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Dr.K.Nedunchelian Editor-in-Chief
Dr. S. Thangavelu Executive Editor

CONTENTS
FROM THE EDITOR'S DESK .......................................................... 109

TOPIC OF INTEREST - ORGAN TRANSPLANTATION ...
Medico legal aspects of cadaveric organ donation and transplantation in India .................................................. 112
  - Chavda M, Cherian A, Abraham BK, Ramakrishnan N

Renal transplantation in children .............................................. 117
  - Anil Vasudevan, Arpana Iyengar, Kishore Phadke

Stem cell transplantation .......................................................... 127
  - Nita Radhakrishnan, Yadav SP, Anupam Sachdeva

Pediatric cardiothoracic transplantation: An update ............... 136
  - Rathinam S, Margabanthu G

Hematopoietic stem cell transplantation in children with special reference to Indian Scenario ......................... 140
  - Shipra Kaicker, Gauri Kapoor

Corneal transplantation in children ......................................... 153
  - Priye Suman Rastogi, Bina John, Sujatha Mohan, Srinivas K Rao

Pediatric liver transplantation with special reference to scenario in India ...................................................... 159
  - Neelam Mohan

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INFECTION DISEASES

Update on rickettsial infections 172
- Arun Shah

NEUROLOGY

Febrile Seizures 177
- Kumaresan G

DERMATOLOGY

Childhood vitiligo - An overview 185
- Jayakar Thomas

PICTURE QUIZ 190

RADIOLOGIST TALKS TO YOU

Disorders of ventral induction and similar conditions - II 191
- Vijayalakshmi G, Elavarasu E, Vijayalakshmi M, Venkatesan MD

CASE STUDY

Stroke after primary varicella zoster virus infection 194
- Jayasree P, Pradeep, Chitra, Anand, Sukumaran TU
Open lip schizencephaly causing childhood hemiparesis 197
- A case report
- Basu M, Saha S, Banerjee T

QUESTION AND ANSWER 200

CLIPPINGS 126, 139, 152, 158, 171, 184, 193

NEWS AND NOTES 176, 199

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This issue is dedicated to the subject of “Human organ and tissue transplantation”, a fascinating field and emerging as treatment option for many end organ failures. Transplantation of human organs and tissues can be life saving and helps to restore vital functions of otherwise incurable patients.

The harvesting of organs for transplantation is dependent on a stringent definition of brain death. World Health Assembly sets guiding principles emphasizing voluntary donation, non-commercialisation, preference of cadaver over living donors and genetically related over non-related donors. The person whether recipient or donor must be the main concern both as patient and human being. The following general principles may be adhered to: i) The organ to be recovered from deceased person for the purpose of transplantation after obtaining consent. ii) Physician certifying death of potential donor should not be directly involved in the organ removal or subsequent transplantation and care of recipient. iii) Cadaver donation is preferable. In case of living donor, genetically related one is better and exception may be bone marrow or other regenerative tissue transplantation. Donors should be explained the risks, benefits and consequences. iv) No organ is removed from living minor, exception being the case of regenerative tissues. v) Human body and tissues can not be the subject of commercial transactions; one should not engage in organ transplantation if there is commercial transactions. vi) Advertising the need for an organ is prohibited. vii) Not to receive any payment that exceeds which is justifiable for the service rendered. viii) Donor organs should be available to patients on the basis of medical need and not on financial or other considerations.

The organ transplantation once was considered almost synonym with renal transplantation. At the present context it is considered as “organ and tissue transplantation” extending to many more organs like liver, heart, pancreas, etc and tissues like cornea as well as other regenerative tissues like hematopoietic stem cell transfusion. Many principles are involved with human organ and tissue transplantation, necessitating very stringent ethical issues to be adhered with legal implications. Even though the indications for various organ transplantation are same universally, the practice of opting for it is very meager in developing countries when compared to developed ones. Reasons may be sociocultural unacceptability, financial constraint, lack of expertise, etc. For the organ transplantation to be successful it is mandatory to follow steps required, starting from donor as well as recipient selection, preparation, surgery and life long immune suppression all of which make the procedure tedious and expensive, leading to failure if not adhered to strictly. In this issue, medicolegal aspects of organ and tissue transplantation in general, information on commonly practiced organ and tissue transplantation are given.

Febrile seizures is one of the commonest neurological problems which creates anxiety among parents and dilemma to pediatricians in diagnosis and to decide on treatment options. The article on “Febrile seizures” will answer many such queries. Some infections are not thought of routinely, among which rickettsial infections is an important one. A brief description of this infection is done in the article “Update on rickettsial infections”.

Under the “Radiologist talks to you” column “Disorders of ventral induction and similar conditions” and under dermatology column, “Vitiligo” are included. Two interesting cases, primary varicella zoster infection presenting as stroke and schizencephaly presenting with seizures and hemiparesis are covered under the column of case studies. As this issue contains most recent update on the subject of interest, we hope it will serve as a useful desk top reference for years to come.

Dr. K. Nedunchelian,
Editor-in-Chief.
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MEDICO LEGAL ASPECTS OF CADAVERIC ORGAN DONATION AND TRANSPLANTATION IN INDIA

*Chavda M  
**Cherian A  
***Abraham BK  
****Ramakrishnan N

Abstract: Organ transplantation is a preferred therapeutic option for patients with end-stage organ failure and has been one of the greatest advances of modern medical science that has resulted in many patients getting a renewed lease of life. Organs can be donated by a living person, after natural death or after “brain death”. After natural death only a few tissues can be donated (like cornea, bone, skin, heart valves and blood vessels) whereas after brain death almost 37 different organs and tissues can be donated including critical solid organs like heart, lungs, liver and kidneys. This article aims to review the medico legal aspects of cadaveric organ donation in India.

Key words: Organ transplantation, Cadaver donor, Transplantation of Human Organ (THO) act, Brain stem death, Transplant coordinator.

Historical background

The technical basis for modern organ transplantation was laid by the French surgeon Alexis Carrel in a series of animal experiments conducted from 1902. Later in 1906 Edward Zirm performed the first corneal transplant. The first living related kidney transplantation was done by Joseph Murray and John Harrison in 1954 in which donor and recipient were identical twins. Subsequently, the first successful cadaveric kidney transplant was performed at Brigham Hospital in Boston in 1962. A year later in 1963, Thomas Starzl from University of Colorado performed the first liver transplantation. Since then, transplantation surgery has been progressive and the first complex heart lung transplantation was performed in 1981. Transplantation Surgery is now recognized by the World Health Organization (WHO) as an established therapeutic option for end stage organ failure of several organs including more recently for pancreas and small intestine.

The first successful cadaver kidney transplant in India was carried out at KEM Hospital, Bombay (now called Mumbai) almost 4 decades ago in 1967. First heart transplantation was performed in All India Institute of Medical Sciences (AIIMS), New Delhi in 1994. Subsequently transplantation in India advanced to first successful multi organ transplantation in 1995 at Apollo Hospitals, Chennai and lung transplantation was successfully done at Madras Medical Mission, Chennai in 1998.

Need for transplantation

The prevalence of chronic kidney disease, in India has been reported between 0.78% and
Although renal transplantation may be a less expensive option than chronic dialysis, only about 5% of all patients with End Stage Renal disease (ESRD) undergo transplantation. Living related donor transplants constitute 30 to 40% of all transplants, while cadaveric transplantation accounts for less than 2% of all transplants. However, in Europe and the United States, cadaver kidney donations contribute 95% and 70% of transplants, respectively. Such a wide disparity between India and Western world is primarily because of myths regarding cadaveric organ donation and lack of understanding about brain death and potential organ donors even amongst the medical community.

Until the 1990s the situation regarding end stage liver disease (ESLD) was not significantly different. More than 200,000 people were dying in India every year from liver failure without any hope of receiving a transplant. However, in the past decade 22 centers in India have performed liver transplants, of which 14 have performed at least one living donor liver transplant (LRLT) procedure. Data from 25 hospitals from Indian transplant registry, during its first phase confirms 14,331 renal transplants (1971-2007) and 291 liver transplants. Interestingly, more than 70% of liver transplants in India is LRLT, suggesting that it has emerged as a more common option than cadaver organ transplantation once again due to lack of cadaver donors.

The transplantation of human organ act

For years, India had the reputation of being a “warehouse for kidneys” and an “organ bazaar” as poverty forced people to sell their kidneys commercially. While organ transplantation remains the best option for some of the patients with end stage organ disease, the inappropriate commercialization involved in the process had to be taken seriously and abolished. With this in view, the Indian Government passed “The Transplantation of Human Organ Act” (THO) in July 1994 which came to effect from February 1995. This act was written along similar lines as the “UK Transplant Act” and legalized the concept of “Brain stem death” or “Brain Death”.

Main features of THO act

1. Definitions
- “Brain stem death” is defined as a state at which the functions of the brain stem have permanently and irreversibly ceased.
- “Transplantation” means the grafting of any human organ from any living person or deceased person to some other living person for therapeutic purposes.
- “Therapeutic purpose” implies systemic treatment of any disease or measures to improve health according to any particular method or modality.
- “Near relative” refers to spouse, son, daughter, father, mother, brother or sister.

2. Brain death certification

The following criteria are required for certification of brain stem death:
- Presence of coma to be confirmed after excluding any reversible causes including but not limited to alcohol intoxication, respiratory depressant drugs and neuromuscular relaxing agents. Cessation of spontaneous respiration which may be confirmed by performing formal apnea tests.
- Absence of pupillary light reflexes
- Absence of Doll’s eye movement
- Absence of corneal reflex
- Absence of motor response in any cranial nerve distribution and lack of response to stimulation of face, limb or trunk
- Absence of gag reflex and cough reflex
• Bilateral absence of eye movements on caloric testing

All these tests are carried out twice, at an interval of at least six hours. The legal time of death is the time at which the second formal testing is completed.

3. Authority for the removal of human organs

In living donors retrieval of organs is legal only from ‘live related donors’ after appropriate informed consent. Human organs may be removed for therapeutic purpose following death in the following situations:

• From any donor who had authorized removal of organ from his body before his death in writing and in presence of two or more witnesses, one of whom should be a near relative.

• When such an authorization is not available, person lawfully in possession of the dead body may give authority.

• In case of unclaimed bodies in hospital or prison, not claimed by any of the near relatives of the deceased person within 48 hours from the time of the death, the person in charge of the management or control of the hospital or prison may give authority.

• In case of brain stem death of a person aged less than 18 yrs, any of the parents of the deceased person may give authority.

• Human organs shall not be retrieved unless brain death is certified by board of medical experts defined as follows:

  • A registered medical practitioner in charge of the hospital in which brain-stem death has occurred

  • An independent registered medical practitioner, from the panel of names approved by the appropriate authority

  • A neurologist or a neurosurgeon from the panel of names approved by the appropriate authority

  • The registered medical practitioner treating the person whose brain-stem death has occurred

4. Regulations for hospitals providing transplantation services

All hospitals offering organ retrieval and transplantation services must be appropriately registered with local health authorities under this act. The exception to this rule are cornea and ear (tympanic membrane or bones) which may be legally retrieved at any place (including home) from dead body of the donor for therapeutic purpose only by registered medical practitioners.

5. Offences and penalties

Commercial dealings related to retrieval and transplantation of human organs is punishable under law with a fine and also minimum imprisonment of two years which may be extended up to seven years. Registered medical practitioners who are found guilty in this process may lose their licensure to practice medicine and removal of name from the Medical Council Register.

Pitfall of THO act

The process of declaring brain death requires two doctors to concur on lack of brainstem functions on two different examinations at least six hours apart. While this ensures accuracy and reliability, it may sometimes delay the process as it may be difficult to find two appropriately authorized specialists.

Sub Clause (3), Clause 9 of Chapter II states: “If any donor authorizes the removal of any of his human organs before his death under sub-section (1) of section 3 for transplantation into the body of such recipient, not being a near relative as is specified by the donor, by reason of affection
or attachment towards the recipient or for any other special reasons, such human organ shall not be removed and transplanted without the prior approval of the Authorization Committee”. As with any other law, the lack of clarity has been misused and created a loophole for transplantation from unrelated donors.

**Current barriers to cadaveric organ transplantation in India**

Broadly, there are three major categories that impede cadaveric organ transplantation in India. Firstly, the lack of awareness in the community about the concept of brain death combined with myths about organ donation. Secondly, the lack of enthusiasm and commitment from medical community in identifying and maintaining brain dead donors and approaching them for potential donation. And, thirdly, the lack of funding (public and private) to facilitate the program with appropriate staffing.

According to a “Public Attitude Survey to Organ Donation”, less than 50 per cent of the populations were willing to consider solid organ donation and the concept of “brain death” was new to most people surveyed. Successful implementation of this program would depend on creating widespread awareness programs to educate the public. It appears that educational level of the family is a key factor in their decision to donate the organs of a deceased relative. Another vital factor is familiarity with the organ donation procedure. In countries with well developed cadaveric donor program it has been observed that prior information about the donation process helps in the decision-making process. Print and electronic media can be vital allies in promoting awareness on organ donation. Introducing these concepts in our high school and college education will also be helpful.

Professional awareness programs are also very important. Educating the hospital medical, nursing and administrative personnel would be a key factor. A review committee appointed by the Delhi High Court has recommended that hospitals and centers with transplantation activity should be advised to have a post of a coordinator in the ICU (who may be a doctor or a senior nursing staff member) independent of the transplant team who receives specialized training and can be a key link between the treating physician, the family of the potential donor and the ORBO (Organ Retrieval and Banking Organization). Such coordinators should possess skills to communicate with the relatives and friends of the patient with a view to explain to them the merits of cadaver donation and possess adequate knowledge to answer queries with regards to the procedures involved and also ensure confidentiality about recipients. While there is a tremendous need for such personnel, there is no structured training currently available.

**Future**

Organ transplantation is well accepted as a therapeutic option for patients with end stage organ disease, but has raised several ethical, legal, moral and social issues in India. There is a need for transparency of law, awareness and education regarding concept of brain death and cadaver organ donation not only amongst lay public but also among medical professionals. The success of the program would rely on support from government, NGOs and media.

In spite of more than a decade of THO act, our transplantation program is still in infancy. THO Act was a great step to streamline the process of organ donation but it needs to be reviewed and appropriately amended. It would be worthwhile to modify THO act to accommodate the following changes:

- Changing its name from ‘Transplantation of Human Organs Act’ to ‘Transplantation of Human Organs and Tissues Act’ which appears more appropriate in the current scenario
• The term ‘near relative’ to be expanded to include grandparents and grand children.

• It should be made mandatory for the treating medical staff and Intensive Care Unit (ICU) staff to request relatives of brain dead patients for organ donation. A centralized record of all patients declared brain dead and their next of kin who made a decision regarding organ donation would help us to better delineate barriers in convincing about organ donation.

• We should increase the panel of authorized specialists who may formally declare brain death as non-availability of neurologists and neurosurgeons may be one of the reasons for delay in the process, which in turn may decrease the chances of maintaining organ viability in the donor.

• Formal training of transplant coordinators and integrating them in the team would greatly help in appropriately educating families of potential donors. Combining empathy, compassion, education, scientific knowledge and most importantly being unbiased and non-judgmental would be key factors for successful transplant coordinators.

