status).	17D: 8–11 years  16D: 12–15  15D: 16–23 years	1  1997	1 study 1997  312	1 study 1997  312	1 study 1997  312
Child Health Questionnaire	A measure of functional status.  Recommended for assessing functional status of pediatric transplant patients transplanted years ago and now on verge of adulthood.	5–18 years	0  but recommended by expert			

<b>Instrument name</b>	<b>Variables measured in cited studies</b>	<b>Age range</b>	<b>Number of times used (all organs) &amp; latest year used</b>	<b>KIDNEY Number of times used, dates of studies reference numbers</b>	<b>LIVER Number of times used, dates of studies reference numbers</b>	<b>HEART Number of times used, dates of studies reference numbers</b>
Functional Disability Inventory (FDI)	Measure of physical function. Assess impact of chronic illness on child's everyday physical and social activities.	school-age children and adolescents	1  1995		1 study 1995  30	
Health Utilities Index Mark II (HUI-II or HUI2)	A health status classification system that measures health status and HRQOL across seven domains – sensation, mobility, emotion, cognition, self-care, pain, and fertility. Yields utility scores.	children and adults	1  2000		1 study 2000  313	
RAND 36-Item Health Survey-Short Form (SF-36)	Measure of self-perceived overall QOL, including physical, social, emotional, and psychological functioning.  Recommended for assessing functional status of pediatric transplant patients transplanted several years ago and now on verge of adulthood.	14 years +	0  but recommended by expert			
Sickness Impact Profile (SIP)	A measure of the impact of illness on general functioning, social interaction and disengagement, recreation, everyday activities, and cognitive function.  Recommended for assessing functional status of pediatric transplant patients transplanted years ago and now on verge of adulthood.	adults	0  but recommended by expert			

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Side Effect Severity Scale (SESS)	A measure of side effect severity, including both observable and nonobservable side effects. Also looks at frequency of outpatient visits, hospitalizations, and biopsies.	children and adults	1  1995			1 study 1995  50
Zamberlan's Quality of Life Questionnaire for School-Age Children after Liver Transplantation	Validated, open-end questionnaire for eliciting child's views on liver transplantation, physical, emotional, and psychosocial adjustment, and impact of transplantation on QOL. Includes measures of knowledge about transplantation, psychosocial adjustment, internalization, physical appearance/functioning, emotions, fears of graft rejection, and satisfaction with life. Specific to liver transplantation.	school age	1  1992		1 study 1992  31	
<b>OVERALL PSYCHOSOCIAL</b>						
Bayley Scales of Infant Development (BSID and BSID-II)	Widely used measure of mental, motor and behavioral development in infants. Consists of two major scales, the Psychomotor Developmental Index (PDI), which measures behavioral and motor development, and the Mental Development Index (MDI), which measures mental development.	BSID: 0 –2.5 years  BSID-II: 1 month– 3.5 years	16  2001	3 studies 1990, 1987, 1985  196,200,201	4 studies 1999, 1997, 1995, 1989  22,23,34,214	9 studies 2001, 1999, 1999, 1998, 1997, 1993, 1991, 1991, 1985  35-37,41- 43,227,231,245

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Children's Global Assessment Scale (C-GAS)	A measure of overall psychosocial functioning that condenses data gathered on child's psychiatric and social disturbance into one, clinically significant index.	wide age range covering childhood and adolescence	2  1997		1 study 1997  317	1 study 1995  50
Global Assessment of Functioning Scale (GAF scale)	A measure of overall psychosocial functioning that condenses data gathered on subject's psychiatric and social disturbance into one, clinically significant index. Includes measures of social, occupational, academic, and other areas of psychosocial adjustment.  Diagnoses are based on criteria contained in the Diagnostic and Statistical Manual of Mental Disorders (DSM).	Children and adults.  Children's version should be used in children.	3  1999			3 studies 1999, 1998, 1997  44,51,334
Minnesota Child Development Inventory (MCDI)	Developmental test for infants and young children situation comprehension, self-help, personal-social skills, gross and fine motor, expressive language, and comprehension-conceptual.	3 months–6 years	2  1989		2 studies 1989, 1987  25,34	
<b>COPING</b>						
Adolescent Coping Orientation for Problem Experiences (A-COPE)	Inventory identifying coping strategies used by adolescents for managing difficult situations.	11–18 years	1  1992			1 study 1992  324

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
<b>ADHERENCE</b>						
Patient Adherence Form for the Physician (PAEF-P)	Completed by a physician, this instrument rates perceived compliance with medications.	completed by physician	1  1996	1 study  10		
Patient Adherence Form for the Dietician (PAEF-D)	Completed by a dietician, this instrument rates perceived compliance with dietary regimen.	completed by dietician	1  1996	1 study  10		
Patient Adherence Form for the Appointment Clerk (PAEF-AC)	Completed by a dietician, this instrument rates compliance with appointments.	completed by dietician	1  1996	1 study  10		
<b>FAMILY FUNCTIONING</b>						
Camberwell Family Interview Schedule (CFI)	Semistructured standardized interview with parents. Assesses the emotional climate of the family by evaluating other family members' critical attitudes and emotional involvement.	parents and other family members	2  1998			2 studies 1998, 1997  44,334

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Family Assessment Device (FAD)  (also known as the “McMaster Family Assessment Device”)  <i>Note: Recommended by expert.</i>	Brief, self-report measure of family functioning. Assesses emotional relationships and functioning within the family.	family members	0  but recommended by expert			
Family Crisis Oriented Personal Evaluation Scales (F-COPES)	Used to identify coping strategies used by families, including acquiring social support, reframing, seeking spiritual support, and passive appraisal.	parents and other family members	2  1998	1 study 1998  279		1 study 1997  333
Family Environment Scale (FES)	This “social climate” scale measures several aspects of family functioning and levels of agreement among family members. Variables include interpersonal relationships, cohesion, conflict, expressiveness, and personal growth.	adolescent and adult family members	3  2001	3 studies 2001, 2000, 1995  17,271,302		
Family Inventory of life Events and Stresses/Changes (FILE)	This index of family stress assesses the “pile-up” of life events experienced by a family, the psychologic and physical health of family members, and their adaptation.	family members	2  1997			2 studies 1997, 1992  324,333



<b>Instrument name</b>	<b>Variables measured in cited studies</b>	<b>Age range</b>	<b>Number of times used (all organs) &amp; latest year used</b>	<b>KIDNEY Number of times used, dates of studies reference numbers</b>	<b>LIVER Number of times used, dates of studies reference numbers</b>	<b>HEART Number of times used, dates of studies reference numbers</b>
Family Inventory of Resources for Management (FIRM)	A measure of the family's perceived personal resources, family system internal resources, and social support.	parents and other family members	1  1992			1 study 1992  324
Family Relationship Index (FRI)	A measure of relationships within the family, namely, cohesion, expressiveness, and conflict.	parents and other family members	1  1996	1 study 1996  10		
Feetham Family Function Survey (FFFS)	Clinical, systematic assessment of relationships affecting or affected by family functioning.	parents and other family members	1  1989			1 study 1989  336
Global Assessment of Family Relational Functioning scale (GARF)	Measure of family QOL and parents' psychological adjustment.	parents	2  1997		1 study 1997  317	1 study 1995  50
Impact on Family Scale	Self-report instrument for determining stress levels in families with chronically ill children. Dimensions assessed include economic, social/familial, personal strain (psychological burden), and mastery (coping strategies).	parents	3  2001		3 studies 2001, 1995, 1990  3,30,33	

<b>Instrument name</b>	<b>Variables measured in cited studies</b>	<b>Age range</b>	<b>Number of times used (all organs) &amp; latest year used</b>	<b>KIDNEY Number of times used, dates of studies reference numbers</b>	<b>LIVER Number of times used, dates of studies reference numbers</b>	<b>HEART Number of times used, dates of studies reference numbers</b>
Parental Bonding Instrument (PBI)	Instrument for capturing subject's own memories of mother's parenting habits, and the emotions associated with these memories.	child as adult	1  1984	1 study 1994  278		
Schneiderman categories	Clinical assessment of family functioning by such clinicians as a psychiatrist, clinical nurse specialist, and social worker.	completed by clinicians	1  1997			1 study 1997  334
<b>PARENTAL FUNCTIONING</b>						
Chronic Illness Coping Inventory: Parent Questionnaires (CICI:PQ)	A measure of parental perceptions of stressors and problem situations and their coping strategies for managing them.	parents	1  1992			1 study 1992  324
Coping Health Inventory for Parents (CHIP)	Used to assess parents' perception of their own coping behaviors for managing a family with a sick child. Includes measures of internal family strength, external support, and relationship with health professionals.	parents	3  2001	1 study 1998  279	1 study 2001  3	1 study 1992  324
Diagnostic, structured clinical interviews based on the Diagnostic and Statistical Manual of Mental Disorders (DSM).	These interviews have been used to identify psychiatric disorders in mothers of children with kidney transplants (see right).	all ages	1  1995	1 study 1995  205		