• Significant enhancements in penalties for offences may be necessary.

• Most importantly, guidelines need to be formed for appropriate organ sharing along the lines of United Network for Organ Sharing (UNOS) in the United States. Mandatory reporting to such an agency would play a key role in not ‘wasting’ organs when other hospitals in the region may be having potential recipients who may benefit.

Points to Remember

• Wide disparity in organ transplantation between India and western world is primarily due to lack of understanding in this field.

• In India “The Transplantation of Human Organ Act” (THO) came in to effect from 1995.

• Lack of awareness, enthusiasm and commitment from medical community as well as lack of funding to facilitate the programme are the barriers to cadaveric organ transplantation in India.

• There is a need to consider some changes in THO act.

References


8. The Transplantation of Human Organ Act, 1994


RENAL TRANSPLANTATION
IN CHILDREN

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Abstract: Renal transplantation is the treatment of choice for children with end-stage renal disease (ESRD). The true burden of ESRD in children in India is unknown. Pediatric renal transplantation presents many unique challenges. It needs a highly skilled team of specialists including pediatric nephrologists, transplant surgeons and trained nursing staff. The evaluation of the donor and recipient and the transplant procedure has been described in brief. The complications after renal transplantation and their management have been described in this review. In addition, factors limiting the development of pediatric renal transplant programme in our country is also highlighted.

Key words: Pediatric Renal transplantation, Complications.

End stage renal disease (ESRD) is defined as irreversible decline in renal function (glomerular filtration rate less than 15ml/min/1.73m²). Renal replacement therapy (dialysis or transplantation) is essential for survival of a child with ESRD. Renal transplantation is considered the best therapeutic option for ESRD. Pediatric patients have a better graft survival as compared to adults. These remarkable results are due to development of specialized pediatric transplant centers, improved surgical techniques and use of newer immunosuppressive drugs. Developing countries like India are not only lagging behind in diagnosing chronic kidney disease at an early stage but also in providing the optimum treatment which is often expensive and beyond the reach of the general population.

The prevalence of ESRD in pediatric population is around 55 per million children.1 Children between 11 to 16 years constitute 50% of the pediatric ESRD population2. There is no pediatric ESRD data registry in India. Hence the exact prevalence of ESRD in pediatric population in our country is not known. According to a rough estimate, only around 500 pediatric transplants have been performed in India so far. Review of the data from India shows that the mean age of transplant was 10-15 years.3, 4, 5 Pre-emptive transplants accounted for only 5% of total transplants in the above reports. Only few transplants were with cadaveric donors (CD).

The causes of ESRD among patients who underwent renal transplantation vary with age. Congenital and hereditary diseases are major causes of ESRD. Urinary tract malformations (hypoplastic, obstructive uropathy) have a higher incidence in the recipients in 0-5 year category than the older age group. Glomerular diseases are the major cause of ESRD in the older age group. Among the glomerular diseases, focal
segmental glomerulo sclerosis (FSGS) is the most common cause. Analysis of 37 cases of pediatric renal transplants by Phadke, et al revealed that glomerular and tubular interstitial diseases accounted for almost equal number of cases.\textsuperscript{3} Gulati, et al could not pin point etiology of native kidney disease in 70% of children transplanted, probably because they presented in late stages.\textsuperscript{4}

**Preparation for transplantation (Table. 1)**

**Pretransplant recipient evaluation**

A detailed history and physical examination along with a number of blood investigations are performed to identify whether the child is fit to undergo transplantation. Compatibility for ABO and tissue cross match are crucial as fewer number of HLA mismatches improve long term graft survival.

It is important to identify the patient’s immunization status. Given the variable response to immunizations and risks associated with live virus vaccines in immunocompromised patients, every effort should be made to fully immunize the child with chronic kidney disease prior to transplantation. Pre-transplant serologic evaluation to document exposure to various viruses (hepatitis B and C, HIV, CMV, varicella and EBV). Underlying tuberculosis should be ruled out.

Nutritional status must be optimized. Steps must also be taken to ensure that children awaiting transplant are adequately dialysed to prevent intra-operative and post-operative morbidity associated with uremia. Children should undergo a detailed neurodevelopmental assessment while cardiac, pulmonary, dental and ophthalmologic evaluation may be sought whenever required. Blood transfusions are generally avoided during pre-transplant period to avoid sensitization. This has become possible with use of erythropoietin for correction of anemia. More than five blood transfusions was associated with greater graft loss with a relative risk (RR) of 1.7 for living donor (LD) grafts and 1.3 for cadaver donor (CD) grafts.\textsuperscript{6}

A thorough evaluation of lower urinary tract in children with abnormal urinary tract with deranged bladder function by a pediatric urologist is essential. Interventions to maximize bladder function like augmentation surgery may be required before transplant. Pre-transplant native nephrectomy may be considered in patients with massive proteinuria, uncontrolled hypertension and to accommodate large donor kidneys in small children.

A detailed counseling with the help of a medical social worker to assess the family dynamics and to find out the child and family’s ability and motivation to comply with immunosuppression and medical therapy is an important part of pre-transplant evaluation.

**Donor evaluation**

Donors can be either living related (parents or siblings older than 18 years) or cadaveric. The live donor has to be medically fit to be eligible for donation. Human organ transplantation act (HOTA) was passed in India in 1994. HOTA provided legal definition of brain death, making cadaveric transplantation feasible. It was also aimed at curbing commercial organ trafficking. Renal angiogram to delineate renal vessels is an essential part of donor work up.

**Contraindications to transplantation**

Children in advanced stages of HIV infection or with devastating neurological or cardiac dysfunction may not be suitable candidates for renal transplantation. A child with malignancy who is completely treated and has no recurrence
### Table 1. Standard preparation of pediatric renal transplant candidates (recipient and donor)

<table>
<thead>
<tr>
<th><strong>Recipient</strong></th>
<th></th>
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<tbody>
<tr>
<td><strong>History and physical examination</strong></td>
<td></td>
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<tr>
<td><strong>Laboratory tests</strong></td>
<td></td>
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<tr>
<td>Hematology (CBC, platelets, differential counts)</td>
<td></td>
</tr>
<tr>
<td>Coagulation parameters (PT, APTT)</td>
<td></td>
</tr>
<tr>
<td>Biochemistry (BUN, Serum creatinine, LFT, S Ca and PO4, PTH, electrolytes)</td>
<td></td>
</tr>
<tr>
<td>Urine volume, 24 hour protein excretion, culture, urine analysis</td>
<td></td>
</tr>
<tr>
<td>Immunology (ABO blood type, HLA type, histocompatibility testing, panel reactive antibodies, tissue cross match)</td>
<td></td>
</tr>
<tr>
<td>Virology (Hepatitis B and C, HIV, CMV, EBV)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiography</strong> (VCUG, Chest X ray, bone age)</td>
<td></td>
</tr>
<tr>
<td><strong>Consultations</strong> (Pediatric surgeon, dentist, social worker, dietician)</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccines</strong> (DPT, polio, HBV double dose, varicella, pneumococcus)</td>
<td></td>
</tr>
<tr>
<td>Mantoux test</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
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</tbody>
</table>

| **Donor** |  |
| **Educate patient and family regarding live donation** |  |
| **Detailed family and social history** |  |
| **ABO compatibility of potential donor** |  |
| **Tissue type and cross match** |  |
| **Complete physical examination** |  |
| **Laboratory investigations** |  |
| Complete blood count, BUN, serum creatinine, electrolytes, liver function tests, lipid profile, thyroid function tests, glucose tolerance test. |  |
| Urine analysis, urine culture, 24 hour urine protein and creatinine excretion |  |
| Chest x-ray, renal angiogram, cardiac angiogram if indicated |  |
| ECG, treadmill test |  |
| **Consultations:** Cardiology, physician, psychiatry, gynecology (in females) |  |

CBC- Complete blood count, PT- Prothrombin time, APTT- Activated prothrombin time  
BUN- Blood urea nitrogen, LFT- Liver function tests, S Ca- Serum calcium,  
PO4- Phosphate, PTH- Parathyroid hormone, HIV-Human immunodeficiency virus,  
CMV- Cytomegalovirus, EBV- Ebstein Barr virus, VCU- Voiding cysto urethrogram,  
DPT-Diptheria-Pertussis-Tetanus  
BUN- Blood urea nitrogen, ECG-Electrocardiogram
for 2 years may be considered for transplant. Transplantation should be deferred for children who have active infection or evidence of active disease (eg: anti-GBM disease or other vasculitis syndromes). Transplantation is usually considered when the weight of the child is above 10 kgs. There are very few centers in the world who can take up children weighing 5 - 10 kgs for transplantation. Because of high risk of recurrence, a child with hyperoxaluria should undergo combined liver and kidney transplantation.

**Transplant surgery**

The operative technique for a transplant may differ depending on the weight of the child. For children less than 15 kgs, the transplant is performed through a midline incision and larger vessels like aorta and inferior vena cava are used for anastomosis with donor kidney blood vessels. The transplantation technique for children with body weight greater than 15 kgs is similar to adults. Close attention to fluid administration is vital during the intra operative period. Central venous pressure should be around 10-15 cms of water before the clamps are removed, to ensure good flow to the graft. Post operatively the urine output is replaced with normal saline.

**Immunosuppression in renal transplantation**

Advances in immunosuppressive therapy over the past decade have led to dramatic improvements in patient and graft survival. Commonly used immunosuppressive drugs are listed in Table 2. The immunosuppressive regimen can be classified into induction therapy and maintenance therapy.

**Induction therapy**

The goal of induction therapy is to prevent T cell activation by using T cell antibodies or IL-2 receptor antibodies.

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### Table 2. Immunosuppressive medications currently used in pediatric transplantation

<table>
<thead>
<tr>
<th>Medication</th>
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<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
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<tr>
<td><strong>Calcineurin inhibitors</strong></td>
</tr>
<tr>
<td>- Cyclosporine</td>
</tr>
<tr>
<td>- Tacrolimus</td>
</tr>
<tr>
<td><strong>Antiproliferative agents</strong></td>
</tr>
<tr>
<td>- Azathioprine</td>
</tr>
<tr>
<td>- Mycophenolate mofetil</td>
</tr>
<tr>
<td><strong>TOR inhibitors</strong></td>
</tr>
<tr>
<td>- Sirolimus (Rapamune)</td>
</tr>
<tr>
<td>- Everolimus</td>
</tr>
<tr>
<td><strong>T cell antibodies</strong></td>
</tr>
<tr>
<td>- Monoclonal antibodies (OKT3)</td>
</tr>
<tr>
<td>- Polyclonal antibodies (Thymoglobulin, ATGAM)</td>
</tr>
<tr>
<td><strong>IL 2 receptor blockade</strong></td>
</tr>
<tr>
<td>- Basiliximab (Simulect)</td>
</tr>
<tr>
<td>- Daclizumab (Zenapax)</td>
</tr>
</tbody>
</table>

**T cell antibodies**: OKT3 (Muronab-CD3) is a monoclonal antibody that binds to lymphocyte-CD3 complex. It is administered as a bolus injection iv for 10-14 days at a dose of 5 mg for children greater than 30 kg and 2.5 mg for children weighing less than 30 kg. Calcineurin inhibitors are withheld during the use of OKT3.

Antithymocyte globulin (ATGAM) and thymoglobulin are the two polyclonal antibodies available. ATGAM is given through a central venous catheter for 10-15 days. Dosage used is 15 mg/kg per dose. Thymoglobulin is given at 1.5-2 mg/kg per dose through a peripheral vein.

**IL 2 receptor antibodies**: Two IL 2 receptor antibodies are currently available. Basiliximab (Simulect) is a chimeric human 1
monocyte monoclonal antibody. It is given as a two dose regimen (10 mg for children less than 40 kg and 20 mg for those greater than 40 kg) on day 0 and 4 after transplantation. Daclizumab (Zenapax) is a humanized monoclonal antibody. The dosing regimen consists of 5 doses of 1 mg/kg every 14 days starting from the day of transplantation. It is well tolerated and has fewer side effects.

**Maintenance immunosuppression**

**Calcineurin inhibitors:** Cyclosporine (CsA): Use of CsA since the early 1980s has led to a decrease in acute rejection episodes and has improved graft survival rates. It inhibits T cell proliferation and differentiation. During the induction therapy, it can be given intravenously at 165 mg/m² per day for children less than 6 years and 4.5 mg/kg per dose for those above 6 years. The drug is preferably given either by continuous infusion or every 8 hourly. Intravenous therapy is continued for 48 hours. The subsequent recommended oral dose is 500 mg/m² per day 8 hourly for children less than 6 years and 8-10 mg/kg per day every 12 hours for children older than 6 years. The maintenance dosage recommended is 5-8 mg/kg per day. Because of erratic drug absorption profile, CsA drug levels have to be closely monitored. Appropriate trough drug levels are 100-200 ng/ml by high power liquid chromatography (HPLC). Higher levels are maintained during the first three months after transplantation. CsA concentration measured 2 hours after administration is an alternate technique but pediatric experience regarding this is limited. The major toxicities with CsA use are nephrotoxicity, hypertension, hepatotoxicity and hyperlipidemia, hypertrichosis, gingival hyperplasia and facial dysmorphism. Metabolic complications include hyperkalemia, hypomagnesemia and hyperuricemia. Another major concern has been the interactions with other drugs. Rifampicin, carbamazepine, phenytoin and phenobarbitone decrease the CsA level. Concomitant use of ketoconazole, itraconazole, erythromycin, methylprednisolone, metaclopramide, omeprazole and grape juice increases CsA levels.

Tacrolimus: It is a macrolide which was introduced in mid 1990s. It interacts with FK binding protein and inhibits T cell derived lymphokines. It can be given as a continuous infusion at a dose of 0.1 mg/kg per day. The oral dosage should not exceed 0.15 mg/kg/day and should be reduced to 0.1 mg/kg per day as a maintenance dose. The whole blood trough level range from 7-20 ng/ml for first 3 months post transplant and 5-15 ng/ml subsequently. Along with mycophenolate (MMF), dosing and target levels are less compared to the standard protocol. The adverse effect profile is almost similar to that of CsA. The degree of nephrotoxicity, hypertension and cosmetic side effects are lesser while the incidence of hyperglycemia, neurological effects and alopecia are much more as compared to CsA.

**Corticosteroids:** They inhibit the inflammatory process via multiple phenotypic effects of glucocorticoid receptors on signalling pathways. These include induction and activation of genomic anti-inflammatory proteins and through non genomic mechanism involving activation of endothelial nitric oxide synthetase (e-NOS). The dosage of prednisolone is 2 mg/kg per day initially with gradual reduction to 0.2-0.3 mg/kg per day within 6 months to 1 year period post transplant. The side effects include growth retardation, increased susceptibility to infection, impaired wound healing, aseptic necrosis of femoral head, cataracts, hyperglycemia, hypertension and Cushingoid features.

**Antiproliferative agents:** Azathioprine (AZA): AZA is a 6-mercaptopurine derivative and acts by directly inhibiting the growth and differentiation
of immune cells. It also inhibits primary antibody synthesis. The dose is 1-2 mg/kg per day. The major side effects of AZA are leucopenia, thrombocytopenia and megaloblastic anemia. Uncommon side effects include hepatotoxicity, pancreatitis and alopecia.

Mycophenolate mofetil (MMF): MMF is increasingly replacing AZA as the first line drug of standard triple therapy. It is an antimetabolite and acts by inhibiting denovo purine synthesis in lymphocytes. The current recommended dose is 1,200 mg/m² per day in two or three doses. Hematological and gastrointestinal side effects are the main concerns.

Other immunosuppressives that are available but not extensively used in children are sirolimus and everolimus.

**Changing trends in immunosuppression**

The standard triple therapy protocol consists of prednisolone, CsA and AZA. Over the last decade, many changes have taken place in the above protocol. MMF has superseded AZA while tacrolimus is being widely used as compared to CsA over the last five years. The debate involving steroid withdrawal or avoidance regimens continues. More firm evidence needs to be available before steroids can be eliminated from the immunosuppressive protocol.

**Post-transplant complications**

**Primary non-function of allograft**

Primary non-function of allograft is more common with cadaveric kidneys because of prolonged cold ischemia time. Other causes include hyperacute allograft rejection and renal artery thrombosis. Surgical causes like obstruction and urinary leak should also be considered in cases of primary allograft dysfunction. Graft thrombosis is a unique complication of pediatric transplantation.

**Allograft rejection**

Rejections are classified as hyperacute (occurs within minutes to hours of transplant), accelerated acute (occurring within the first week after transplant), acute (occurring within the first year of transplant), late acute (occurring after the first year) and chronic (usually years later in the course of transplant).

Hyper acute rejection is the result of specific anti-donor antibodies against HLA, ABO or other antigens. Fortunately it is rare. Allograft biopsy reveals glomerular thrombosis, fibrinoid necrosis and polymorphonuclear infiltration. Surgical removal of allograft is mandatory in such cases.

Accelerated acute rejection can occur when the recipient has been sensitized by blood transfusions. Acute rejection is a systemic inflammatory disorder associated with constitutional symptoms. Risk factors for acute rejection include absence of prophylactic T-cell antibody therapy, cadaveric donor age less than 5 years, no DR matches and presence of acute tubular necrosis (ATN).

Rejection is suspected when there is decreasing urinary output and rising serum creatinine. Renal biopsy confirms acute rejection. The severity of rejection is classified according to the Banff criteria.

Standard treatment for an episode of acute rejection is intravenous methylprednisolone (20-25 mg/kg, max 1 gm) for 3 consecutive days. Steroid resistant rejection episodes are treated with T-cell antibodies (OKT3, ATGAM and Thymoglobulin). In those patients who have steroid resistant and antibody resistant rejection episodes, conversion to an alternative calcineurin inhibitor or other immunosuppressants may be warranted.

Among LD kidneys, 55% of rejection episodes are completely reversed, 40% are
partially reversed and 5% end in graft failure. Similar figures for CAD kidneys are 48%, 45%, 7% respectively.

**Chronic allograft dysfunction:** It is the most common cause of graft failure beyond the early post transplant period. The clinical picture is that of gradually declining renal function along with proteinuria and hypertension. Morphological findings associated with chronic allograft dysfunction are characterized by widespread obliterative vasculopathy, glomerulosclerosis and interstitial fibrosis with tubular atrophy. Immune mediated injury, ischemia and non – immunologic injury also influence the development of chronic allograft nephropathy.

**Infections**

The most common cause of hospitalization post-transplantation is related to infectious complications rather than rejections. Different infections occur at different times during post-transplant period. (Table 3)

**Other complications**

Hypertension is common in children after transplantation and is often associated with decreased allograft function. Most of them are hypertensive prior to transplantation which is related to their native kidney disease. Possible causes of hypertension after transplantation include use of corticosteroids and calcineurin inhibitors as part of immunosuppressive protocol, recurrence of disease, chronic allograft dysfunction, renal artery stenosis and essential hypertension.

Multiple factors contribute to growth failure during post transplant period. Optimal management of growth retardation would entail assiduous attention to correcting fluid and electrolyte imbalances and acidosis, ensuring adequate nutrition and control of secondary hyperparathyroidism prior to transplantation. Recombinant growth hormone (rGH) may be used in children with height less than 2 SD (standard deviation).

The current incidence of post transplant lymphoproliferative disorders (PTLD) is 1 -2 % of all pediatric renal transplant patients. Age less than 18 years, male gender and intense immunosuppression are significant risk factors.

Recurrence of native kidney disease is a significant cause of allograft loss and morbidity. Recurrences of FSGS occur in 40% of grafts. Age less than 6 years, rapid progression to ESRD, mesangial hypercellularity on native biopsy and recurrence in previous transplant markedly increase the risk of recurrence. The other

---

**Table 3. Timetable of infections after organ transplantation**

| Infection in the first month post-transplant | Infection conveyed with a contaminated allograft. |
| Infection caused by residual infection in the recipient | 95% are wound infections, urinary and respiratory infections, catheter related infections. |
| Viruses (Cytomegalovirus, Ebstein Barr virus, hepatitis B and C) | Opportunistic infections |
| Pneumocystis jiroveci | Aspergillus, candida |
| Infection more than 6 months post transplant | Community acquired infections |
| Urinary tract infections | Cryptococcus neoformans |
glomerular disease which recurs in transplanted kidney are IgA nephropathy, membrano-proliferative glomerulonephritis and hemolytic uremic syndrome. Because of almost 100% risk of recurrence with isolated renal transplantation in patients with primary hyperoxaluria, combined liver and kidney transplantation is indicated in these patients.

Non-compliance with therapeutic regimen is an important cause of delayed graft dysfunction in adolescents. A major reason for non-compliance is cosmetic side effects like cushingoid facies, hypertrichosis and gum hypertrophy associated with steroid and cyclosporine therapy. Other factors include poor socioeconomic status and family stress.

Transplant experience at our center

At our center, 38 pediatric renal transplants were performed over last 8 years. The mean age and weight at the time of transplantation was 13.8 +/- 2.58 years and 30.85 +/- 7.44 kg, respectively. Twenty-nine children were boys and 9 were girls. Fifteen children had underlying glomerular disease and 23 had tubulointerstitial disease. All transplants were living related except two, which were from deceased donors. The median duration of hemodialysis and peritoneal dialysis before transplantation were 2.75 and 4 months, respectively. Pre-emptive transplant accounted for 12% of our transplant.

Immunosuppression medications in the majority included cyclosporine, azathioprine, and corticosteroids. The most common post-transplant complication was urinary tract infection. Acute rejection was seen in 4 patients (18.1%) and was reversed in three. Hypertension after transplant persisted in three fourth of our children. Actual graft survivals at 1, 3, and 5 years were 94%, 90%, and 82%, respectively which is comparable to the data from the developed countries. The outcomes from various centers in India are presented in Table 4. In US, the graft survival rates for index transplantation at 1, 3 and 5 years are 95%, 90% and 83% for LD Kidneys and 91%, 82% and 73% for CD kidneys. These values represent a significant improvement in survival rates as compared to a decade back.

Challenges facing renal transplantation programme in India

In the absence of a renal registry in India, the true magnitude of CKD/ESRD is not known. It is estimated that in India every year over 152,000 people are diagnosed to have end-stage renal failure needing renal transplantation. However, only a fraction of these individuals (2-3%) receive a kidney transplant. One of the major reasons is the high cost of transplant. The cost of renal transplant procedure varies between 1.0-3.0 lakhs. The cost of immunosuppression with basic triple immunosuppression

Table 4. Comparison of graft survival – Indian data

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Mean age (Years)</th>
<th>Follow up (months)</th>
<th>1 year graft survival</th>
<th>5 year graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulati et al</td>
<td>39</td>
<td>15 + 1</td>
<td>31</td>
<td>89%</td>
<td>53%</td>
</tr>
<tr>
<td>Chacko et al</td>
<td>90</td>
<td>15 + 3</td>
<td>42 + 33</td>
<td>98%</td>
<td>85%</td>
</tr>
<tr>
<td>Phadke et al</td>
<td>37</td>
<td>13.8 + 2.5</td>
<td>40 + 29.0</td>
<td>94%</td>
<td>82%</td>
</tr>
</tbody>
</table>
drugs (cyclosporine, steroid and azathioprine) is around Rs 10,000-15,000 per month. In absence of government support and lack of insurance cover, transplantation remains a distant dream. In one study, it was concluded that 63% had help from their employer or charity, 26% took loans and 34% sold assets or pooled their family resources. Besides inadequate finance, lack of appropriate donor is another major obstacle. Deceased organ transplant program is very poorly organized in our country and accounts for less than 1% of total renal transplantations. Creating a positive attitude among the public and medical professionals, early brain death identification, and certification, adequate counseling to obtain consent for organ donation, are essential for successful deceased organ transplantation. The other hindrances are ignorance among the general public and medical fraternity, passive attitudes of the society towards organ transplantation and lack of proper medical infrastructure and support. Treatment of chronic diseases in children is accorded low priority in public health domain where malnutrition, acute infectious diseases are considered major issues.

**Future trends and conclusions**

Pediatric renal transplantation is at crossroads. Progress in tissue typing, clinical care and immunosuppression has made renal transplantation a safe and reliable therapy. Creating public awareness on chronic kidney disease and organ donation, sensitizing the medical fraternity of the process of organ donation, early detection and timely referral of children with chronic kidney disease will go a long way in improving the outcome of pediatric renal transplantation in India. With improvement in health care infrastructure and technical capabilities and more numbers of centers performing pediatric transplants, the future appears brighter.

**Points to Remember**

- The optimal treatment for end-stage renal disease in children is transplantation and child can lead a near normal life after transplantation.
- Living related donors such as parents are the source of organ for a child and all efforts should be made to promote deceased organ programme.
- The long term results of renal transplantation in our country is as good as anywhere else.
- Early detection of chronic kidney disease, close follow up at specialized centers and positive attitudes should spell a bright future for pediatric renal transplantation in our country.

**References**


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**CLIPPINGS**

**Acyclovir for treating varicella in otherwise healthy children and adolescents**

Chickenpox (varicella) usually affects children from one to 14 years. In young babies, adults or people with impaired immune system, chickenpox is more severe. Treatments include lotions to relieve itchiness, paracetamol (acetaminophen) for fever and the antiviral drug acyclovir. The review of trials found that acyclovir reduces the number of days of fever from chickenpox in otherwise healthy children, usually without adverse effects. It is not clear whether it improves sores and itching.


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**Nebulized hypertonic saline solution for acute bronchiolitis in infants**

Acute viral bronchiolitis is the most common lower respiratory tract infection in infants, but the standard treatment remains supportive care. This review was conducted to assess the effects of nebulized hypertonic saline, which can increase clearance of mucus, in these patients. Four randomized trials involving 254 infants were included. Analysis of the pooled data suggests that nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis. There were no adverse effects noted with nebulized hypertonic saline when administered along with bronchodilators.

ORGAN TRANSPLANTATION

STEM CELL TRANSPLANTATION

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**Yadav SP  
***Anupam Sachdeva

Abstract: Amongst the organ transplantation stem cell transplantation helps in many disease conditions. It has grown in leaps and bounds throughout the world bringing about permanent cure for many devastating illnesses. The article covers the origin and types of stem cells and their clinical application.

Keywords: Stem cell, Transplantation.

Stem cells

Stem cells are primitive cells that are pluripotent, capable of self-renewal and can remain undifferentiated. Stem cells can aid in treating many previously devastating diseases. Based on their origin, they are divided into three categories.

1. Embryonal stem (ES) cells: ES cells are derived from developing embryos and can be maintained in culture while retaining their ability to generate virtually any tissue in the body. There are substantial scientific and ethical hurdles for human ES cells to be used clinically.

2. Tissue specific stem cells: Stem cells have been found in blood, skin, gut, liver and perhaps brain and pancreas. They exist in small numbers in the tissue and have self-renewal potential. Hematopoietic stem cells are the longest studied and the best-known examples of tissue specific stem cells.

3. Multipotent adult stem cells: These are isolated from adult bone marrow and are characterized by their ability to differentiate into any body tissue under appropriate conditions.

Clinical application of hematopoietic stem cells

Hematopoietic stem (HS) cells reside primarily in the bone marrow but do circulate in the peripheral blood. These cells may replenish damaged or missing components of the hematopoietic and immunologic system. The clinical uses of hematopoietic stem cells can be discussed under the following headings.

1) HS cell transplantation, 2) HS cell gene therapy and 3) HS cell plasticity.

1. Hematopoietic stem cell transplantation

History

Hematopoietic stem cell transplantation (HSCT) was originally conceived more than 50 years ago. Initial studies done in animals showed that transplantation of genetically identical material or the animal’s own marrow averted death. Studies in animals later translated to work in humans and this was pioneered by a team led by Dr. E Donnall Thomas. In 1959, he reported that a patient with end stage leukemia sustained a remission for more than three months.
following total body irradiation and infusion of bone marrow from her identical twin. Later in 1970’s HLA identical sibling transplant was performed in leukemic patients by the same group. This work laid the foundation for further advances in hematopoietic stem cell transplantation and this was recognized by the 1990 Nobel Prize awarded to Dr. E. Donnall Thomas.

Graft types in HSCT

**Autologous transplants** use stem cells derived from the patient’s own marrow or peripheral blood. Initially this was developed in order to rescue the bone marrow of patients undergoing chemotherapy. Now autologous transplants are being increasingly incorporated in protocols for solid tumors like neuroblastoma. This method thus forms the most important form of stem cell transplantation performed worldwide. Stem cells can be stored without loss of viability and mortality is low with this procedure. In addition, there is no risk of graft versus host disease.

**Allogeneic transplants** are hemopoietic stem cells from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor matched for HLA type, who may be a family member or an unrelated volunteer. Initially allogeneic transplant was developed for treatment of hematological malignancies. Now it is being utilized for a variety of hematological disorders and for non-hematological disorders like inborn errors of metabolism and autoimmune diseases.

**Syngeneic transplants** involve transplantation from a person sharing identical genetic material i.e., an identical twin.

**Sources of stem cells**

1. **Bone Marrow:** Bone marrow obtained by repeated aspiration of posterior iliac crests while donor is under general or local anesthesia is the traditional source of stem cells. This does not cause any side effects to the donor except for slight discomfort at the site of aspiration and the requirement of packed cell transfusion in some cases of pediatric donors.

2. **Peripheral blood stem cells (PBSC):** It was noted in early 1980’s that marrow stem cells circulated in the peripheral blood. Stem cell yield from peripheral blood can be increased by giving bone marrow growth factors like granulocyte colony stimulating factor (G-CSF). Stem cells are then harvested by leukopheresis. CD 34 cell surface molecule is used as a surrogate marker of stem cells. G-CSF increases the proliferation of neutrophils and causes release of proteases. Proteases degrade the proteins that anchor stem cells to the marrow stroma, thus freeing the cells to enter circulation. PBSCs cause the most rapid hematopoietic reconstitution but contains more T2 cells than bone marrow due to which they are associated with increased risk of chronic GVHD.