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Golomok-Rust Inventory of Marital Status (GRIMS)	Assesses quality of relationship between partners, and identifies areas of conflict.	adults	2  1998			2 studies 1998, 1997  44,334
Hymovich Chronicity Impact and Coping Instrument (CICI)	Parent-completed clinical assessment of parental coping and parental perceptions of child's illness.	parents	1  1989			1 study 1989  336
Leeds scale for self-assessment of anxiety and depression (Leeds SAD) <i>(British)</i>	Self-assessment tool for measuring general anxiety and general depression.	Has been used in parents of children with end-stage renal disease.	1  1991	1 study 1991  272		
Parenting Stress Index (PSI) or Parenting Stress Index-Short Form (PSI-SF)	Measures the degree of stress in the parent-child interaction and the strengths and weakness of parenting skills. Parenting skills measured include responsiveness to the child and the ability to identify problems, solutions, and productive ways of communicating with the child.	parents	2  2000	2 studies 2000, 1998  17,279		
Parents' Perception of the Transplant Experience <i>Note: Specific to heart transplantation.</i>	A measure of various aspects of the parents' perception of the heart transplant experience. Measures include perceived family emotional well being, strengths, finances, and roles; guilt over donor death; understanding of cause of heart disease; and perception of child's survival and prognosis.	parents	1  1997			1 study 1997  333

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
Primary Communication Inventory (PCI)	A measure of verbal and non-verbal communication practices used by a married couple.	adults	1  1996	1 study 1996  10		
<b>SOCIOECONOMIC STATUS (SES)</b>						
Hollinghead's index of social status	Widely used measure of Socioeconomic status (SES) in American studies.		16  2001	8 studies 1999, 1997, 1995 1995 1990 1992 1991 1991 1,22- 24,28,30,33,214	5 studies 2001, 2000 1990, 1989 1982  17,34,200,204,302	3 studies 1995, 1985, 1983  50,230,245
<b>OUTDATED/ SUPERSEDED TESTS</b>						
Offer Self-Image Questionnaire (OSIQ)  <i>Current version is the OSIQ-R.</i>	Self-report measure of adolescent self-image. Provides measures of self-perceived impulse, control, family functioning, emotional tone, self confidence, body image, vocational attitudes, social functioning, ethical values, self reliance, mental health, sexuality, and idealism. Applications include use in normal teens, those at risk for depression or suicide, delinquent youths, and teens with eating disorders.  Superseded by the OSIQ-R ("R" = revised.)	12–19 years	1  1987			1 study 1987: 242

Instrument name	Variables measured in cited studies	Age range	Number of times used (all organs) & latest year used	KIDNEY Number of times used, dates of studies reference numbers	LIVER Number of times used, dates of studies reference numbers	HEART Number of times used, dates of studies reference numbers
-----------------	-------------------------------------	-----------	--	---	--	--

The following are also considered outdated tests:

- Cornell Index: psychiatric/psychosomatic screening inventory (adults)
- Maudsley Personality Inventory: superseded by EPI & EPQ (adults)
- The Personal Audit: Superseded by the 1991 revised edition. Measure of personal adjustments required for job success for those of working age.
- Rotter Incomplete Sentences Blank: Measure of personality.

The following are non-validated instruments of psychosocial and/or physical functioning used in studies included in the literature review:

- Liver Transplant Disability Scale (LTDS): Clinical measure of medical disability due to liver transplantation. Includes measures of infections, liver synthetic function, cholestasis, growth, portal hypertension, and hospitalization frequency. Used in one pilot study, in 2000.<sup>313</sup>
- Index of Physical Ability: Investigator-developed for assessing active functioning of European children in grades 1–4. Looks at school attendance, participation in sports and other recreational activities, and walking ability. Used in one study, in 1997.<sup>334</sup>

## References

1. Windsorova D, Stewart SM, Lovitt R, et al: Emotional adaptation in children after liver transplantation. *Journal of Pediatrics* 119:880-7, 1991
2. House R, Dubovsky SL, Penn I: Psychiatric aspects of hepatic transplantation. *Transplantation* 36:146-50, 1983
3. Schulz K, Hofmann C, Sander K, et al: Comparison of quality of life and family stress in families of children with living-related liver transplants versus families of children who received a cadaveric liver. *Transplantation Proceedings* 33:1496-7, 2001
4. Lawry KW, Brouhard BH, Cunningham RJ: Cognitive functioning and school performance in children with renal failure. *Pediatric Nephrology* 8:326-9, 1994
5. Qvist E, Pihko H, Fagerudd P, et al: Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood [pre-publication]. *Pediatric Transplantation* 5:in press, 2001
6. Mendley SR, Zelko FA: Improvement in specific aspects of neurocognitive performance in children after renal transplantation. *Kidney International* 56:318-23, 1999
7. Williams BL, Schneider JA, Trauner DA: Global intellectual deficits in cystinosis. *American Journal of Medical Genetics* 49:83-7, 1994
8. Town M, Jean G, Cherqui S, et al: A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nature Genetics* 18:319-24, 1998
9. Fennell EB, Fennell RS, Mings E, et al: The effects of various modes of therapy for end stage renal disease on cognitive performance in a pediatric population--a preliminary report. *International Journal of Pediatric Nephrology* 7:107-12, 1986
10. Davis MC, Tucker CM, Fennell RS: Family behavior, adaptation, and treatment adherence of pediatric nephrology patients. *Pediatric Nephrology* 10:160-6, 1996
11. Grushkin CM, Korsch BM, Fine RN: The outlook for adolescents with chronic renal failure. *Pediatric Clinics of North America* 20:953-63, 1973
12. Zarinsky I: Psychological problems of kidney transplanted adolescents. *Adolescence* 10:101-9, 1975
13. Simmons RG, Kamstra L: Long-term rehabilitation of transplant patients. *Proceedings of the Clinical Dialysis & Transplant Forum* 10:43-6, 1980
14. Taber VB, Lee HA, Slapak M: A rehabilitation assessment of renal transplantees (based on United Kingdom experience). *Nephrology Nurse* 5:9-14, 1982
15. Landes LE, Holman JM, Maxwell JG: Rehabilitation of the end stage renal disease patients through transplantation. *Dialysis and Transplantation* 12:580-3, 1983
16. Devins GM, Mann J, Mandin H, et al: Psychosocial predictors of survival in end stage renal disease. *The Journal of Nervous and Mental Disease* 178:127-33, 1990
17. Soliday E, Kool E, Lande MB: Psychosocial adjustment in children with kidney disease. *Journal of Pediatric Psychology* 25:93-103, 2000

18. McDiarmid SV: Liver transplantation. The pediatric challenge. *Clinics in Liver Disease* 4:879-927, 2000
19. Reding R: Steroid withdrawal in liver transplantation: benefits, risks, and unanswered questions. *Transplantation* 70:405-10, 2000
20. Sarna S, Hoppu K, Neuvonen PJ, et al: Methylprednisolone exposure, rather than dose, predicts adrenal suppression and growth inhibition in children with liver and renal transplants. *Journal of Clinical Endocrinology & Metabolism* 82:75-7, 1997
21. Balistreri W, JC B, FC R: The effect of immunosuppression on growth and development. *Liver Transplant Surg* 1:64, 1995
22. Wayman KI, Cox KL, Esquivel CO: Neurodevelopmental outcome of young children with extrahepatic biliary atresia 1 year after liver transplantation. *Journal of Pediatrics* 131:894-8, 1997
23. Kennard BD, Stewart SM, Phelan-McAuliffe D, et al: Academic outcome in long-term survivors of pediatric liver transplantation. *Journal of Developmental & Behavioral Pediatrics* 20:17-23, 1999
24. Stewart SM, Campbell RA, McCallon D, et al: Cognitive patterns in school-age children with end-stage liver disease. *Journal of Developmental & Behavioral Pediatrics* 13:331-8, 1992
25. Stewart SM, Uauy R, Waller DA, et al: Mental and motor development correlates in patients with end-stage biliary atresia awaiting liver transplantation. *Pediatrics* 79:882-8, 1987
26. Stewart SM, Uauy R, Kennard BD, et al: Mental development and growth in children with chronic liver disease of early and late onset. *Pediatrics* 82:167-72, 1988
27. Hattori H, Higuchi Y, Tsuji M, et al: Living-related liver transplantation and neurological outcome in children with fulminant hepatic failure. *Transplantation* 65:686-92, 1998
28. Stewart SM, Silver CH, Nici J, et al: Neuropsychological function in young children who have undergone liver transplantation. *Journal of Pediatric Psychology* 16:569-83, 1991
29. Tarter RE, Van Thiel DH, Hegedus AM, et al: Neuropsychiatric status after liver transplantation. *Journal of Laboratory & Clinical Medicine* 103:776-82, 1984
30. DeBolt AJ, Stewart SM, Kennard BD, et al: A survey of psychosocial adaptation in long-term survivors of pediatric liver transplants. *Children's Health Care* 24:79-96, 1995
31. Zamberlan KE: Quality of life in school-age children following liver transplantation. *Maternal-Child Nursing Journal* 20:167-229, 1992
32. Gritti A, Di Sarno AM, Comito M, et al: Psychological impact of liver transplantation on children's inner worlds. *Pediatric Transplantation* 5:37-43, 2001
33. Kennard BD, Petrik K, Stewart SM, et al: Identifying factors in post-operative successful adaptation to pediatric liver transplantation. *Social Work in Health Care* 15:19-33, 1990
34. Stewart SM, Uauy R, Waller DA, et al: Mental and motor development, social competence, and growth one year after successful pediatric liver transplantation. *Journal of Pediatrics* 114:574-81, 1989

35. Baum M, Chinnock R, Ashwal S, et al: Growth and neurodevelopmental outcome of infants undergoing heart transplantation. *Journal of Heart & Lung Transplantation* 12:S211-7, 1993
36. Freier MC, Mallery S, Baum MF, et al: Medical and surgical variables influence neurodevelopmental outcome in infant heart transplant recipients (Abstract), 11th Annual Convention of the American Psychological Society. Denver, CO, 1999
37. Fortuna RS, Chinnock RE, Bailey LL: Heart transplantation among 233 infants during the first six months of life: the Loma Linda experience. Loma Linda Pediatric Heart Transplant Group. *Clinical Transplants*:263-72, 1999
38. Miller G, Tesman JR, Ramer JC, et al: Outcome after open-heart surgery in infants and children. *Journal of Child Neurology* 11:49-53, 1996
39. Miller G, Mamourian AC, Tesman JR, et al: Long-term MRI changes in brain after pediatric open heart surgery. *Journal of Child Neurology* 9:390-7, 1994
40. Bellinger DC, Wypij D, Kuban KC, et al: Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation* 100:526-32, 1999
41. Bellinger DC, Rappaport LA, Wypij D, et al: Patterns of developmental dysfunction after surgery during infancy to correct transposition of the great arteries. *Journal of Developmental & Behavioral Pediatrics* 18:75-83, 1997
42. Bellinger DC, Wernovsky G, Rappaport LA, et al: Cognitive development of children following early repair of transposition of the great arteries using deep hypothermic circulatory arrest. *Pediatrics* 87:701-7, 1991
43. Bellinger DC, Wypij D, du Plessis AJ, et al: Developmental and neurologic effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. *Journal of Thoracic & Cardiovascular Surgery* 121:374-83, 2001
44. Serrano-Ikkos E, Lask B, Whitehead B, et al: Incomplete adherence after pediatric heart and heart-lung transplantation. *Journal of Heart & Lung Transplantation* 17:1177-83, 1998
45. Todaro JF, Fennell EB, Sears SF, et al: Review: cognitive and psychological outcomes in pediatric heart transplantation. *Journal of Pediatric Psychology* 25:567-76, 2000
46. Wray J, Radley-Smith R, Yacoub M: Effect of cardiac or heart-lung transplantation on the quality of life of the paediatric patient. *Quality of Life Research* 1:41-6, 1992
47. Wray J, Long T, Radley-Smith R, et al: Returning to school after heart or heart-lung transplantation: how well do children adjust? *Transplantation* 72:100-6, 2001
48. Baum M, Freier K, Chinnock R: Growth and Cognitive Development, in Tejani A, Harmon W, Fine R (eds): *Pediatric Solid Organ Transplantation* (ed 1st edition). Copenhagen, Munksgaard, 2000, pp 433-9
49. Higgins SS: Parental considerations for children undergoing cardiac transplantation. *Critical Care Nursing Clinics of North America* 12:79-85, 2000
50. DeMaso DR, Twente AW, Spratt EG, et al: Impact of psychologic functioning, medical severity, and family functioning in pediatric heart transplantation. *Journal of Heart & Lung Transplantation* 14:1102-8, 1995



51. Serrano-Ikkos E, Lask B, Whitehead B, et al: Heart or heart-lung transplantation: psychosocial outcome. *Pediatric Transplantation* 3:301-8, 1999
52. Janssen F, Van Damme-Lombaerts R, Van Dyck M, et al: Impact of growth hormone treatment on a Belgian population of short children with renal allografts. *Pediatric Transplantation* 1:190-6, 1997
53. NAPRTCS: 2001 annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS).:Section 6, 2001
54. Fine RN: Growth following solid organ transplantation [pre-publication]. *Pediatric Transplantation*, February, 2002
55. Fine R: Rehabilitation and Growth Post Transplant in Infants and Adolescents, in Tejani A, Harmon W, Fine R (eds): *Pediatric Solid Organ Transplantation* (ed 1st edition). Copenhagen, Munksgaard, 2000, pp 227-36
56. Melter M, Briscoe DM: Challenges after pediatric transplantation. *Seminars in Nephrology* 20:199-208, 2000
57. Haffner D, Schaefer F: Does recombinant growth hormone improve adult height in children with chronic renal failure? *Seminars in Nephrology* 21:490-7, 2001
58. Hokken-Koelega AC, Van Zaal MA, de Ridder MA, et al: Growth after renal transplantation in prepubertal children: impact of various treatment modalities. *Pediatric Research* 35:367-71, 1994
59. Ingelfinger JR, Grupe WE, Harmon WE, et al: Growth acceleration following renal transplantation in children less than 7 years of age. *Pediatrics* 68:255-9, 1981
60. Maxwell H, Haffner D, Rees L: Catch-up growth occurs after renal transplantation in children of pubertal age. *Journal of Pediatrics* 133:435-40, 1998
61. Maxwell H, Rees L: Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients. *British Association for Pediatric Nephrology. Archives of Disease in Childhood* 79:481-7, 1998
62. Tejani A, Fine R, Alexander S, et al: Factors predictive of sustained growth in children after renal transplantation. The North American Pediatric Renal Transplant Cooperative Study. *Journal of Pediatrics* 122:397-402, 1993
63. de Broux E, Huot CH, Chartrand S, et al: Growth and pubertal development following pediatric heart transplantation: a 15-year experience at Ste-Justine Hospital. *Journal of Heart & Lung Transplantation* 19:825-33, 2000
64. Chantler, Holliday MA: Growth in children with renal disease with particular reference to the effects of calorie malnutrition: a review. *Clinical Nephrology* 1:230-42, 1973
65. Betts PR, Magrath G: Growth pattern and dietary intake of children with chronic renal insufficiency. *Bmj* 2:189-93, 1974
66. West CD, Smith WC: An attempt to elucidate the cause of growth retardation in renal disease. *American Journal of Diseases of Children* 91:460-76, 1956
67. Betts PR, Magrath G, White RH: Role of dietary energy supplementation in growth of children with chronic renal insufficiency. *Bmj* 1:416-8, 1977

68. Mehls O, Ritz E, Oppermann HC, et al: Femoral head necrosis in uremic children without steroid treatment or transplantation. *Journal of Pediatrics* 99:926-9, 1981
69. Tonshoff B, Schaefer F, Mehls O: Disturbance of growth hormone--insulin-like growth factor axis in uraemia. Implications for recombinant human growth hormone treatment. *Pediatric Nephrology* 4:654-62, 1990
70. Kleinknecht C, Broyer M, Gagnadoux MF, et al: Growth in children treated with long-term dialysis. A study of 76 patients. *Advances in Nephrology From the Necker Hospital* 9:133-63, 1980
71. Stefanidis CJ, Koulieri A, Siapera D, et al: Effect of the correction of anemia with recombinant human erythropoietin on growth of children treated with CAPD. *Advances in Peritoneal Dialysis* 8:460-3, 1992
72. Abitbol CL, Zilleruelo G, Montane B, et al: Growth of uremic infants on forced feeding regimens. *Pediatric Nephrology* 7:173-7, 1993
73. Chan JC, McEnery PT, Chinchilli VM, et al: A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *The Growth Failure in Children with Renal Diseases Investigators. Journal of Pediatrics* 124:520-8, 1994
74. Tom A, McCauley L, Bell L, et al: Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. *Journal of Pediatrics* 134:464-71, 1999
75. Hokken-Koelega AC, van Zaal MA, van Bergen W, et al: Final height and its predictive factors after renal transplantation in childhood. *Pediatric Research* 36:323-8, 1994
76. Guest G, Berard E, Crosnier H, et al: Effects of growth hormone in short children after renal transplantation. *French Society of Pediatric Nephrology. Pediatric Nephrology* 12:437-46, 1998
77. McDonald R, Donaldson L, Emmett L, et al: A decade of living donor transplantation in North American children: the 1998 annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatric Transplantation* 4:221-34, 2000
78. Sheldon CA, McLorie GA, Churchill BM: Renal transplantation in children. *Pediatric Clinics of North America* 34:1209-32, 1987
79. Ingulli E, Tejani A: An analytical review of growth hormone studies in children after renal transplantation. *Pediatric Nephrology* 9:S61-5, 1995
80. Feld LG, Stablein D, Fivush B, et al: Renal transplantation in children from 1987-1996: the 1996 Annual Report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatric Transplantation* 1:146-62, 1997
81. Fine RN: Growth post renal-transplantation in children: lessons from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatric Transplantation* 1:85-9, 1997
82. Jabs K, Van Dop C, Harmon WE: Growth hormone treatment of growth failure among children with renal transplants. *Kidney International - Supplement* 43:S71-5, 1993
83. Jabs KL, Van Dop C, Harmon W: Assessment of long-term growth in children with renal allografts (abstr). *Kidney International* 37:607A, 1990