3. **Umbilical cord blood stem cells:** Cord blood of neonates contains substantial numbers of hematopoietic stem cells that can be harvested at delivery, frozen and then transplanted to patients. They can be matched with potential donors without much delay. First cord blood transplant was performed by Gluckmann and colleagues in 1989 for Fanconi’s anemia. Cord blood requires less stringent HLA matching than marrow/ peripheral blood stem cells. With the emergence of cord blood banks with public cord blood banking facilities, they form an important source of stem cells especially for ethnic minorities and countries where marrow donor registries do not exist. Cord blood is also associated with minimal GVHD due to naïve T cells in it. The disadvantage with cord blood is delayed engraftment due to the small number of stem cells; hence infections are more common during the prolonged period of neutropenia.
Also, the cell dose in one cord blood unit may not be sufficient for an older child or an adult. The use of double cord blood has overcome this problem.

**Donor selection**

**HLA matching**

Allogeneic transplantations became feasible with the identification and typing of HLA (human leukocyte antigen) located on major histocompatibility locus on chromosome 6. There are 2 sets of genes on both alleles and hence they are inherited as haplotypes. Thus two siblings have one chance in four of being HLA identical. With the establishment of international marrow donor registries there are good chances of finding a matched unrelated donor depending on the ethnic group. For patients from Asia and Indian subcontinent, the probability of finding a donor of Asian origin is low due to the poor representation in these registries and due to the absence of local registries. The strongest transplant reactions occur when the major histocompatibility antigens of the donor and of the recipient are incompatible. The indication of stem cell transplantation are given in Table 1.

**Donor registries**

Only 20-25% of patients eligible for allogeneic transplantation will have suitable sibling donors. To make transplants available to a greater number of eligible patients, bone marrow donor registries have been established in several countries. This will identify unrelated but matched donors for prospective patients.

**Collection of hematopoietic stem cells**

Bone marrow is harvested from posterior iliac crest and is generally well tolerated. In case of ABO incompatibility, it is necessary to remove mature erythrocytes from the graft to avoid a hemolytic reaction. Peripheral blood (PB) stem cells are mobilized from the bone marrow by G-CSF given at a dose of 10 μg/kg/day for 4-5 days. PB stem cells are then collected by leukopheresis. Neither anesthesia nor hospitalization is required for the donor. Umbilical cord blood is collected at the time of delivery by clamping the cord and cutting the umbilical cord. The median volume collected is around 60-70ml. Once collected, it is then processed and stored in liquid nitrogen till further use.

**Preparative regimens / Conditioning regimens for the recipient**

The objective of myeloablation of the recipient prior to transplant is to eradicate the cancer cells in case of malignancies. The preparative regimen also augments the antitumor immune response by causing a breakdown of tumor cells, which results in flood of tumor antigens into the antigen presenting cells. This results in proliferation of T cells that attack the surviving malignant cells. In non malignant indications, myeloablation helps in inducing immunosuppression.

1. **Total body irradiation:** It is both myeloablative and immunosuppressive. The effects are independent of blood supply and the effects reach sites that are not accessible by chemotherapy. It is also not associated with cross resistance to chemotherapy. Local shielding of organs and fractionation of the total dose can reduce toxicity. The toxicity and scarcity of facilities for TBI have led to development of radiation free regimens.

2. **Busulphan- Cyclophosphamide (Bu-Cy):** In 1983, a regimen of Bu with high doses of Cy proved effective in treatment of acute myeloid leukemia. Acute adverse effects are associated with high plasma levels of busulphan and metabolites of cyclophosphamide. The dose of cyclophosphamide was later lowered to reduce
Table 1. Common indications for hematopoietic stem cell transplantation

<table>
<thead>
<tr>
<th>Diseases commonly treated with hematopoietic stem cell transplantation</th>
<th>Malignant conditions</th>
<th>Non malignant conditions</th>
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<tbody>
<tr>
<td><strong>AUTOLOGOUS</strong></td>
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<tr>
<td>Acute myeloid leukemia</td>
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<tr>
<td>Hodgkin’s disease</td>
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<td></td>
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<tr>
<td>Non Hodgkin’s lymphoma</td>
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<td></td>
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<tr>
<td>Neuroblastoma, Ewing’s sarcoma</td>
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<tr>
<td><strong>ALLOGENEIC</strong></td>
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<tr>
<td>Acute myeloid leukemia</td>
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<tr>
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<td>Chronic myeloid leukemia</td>
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<tr>
<td>Myelodysplastic syndromes</td>
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</tr>
<tr>
<td>Myeloproliferative syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Hodgkin’s lymphoma</td>
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</tbody>
</table>

Toxicity. Toxicity can also be reduced by adjusting the dose of busulphan according to the plasma levels or by using intravenous instead of oral busulphan⁵.

**Reduced intensity conditioning**

It is widely recognized that immunocompetent cells in the donor can also help clear the recipient’s residual tumor cells, a “graft versus tumor” effect. Hence it may not always be necessary to completely eradicate the disease with conditioning to achieve a cure. This observation led to experimentation with reduced intensity protocols sometimes followed by immunotherapy. Such non-myeloablative transplants are variously called mini-transplants or low intensity transplants.

After the preparative regimen, the processed stem cells are infused intravenously. The patients are kept in high efficiency particulate air filter (HEPA) filtered rooms and are on prophylactic antifungals, antibiotics and antiviral agents.
Engraftment is defined as absolute neutrophil count more than 500/cumm for more than 3 days consecutively.

**Complications**

**Early effects**

1. **Mucositis:** It is the most common complication of myeloablative preparative regimes and methotrexate (for prevention of GVHD). Oropharyngeal mucositis results in painful ulcers in the mouth and throat. It can also lead to mucoid diarrhea and crampy pain abdomen.

2. **Sinusoidal obstruction syndrome (SOS)/Veno occlusive disease:** Potentially fatal syndrome of painful hepatomegaly, jaundice and fluid retention. Total body irradiation, busulphan, cyclophosphamide and many other preparative regimens cause SOS. The metabolites of these drugs and irradiation results in sloughing of the sinusoidal endothelium which results in obstruction of hepatic circulation and injury to the centrilobular hepatocytes. The recognized pre-transplant risk factors include extremes of age, prior liver disease and preexisting poor physiological status. Because there is no effective treatment of this complication, prevention is critical. Use of reduced intensity conditioning regimens and the substitution of fludarabine for cyclophosphamide appear to reduce the risk.

Defibrotide is a mixture of single stranded oligonucleotides that have local antithrombotic, anti ischemic and anti inflammatory properties. It protects the sinusoidal endothelium without compromising the cytotoxic therapy. Hence it is used now for prophylaxis as well as treatment of SOS.

3. **Acute graft versus host disease (aGVHD):** is the most important complication of allogeneic transplantation. Acute GVHD damages the skin, gut and liver. A pruritic maculopapular rash can affect the palms, soles or face and may become generalized. Nausea, vomiting, abdominal pain, bloody diarrhea and jaundice may occur. The most commonly used grading system for disease (aGVHD) was introduced by Glucksberg. 30 years ago; the International Bone Marrow Transplant Registry (IBMTR) developed a revised system in 1997. The two classifications performed similarly in explaining variability in survival by aGVHD grade, although the Glucksberg classification predicted early survival better. There was less physician bias or error in assigning grades with the IBMTR scoring system.

The principal risk factor for aGVHD is HLA mismatch, but it can occur despite a full HLA match. Prophylaxis for GVHD is provided with short-term methotrexate plus cyclosporine for several months. The incidence of GVHD can also be reduced by in vitro T cell depletion of the graft before transplantation.

4. **Transplantation associated lung injury:** This usually occurs within four months of the procedure and the mortality exceeds 60%. Risk factors include TBI, allogeneic transplantation and acute GVHD suggesting that donor lymphocytes target the lung. Treatment with etanercept that blocks tumour necrosis factor, combined with corticosteroids may reduce the injury promptly.

5. **Infections:** Transplant related infections result from damage to the mouth, gut and skin from preparative regimens as well as from catheters, neutropenia and immunodeficiency. Prolonged neutropenia, GVHD and the administration of corticosteroids predispose patients to fungal infections. Cytomegalovirus is an important cause of morbidity during this period.

**Delayed effects**

1. **Chronic GVHD:** Risk of chronic GVHD increases with recipient and donor age. Chronic
GVHD is associated with loss of self-tolerance and often resembles Sjogren’s syndrome or scleroderma. Chronic GVHD can cause bronchiolitis, keratoconjunctivitis sicca, esophageal stricture, malabsorption, cholestasis, hematocytopenia, and generalized immunosuppression. Treatment with corticosteroids may be needed for two years or longer.

2. **Growth and development** are impaired in children who undergo transplantation as a result of myeloablative preparative regimens. Growth hormone therapy increases height in these children.

3. **Fertility** in adulthood may be impaired in children undergoing transplantation. Young men may recover their fertility later in life. Semen cryopreservation and oocytes cryopreservation can be done to aid in fertility later in life.

4. **Secondary cancers** increase after transplantation. Myelodysplasia and acute leukemia are complications of autologous transplantation for Hodgkin’s and non-Hodgkin’s lymphoma. Survivors of transplantation should be followed indefinitely to detect early cancer or precursor lesions.

**Advances in stem cell transplantation**

1. Reduced intensity conditioning
2. Donor lymphocyte infusions
3. Improved HLA typing
4. Improved supportive care
5. Ex-vivo manipulation of stem cells

**Hematopoietic stem (HS) cell transplantation in developing world**

Developing countries of Middle East and Africa have large numbers of patients affected by lethal red cell disorders. The first bone marrow transplantation done in India was in 1983 at Tata memorial hospital, Mumbai. There are around 10 centers in India that perform allogeneic transplants. Published results from these centres show that it is possible to achieve results similar to international standards.

**HS cell gene therapy**

Gene therapy offers an alternative to stem cell transplantation from healthy donors for the treatment of certain genetic diseases of the blood. In this, the patient’s own HS cells are isolated from bone marrow or blood, genetically engineered to express a normal copy of the gene responsible for the disease and then transplanted back into the patient. Since 1990’s this has been used to treat severe combined immunodeficiencies (SCIDs), using viral vectors to carry a healthy gene into the genome of the patient’s HS cells. Patients affected by the X-linked variant, the adenosine deaminase (ADA)-deficient variant and chronic granulomatous disease seem to be permanently cured of their defects using this strategy.

But despite the initial success, this had not progressed at the expected pace. One reason is the difficulty in appropriately regulating transferred globin genes. Moreover, in the study involving X linked SCID, 3 patients ultimately progressed to acute leukemia due to uncontrolled lymphoid proliferation. This was linked to the insertion of the viral vector used for gene transfer, into the stem cell genome near an oncogene. But this has not been seen in other similar studies. With the introduction of safer and more efficient vectors, HS cell based gene therapy will prove beneficial in a number of other genetic diseases. In particular, neurodegenerative disorders caused by the absence of specific enzymes, such as lysosomal enzymes, are good candidates for HS-cell gene therapy, as replacement enzymes can potentially be produced by cells generated from genetically engineered HS cells.
**HS cell plasticity**

Of late, there has been a great deal of interest in the use of HS cells to treat diseases of other organs and tissue. Initially it was thought that HS cells transdifferentiated into mature cells of the recipient organ in the presence of local tissue factors. Later it has been found that cell fusion was probably the major mechanism.

**Stem cells in heart disease**

Many types of stem/progenitor cells have been used in an attempt to regenerate the infarcted heart. Embryonic stem cells represent the most promising type of cells to rely on for a future tool in heart failure treatment. Currently, however, these cells are available only in limited numbers and their therapeutic use would likely introduce ethical and regulatory dilemmas, as well as the risk of allograft immunologic reactions. Bone marrow contains mesenchymal stem and progenitor cells that have the ability to differentiate into multiple mesoderm-type cell lineages, e.g., endothelial-cells, osteoblasts and chondrocytes. Cellular cardiomyoplasty is the technique of using autologous stem cells for myocardial regeneration.

**Stem cells in GI disease**

The continued need for an alternative means of replacing beta-cells in people with diabetes has fostered scientific and public interest in the potential of embryonic stem cells as a potential therapy. The role of adult stem cells in the formation of new beta-cells is controversial and the origin of such cells is unclear.

Stem cell based research is also on for the treatment of several disorders, such as inflammatory bowel diseases, celiac disease and acute or chronic hepatopathies. Nonetheless, critical aspects need to be further addressed, including the long-term safety, tolerability and efficacy of cell-based treatments, as well as their carcinogenic potential.

**Stem cell therapy in renal disease**

Currently, most renal stem cell research is focussed on models of acute renal injury. Acute renal failure has 50-80% mortality. Currently, the only treatment options are dialysis and other supportive measures while waiting for return of renal function. Stem cells offer an exciting potential for kidney regeneration. Because stem cells have diverse developmental potential, they have opened a new avenue for potential effective treatment of acute renal failure. Because bone marrow stem cells are readily accessible, they remain an important source for autologous cell replacement therapy. More research needs to be conducted to determine the type of bone marrow cells, dose and route of administration of the cells.

**Stem cells in CNS disease**

Stroke and traumatic brain injury leads to cell death, characterized by a loss of neurons and oligodendrocytes within the brain. Healthy adult brain contains neural stem cells, these divide and act to maintain general stem cell numbers or become progenitor cells.

New insights into the biology of neural stem cells (NSCs) have raised expectations for their use in the treatment of neurologic diseases. Originally, NSC transplantation was proposed as a means of replacing cells in central nervous system diseases that result in cell loss. However, recent data regarding their beneficial effects in various animal models of neurologic diseases indicate that transplanted NSCs may also attenuate deleterious inflammation, protect the central nervous system from degeneration and enhance endogenous recovery processes. Recent studies have shown that neurons suitable for transplantation can be generated from stem cells in culture and that, in response to injury the
adult brain produces new neurons from endogenous stem cells. These findings indicate the possibility of developing stem cell therapies to treat human neurodegenerative disorders\textsuperscript{12, 13, 14}.

**Stem cells in lung diseases**

Bronchopulmonary dysplasia (BPD) and cystic fibrosis (CF) are two common serious chronic respiratory disorders without specific treatments affecting children. Stem cells have the potential to act as a vehicle for corrective gene therapy, thereby restoring normal organ function. Ultimately, lung stem cell therapy may also be applicable to other devastating lung disorders such as pulmonary hypoplasia. The use of exogenous cells to supplement the natural repair mechanisms or the possibility of genetic manipulation in vitro before administration are appealing therapeutic options for these diseases. Increasing attention has been focussed on the use of adult bone marrow-derived stem cells to regenerate damaged organs. Initial work suggests that BMSC can engraft and differentiate into a variety of lung cells, but these findings have been challenged recently. This highlights the need for more reliable techniques and assays to assess adult BM-derived cells lung engraftment and transdifferentiation\textsuperscript{15}.

**Stem cells in skin diseases**

Extensive stem cell research and potential clinical applications have provided new perspectives in the use of stem cells in the treatment of human skin disorders such as severe burns and wounds, as well as skin cancer and alopecia. Adult, tissue-specific stem cells are required for tissue homeostasis as well as for the ability to respond to insults such as during wound healing. Fetal wounds can heal rapidly without scars, while in adults wound healing decreases with aging, and this likely represents changes in the functional status of stem cells. A better understanding of cell signaling during wound-induced activation of fetal and adult stem cells should lead to improved therapeutic strategies to make adult skin heal more like the fetal tissue\textsuperscript{16}.