84. NAPRTCS: 1999 annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS)., 1999
85. Tejani A, Sullivan K: Long-term follow-up of growth in children post-transplantation. *Kidney International - Supplement* 43:S56-8, 1993
86. Grushkin CM, Fine RN: Growth in children following renal transplantation. *American Journal of Diseases of Children* 125:514-6, 1973
87. van Diemen-Steenvoorde R, Donckerwolcke RA, Brackel H, et al: Growth and sexual maturation in children after kidney transplantation. *Journal of Pediatrics* 110:351-6, 1987
88. Haffner D, Schaefer F, Nissel R, et al: Effect of growth hormone treatment on the adult height of children with chronic renal failure. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *New England Journal of Medicine* 343:923-30, 2000
89. Schaefer F, Seidel C, Binding A, et al: Pubertal growth in chronic renal failure. *Pediatric Research* 28:5-10, 1990
90. Hokken-Koelega AC, Stijnen T, de Jong RC, et al: A placebo-controlled, double-blind trial of growth hormone treatment in prepubertal children after renal transplant. *Kidney International - Supplement* 53:S128-34, 1996
91. Schaefer F, Mehls O: Endocrine and growth disorders, in Barratt TM, Avner ED, Harmon W (eds): *Pediatric Nephrology* (ed 4th). Baltimore, MD, Williams & Wilkins, 1998, pp 1197-1230
92. Hokken-Koelega AC, Stijnen T, de Ridder MA, et al: Growth hormone treatment in growth-retarded adolescents after renal transplant. *Lancet* 343:1313-7, 1994
93. Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM, et al: Levels of growth hormone, insulin-like growth factor-I (IGF-I) and -II, IGF-binding protein-1 and -3, and cortisol in prednisone-treated children with growth retardation after renal transplantation. *Journal of Clinical Endocrinology & Metabolism* 77:932-8, 1993
94. Ferraris JR, Day PF, Gutman R, et al: Effect of therapy with a new glucocorticoid, deflazacort, on linear growth and growth hormone secretion after renal transplantation. *Journal of Pediatrics* 121:809-13, 1992
95. Mentser M, Breen TJ, Sullivan EK, et al: Growth-hormone treatment of renal transplant recipients: the National Cooperative Growth Study experience--a report of the National Cooperative Growth Study and the North American Pediatric Renal Transplant Cooperative Study. *Journal of Pediatrics* 131:S20-4, 1997
96. Benfield MR, Parker KL, Waldo FB, et al: Growth hormone in the treatment of growth failure in children after renal transplantation. *Kidney International - Supplement* 43:S62-4, 1993
97. Van Es A: Growth hormone treatment in short children with chronic renal failure and after renal transplantation: combined data from European clinical trials. The European Study Group. *Acta Paediatrica Scandinavica - Supplement* 379:42-8; discussion 49, 1991
98. Benfield MR, Kohaut EC: Growth hormone is safe in children after renal transplantation. *Journal of Pediatrics* 131:S28-31, 1997

99. Fine RN, Yadin O, Moulten L, et al: Extended recombinant human growth hormone treatment after renal transplantation in children. *Journal of the American Society of Nephrology* 2:S274-83, 1992
100. Friedman AL: Growth hormone is not safe for children with renal transplants. *Journal of Pediatrics* 131:S25-7, 1997
101. Mehls O, Wuhl E, Haffner D, et al: Growth hormone treatment of short children with chronic renal failure before and after renal transplantation: rationale and recent results. *Nephrology, Dialysis, Transplantation* 11:1747-50, 1996
102. Fine R, Sullivan EK, Tejani A: The impact of recombinant human growth hormone treatment on final adult height. *Pediatric Nephrology* 14:679-81, 2000
103. Fine RN, Sullivan EK, Kuntze J, et al: The impact of recombinant human growth hormone treatment during chronic renal insufficiency on renal transplant recipients. *Journal of Pediatrics* 136:376-82, 2000
104. Rees L, Ward G, Rigden SP: Growth over 10 years following a 1-year trial of growth hormone therapy. *Pediatric Nephrology* 14:309-14, 2000
105. Fine RN, Stablein D, Cohen A, et al: rgGH post-transplant: one-year randomized controlled study of NAPRTCS (abstr). *Pediatric Research* 49:422A, 2001
106. Van Dop C, Jabs KL, Donohoue PA, et al: Accelerated growth rates in children treated with growth hormone after renal transplantation. *Journal of Pediatrics* 120:244-50, 1992
107. Tonshoff B, Haffner D, Albers N, et al: Predictors of the response to growth hormone in short prepubertal children post-renal transplant. German Study Group for Growth Hormone Treatment in Children Post Renal Transplantation Study Group Members. *British Journal of Clinical Practice. Supplement* 85:34-7, 1996
108. Broyer M: Results and side-effects of treating children with growth hormone after kidney transplantation--a preliminary report. Pharmacia & Upjohn Study Group. *Acta Paediatrica. Supplement* 417:76-9, 1996
109. Benfield MR, Vail A, Waldo FB, et al: The effect of recombinant human growth hormone on responses to alloantigens in the pediatric transplant patient. *Pediatric Nephrology* 10:280-2, 1996
110. Hokken-Koelega AC: Growth hormone treatment in children before and after renal transplantation. *Journal of Pediatric Endocrinology & Metabolism* 9:359-64, 1996
111. Hokken-Koelega AC, de Jong RC, Donckerwolcke RA, et al: Use of recombinant human growth hormone (rhGH) in pubertal patients with CRI/dialysis/post-transplant: Dutch data. Dutch Study Group on Growth in Children with Chronic Renal Disease. *British Journal of Clinical Practice. Supplement* 85:5-6, 1996
112. Laine J, Krogerus L, Sarna S, et al: Recombinant human growth hormone treatment. Its effect on renal allograft function and histology. *Transplantation* 61:898-903, 1996
113. Fine RN, Stablein DM, Tejani A: Do children exhibit catch-up growth post transplant: North American Pediatric Renal Transplant Cooperative Study special study. *Pediatric Nephrology* 9:S66-8, 1995

114. Fine RN: Growth hormone treatment of children with chronic renal insufficiency, end-stage renal disease and following renal transplantation--update 1997. *Journal of Pediatric Endocrinology & Metabolism* 10:361-70, 1997
115. Mehls O, Ritz E: Skeletal growth in experimental uremia. *Kidney International - Supplement* 15:S53-62, 1983
116. Fine RN, Kohaut EC, Brown D, et al: Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. Genentech Cooperative Study Group. *Journal of Pediatrics* 124:374-82, 1994
117. Tyden G, Berg U, Reinholt F: Acute renal graft rejection after treatment with human growth hormone. *Lancet* 336:1455-6, 1990
118. Schwartz ID, Warady BA: Cadaveric renal allograft rejection after treatment with recombinant human growth hormone. *Journal of Pediatrics* 121:664-6, 1992
119. Bartosh S, Kaiser B, Rezvani I, et al: Effects of growth hormone administration in pediatric renal allograft recipients. *Pediatric Nephrology* 6:68-73, 1992
120. Benfield MR, Parker KL, Waldo FB, et al: Treatment of growth failure in children after renal transplantation. *Transplantation* 55:305-8, 1993
121. Fine RN, Kohaut E, Brown D, et al: Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone. *Kidney International* 49:781-5, 1996
122. Haffner D, Wuhl E, Schaefer F, et al: Factors predictive of the short- and long-term efficacy of growth hormone treatment in prepubertal children with chronic renal failure. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *Journal of the American Society of Nephrology* 9:1899-907, 1998
123. Tonshoff B, Mehls O, Heinrich U, et al: Growth-stimulating effects of recombinant human growth hormone in children with end-stage renal disease. *Journal of Pediatrics* 116:561-6, 1990
124. Koch VH, Lippe BM, Nelson PA, et al: Accelerated growth after recombinant human growth hormone treatment of children with chronic renal failure. *Journal of Pediatrics* 115:365-71, 1989
125. Rees L, Rigden SP, Ward G, et al: Treatment of short stature in renal disease with recombinant human growth hormone. *Archives of Disease in Childhood* 65:856-60, 1990
126. Tyden G, Wernersson A, Sandberg J, et al: Development of renal cell carcinoma in living donor kidney grafts. *Transplantation* 70:1650-6, 2000
127. Darendeliler F, Hindmarsh PC, Preece MA, et al: Growth hormone increases rate of pubertal maturation. *Acta Endocrinologica* 122:414-6, 1990
128. Kawai M, Momoi T, Yorifuji T, et al: Unfavorable effects of growth hormone therapy on the final height of boys with short stature not caused by growth hormone deficiency. *Journal of Pediatrics* 130:205-9, 1997
129. Simon D, Rosilio M, Maisin A, et al: Post graft development of short children treated with growth hormone before kidney graft. *Pediatric Nephrology* 13:723-9, 1999

130. Hokken-Koelega A, Mulder P, De Jong R, et al: Long-term effects of growth hormone treatment on growth and puberty in patients with chronic renal insufficiency. *Pediatric Nephrology* 14:701-6, 2000
131. Mehls O, Berg U, Broyer M, et al: Chronic renal failure and growth hormone treatment: Review of the literature and experience in KIGS, in Ranke MB, Wilton P (eds): *Growth hormone therapy in KIGS-10 years experience* (ed 11th). Heidelberg, Germany, Barth, 1999, pp 327-40
132. Berard E, Crosnier H, Six-Beneton A, et al: Recombinant human growth hormone treatment of children on hemodialysis. *French Society of Pediatric Nephrology. Pediatric Nephrology* 12:304-10, 1998
133. Ettenger RB, Blifeld C, Prince H, et al: The pediatric nephrologist's dilemma: growth after renal transplantation and its interaction with age as a possible immunologic variable. *Journal of Pediatrics* 111:1022-5, 1987
134. Pennisi AJ, Costin G, Phillips LS, et al: Somatomedin and growth hormone studies in pediatric renal allograft recipients who receive daily prednisone. *American Journal of Diseases of Children* 133:950-4, 1979
135. Blodget FM, Burgin L, Iezzoni D, et al: Effects of prolonged cortisone therapy on the statural growth, skeletal maturation, and metabolic status of children. *New England Journal of Medicine* 254:636-41, 1956
136. Dearden LC, Mosier HD, Jr., Brundage M, et al: The effects of different steroids on costal and epiphyseal cartilage of fetal and adult rats. *Cell & Tissue Research* 246:401-12, 1986
137. Chyun YS, Kream BE, Raisz LG: Cortisol decreases bone formation by inhibiting periosteal cell proliferation. *Endocrinology* 114:477-80, 1984
138. Wehrenberg WB, Bergman PJ, Stagg L, et al: Glucocorticoid inhibition of growth in rats: partial reversal with somatostatin antibodies. *Endocrinology* 127:2705-8, 1990
139. Robinson IC, Gabrielsson B, Klaus G, et al: Glucocorticoids and growth problems. *Acta Paediatrica. Supplement* 411:81-6, 1995
140. Saenger P, Wiedemann E, Schwartz E, et al: Somatomedin and growth after renal transplantation. *Pediatric Research* 8:163-9, 1974
141. Schaefer F, Hamill G, Stanhope R, et al: Pulsatile growth hormone secretion in peripubertal patients with chronic renal failure. Cooperative Study Group on Pubertal Development in Chronic Renal Failure. *Journal of Pediatrics* 119:568-77, 1991
142. Shapiro R: Tacrolimus in pediatric renal transplantation: a review. *Pediatric Transplantation* 2:270-6, 1998
143. Ellis D: Growth and renal function after steroid-free tacrolimus-based immunosuppression in children with renal transplants. *Pediatric Nephrology* 14:689-94, 2000
144. Klare B, Strom TM, Hahn H, et al: Remarkable long-term prognosis and excellent growth in kidney-transplant children under cyclosporine monotherapy. *Transplantation Proceedings* 23:1013-7, 1991
145. Kovarik J, Mentser M, Broyer M, et al: Disposition of basiliximab, a chimeric IL-2 receptor (CD25) monoclonal antibody, in pediatric renal transplant patients (abstr). *Pediatric Transplantation* 2:91, 1998

146. Kovarik JM, Melter M, Dunn S, et al: Disposition of Basiliximab, an IL-2 receptor (CD25) chimeric monoclonal antibody, in pediatric liver transplant patients (abstr). *Transplantation* 67:S124, 1999
147. Nashan B, Moore R, Amlot P, et al: Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. *Lancet* 350:1193-8, 1997
148. Nashan B, Light S, Hardie IR, et al: Reduction of acute renal allograft rejection by daclizumab. Daclizumab Double Therapy Study Group. *Transplantation* 67:110-5, 1999
149. Kirk AD, Burkly LC, Batty DS, et al: Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates. *Nature Medicine* 5:686-93, 1999
150. Chandraker A, Russell ME, Glysing-Jensen T, et al: T-cell costimulatory blockade in experimental chronic cardiac allograft rejection: effects of cyclosporine and donor antigen. *Transplantation* 63:1053-8, 1997
151. Denton MD, Reul RM, Dharnidharka VR, et al: Central role for CD40/CD40 ligand (CD154) interactions in transplant rejection. *Pediatric Transplantation* 2:6-15, 1998
152. Sarwal MM, Yorgin PD, Alexander S, et al: Promising early outcomes with a novel, complete steroid avoidance immunosuppression protocol in pediatric renal transplantation. *Transplantation* 72:13-21, 2001
153. Benfield MR, Symons JM, Bynon S, et al: Mycophenolate mofetil in pediatric renal transplantation. *Pediatric Transplantation* 3:33-7, 1999
154. Neu AM, Benfield M: What is the role for mycophenolate mofetil in pediatric renal transplantation? *Pediatric Transplantation* 3:83-7, 1999
155. Ghio L, Tarantino A, Edefonti A, et al: Advantages of cyclosporine as sole immunosuppressive agent in children with transplanted kidneys. *Transplantation* 54:834-8, 1992
156. Ingulli E, Sharma V, Singh A, et al: Steroid withdrawal, rejection and the mixed lymphocyte reaction in children after renal transplantation. *Kidney International - Supplement* 43:S36-9, 1993
157. Jabs K, Sullivan EK, Avner ED, et al: Alternate-day steroid dosing improves growth without adversely affecting graft survival or long-term graft function. A report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation* 61:31-6, 1996
158. Broyer M, Guest G, Gagnadoux MF: Growth rate in children receiving alternate-day corticosteroid treatment after kidney transplantation. *Journal of Pediatrics* 120:721-5, 1992
159. Kaiser BA, Polinsky MS, Palmer JA, et al: Growth after conversion to alternate-day corticosteroids in children with renal transplants: a single-center study. *Pediatric Nephrology* 8:320-5, 1994
160. Tejani A, Cortes L, Sullivan EK: A longitudinal study of the natural history of growth post-transplantation. *Kidney International - Supplement* 53:103-8, 1996
161. Pasqualini T, Ferraris JR, Jasper H, et al: Differences in anthropometric parameters and the IFG-I-IGFBP3 axis between liver and renal transplant children. *Transplantation* 70:472-6, 2000

162. Sarna S, Laine J, Sipila I, et al: Differences in linear growth and cortisol production between liver and renal transplant recipients on similar immunosuppression. *Transplantation* 60:656-61, 1995
163. Chand DH, Southerland SM, Cunningham RJ, 3rd: Tacrolimus: the good, the bad, and the ugly. *Pediatric Transplantation* 5:32-6, 2001
164. Kelly DA: Posttransplant growth failure in children. *Liver Transplantation & Surgery* 3:S32-9, 1997
165. Everson GT, Trouillot T, Wachs M, et al: Early steroid withdrawal in liver transplantation is safe and beneficial. *Liver Transplantation & Surgery* 5:S48-57, 1999
166. Maes M, Sokal E, Otte JB: Growth factors in children with end-stage liver disease before and after liver transplantation: a review. *Pediatric Transplantation* 1:171-5, 1997
167. Group SR: Studies of Pediatric Liver Transplantation (SPLIT): year 2000 outcomes. *Transplantation* 72:463-76, 2001
168. McDiarmid SV, Gornbein JA, DeSilva PJ, et al: Factors affecting growth after pediatric liver transplantation. *Transplantation* 67:404-11, 1999
169. Andrews WS, Wanek E, Fyock B, et al: Pediatric liver transplantation: a 3-year experience. *Journal of Pediatric Surgery* 24:77-82, 1989
170. Beath SV, Brook GD, Kelly DA, et al: Successful liver transplantation in babies under 1 year. *Bmj* 307:825-8, 1993
171. Codoner-Franch P, Bernard O, Alvarez F: Long-term follow-up of growth in height after successful liver transplantation. *Journal of Pediatrics* 124:368-73, 1994
172. Moukarzel AA, Najm I, Vargas J, et al: Prediction of long-term linear growth following liver transplantation. *Transplantation Proceedings* 22:1558-9, 1990
173. Viner RM, Forton JT, Cole TJ, et al: Growth of long-term survivors of liver transplantation. *Archives of Disease in Childhood* 80:235-40, 1999
174. Asonuma K, Inomata Y, Uemoto S, et al: Growth and quality of life after living-related liver transplantation in children. *Pediatric Transplantation* 2:64-9, 1998
175. Sarna S, Sipila I, Ronnholm K, et al: Recombinant human growth hormone improves growth in children receiving glucocorticoid treatment after liver transplantation. *Journal of Clinical Endocrinology & Metabolism* 81:1476-82, 1996
176. Sarna S, Sipila I, Vihervuori E, et al: Growth delay after liver transplantation in childhood: studies of underlying mechanisms. *Pediatric Research* 38:366-72, 1995
177. Dunn SP, Falkenstein K, Lawrence JP, et al: Monotherapy with cyclosporine for chronic immunosuppression in pediatric liver transplant recipients. *Transplantation* 57:544-7, 1994
178. McDiarmid SV, Farmer DA, Goldstein LI, et al: A randomized prospective trial of steroid withdrawal after liver transplantation. *Transplantation* 60:1443-50, 1995
179. Gonwa TA, Mai ML, Melton LB, et al: End stage renal disease (ESRD) following orthotopic liver transplantation (OLT) utilizing calcineurin inhibitor (CNI) based immunotherapy: risk of development and treatment, *Transplant 2001: The Joint American Transplant Meeting*. Chicago, IL, The American Society of Transplantation (AST), 2001