**Stem cells and human reproduction**

Human embryonic stem (hES) cells herald a new era of stem cell research. The identification of germ stem cells in the testes and perhaps in the ovary raises the possibility of improving treatments for the increasing number of infertile couples. This opens us to the possibility that postnatal oogenesis could be stimulated in human ovaries and will be of benefit in reproductive-age women, particularly those who are cancer survivors. Evidence for the existence of adult stem cells in the endometrium is steadily accumulating; however, more research is required to define them. This would in future offer the possibility of a new understanding of gynecological disease and the possibility for their potential use in restoring damaged or inadequate endometrium. The explosion in stem cell research is also likely to have a major impact in advancing therapeutics in the field of reproductive medicine\textsuperscript{17}.

In spite of the promising uses of stem cells in many human diseases, it raises several ethical and social issues such as destruction of human embryos to create human embryonic stem (hES) cell lines, potential for introducing co-modification in human tissues and organs with inherent barriers of access to socioeconomically deprived and possible use of technology for germ-line engineering and reproductive cloning. The research in this field, therefore, needs to be regulated to strike a balance. As stem cell therapy is poised to enter into clinical practice, different investigating countries have formulated guidelines for stem cell research and therapy\textsuperscript{18}.

Several ongoing projects in the field of biotechnology, include the efficacy of autologous stem cells in prevention of amputation in chronic
critical limb ischemia, efficacy of autologous bone marrow stromal cells in patients with acute ischemic stroke and limbal stem cells in corneal transplant.

**Conclusion**

It is remarkable that, through bone marrow and HS-cell transplants, stem-cell therapies have brought about permanent cures for many patients suffering from hematological disorders. There are efforts underway to develop therapies using alternative sources of stem cells, such as embryonic stem cells. However, because HS cells are relatively abundant and accessible, alternative sources might be less crucial for treating common blood disorders than for diseases of other organs and tissues. Advances in HS cell based therapies would probably be the answer for the many incurable diseases of today.

**Points to Remember**

- **Stem cell therapy has brought permanent cure for many hematologic disorders.**

- **Efforts are underway to develop therapies for various disorders using alternative sources of stem cell like embryonic stem cells.**

**References**

18. Guidelines for stem cell research and therapy ICMR & DBT Document 2007
ORGAN TRANSPLANTATION

PEDiatric cardiothoracic transplantation: an update
*Rathinam S
**Margabanthu G

Abstract: Pediatric cardiothoracic transplantation is a specialized field which involves complex decision making and management. Pediatric cardiothoracic transplant patients present many challenges both to the pediatricians and the specialists. Indications, trends and developments in this area are reviewed.

Keywords: Pediatric cardiac transplant, Pediatric lung transplant, Pediatric mechanical support, Post-transplant.

Cardiothoracic transplantation is a rapidly evolving field. Pediatric cardiac transplantation is a challenging field which is now widely available for children with end-stage heart disease. From the time of the first successful transplant, more than 60,000 cardiac transplants have been performed around the world, of which the pediatric cardiac transplant rate is only 350 per year1.

This is due to the fact that pediatric heart transplantation is a difficult area with a variety of anatomic cardiac configurations of the congenital heart disease, the small size of the organs and the peculiarities of the immature immune system. The limitations on the use of pediatric assist devices and the intense involvement of parents in the decision making process complicate matters further2.

Pediatric cardiothoracic transplantation is managed by two different teams. The surgical team is common for the two different patient groups. The heart transplant group is managed by cardiologists and the heart-lung transplant group is best managed by the respiratory physicians.

HEART TRANSPLANT

Indications

The indications for a pediatric heart transplant vary according to different age groups and these include congenital cardiac anomalies, cardiomyopathies and retransplant. The main indication for children under 1 year of age who undergo a transplant is congenital anomalies (75%), whereas for children 11 to 17 years of age, the primary indication is cardiomyopathy (63%)3. Children with previous palliative procedures with progressive heart failure, children with univentricular hearts who are not candidates for systemic venous-to-pulmonary artery anastomoses and children with anatomy unsuitable and risky for surgical palliation are offered transplant in preference.

A heart transplant is a palliative procedure which is offered only when no other medical or surgical options remain for the child. The selection criteria for pediatric heart transplant recipients include the following:- complex congenital heart
disease not amenable to surgical intervention with a chance for acceptable outcome or survival; end-stage cardiomyopathy despite maximal medical therapy; conceptional age greater than 36 weeks and a current weight greater than 2 kg; failure to thrive or growth retardation due to heart failure; malignant arrhythmias unresponsive to therapy or defibrillator placement; documentation of progressive rise in pulmonary vascular resistance that would prevent a later successful heart transplant; and unacceptably poor quality of life due to heart failure.

**LUNG TRANSPLANT**

Heart and lung transplant is offered to children with cardiac pathologies with a non reactive pulmonary bed. Isolated causes of lung transplant are listed in Table. 1.

**Evaluation of candidates**

A child referred to the transplant team, undergoes a thorough, multispeciality evaluation to rule out any condition that would preclude transplantation. They must be free from chromosomal abnormalities or syndromes that limit survival or the benefit from transplant. A satisfactory neurological examination is mandatory. The candidate and family must undergo a rigorous psychosocial evaluation to ensure that family can provide long-term supportive care and handle medical needs during the follow-up period. The cardiovascular evaluation includes echocardiography and cardiac catheterization, and possibly V/Q scan and chest CT or MRI. These are performed to define the anatomy as well as to evaluate the pulmonary vascular resistance and delineation of the pulmonary blood flow

The reactivity of the pulmonary vascular bed will decide the nature of the transplant. If the pulmonary vascular bed is nonreactive, the only option for the child is to be listed for a heart-lung transplant. The child also has to undergo various immunological testing for ABO and Rh compatibilities with the potential donor.

**Recent advances**

There are new developments which may have impact on the transplant services.

**Advances in the management of heart failure**

The COCPIT study in adults showed that only patients with severe heart failure had a survival benefit from transplantation, which has major implications for heart transplantation. Though the study has been criticised for the short observation period and incomplete data it has encouraged the permeation of the process of new treatments for heart failure into pediatrics.

In a recent study from UK, it has been found that the use of maximal oxygen consumption is

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**Table 1. Indications for lung / heart lung transplant**

<table>
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<tr>
<th>Indications</th>
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<tr>
<td>Emphysema/COPD</td>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Idiopathic pulmonary fibrosis</td>
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<tr>
<td>Primary pulmonary hypertension</td>
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<tr>
<td>Alpha-1-antitrypsin deficiency</td>
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<tr>
<td>Others : Sarcoidosis</td>
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<tr>
<td>Interstitial lung disease</td>
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<tr>
<td>Bronchiectasis</td>
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<tr>
<td>Pulmonary fibrosis</td>
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<tr>
<td>Lymphangioleiomyomatosis</td>
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<tr>
<td>Obliterative bronchiolitis (Non-retransplant)</td>
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<tr>
<td>Pulmonary vascular disease</td>
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<tr>
<td>Occupational lung disease</td>
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<tr>
<td>Inhalation burns / Trauma</td>
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<tr>
<td>Rheumatoid disease</td>
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helpful in assessment of severity of heart failure and a cut off value of 14 ml/kg/min has been shown to be of prognostic use\(^4\). This has also been used in the timing of pediatric heart transplantation referral.

The use of angiotensin converting enzyme inhibitors and \(\beta\) blockers has improved survival in heart failure. Like wise cardiac resynchronisation therapy which has been successful in adults with heart failure is making its way into the pediatric population to optimize the cardiac status.

**Mechanical support**

Extracorporeal membrane oxygenation (ECMO) has been successfully used as a bridge to transplantation in the category of children needing significant inotropes and mechanical assistance. Though this is not a long term support, it is an option for several weeks\(^5\). ECMO bridging to transplant does require the increased use of marginal donor hearts and has the substantial morbidity of ECMO, often requiring tracheostomy, renal dysfunction requiring hemofiltration and muscle weakness postoperatively leading to delayed mobilisation.

**ABO mismatch and infant transplantation**

20% of pediatric transplants are infants where there is paucity of suitable donors. The Toronto group have reported successful transplantation with ABO incompatible heart\(^6\). Though hyperacute rejection has been a strong contraindication for ABO incompatible heart transplantation they were successful because the infants in the first year of life do not produce isohemagglutinins and titres of anti-A or anti-B antibody titres are low. However if the titre is high before transplantation it is wise to stop the process. The whole process is very motivating and available donor pool has greatly widened.

**Survival after heart transplantation**

There have been great advances in pediatric intensive care with ECMO to support failing hearts and this has reduced the peri-operative mortality significantly. Newer immuno-suppressive drugs like tacrolimus (calcineurin inhibitor) and mycophenolate mofetil are being widely used instead of cyclosporin. Reduced use of steroids has decreased incidence of hypertension, obesity and coronary disease. The use of statins has reduced the incidence of coronary heart disease and also has a positive input with the reduction of acute rejection in the adults and this practice is now used in pediatrics. The combination of all these strategies has resulted in improved outcomes.

**Lung or heart-lung transplantation**

There has been a change in trend from heart lung transplantation towards bilateral or double lung transplantation in the last few decades. The various options available are Domino’s procedure which was in vogue in the 80’s where a heart lung transplant is performed with cardiac bypass, with the explanted heart used for patient with terminal cardiac disease. Double lung transplantation where both the lungs are transplanted is performed under cardiopulmonary bypass. Bilateral sequential lung transplantation is increasingly preferred with one lung being transplanted followed by the other without the need for bypass\(^7\).

**Outcome following transplantation**

The survival figure internationally for the heart transplant is around 90% for the first year and at five years it is reduced to 80%\(^8\). Infection with background suppression of the immune responses is the other main cause of death. Congenital disease, retransplant, recipient age, creatinine, donor age,
donor body surface area (BSA) and pediatric transplant volume are factors affecting one year survival.

Lung transplant still has poor outcomes. The outcome is affected by the early deaths caused by acute graft rejection and latter as part of the chronic rejection or acute rejection with respiratory infection in the form of bronchiolitis obliterans which is a condition poorly understood.

**Points to Remember**

- **Pediatric cardiothoracic transplantation is a complex area with complex decision making.**
- **The indications have evolved over the decades.**
- **Better management of heart failure, mechanical support and immuno suppression have improved outcomes.**

**References**


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**Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma**

In acute asthma attacks, higher doses of inhaled \( \beta_2 \)-agonists (reliever inhalers) are used to overcome the narrowing of the passages in the lungs. The medication can be given by wet nebulisation or from an inhaler with a spacer device (holding chamber). This review now includes in-patient studies, as well as those in casualty and community setting, comparing these two delivery methods in acute asthma attacks. In adults, no important differences were found between the two methods, whilst in children those randomised to wet nebulisation spent longer in casualty. Metered-dose inhalers with a spacer can perform at least as well as wet nebulisation in delivering \( \beta_2 \)-agonists in acute asthma.

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH SPECIAL REFERENCE TO INDIAN SCENARIO

* Shipra Kaicker
** Gauri Kapoor

Abstract: Hematopoietic stem cell transplantation (HSCT) has the capacity to achieve cure for many pediatric malignant and non-malignant diseases. Improved selection of donors using better HLA matching techniques, a wider selection of donor sources for unrelated transplants, newer regimens for immunosuppressive therapy and improved supportive care for complications related to the post transplant period have all led to improved outcomes. Clinicians should be aware of current indications for stem cell transplantation and patients should be referred early to transplant centers. In India, there is a need for capacity building in terms of developing transplant centers to cope with the large number of patients who need HSCT as well as training transplant physicians and nurses.

Keywords: Hematopoietic stem cell transplantation, Children, BMT

Hematopoietic stem cell transplantation is now used worldwide to treat a variety of pediatric malignant and non-malignant diseases. This discipline has expanded rapidly over the past 50 years. New advances related to improved techniques of HLA matching, sources of stem cells used and supportive care have led to improved outcome and a decrease in morbidity and mortality related with transplantation.

Bone marrow transplantation was first successfully used in the 1960’s. The initial transplants were done for patients with immunodeficiencies. Since then the benefit of transplantation has been demonstrated in a variety of diseases which now have a potential for cure with transplantation.

Bone marrow transplantation in malignant diseases (hematological malignancies and solid tumors) was designed initially with the goal of rescuing the recipient’s marrow from the effects of myelo-ablative chemotherapy that was administered to destroy malignant cells. This was achieved by ablating the marrow with high dose chemotherapy alone or in combination with total body irradiation followed by intravenous infusion of hematopoietic stem cells. In the more recent past, the additional immune mediated effects of the donor allograft have begun to be recognized. Immune effector cells from the donor are thought to potentiate anti-tumor activity by creating a graft versus tumor effect.

In India, the number of children requiring bone marrow transplantation far exceeds the number of transplants that are actually being performed. The major limiting factor is the high
cost of transplantation (autologous transplant costs approximately Rs 3-5 lakh and allogeneic Rs 10-15 lakh with very few of these transplants being reimbursed by insurance). There are also limited centers with the expertise for performing transplantation and they may have a long waiting list for patients requiring transplantation. There may be additional difficulties in finding suitable unrelated donors for allogeneic transplant if no matched donors exist within the family. Setting up of national bone marrow registries and donor banks and drives in the community for voluntary marrow donation would be important steps to improve the availability of unrelated marrow sources. Setting up of umbilical cord blood banks as a source of stem cells may also be an important way to expand the unrelated donor pool since this would not require voluntary donation. Moreover identifying and mobilizing sources of funding for patients with life threatening conditions where hematopoietic stem cell transplantation is the only curative option is another area that needs prioritization.

Types of transplantation

This depends on the source of hematopoietic stem cells. When obtained from a genetically identical twin it is called syngeneic, from a sibling or unrelated human donor it is termed as allogeneic and when obtained from the patient’s own bone marrow or peripheral blood it is autologous.

Autologous transplantation

Autologous transplants use stem cells obtained from the patient that are used to rescue the patient’s bone marrow from the myeloablative effects of high dose chemotherapy. Many chemo-sensitive solid tumors exhibit a steep dose-response curve for chemotherapeutic agents to achieve effective cell kill. The main dose limiting toxicity of high dose chemotherapy is often life threatening myelo-suppression. This limits the dose of chemotherapeutic agents that can safely be administered. With the use of autologous transplantation the recipient’s own stem cells are infused intravenously after treatment with myeloablative doses of chemotherapy. The stem cells are typically collected early on in therapy (usually after the first 2-3 cycles of chemotherapy). They are stored with DMSO (Dimethyl Sulfoxide) and frozen at −80 °C and can be thawed for use when required. Peripheral blood stem cells (PBSCs) are used for most autologous transplants. These are collected from the patient after mobilization from the bone marrow into peripheral blood with the use of growth factors such as G-CSF (granulocyte colony stimulating factor). The collected stem cells can be concentrated using CD34 antigen labeled columns (CD34 is a marker for hematopoietic stem cells) to get a purer product. The cells may also on occasion be treated ex vivo with cytotoxic drugs or monoclonal antibodies, in an attempt to decrease contamination with tumor cells. Autologous transplant – single or in tandem is usually performed towards the tail end of therapy as consolidation for high risk tumors with the aim of eliminating potentially resistant tumor cells that may have survived beyond the initial chemotherapy cycles. Immuno-suppression is not required after autologous transplantation since the stem cells are the patient’s own and there is no risk of graft versus host disease. Pediatric diseases for which autologous transplants are most often utilized are listed in Table 1.