180. Baum D, Bernstein D, Starnes VA, et al: Pediatric heart transplantation at Stanford: results of a 15-year experience. *Pediatrics* 88:203-14, 1991
181. de Broux E, Huot CH, Chartrand S, et al: Growth after pediatric heart transplantation. *Transplantation Proceedings* 33:1735-7, 2001
182. Au J, Gregory JW, Colquhoun IW, et al: Paediatric cardiac transplantation with steroid-sparing maintenance immunosuppression. *Archives of Disease in Childhood* 67:1262-6, 1992
183. Chinnock R, Baum M: Somatic growth in infant heart transplant recipients. *Pediatric Transplantation* 2:30-4, 1998
184. Ferrazzi P, Fiocchi R, Gamba A, et al: Pediatric heart transplantation without chronic maintenance steroids. *Journal of Heart & Lung Transplantation* 12:S241-5, 1993
185. Hirsch R, Huddleston CB, Mendeloff EN, et al: Infant and donor organ growth after heart transplantation in neonates with hypoplastic left heart syndrome. *Journal of Heart & Lung Transplantation* 15:1093-100, 1996
186. Parisi F, Squitieri C, Carotti A, et al: Ten-year follow-up after pediatric transplantation. *Journal of Heart & Lung Transplantation* 18:275-7, 1999
187. Hobbs S, Sexson S: Cognitive development and learning in the pediatric organ transplant recipient. *Journal of Learning Disabilities* 26:104-13, 1993
188. Stewart SM, Kennard BD, Waller DA, et al: Cognitive function in children who receive organ transplantation. *Health Psychology* 13:3-13, 1994
189. Frauman AC, Myers JT: Cognitive, psychosocial, and physical development in infants and children with end-stage renal disease. *Advances in Renal Replacement Therapy* 1:49-54, 1994
190. Warady BA, Belden B, Kohaut E: Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. *Pediatric Nephrology* 13:759-65, 1999
191. Geary DF, Haka-Ikse K: Neurodevelopmental progress of young children with chronic renal disease. *Pediatrics* 84:68-72, 1989
192. Warady BA, Kriley M, Lovell H, et al: Growth and development of infants with end-stage renal disease receiving long-term peritoneal dialysis. *Journal of Pediatrics* 112:714-9, 1988
193. Brouhard BH, Donaldson LA, Lawry KW, et al: Cognitive functioning in children on dialysis and post-transplantation. *Pediatric Transplantation* 4:261-7, 2000
194. Fennell RS, Rasbury WC, Fennell EB, et al: Effects of kidney transplantation on cognitive performance in a pediatric population. *Pediatrics* 74:273-8, 1984
195. Fennell RS, Fennell EB, Carter RL, et al: Association between renal function and cognition in childhood chronic renal failure. *Pediatric Nephrology* 4:16-20, 1990
196. Crittenden MR, Holliday MA, Piel CF, et al: Intellectual development of children with renal insufficiency and end stage disease. *International Journal of Pediatric Nephrology* 6:275-80, 1985

197. Rasbury WC, Fennell RS, 3rd, Fennell EB, et al: Cognitive functioning in children with end stage renal disease pre- and post-dialysis session. *International Journal of Pediatric Nephrology* 7:45-50, 1986
198. Fennell RS, Fennell EB, Carter RL, et al: A longitudinal study of the cognitive function of children with renal failure. *Pediatric Nephrology* 4:11-5, 1990
199. Rasbury WC, Fennell RS, 3rd, Morris MK: Cognitive functioning of children with end-stage renal disease before and after successful transplantation. *Journal of Pediatrics* 102:589-92, 1983
200. Davis ID, Chang PN, Nevins TE: Successful renal transplantation accelerates development in young uremic children. *Pediatrics* 86:594-600, 1990
201. So SK, Chang PN, Najarian JS, et al: Growth and development in infants after renal transplantation. *Journal of Pediatrics* 110:343-50, 1987
202. McGraw ME, Haka-Ikse K: Neurologic-developmental sequelae of chronic renal failure in infancy. *Journal of Pediatrics* 106:579-83, 1985
203. Nevins TE: Transplantation in infants less than 1 year of age. *Pediatric Nephrology* 1:154-6, 1987
204. Wolff G, Ehrich JH, Offner G, et al: Psychosocial and intellectual development in 12 patients with infantile nephropathic cystinosis. *Acta Paediatrica Scandinavica* 71:1007-11, 1982
205. Fukunishi I, Honda M: School adjustment of children with end-stage renal disease. *Pediatric Nephrology* 9:553-7, 1995
206. Fennell RS, 3rd, Fennell EB, Carter RL, et al: Effects of changing therapy on cognition of children in renal failure. *Child Nephrology & Urology* 9:211-9, 1988
207. Broyer M, Chantler C, Donckerwolcke R, et al: The paediatric registry of the European Dialysis and Transplant Association: 20 years' experience. *Pediatric Nephrology* 7:758-68, 1993
208. Fine RN, Malekzadeh MH, Pennisi AJ, et al: Long-term results of renal transplantation in children. *Pediatrics* 61:641-50, 1978
209. Morel P, Almond PS, Matas AJ, et al: Long-term quality of life after kidney transplantation in childhood. *Transplantation* 52:47-53, 1991
210. Lewis DJ, McIver M, Scott DF, et al: Dialysis and renal transplantation in children: long term and recent experience. *Journal of Paediatrics & Child Health* 26:276-9, 1990
211. Hodson EM, Knight JF, Sheil AG, et al: End-stage renal failure in children: 16 years' experience at one Australian centre. *Medical Journal of Australia* 152:245-50, 1990
212. Stewart SM, Hildebeitel C, Nici J, et al: Neuropsychological outcome of pediatric liver transplantation. *Pediatrics* 87:367-76, 1991
213. Wayman K: Neurodevelopmental Status of Young Children with End-Stage Liver Disease. *Liver Bulletin*, a quarterly publication of the Liver Transplant Program at Stanford University 2 (Summer), 1997
214. Hopkins J, Roizen NJ, Lindsay D, et al: Development and treatment of infants with biliary atresia. *Children's Health Care* 24:97-106, 1995

215. Hall WA, Martinez AJ: Neuropathology of pediatric liver transplantation. *Pediatric Neuroscience* 15:269-75, 1989
216. Fletcher JM, Couper R, Moore D, et al: Liver transplantation for citrullinaemia improves intellectual function. *Journal of Inherited Metabolic Disease* 22:581-6, 1999
217. van Mourik ID, Beath SV, Brook GA, et al: Long-term nutritional and neurodevelopmental outcome of liver transplantation in infants aged less than 12 months. *J Pediatr Gastroenterol Nutr* 30:269-75., 2000
218. Newburger JW, Silbert AR, Buckley LP, et al: Cognitive function and age at repair of transposition of the great arteries in children. *New England Journal of Medicine* 310:1495-9, 1984
219. Sokol RJ, Guggenheim MA, Heubi JE, et al: Frequency and clinical progression of the vitamin E deficiency neurologic disorder in children with prolonged neonatal cholestasis. *American Journal of Diseases of Children* 139:1211-5, 1985
220. Sokol RJ: Vitamin E deficiency and neurologic disease. *Annual Review of Nutrition* 8:351-73, 1988
221. Busuttil AA, Goss JA, Seu P, et al: The role of orthotopic liver transplantation in the treatment of ornithine transcarbamylase deficiency. *Liver Transplantation & Surgery* 4:350-4, 1998
222. Butterworth RF: Effects of hyperammonaemia on brain function. *Journal of Inherited Metabolic Disease* 21:6-20, 1998
223. Buschle KN, O'Connor A, Ryckman FC, et al: Hearing impairment in children after liver transplantation, 14th Annual Meeting of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), Gastroenterology, Hepatology & Nutrition, Children's Hospital Medical Center, Cincinnati, Ohio, 2001
224. Wray J, Pot-Mees C, Zeitlin H, et al: Cognitive function and behavioural status in paediatric heart and heart-lung transplant recipients: the Harefield experience. *Bmj* 309:837-41, 1994
225. Baum MF, Freier MC, Allen J, et al: Neurodevelopmental impact of transplantation: infant., 3rd Loma Linda International Conference for Pediatric Heart and Lung Transplantation. Rancho Mirage, CA, 1997
226. Wray J, Yacoub M: Psychosocial evaluation of children after open heart surgery versus cardiac transplantation, in Yacoub M, Pepper JR (eds): *Annual of cardiac surgery* 90-91. London, Current Science Publications, 1991, pp 50-5
227. Baum MF, Cutler DC, Fricker FJ, et al: Session VII: Physiologic and psychological growth and development in pediatric heart transplant recipients. *Journal of Heart & Lung Transplantation* 10:848-55, 1991
228. Backer CL, Zales VR, Harrison HL, et al: Intermediate term results of infant orthotopic cardiac transplantation from two centers. *Journal of Thoracic & Cardiovascular Surgery* 101:826-32, 1991
229. Dunn JM, Cavarocchi NC, Balsara RK, et al: Pediatric heart transplantation at St. Christopher's Hospital for Children. *Journal of Heart Transplantation* 6:334-42, 1987
230. O'Dougherty M, Wright FS, Garmezny N, et al: Later competence and adaptation in infants who survive severe heart defects. *Child Development* 54:1129-42, 1983