Allogeneic transplantation

Allogeneic transplantation utilizes a stem cell source that is different from the patient’s own stem cells. As mentioned above the donor of stem cells could be a twin, a sibling or an unrelated person. Hematopoietic stem cells for allogeneic transplants are currently available from 3 main sources: Bone marrow (BM), peripheral blood stem cells (PBSCs) and umbilical cord blood (UCB) which is a rich source of hematopoietic
Table 1. Indications for autologous transplantation in children

<table>
<thead>
<tr>
<th>Hematological malignancies</th>
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<tbody>
<tr>
<td>1. Hodgkin’s lymphoma - relapse or partial remission</td>
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<tr>
<td>2. Non Hodgkin’s lymphoma - relapse or partial remission</td>
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<tr>
<td>3. Acute myeloid leukemia (AML) and Chronic myeloid leukemia (CML) - investigational</td>
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<table>
<thead>
<tr>
<th>Solid tumors</th>
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<tbody>
<tr>
<td>1. Neuroblastoma stage IV</td>
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<tr>
<td>2. Ewing’s sarcoma, Primitive neurectodermal tumors (PNET) - metastatic*</td>
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<tr>
<td>3. Rhabdomyosarcoma*</td>
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<tr>
<td>4. Wilms tumor*</td>
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<tr>
<td>5. Brain tumor</td>
</tr>
<tr>
<td>6. Germ cell tumor*</td>
</tr>
</tbody>
</table>

*For solid tumors with metastatic disease at presentation or relapse that is chemo sensitive. Among solid tumors other than brain tumor and neuroblastoma, autologous transplant has not been shown to improve survival and remains an investigational modality of treatment.

stem cells. Traditionally, BM has been used as a source of stem cells for allogeneic HSCT and more recently PBSCs are gaining popularity.

**Donor selection and histocompatibility testing**

The first and most important step to successful allogeneic transplantation is the understanding of polymorphisms in histocompatibility antigens among different ethnic populations. HLA matching between the recipient and potential donors has to be carried out to choose the best compatible donor to ensure successful allogeneic transplantation. Two major types of histocompatibility antigens exist on human cells- class 1 molecules which include HLA A, B and C and type 2 molecules HLA- DR, DQ. Matching for HLA has traditionally been done using serological techniques. More recently high resolution typing is done using molecular methodology. High resolution typing uses techniques such as SSOP (sequence specific oligonucleotide probes) or SSP (sequence specific primers). Matching at the allelic level by these techniques allows for identification in disparities not picked up by conventional serological techniques. A low incidence of graft versus host disease can be achieved when children receive hematopoietic stem cell transplant after matching with high resolution typing.

A HLA matched sibling (6/6 HLA match) if available remains the best donor source. About 60% - 75% patients will not have an available matched family donor and will require an alternative donor source. International marrow registries and banks now allow most patients at least in the developed countries to find a suitable donor. However, the availability of donors of Asian origin remains limited in the international registries.

ABO incompatibility can exist between donor and recipient and this does not preclude donation. For an unrelated transplant a fully matched donor is ideal. A one or two antigen mismatched cord
blood unit is permissible since cord blood represents a more immunologically naïve source of stem cells\(^5\).

Recipients and donor screening is done for any major organ dysfunction as pre-transplant evaluation. This always involves screening for many infectious agents that may be problematic to the recipient during transplantation: Hepatitis, EBV, CMV, HSV 1 and 2, HTLV and HIV viruses.

**Hematopoietic stem cell collection**

(1) **Bone Marrow**: Donor marrow is collected by repeated aspirations from posterior iliac crests into a heparinized saline container. The quantity of nucleated bone marrow cells collected must be at least 2-5 x 10\(^8\)/kg of recipient weight or CD34 + cells more than 5 x 10\(^6\) to ensure engraftment. The usual volume of marrow to achieve this cell yield is about 10-15 ml/kg of recipient body weight. After processing, the marrow is infused intravenously into the recipient.

(2) **Umbilical cord blood stem cells**: The recognition that umbilical cord blood is a rich source of hematopoietic stem cells (HSCs) led to the first successful cord blood transplantation in a Fanconi’s anemia patient in 1988\(^6\). This spurred the development of cord blood banks where cord blood units can be frozen and stored for future use. Cord blood is easy to obtain at the time of delivery and can be done by a trained medical professional. Cord blood now represents an excellent source of stem cells that is quickly and readily available.

**Advantages of cord blood stem cells**: (1) Due to their decreased allo-reactivity there is a decreased chance of graft versus host disease with umbilical cord blood transplants. (2) Cord blood is also easily collected and readily available when required as compared to a time lag for living donor selection, testing and donation and there is no risk of donor loss at the time of transplantation. (3) There is also a decreased risk for infections such as EBV and CMV (4) Increased tolerance to HLA-mismatch with cord blood using a 1 or 2 antigen mismatched donor.

**Disadvantages of UCB**: (1) Low cell dose which increases chances of graft failure, (2) slower engraftment with delay in recovery of neutrophils and platelets (3) absence of transfer of adoptive immunity and (4) lack of knowledge of the genetic history of the donor.

Currently about 300000 units of cord blood have been banked worldwide of which 3000 units have already been used for transplantation. In India storage of umbilical cord blood has been started by Reliance Life Sciences for public banking. Life Cell is a private cord blood bank that has opened collection sites in several cities in India. Histostem (a Korean company) also has plans of setting up cord blood banks in India. Cord blood banking will improve availability of unrelated donor units.

(3) **Peripheral blood stem cells**: In the 1990’s it was also realized that hematopoietic stem cells (HSCs) from the marrow could be mobilized into the peripheral blood of the donor after a few days of use of cytokines such as granulocyte colony stimulating factor (G-CSF) or granulocyte-monocyte colony stimulating factor (GM-CSF). This allowed the collection of peripheral blood stem cells (PBSCs) instead of bone marrow. Collection of PBSCs has the advantage of making donation much less painful for the donor. PBSCs are collected via an apheresis procedure from the peripheral blood after mobilization into the circulation with G-CSF or GM-CSF. Peripheral blood stem cell collection usually gives a product with a higher stem cell yield. Engraftment occurs faster with PBSCs due to a higher percentage of HSCs in the product as compared to other donor sources. The collected...
product is also thought to have a lower risk of tumor contamination. However there is a concern of increased risk of graft versus host disease particularly chronic GVHD. Peripheral blood stem cell transplantation is being used with increasing frequency nowadays for most autologous and many allogeneic transplants.

**Pre-transplantation conditioning regimens**

A variety of different conditioning regimens are used that may or may not involve total body irradiation. Most commonly used drugs for conditioning are cyclophosphamide and busulfan. Two of the more commonly used regimens for leukemia are TBI/Cy (total body irradiation/cyclophosphamide) and Bu/Cy (busulfan/cyclophosphamide). In aplastic anemia anti-thymocyte globulin is often used as part of initial conditioning regimen. Non-myeloablative regimens have recently been employed that utilize the ability of donor T cells to ablate host hematopoiesis or malignancy with some success.

**Role of allogeneic transplants in children (Table 2)**

**Beta thalassemia and sickle cell anemia**

Both beta-thalassemia and sickle cell anemia are lifelong disorders that decrease quality of life and overall lifespan. Bone marrow transplantation remains the only curative option for these diseases. Transplantation has a better outcome in younger patients (<17 years) particularly those who have been well chelated for iron overload and ideally should be recommended for a patient with a matched sibling donor. Outcome of transplantation for beta-thalassemia patients from a matched sibling donor varies with patient characteristics. The Pesaro classification assigns patients to risk groups based on their liver size, presence or absence of portal fibrosis on liver biopsy and adherence to regular chelation therapy. Class 1 patients (with none of the above listed risk factors) and class 2 patients (with one or two risk factors) have better outcomes after transplantation. Lucarelli et al reported thalassemia free survival of 94% in class 1 and 77 % in class 2 patients. Patients in class 3 have a less favorable outcome (53%) with an increased rate of transplant related mortality. Pre-transplant conditioning for transplants in thalassemia is typically done with a combination of busulfan and cyclophosphamide. In an attempt to improve transplant related mortality and decrease rejection in group 3 patients, the same group of investigators used a modified regimen using pre-transplant immunosupression with hydroxyurea and azathioprine. Fludarabine was also added to the conditioning regimen and a program of hypertransfusion and chelation was done prior to transplantation. All these measures appeared to improve survival for class 3 patients.

In India, the largest cohort of patients who have received transplants for beta thalassemia is at CMC Vellore. To date this group has performed transplants for about 300 thalassemia patients. Since a large number of thalassemia patients sent to this center have not received adequate medical treatment prior to referral, many will fall into Pesaro class 3 risk group. A recent observation of this group was that class 3 patients represent a heterogeneous group and not all will fare poorly. On retrospective multivariate analysis of their patient population they found that 2 significant variables emerged. Patients with liver size 5 cm or more and age 7 years or more had a worse outcome as compared to the group that did not have these factors who did significantly better.

In a very small group of patients with hemoglobinopathies a non-myeloablative, reduced intensity approach that gives rise to a mixed donor-recipient chimera has been tried. The rationale behind this is that cure may occur with a mixed chimeric state of donor and recipient marrow. Reduced intensity transplants have the advantage of decreasing the long term side effects of growth.
Table 2. Indications for allogeneic transplantation in children

<table>
<thead>
<tr>
<th>Malignant conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Leukemia.</td>
</tr>
<tr>
<td>a. Acute lymphoblastic leukemia (ALL) in first remission with very high risk features e.g. Philadelphia chromosome-positive ALL, low hypodiploidy</td>
</tr>
<tr>
<td>b. ALL in second or third or subsequent remissions</td>
</tr>
<tr>
<td>c. Acute myeloid leukemia in first remission with an available matched related donor or unrelated donor for patients in second or subsequent remission</td>
</tr>
<tr>
<td>d. Chronic myeloid leukemia</td>
</tr>
<tr>
<td>e. Myelodysplasia</td>
</tr>
<tr>
<td>f. Juvenile chronic myeloid leukemia (JCML)</td>
</tr>
<tr>
<td>g. Juvenile myelomonocytic leukemia (JMML)</td>
</tr>
<tr>
<td>2) Lymphoma- Hodgkin’s and Non-Hodgkin’s in second remission</td>
</tr>
<tr>
<td>3) Myelodysplasia/myelofibrosis</td>
</tr>
<tr>
<td>4) Hemophagocytic lymphohistiocytosis</td>
</tr>
<tr>
<td>5) Selected solid tumors such as very high risk Ewing’s, stage 4 neuroblastoma, renal cell carcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-malignant conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Hemoglobinopathies – e.g. Thalassemia major and sickle cell anemia</td>
</tr>
<tr>
<td>2) Immunodeficiency syndromes- SCID, Immunodeficiency with hyper IgM, Leucocyte adhesion deficiency, Wiskott Aldrich, Chediak Higashi, X linked lymphoproliferative disorder, Kostmann syndrome, chronic granulomatous disease, other severe neutrophil defects (Schwachmann syndrome), Omenn syndrome</td>
</tr>
<tr>
<td>3) Diamond Blackfan anemia</td>
</tr>
<tr>
<td>4) Acquired aplastic anemia</td>
</tr>
<tr>
<td>5) Fanconi anemia</td>
</tr>
<tr>
<td>6) Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>7) Mucopolysaccharidosis</td>
</tr>
<tr>
<td>8) Osteopetrosis</td>
</tr>
</tbody>
</table>

and endocrine problems that occur post transplant with the use of myelo-ablative conditioning regimens.

Many iron overloaded thalassemia patients benefit from continued iron chelation/ phlebotomy after successful transplantation.

Sickle cell patients similarly have an excellent chance for cure with a transplant from an HLA matched sibling. However, since the clinical features of this disease may be diverse, transplant is usually reserved for patients with severe disease such as stroke.\textsuperscript{11}
**Transplantation for primary immunodeficiencies in childhood**

Early transplantation (age < 6 months) for primary immunodeficiency syndromes such as SCID (sub acute combined immunodeficiency syndrome) from a matched sibling donor if available leads to the best outcomes with an overall survival >90% if performed at an early age. Delay in transplantation is complicated by significant infectious complications particularly pulmonary infections that may have already occurred in the host prior to transplantation. In one study infants transplanted at <3.5 months of age had a 95 % overall survival (OS) as compared to 76% OS for older children. If a matched sibling donor is not available, a T-cell depleted haplo-identical donor (often the patient’s mother) has been used. In a SCID patient who shows evidence of maternal engraftment the child is already tolerant to maternal cells. It is important to ensure adequate T cell depletion in such cases to prevent development of graft versus host disease. T cell depleted grafts run the risk of development of significant opportunistic infections and EBV associated lymphoproliferative disease in the post transplant period due to slow recovery of T cells. Reduced intensity non-myeloablative regimens may also be employed in future to avoid the problems related with myeloablative conditioning.

In such cases however, although T cell function reconstitution occurs, true stem cell grafting from the donor probably does not occur since B cells, erythroid and myeloid cells often remain of recipient origin. In some other immunodeficiencies such as reticular dysgenesis prior conditioning is always required to prevent failure of engraftment. Other immunodeficiencies for which transplantation has been used successfully are Wiskott Aldrich syndrome, familial hemophagocytic lymphohistiocytosis, severe congenital neutropenia and many others. In families with a history of immunodeficiency, where a genetic diagnosis has already been made prenatal diagnosis can enable early transplantation. Early transplantation remains the key factor in predicting successful outcome in these patients. Reduced intensity non-myeloablative regimens may also be employed in future to avoid the problems related with myeloablative conditioning.

**Transplantation for aplastic anemia and bone marrow failure syndromes**

Acquired aplastic anemia can be cured by transplantation from a fully matched sibling donor and all such patients should be referred early for transplantation since they have excellent outcomes. Transfusion of multiple blood products can adversely affect transplant outcome by leading to allo-immunization. In particular such patients should not receive blood products from an immediate family member. Young patients (less than 17 years) with no other co-morbidities have a more than 80% chance of cure. Other bone marrow failure syndromes such as Fanconi anemia can also be transplanted if a suitable donor is available. Modified conditioning regimens often have to be used in such patients to avoid the toxicity of the conditioning regimens.
Transplantation in childhood acute leukemias

Most patients with acute lymphoblastic leukemia can be cured with current chemotherapy regimens. Indications for transplantation include poor prognostic factors where survival is sub-optimal with high dose chemotherapy regimens alone. For most cases of ALL with poor prognostic factors the advantage of bone marrow transplantation is still controversial. A conditioning regimen that includes radiation seems to confer a survival advantage over conditioning with chemotherapy alone since the use of radiation appears to improve chances of preventing subsequent leukemia relapse. Evaluation of minimal residual disease status by techniques such as flow cytometry after chemotherapy and gene expression profiling will identify subsets of patients who are at an increased risk of relapse and incorporation of upfront transplantation strategies in the future for such high risk patients may improve chances of leukemia free survival. Umbilical cord blood has been successfully used for transplants in children with leukemia.