231. Rappaport LA, Wypij D, Bellinger DC, et al: Relation of seizures after cardiac surgery in early infancy to neurodevelopmental outcome. Boston Circulatory Arrest Study Group. *Circulation* 97:773-9, 1998
232. Haneda K, Itoh T, Togo T, et al: Effects of cardiac surgery on intellectual function in infants and children. *Cardiovascular Surgery* 4:303-7, 1996
233. Clarkson PM, MacArthur BA, Barratt-Boyes BG, et al: Developmental progress after cardiac surgery in infancy using hypothermia and circulatory arrest. *Circulation* 62:855-61, 1980
234. Hovels-Gurich HH, Seghaye MC, Dabritz S, et al: Cognitive and motor development in preschool and school-aged children after neonatal arterial switch operation. *Journal of Thoracic & Cardiovascular Surgery* 114:578-85, 1997
235. Wells FC, Coghill S, Caplan HL, et al: Duration of circulatory arrest does influence the psychological development of children after cardiac operation in early life. *Journal of Thoracic & Cardiovascular Surgery* 86:823-31, 1983
236. Kern JH, Hinton VJ, Nereo NE, et al: Early developmental outcome after the Norwood procedure for hypoplastic left heart syndrome. *Pediatrics* 102:1148-52, 1998
237. Mahle WT, Wernovsky G, Gerdes M, et al: Neurodevelopmental outcome of school-age children with hypoplastic left heart syndrome. *Circulation Suppl* 1:1785, 1998
238. Rogers BT, Msall ME, Buck GM, et al: Neurodevelopmental outcome of infants with hypoplastic left heart syndrome. *Journal of Pediatrics* 126:496-8, 1995
239. Mahle WT, Clancy RR, Moss EM, et al: Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. *Pediatrics* 105:1082-9, 2000
240. Silbert A, Wolff PH, Mayer B, et al: Cyanotic heart disease and psychological development. *Pediatrics* 43:192-200, 1969
241. Blackwood MJ, Haka-Ikse K, Steward DJ: Developmental outcome in children undergoing surgery with profound hypothermia. *Anesthesiology* 65:437-40, 1986
242. Lawrence KS, Fricker FJ: Pediatric heart transplantation: quality of life. *Journal of Heart Transplantation* 6:329-33, 1987
243. Hangard-Patton L, Lawrence KS: Psychosocial Implications of Heart Transplantation, in Tejani A, Harmon W, Fine R (eds): *Pediatric Solid Organ Transplantation* (ed 1st edition). Copenhagen, Munksgaard, 2000, pp 440-3
244. Wright M, Nolan T: Impact of cyanotic heart disease on school performance. *Archives of Disease in Childhood* 71:64-70, 1994
245. Aram DM, Ekelman BL, Ben-Shachar G, et al: Intelligence and hypoxemia in children with congenital heart disease: fact or artifact? *Journal of the American College of Cardiology* 6:889-93, 1985
246. O'Dougherty M, Wright FS, Loewenson RB, et al: Cerebral dysfunction after chronic hypoxia in children. *Neurology* 35:42-6, 1985
247. Linde LM, Rasof B, Dunn OJ: Mental development in congenital heart disease. *Journal of Pediatrics* 71:198-203, 1967

248. Linde LM, Rasof B, Dunn OJ: Longitudinal studies of intellectual and behavioral development in children with congenital heart disease. *Acta Paediatrica Scandinavica* 59:169-76, 1970
249. Hesz N, Clark EB: Cognitive development in transposition of the great vessels. *Archives of Disease in Childhood* 63:198-200, 1988
250. Ferry PC: Neurologic sequelae of open-heart surgery in children. An 'irritating question'. *American Journal of Diseases of Children* 144:369-73, 1990
251. Shaben TR: Psychosocial issues in kidney-transplanted children and adolescents: literature review. *Anna Journal* 20:663-8, 1993
252. Davis ID: Pediatric renal transplantation: back to school issues. *Transplantation Proceedings* 31:61S-62S, 1999
253. Bradford R: Children's psychological health status--the impact of liver transplantation: a review. *Journal of the Royal Society of Medicine* 84:550-3, 1991
254. Burdelski M, Nolkemper D, Ganschow R, et al: Liver transplantation in children: long-term outcome and quality of life. *European Journal of Pediatrics* 158:S34-42, 1999
255. Hanton LB: Caring for children awaiting heart transplantation: psychosocial implications. *Pediatric Nursing* 24:214-8, 1998
256. Riley CM: Thoughts about kidney transplantation in children. *Journal of Pediatrics* 65:797, 1964
257. Fine RN, Korsch BM, Stiles Q, et al: Renal homotransplantation in children. *Journal of Pediatrics* 76:347-57, 1970
258. Bernstein DM: After transplantation - The child's emotional reactions. *American Journal of Psychiatry* 127:109, 1971
259. Kahn AU, Herndon CN, Ahmadian SY: Social and emotional adaptation of children with transplant kidneys and chronic hemodialysis. *American Journal of Psychiatry* 127:114, 1971
260. Lilly JR, Giles G, Hurwitz R, et al: Renal homotransplantation in pediatric patients. *Pediatrics* 47:548-57, 1971
261. Najarian JS, Simmons RL, Tallent MB, et al: Renal transplantation in infants and children. *Annals of Surgery* 174:583-600, 1971
262. Tisza VB, Dorsett P, Morse J: Psychological implications of renal transplantation. *Journal of the American Academy of Child Psychiatry* 15:709-20, 1976
263. Levi M: The psychological dilemmas confronting the adolescent transplant patient. *Nephrology Nurse* 4:42-5, 1982
264. Korsch BM, Negrete VF, Gardner JE, et al: Kidney transplantation in children: psychosocial follow-up study on child and family. *Journal of Pediatrics* 83:399-408, 1973
265. Simmons RG, Klein SD, Immons RL: *Gift of life; The social and psychological impact of organ transplantation*. New York, Wiley, 1977
266. Reynolds JM, Morton MJ, Garralda ME, et al: Psychosocial adjustment of adult survivors of a paediatric dialysis and transplant programme. *Archives of Disease in Childhood* 68:104-10, 1993

267. Donckerwolcke RA: Long-term complications of renal transplantation. *Child Nephrology & Urology* 11:179-84, 1991
268. Beck AL, Nethercut GE, Crittenden MR, et al: Visibility of handicap, self-concept, and social maturity among young adult survivors of end-stage renal disease. *Journal of Developmental & Behavioral Pediatrics* 7:93-6, 1986
269. Lee HM, Mendez-Picon G, Posner MP: The status of rehabilitation, morbidity, and mortality of long-term survivors of pediatric kidney transplants. *Transplantation Proceedings* 21:1989-91, 1989
270. Frauman AC, Gilman CM, Carlson JR: Rehabilitation and social and adaptive development of young renal transplant recipients. *Anna Journal* 23:467-71, 484; discussion 472-3, 1996
271. Fukunishi I, Kudo H: Psychiatric problems of pediatric end-stage renal failure. *General Hospital Psychiatry* 17:32-6, 1995
272. Brownbridge G, Fielding DM: Psychosocial adjustment to end-stage renal failure: comparing haemodialysis, continuous ambulatory peritoneal dialysis and transplantation. *Pediatric Nephrology* 5:612-6, 1991
273. Brem AS, Brem FS, McGrath M, et al: Psychosocial characteristics and coping skills in children maintained on chronic dialysis. *Pediatric Nephrology* 2:460-5, 1988
274. Brouhard BH, Lawry K, Davis I, et al: *Journal of Investigative Medicine* 45:309A, 1997
275. Karrfelt HM, Berg UB, Lindblad FI: Renal transplantation in children: psychological and donation-related aspects from the parental perspective. *Pediatric Transplantation* 4:305-12, 2000
276. Eisenhauer GL, Arnold WC, Livingston RL: Identifying psychiatric disorders in children with renal disease. *South Med J* 81:572-6, 1988
277. Garralda ME, Jameson RA, Reynolds JM, et al: Psychiatric adjustment in children with chronic renal failure. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 29:79-90, 1988
278. Morton MJ, Reynolds JM, Garralda ME, et al: Psychiatric adjustment in end-stage renal disease: a follow up study of former paediatric patients. *Journal of Psychosomatic Research* 38:293-303, 1994
279. Douglas JE, Hulson B, Trompeter RS: Psycho-social outcome of parents and young children after renal transplantation. *Child: Care, Health & Development* 24:73-83, 1998
280. Korsch BM, Fine RN, Negrete VF: Noncompliance in children with renal transplants. *Pediatrics* 61:872-6, 1978
281. Beck DE, Fennell RS, Yost RL, et al: Evaluation of an educational program on compliance with medication regimens in pediatric patients with renal transplants. *Journal of Pediatrics* 96:1094-7, 1980
282. Fine RN: The adolescent with end-stage renal disease. *American Journal of Kidney Diseases* 6:81-5, 1985

283. Fine RN, Salusky IB, Ettenger RB: The therapeutic approach to the infant, child, and adolescent with end-stage renal disease. *Pediatric Clinics of North America* 34:789-801, 1987
284. Fine RN, Tejani A: Renal transplantation in children. *Nephron* 47:81-6, 1987
285. Offner G, Aschendorff C, Hoyer PF, et al: End stage renal failure: 14 years' experience of dialysis and renal transplantation. *Archives of Disease in Childhood* 63:120-6, 1988
286. Reznik VM, Durham BL, Lyons Jones K, et al: Changes in facial appearance during cyclosporin treatment. *Lancet* 1:1405-7, 1987
287. Reynolds JM, Garralda ME, Postlethwaite RJ, et al: Changes in psychosocial adjustment after renal transplantation. *Archives of Disease in Childhood* 66:508-13, 1991
288. Ettenger RB, Rosenthal JT, Marik J, et al: Long-term results with cyclosporine immune suppression in pediatric cadaver renal transplantation. *Transplantation Proceedings* 23:1011-2, 1991
289. Conrad P: The meaning of medications: Another look at compliance. *Social Science & Medicine* 20:29-37, 1985
290. Pidgeon V: Compliance with chronic illness regimens: School-aged children and adolescents. *Journal of Pediatric Nursing* 4:36-47, 1989
291. Nekolaichuk CL: Learning to live with uncertainty: The role of hope and medication compliance in chronic illness. Edmonton, Canada, University of Alberta, 1990
292. Mongeau JG, Clermont MJ, Robitaille P, et al: Study of psychosocial parameters related to the survival rate of renal transplantation in children. *Pediatric Nephrology* 11:542-6, 1997
293. Henning P, Tomlinson L, Rigden SPA, et al: Long-term outcome of treatment of end stage renal failure. *Archives of Disease in Childhood* 63:35-40, 1988
294. Melzer SM, Leadbeater B, Reisman L, et al: Characteristics of social networks in adolescents with end stage renal disease treated with renal transplantation. *Journal of Adolescent Health Care* 10:308-12, 1989
295. Pozanski EO, Miller E, Salguero C, et al: Quality of life for long-term survivors of end stage renal disease. *Journal of the American Medical Association* 239:2343-7, 1978
296. Potter D, Feduska N, Belzer J, et al: Twenty years of renal transplantation in children. *Pediatrics* 77:465-70, 1986
297. So SKS, Mauer SM, Nevins TE, et al: Current results in pediatric renal transplantation of transplant patients. *Proceedings of the Dialysis Transplant Forum*:43-6, 1986
298. Wallander JL, Varni JW: Effects of pediatric chronic physical disorders on child and family adjustment. *J Child Psychol Psychiatr Allied Discipl* 39:29-46, 1998
299. Silver EJ, Stein RE, Dadds MR: Moderating effects of family structure on the relationship between physical and mental health in urban children with chronic illness. *Journal of Pediatric Psychology* 21:43-56, 1996
300. Kovacs M, Kass RE, Schnell TM, et al: Family functioning and metabolic control of school-aged children with IDDM: the role of family cohesion and conflict. *Diabetes Care* 12:409-14, 1989

301. Manne SL, Lesanics D, Meyers P, et al: Predictors of depressive symptomatology among parents of newly diagnosed children with cancer. *Journal of Pediatric Psychology* 20:491-510, 1995
302. Soliday E, Kool E, Lande MB: Family environment, child behavior, and medical indicators in children with kidney disease. *Child Psychiatry & Human Development* 31:279-95, 2001
303. Crittenden MR, Holaday B: Psychosocial factors associated with physical growth and behavior adaptations of children with renal dysfunction. *Percept Mot Skills* 62:437-8, 1986
304. Malekzadeh MH, Pennisi AJ, Uittenbogaart CH, et al: Current issues in pediatric renal transplantation. *Pediatric Clinics of North America* 23:857-72, 1976
305. Muslin HL: Psychiatric aspects of renal failure. *American Journal of Psychiatry* 127:1185-8, 1971
306. Penn I, Bunch D, Olenik D, et al: Psychiatric experience with patients receiving renal nad hepatic transplants. *Seminars in Psychiatry* 3:133-44, 1971
307. Burgess DB, Martin HP, Lilly JR: The developmental status of children undergoing the Kasai procedure for biliary atresia. *Pediatrics* 70:624-9, 1982
308. Quiros-Tejeira RE, Ament ME, Heyman MB, et al: Does liver transplantation affect growth pattern in Alagille syndrome? *Liver Transplantation* 6:582-7, 2000
309. Alagille D: Alagille syndrome today. *Clinical & Investigative Medicine - Medecine Clinique et Experimentale* 19:325-30, 1996
310. Tornqvist J, Van Broeck N, Finkenauer C, et al: Long-term psychosocial adjustment following pediatric liver transplantation. *Pediatric Transplantation* 3:115-25, 1999
311. Schwering KL, Febo-Mandl F, Finkenauer C, et al: Psychological and social adjustment after pediatric liver transplantation as a function of age at surgery and of time elapsed since transplantation. *Pediatric Transplantation* 1:138-45, 1997
312. Apajasalo M, Rautonen J, Sintonen H, et al: Health-related quality of life after organ transplantation in childhood. *Pediatr Transplantation* 1:130-7, 1997
313. Midgley DE, Bradlee TA, Donohoe C, et al: Health-related quality of life in long-term survivors of pediatric liver transplantation. *Liver Transplantation* 6:333-9, 2000
314. Zitelli BJ, Gartner JC, Malatack JJ, et al: Pediatric liver transplantation: patient evaluation and selection, infectious complications, and life-style after transplantation. *Transplantation Proceedings* 19:3309-16, 1987
315. Zitelli B, Miller J, Gartner C, et al: Changes in life-style after liver transplantation. *Pediatrics* 82:173-80, 1988
316. Colonna JO, 2nd, Brems JJ, Hiatt JR, et al: The quality of survival after liver transplantation. *Transplantation Proceedings* 20:594-7, 1988
317. Stone RD, Beasley PJ, Treacy SJ, et al: Children and families can achieve normal psychological adjustment and a good quality of life following pediatric liver transplantation: a long-term study. *Transplantation Proceedings* 29:1571-2, 1997



318. Gold LM, Kirkpatrick BS, Fricker FJ, et al: Psychosocial issues in pediatric organ transplantation: the parents' perspective. *Pediatrics* 77:738-44, 1986
319. Weichler N, Hakos L: Information needs of primary caregivers in pediatric liver transplantation. *Transplantation Proceedings* 21:3562, 1989
320. Boutsen C, Gilbert S: Cost of liver transplantation: financing and social aspects. *Transplantation Proceedings* 19:3363-6, 1987
321. Serrano JA, Verougstraete C, Ghislain T: Psychological evaluation and support of pediatric patients and their parents. *Transplantation Proceedings* 19:3358-62, 1987
322. Bradford R, Tomlinson L: Psychological guidelines in the management of paediatric organ transplantation. *Archives of Disease in Childhood* 65:1000-3, 1990
323. Lawrence KS, Fricker FJ, Cardillo S: Pediatric Heart Transplantation: the recipient's perspective., in Walter PJ (ed): *Quality of Life after Open Heart Surgery*. The Hague, Kluwer Academic Publishers, 1992, pp 363-70
324. Uzark KC, Sauer SN, Lawrence KS, et al: The psychosocial impact of pediatric heart transplantation. *Journal of Heart & Lung Transplantation* 11:1160-7, 1992
325. Shapiro PA, Kornfeld DS: Psychiatric outcome of heart transplantation. *General Hospital Psychiatry* 11:352-7, 1989
326. Tebbi CK, Cummings KM, Zevon MA, et al: Compliance of pediatric and adolescent cancer patients. *Cancer* 58:1179-84, 1986
327. Smith SD, Rosen D, Trueworthy RC, et al: A reliable method for evaluating drug compliance in children with cancer. *Cancer* 43:169-73, 1979
328. Collins EG, White-Williams C, Jalowiec A: Spouse stressors while awaiting heart transplantation. *Heart & Lung* 25:4-13, 1996
329. Nolan MT, Cupples SA, Brown MM, et al: Perceived stress and coping strategies among families of cardiac transplant candidates during the organ waiting period. *Heart & Lung* 21:540-7, 1992
330. Porter RR, Bailey C, Bennett GM, et al: Stress during the waiting period: a review of pretransplantation fears. *Critical Care Nursing Quarterly* 13:25-31, 1991
331. Lazarus RS, Folkman S: *Stress, appraisal and coping*. New York, Springer Publishing, 1980
332. DeMaso DR, Campis LK, Wypij D, et al: The impact of maternal perceptions and medical severity on the adjustment of children with congenital heart disease. *Journal of Pediatric Psychology* 16:137-49, 1991
333. Suddaby EC, Flattery MP, Luna M: Stress and coping among parents of children awaiting cardiac transplantation. *Journal of Transplant Coordination* 7:36-40, 1997
334. Serrano-Ikkos E, Lask B, Whitehead B: Psychosocial morbidity in children, and their families, awaiting heart or heart-lung transplantation. *Journal of Psychosomatic Research* 42:253-60, 1997
335. Rodrique JR, Greene AC, Boggs SR: Current status of psychological research in organ transplantation. *Journal of Clinical Psychology in Medical Settings* 1:41-70, 1994

336. Uzark K, Crowley D: Family stress after pediatric heart transplantation. Progress in Cardiovascular Nursing 4:23-7, 1989