Current indications for transplant have recently been reviewed\(^\text{16}\). These include (1) Transplantation in second remission (CR2) in cases of early relapse in ALL (relapse occurring in less than 36 months from initial diagnosis) with a well matched related donor is probably the most clearly defined indication for transplantation\(^\text{17}\). Late relapses (more than 36 months) may be salvaged with chemotherapy alone and transplantation can be deferred if a second relapse occurs and a third remission can be achieved.

(2) ALL with Philadelphia chromosome positivity in first complete remission can be considered for transplant if there is a matched related sibling since this cytogenetic feature portends a very poor prognosis\(^\text{18}\). However, transplantation with a well matched but unrelated donor or with cord blood may also be considered especially if associated high risk features co-exist such as WBC count at diagnosis more than 100,000 or age more than 10 years. With the current use of Imatinib and other newer generation tyrosine kinase inhibitors for Philadelphia chromosome positive ALL in current protocols the role of unrelated transplant in this setting is still evolving.

(3) Hypodiploid ALL (less than 44 chromosome copy number) has a poor prognosis with chemotherapy alone (less than 40 % survival). Thus patients in this subgroup may benefit from early transplant. The role of transplantation in infant ALL with MLL gene re-arrangements has been looked at with mixed results, proving beneficial in some and not in other studies.

Thus a knowledge of the initial leukemia cytogenetics and the patient’s response to therapy serve as important guides to identify which patients may benefit from transplant.

(4) Acute myeloid leukemia in childhood should be transplanted in first complete remission if a HLA matched sibling donor is available. If no sibling donor is available high dose chemotherapy is the standard of care. Unrelated transplantation is done for relapsed AML in second remission.

(5) Chronic myeloid leukemia with a matched sibling donor can be cured by bone marrow transplantation in a young adult even in the era of tyrosine kinase inhibitors such as imatinib and other second generation inhibitors. Graft versus leukemia effect of the donor graft is well documented in CML.

Role of transplantation for pediatric lymphomas

The role of bone marrow transplantation in pediatric lymphomas is still evolving and has recently been reviewed\(^\text{19}\). Currently autologous
transplantation in pediatric lymphoma appears to benefit patients with relapsed Hodgkin’s and Non-Hodgkin’s lymphoma. However, patients with poor prognostic features such as CNS or bone marrow involvement at diagnosis or patients with poor response to first line therapy may benefit from upfront transplantation. About 90% of patients with Hodgkin’s disease are curable with chemotherapy alone even in advanced stages. However, about 10-15% of patients will relapse. The duration of first remission is an important factor and patients who relapse 12 months after diagnosis can often enter remission with standard chemo alone. However patients with refractory disease or with early relapse fare poorly. Progression free survival for this group with high dose chemotherapy followed by autologous transplant is an estimated 5-10 year overall survival of 20-25% and these patients continue to remain at risk for secondary AML and breast carcinoma. Similarly patients with non-Hodgkin’s lymphoma that relapse or have chemo-refractory disease fare poorly even after attempts at autologous transplantation. Allogeneic transplant for such patients has shown promising early results and it is hypothesized that there may be a graft versus lymphoma effect in these cases.

**Complications of transplantation**

Conditioning regimens may lead to complications unique to transplantation such as: toxic vasculitis, severe mucositis, veno-occlusive disease of liver, acute alveolitis, interstitial pneumonitis, obliterative bronchiolitis and multiple organ failure in addition to infectious complications. Clinicians dealing with transplant patients therefore need to have a high index of suspicion for the above conditions.

Infections during the first 30 days post transplant mainly include bacterial gram negative and gram positive infections; invasive fungal infections primarily Aspergillus and reactivation of herpes simplex.

Infections 30-120 days post transplant include protozoal infections with PCP and toxoplasma; viral infections like CMV, adenovirus, human herpes virus-6 (HHV-6) and EBV infections; and fungal infections with candida, aspergillus and fusarium.

Infections occurring more than 120 days post transplant are usually sinopulmonary infections with encapsulated organisms such as pneumococcus and viral infections like cutaneous herpes zoster.

Interstitial pneumonitis is a dreaded transplant related complication. It may occur from infections such as CMV, PCP and fungus, drugs, radiation and could be immune mediated or idiopathic.

Pancytopenia occurs universally and blood component support with red blood cells and platelets is an essential part of supportive care post transplant. Growth factor support with G-CSF is routinely used.

**Graft versus host disease (GVHD)**

GVHD occurs primarily due to allo-reactivity of T cells in the donor graft against the recipient. Its incidence is highest with unrelated donor transplants. GVHD prophylaxis is done routinely in allogeneic transplants with immuno-modulatory drugs such as steroids, cyclosporine, methotrexate etc. The duration of prophylaxis is for about a year with a gradual weaning of the drugs.

Acute GVHD manifests typically within 30-40 days post transplant but can occur up to the first 100 days and manifests most often as fever, rash, gastroenteritis, hepatic dysfunction
and bronchitis. It is managed by stepping up immunosupression post transplant. A biopsy is often required to establish the diagnosis.

Chronic GVHD occurs more than 100 days post transplant. It may be limited to a single organ or may have a more diffuse involvement. It usually manifests with scleroderma like skin lesions, dry eyes, dry mouth, hepatic dysfunction, joint contractures, interstitial pneumonitis and bronchiolitis obliterans.

**Post transplant morbidities**

The pediatric patient may often return to his hometown to be cared for by his primary pediatrician after the initial months post transplant with frequent follow-up visits scheduled by the transplanting facility.

It is important that pediatrician taking care of such patients be aware of the possible late complications that can arise after transplantation so that he/she may communicate with the transplant centre if problems arise. Following are possible late complications that should be monitored for:

1. Chronic GVHD
2. Endocrine problems: hypothyroidism, hypogonadism, growth failure
3. Secondary malignancies
4. Sterility
5. Cataracts
6. Renal insufficiency
7. Dental problems
8. Immunological dysfunction
9. Cardiomyopathy
10. Interstitial and obstructive lung disease
11. Aseptic bone necrosis
12. Post transplant lympho-proliferative disorder
13. Leuco-encephalopathy and neuro-cognitive problems manifesting as school difficulties

**Hematopoietic stem cell transplantation in India**

The first allogeneic stem transplant was done in 1983 at Tata Memorial Hospital, Mumbai. This was followed shortly thereafter by Christian Medical College, Vellore in 1986. Vellore has subsequently gone on to become the single largest transplant centre in the country for adults as well as for children.

Today a number of centers have developed successful BMT programmes like Apollo Speciality Hospital, Chennai, All India Institute of Medical Sciences, Delhi, Army Hospital (Research and Referral), New Delhi, Jaslok Hospital, Mumbai and Rajiv Gandhi Cancer Institute and Research Centre, Delhi to name a few. More than 2000 patients have undergone allogeneic and autologous HSCT at these centres.

Pediatric HSCT are being done in India for various indications as shown in Tables 3 and 4. Christian Medical College, Vellore has the largest series of over 400 transplants of which nearly 350 have been done for thalassemia major followed by aplastic anemia and leukemias.

Tata Memorial Mumbai have done about 76 pediatric transplants for leukemias, aplastic anemias, Fanconi anemia while Apollo Chennai has a series of nearly 60 patients transplanted for similar indications. It is quite apparent that there is a need for more trained transplant physicians and nurses, and for more transplant centres to cope with the large number of patients who need HSCT.

**Summary**

Many diseases are potentially curable by bone marrow transplantation. New techniques have improved outcomes of transplant and availability of wider donor sources makes transplant an option for many patients. Patients
### Table 3. Pediatric transplant data (<18yrs), Tata Memorial Center, Mumbai, 1983-2008.

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allogeneic transplant</th>
<th>PBSC/BM / Un RelCord</th>
<th>Autologous transplant</th>
<th>PBSC/BM</th>
<th>Total (auto+allog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>20</td>
<td>7/12/1</td>
<td>3</td>
<td>2/1</td>
<td>23</td>
</tr>
<tr>
<td>ALL</td>
<td>7</td>
<td>2/5/0</td>
<td>2</td>
<td>2/0</td>
<td>9</td>
</tr>
<tr>
<td>CML</td>
<td>16</td>
<td>5/11/0</td>
<td>1</td>
<td>1/0</td>
<td>17</td>
</tr>
<tr>
<td>Thal major</td>
<td>13</td>
<td>9/1/2/1(BM+ cord related)</td>
<td>NA</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Aplastic An</td>
<td>9</td>
<td>1/8</td>
<td>NA</td>
<td>NA</td>
<td>9</td>
</tr>
<tr>
<td>Fanconi An</td>
<td>10</td>
<td>5/5/0</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>CGD</td>
<td>1</td>
<td>1/0/0</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>0</td>
<td>NA</td>
<td>8</td>
<td>6/0/2(PBSC + BM)</td>
<td>8</td>
</tr>
<tr>
<td>PNET</td>
<td>0</td>
<td>NA</td>
<td>4</td>
<td>3/1</td>
<td>4</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0</td>
<td>NA</td>
<td>6</td>
<td>3/2/1(PBSC + BM)</td>
<td>6</td>
</tr>
<tr>
<td>ARMS</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>1/0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>76</td>
<td>25</td>
<td>101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ARMS-Alveolar Rhabdomyosarcoma; NA-Not applicable; Unrel cord-unrelated cord; CGD-Chronic Granulomatous Disease. [This data is obtained by personal communication from Dr. Navin Khattry, Assistant Professor & BMT Programme Coordinator Tata Memorial Centre, Mumbai].

### Table 4. Pediatric transplant data (<16yrs), Apollo Cancer/ Speciality Hospital, Chennai, 1995 to Aug 2008: Indications and types of grafts

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allogeneic</th>
<th>Autologous</th>
<th>Cord Blood Related</th>
<th>Cord Blood Unrelated</th>
<th>From identical twin</th>
<th>Haplo-identical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>ALL</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>CML</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bilineage Leukemia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thal major</td>
<td>24</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Fanconi’s anemia</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Congenital Erythropoietic</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Congenital Sideroblastic anemia</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Ewing’s Sarcoma</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Hepatoblastoma</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td><strong>Total</strong></td>
<td>58</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>81</td>
</tr>
</tbody>
</table>

AML= acute myeloid leukemia; ALL = acute lymphoblastic leukemia; CML= chronic myeloid leukemia; Thal maj= Thalassemia major. [This data is obtained from personal communication from Dr Jose M Easow, In-charge Blood and Marrow Transplantation Unit at Apollo Cancer / Speciality Hospital, Chennai]
who may benefit from transplantation should be referred early to an established transplant centre. The field of bone marrow transplantation in India is undergoing a dynamic change as more centres are taking up this challenging field. Even so, there is a significant gap between demand and supply often leading to long waiting lists of patients. Hence the health care advisors need to focus on planning to develop more centers and trained personnel. High cost of transplantation remains a deterrent for many families. Public and private insurance agencies and NGOs need to take it up as a priority area.

**Points to Remember**

- Many diseases are potentially curable by bone marrow transplantation.
- New techniques have reduced transplant related morbidity and mortality.
- Patients who may benefit from transplantation should be referred early to an established transplant center.
- Health care advisors need to focus on planning to develop more BMT centers and trained personnel in India.

**References**


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**CLIPPINGS**

**Interventions for treating obesity in children**

Childhood obesity affects both the physical and psychosocial health of children and may put them at risk of ill health as adults. More information is needed about the best way to treat obesity in children and adolescents. In this review, 64 studies were examined including 54 studies on lifestyle treatments (with a focus on diet, physical activity or behaviour change) and 10 studies on drug treatment to help overweight and obese children and their families with weight control. No surgical treatment studies were suitable to include in this review. This review showed that lifestyle programs can reduce the level of overweight in child and adolescent obesity 6 and 12 months after the beginning of the program. In moderate to severely obese adolescents, a reduction in overweight was found when either the drug orlistat, or the drug sibutramine were given in addition to a lifestyle program, although a range of adverse effects was also noted. Information on the long-term outcome of obesity treatment in children and adolescents was limited and needs to be examined in some high quality studies.

CORNEAL TRANSPLANTATION IN CHILDREN

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*Bina John
*Sujatha Mohan
**Srinivas K Rao

Abstract: The child’s eye is not a miniature adult’s eye. It has very different anatomic and functional characteristics and surgery is often technically challenging. The developing visual system in a child is also prone to suppression and often the anatomic results of corneal grafting in children are not commensurate with the visual gains, due to amblyopia. The child is also unable to look after the operated eye, and often does not mention symptoms of early graft rejection or loose sutures, and hence parental support is critical in the perioperative period. These issues need to be addressed in order to obtain good outcome with pediatric penetrating keratoplasty. However, with due attention to these issues, an experienced corneal transplant surgeon, working closely with the pediatrician and anesthetist, can often succeed in improving visual function in children with corneal opacities.

Key words: Amblyopia, Pediatric, Penetrating keratoplasty, Visual outcome.

Pediatric corneal transplantation is not a commonly performed procedure. It is a technically complex surgery and is quite different from such procedures in adults. The outcome of the surgery is also not the same as in adults and often requires close cooperation of a team of professionals for optimal outcome. The team includes ophthalmologists (corneal, pediatric, glaucoma and vitreoretinal specialists), a pediatrician and a pediatric anesthetist. This article explores the indications, surgical caveats, postoperative care procedures and outcome with special emphasis on the role of the pediatrician in the management of children with this problem.

Although the definition of ‘pediatric’ in the context of corneal transplantation varies widely in literature (with 12, 14 or 16 years being the upper limit), it is generally true that the older the child, the closer is the resemblance of surgical technique and outcome to that in adults. It is widely accepted that corneal replacement surgery in infants and very young children (less than 5 years of age), is associated with a worse prognosis. However, it is also paradoxical that current advice is to operate as soon as possible, especially in children with unilateral corneal pathology, to promote the development of the visual system – often as early as 3 months of age. There are various reasons for the age related outcomes. In very young children, there are difficulties in the pre-, intra- and post-operative periods.

Assessment of visual function

Visual function is difficult to assess quantitatively in infants and preschool children. In the latter, an estimate is possible using specially designed cards with cartoon drawings of common objects like the Teller visual acuity cards, which are calibrated to provide a semi-quantitative
measure of visual function.\textsuperscript{2} In infants however, surrogate measures of visual function are often used, which include the presence of a squint (malaligned), nystagmus, resistance to covering one eye (if the right eye has poor vision, the infant will often tolerate covering of the right eye, since the left eye sees; but will become restless if the left eye is covered), and the Franscheschetti sign (the child constantly pokes the eye with a finger – to stimulate the retina, which produces flashes of light called ‘phosphene’). The presence of one or more of these signs in a child should initiate prompt referral to an ophthalmologist. In the context of this article, these signs are present in children with an obvious corneal opacity. However, it is important to remember that such findings can also occur due to problems in the retina or optic nerve in a child with a normal appearing eye.

**Indications for corneal replacement in children**

The cause of the corneal opacity is important – as it has been shown to influence the surgical results of corneal replacement in children. In general, the main reasons for corneal transplants are the following:


Congenital problems (Table 1)\textsuperscript{2} are those that the child is born with and are important since they are often associated with other developmental problems in the eye or other physical ailments. These can influence the surgical process and general anesthesia and influence final visual outcomes and may also help deciding the need for and timing of surgery.

Acquired traumatic opacities in the cornea are often associated with damage to other parts of the eye – specifically the lens and sometimes the retina. They may also be associated with

**Table 1. Common causes of congenital corneal opacities**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
</tr>
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</table>
| Neurocristopathies | a. Peter’s anomaly  
b. Sclerocornea  
c. Anterior staphyloma / Keratectasia  
d. Infantile glaucoma |
| Dystrophic processes | a. Endothelial dystrophies  
  i. Posterior polymorphous dystrophy  
  ii. Congenital hereditary endothelial dystrophy  
 b. Stromal dystrophies  
  i. Congenital hereditary stromal dystrophy |
| Inborn errors of metabolism | a. Mucopolysaccharidoses  
  i. MPS IH (Hurler syndrome)  
  ii. MPS IS (Scheie syndrome)  
  iii. MPS IH-S (Hurler-Scheie syndrome)  
  iv. MPS VIA (Marateaux Lamy syndrome) severe  
  v. MPS VII (Sly syndrome)  
  vi. MPS of Bowman layer  
 b. Mucolipidoses  
  i. MLS IV |
| Infectious embryopathies | a. Syphilis  
 b. Rubella  
 c. Herpes simplex |
| Congenital tumors | a. Corneal / Limbal dermoid |
infections in the eye at the time of injury. These associated changes in the eye can influence the choice, timing and outcomes of surgery. Other causes of trauma include birth injuries (often with forceps assisted delivery) resulting in rupture of the Descemet’s membrane, corneal edema and scarring, and chemical trauma to the ocular surface.

Acquired non-traumatic opacities in the cornea are most often due to healed infections, immunological processes like interstitial keratitis, vitamin A deficiency, or sometimes neurotrophy. In these conditions, the corneal opacities are often associated with vascularization and this can compromise the immunological privilege present in the normal cornea, with resultant increase in the risk of rejection of the corneal graft.

While systemic conditions take precedence in planning the care of the child, it is important that children with corneal opacities are referred quickly to the ophthalmologist for a detailed assessment. If examination reveals a compromise of visual function, then early surgery must be planned to rehabilitate the child, given the constraints mentioned in the earlier sections. While waiting for surgery, it may sometimes be possible to help the child by dilating the pupil in the affected eye. If the corneal opacity is small and/or partially involving the corneal center, dilating the pupil to a size larger than the opacity can help partially ameliorate the deleterious effects of the opacity on the visual system.

**Surgical technique**

It is important that the surgeon be experienced in the management of these small eyes. In addition to a small palpebral fissure, which makes access to the cornea difficult (and requires the use of special miniature instruments like the eye speculum), it is important to remember that the pediatric eye is not a miniature adult eye. The scleral and corneal tissues have very low rigidity and a tendency for collapse of the ocular coats often results in an increased upthrust during surgery. If not managed appropriately, this can sometimes result in a spontaneous extrusion of the lens from the eye. The intraocular tissues also tend to be less well developed and fragile and require extremely careful handling. Even if the above mentioned are taken care of, an increased occurrence of inflammation in the postoperative period is not uncommon. The surgeon must be prepared for intraoperative surprises – due to concomitant changes in other ocular structures and must deal with them appropriately.

**Postoperative care**

The postoperative care of such children offers many challenges. Young children are often averse to repeat examinations and applying medications in the operated eye can also be very difficult. It is important to preoperatively assess the social support systems that exist for the child. Parents and/or close relatives must be counselled at length and if in the surgeon’s opinion, they are unable or unwilling to take on the responsibility of looking after the child in the postoperative period, it may be necessary to avoid surgery. In addition to these difficulties, frequent examinations in the early postoperative period are critical, since corneal healing is rapid in young children, resulting in loosening of the corneal sutures. Such loose sutures must be identified and removed immediately, as they can predispose to mucous accumulation, corneal ulceration, infection and rejection. Parents must be trained to examine the child’s eye every day with a torch and look for the presence of loose sutures or mucus on the eye.

While the schedule for postoperative examination can vary, it is often as frequent as every week in infants – for the first 4 to 6 weeks, until all sutures are removed. Such close monitoring in the early postoperative period is also important to detect other problems such as wound...
misalignment, increased intraocular inflammation, elevated intraocular pressure and other problems which can affect the final outcome. Young children have an active immune system and graft rejection is more common. It has been reported that the highest occurrence of this important complication is in the first 6 months and hence, this defines the period during which close postoperative observation is essential. Although graft rejection will result in symptoms like reduced vision and pain, these will not be reported by children and should be detected by parental or surgeon monitoring.

While topical medications can be used with relative freedom in children, systemic medications have to be used with caution and this limits the options available for management in the postoperative period. However, in those children who undergo a high risk corneal graft, the help of the pediatrician is required to initiate treatment with systemic steroids (in tapering doses over 4 weeks) and immunosuppressants like cyclosporine A, methotrexate, mycofenolate mofetil, and tacrolimus. Hence, it is important that the pediatrician and ophthalmologist work closely together to help achieve optimal outcome in these children.

**Visual rehabilitation**

While the preoperative assessment, surgical technique and appropriate postoperative care are vital, these unfortunately constitute management of only one half of the problem in children with corneal pathology. Proper attention to these details helps achieve a clear corneal graft in these eyes, the rates of which can vary from 50% to 85%, depending chiefly on the corneal condition operated, the expertise of the surgical team and the postoperative care regimen followed.

However, unlike in an adult, achieving a clear cornea does not equate with success in restoring vision to the eye. The immature visual system in young children is extremely sensitive to opacities in the visual pathway and this can result in poor development of the neurological circuits on the affected side. The resultant condition is termed amblyopia or ‘lazy eye’, referring to the poor visual function in an eye, which otherwise looks normal. The longer the period of visual deprivation, the more dense is the amblyopia and lesser the visual recovery after corneal transplantation. Hence, after surgery has resulted in a clear cornea, the pediatric ophthalmologist will need to prescribe appropriate refractive correction and aggressively treat the amblyopia. Patching the normal eye for a few hours each day, which forces the child to use the amblyopic eye, can be attempted. Attempts at stimulating macular function in the affected eye, termed pleoptics, used earlier have largely been abandoned now. If there is a squint, this must be corrected to realign the ocular axes, which allows the two eyes to work together. The visual pathways are believed to mature by 10 to 12 years of age and hence the above efforts should be concentrated on children in this age group.

**Recent advances**

In addition to conventional corneal transplantation techniques, in which the entire thickness of the cornea is replaced, recent technical advances permit component corneal replacement. If only the anterior corneal tissues are affected, a procedure termed Deep Anterior Lamellar Keratoplasty (DALK), is performed. In this approach, the Descemet’s membrane and the endothelium of the recipient are retained and only the anterior corneal tissues transplanted. The advantage of this approach is that endothelial graft rejection (the most serious kind) is avoided. Similarly, if the pathology is limited to endothelial failure, then selective replacement of the posterior corneal layers is now possible, a method termed Descemet’s Stripping Endothelial Keratoplasty (DSEK). Since the graft is performed without
sutures, this improves the safety of the procedure and allows faster visual rehabilitation. The recent recognition that the limbus is the seat of the corneal stem cells and that children with sclerocornea also tend to have limbal insufficiency, allows improved outcomes by combining limbal stem cell grafts with corneal replacement procedures.

**Conclusions**

Pediatric corneal transplants remain a challenge to the ophthalmologist. Despite recent advances in our understanding of the procedure and improvements in surgical technique, the characteristics of the pediatric eye and immune system, result in lesser anatomical success than in adult eyes. Studies in literature report an anatomical success rate that varies between 44.2% and 80%. The failure of a clear cornea to allow good vision in some of these eyes is due to amblyopia, which remains a potent cause of poor visual outcome, with approximately one half of operated eyes achieving functional vision (defined as the ability to count fingers or perform more complex tasks). Achieving good results in these children depends on a multi-disciplinary approach—with pediatricians, anesthetists, and parents providing vital support to the ophthalmologist. Despite these limitations, however, enough success has been reported with the process to make all the efforts worthwhile, when performing corneal transplants in these young children, provided the decision to operate is made carefully and conjointly, by the surgeon and the parents.

**Points to Remember**

- **Congenital corneal opacities can occur in one or both eyes, with or without discernable antenatal insults and with or without concurrent ocular and systemic pathology.**
- **Corneal opacities affecting the visual axis—either due to congenital causes or trauma, must be assessed adequately by an ophthalmologist.**
- **Central corneal opacities often need surgical treatment and surgery must be performed early to help avoid dense amblyopia, especially in unilateral pathology.**
- **Corneal transplantation in children is technically complicated and must be performed by trained and experienced ophthalmologist and anesthetist.**
- **The role of the pediatrician is very important in these conditions as they help identify the problem at an early stage and in assessing the health of the child to rule out associated underlying systemic problems.**

**References**


CLIPPINGS

Once or twice daily doses compared with three or four daily doses of amoxicillin, with or without clavulanate, for the treatment of acute otitis media in children

Acute otitis media is very common disease in children and may cause pain and hearing loss. Amoxicillin, with or without clavulanate, is the most commonly used antibiotic for the treatment of acute otitis media. Currently one or two daily doses are increasingly used, in preference to three or four times daily doses, to aid compliance. We could not claim that the different dosage schedules have the same effectiveness, as the included studies were biased. To study whether both dosing schedules have the same effectiveness, a good quality equivalence trial is necessary.

Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004975. DOI: 10.1002/14651858.CD004975.pub2. This version first published online: October 08. 2008

Traditional birth attendant training for improving health behaviours and pregnancy outcomes

In the developing world, many women give birth at home assisted by family members or traditional birth attendants (TBAs). TBAs lack formal training and governments and other organizations have conducted training programs to improve their skills. There is disagreement that these training programs are effective. This review included four studies and examined the effect of TBA training on TBA behaviour and on pregnancy outcomes. We conclude that the potential of TBA training to decrease newborn death is promising, when combined with improved health services. The number of studies, however, is insufficient to provide the necessary evidence for TBA training effectiveness.

ORGAN TRANSPLANTATION

PEDIATRIC LIVER TRANSPLANTATION - WITH SPECIAL REFERENCE TO SCENARIO IN INDIA

* Neelam Mohan

Abstract: Liver transplantation is an accepted treatment for end stage liver disease for both adults and children. Indications, contraindications and pre-operative evaluation, complications of liver transplantation are dealt with, in this article. Scenario of liver transplantation in India including author’s experience are covered.

Key words: Liver transplantation, Indications, Contraindications, Complications.

Liver transplantation or hepatic transplantation is the replacement of a diseased liver with a healthy liver allograft. The most commonly used technique is orthotopic transplantation, in which the native liver is removed and the donor organ is placed in the same anatomic location as the original liver. Liver transplantation nowadays is a well accepted treatment option for end-stage liver disease and acute liver failure, hepatic tumors and certain metabolic diseases.

History

The first human liver transplant was performed in 1963 by a surgical team led by Dr. Thomas Starzl of Denver, Colorado, United States. Dr. Starzl performed several additional transplants over the next few years before the first short-term success was achieved in 1967 with the first one-year survival post transplantation. Despite the development of viable surgical techniques, liver transplantation remained experimental through the 1970s, with one year patient survival in the vicinity of 25%. The introduction of cyclosporine by Sir Roy Calne markedly improved patient outcome and the 1980’s saw recognition of liver transplantation as a standard clinical treatment for both adult and pediatric patients with appropriate indications. Liver transplantation is now performed at over one hundred centers in the USA, as well as numerous centers in Europe and elsewhere. Since then, there have been considerable advances in both medical and surgical management, with international 1 year survival rates for pediatric liver transplant in excess of 90% and 5-10 year survival rates of 80%.

In India, however, the liver transplant programme picked up only after the year 2000 and gradually gained momentum. The growth was very slow initially, as is expected in any new programme. However, over the last few years there has been a rapid growth in liver transplantation and several centres in India are performing liver transplants. It is now well realized that the infrastructure and expertise are available in our country and the confidence of the referring doctors and patients is gradually building up. Economic burden is however, a major set back in India.

Indications for liver transplantation in children (Fig.1)

I. Chronic liver failure, II. Acute liver failure, III. Certain inborn errors of metabolism, IV. Certain hepatic tumors.

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I. Chronic liver failure

End stage chronic liver disease / chronic liver failure could be secondary to cholestatic liver disease, metabolic liver disease or chronic hepatitis. The underlying causes under this group is given in Table. 1.

(A) Cholestatic liver disease

Cholestatic liver disease is the commonest indication for liver transplantation in children. Of the cholestatic liver diseases, biliary atresia remains the main indication worldwide. Neonatal cholestasis contributes to nearly 30% of the chronic liver disease in children in India and upto 30%-35% of neonatal cholestasis cases are of biliary atresia.

(B) Metabolic liver disease

The common metabolic liver diseases in children for which liver transplant is indicated in west are α1-antitrypsin deficiency, tyrosinemia type I, Wilson’s disease, cystic fibrosis, glycogen storage type IV.

Table 1. Common causes of chronic liver failure requiring liver transplantation

<table>
<thead>
<tr>
<th>Cholestatic liver disease</th>
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<tbody>
<tr>
<td>Biliary atresia</td>
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<tr>
<td>Idiopathic neonatal hepatitis</td>
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<tr>
<td>Alagille syndrome</td>
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<tr>
<td>Progressive familial intrahepatic cholestasis</td>
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<tr>
<td>Nonsyndromic biliary hypoplasia</td>
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<td>Sclerosing cholangitis</td>
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<table>
<thead>
<tr>
<th>Metabolic liver disease</th>
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</thead>
<tbody>
<tr>
<td>α1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Tyrosinemia type I</td>
</tr>
<tr>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Glycogen storage disease type IV</td>
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<table>
<thead>
<tr>
<th>Chronic hepatitis</th>
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<tbody>
<tr>
<td>Autoimmune</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Postviral (hepatitis B, C, other)</td>
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<table>
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<tr>
<th>Cryptogenic cirrhosis</th>
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</thead>
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<tr>
<td>Fibropolycystic liver disease ± Caroli’s disease</td>
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</table>

| Primary immunodeficiency               |

Fig. 1. Primary indications for liver transplantation in children in West. n=3,998 pediatric patients, adapted from the European Liver Transplantation Registry, 2002.
In India the commonest metabolic liver disease seen is Wilson’s disease. Wilson’s disease is a rare autosomal recessive disorder of copper metabolism resulting in excessive accumulation of copper in liver, CNS, kidneys, cornea, skeletal system and other organs. The prevalence of the disorder is 1 in 30,000 worldwide with a carrier frequency of 1 person in 90. Early diagnosis and therapy with d-pencillamine / trientene should be curative but many children will present with established cirrhosis or fulminant liver failure. Indications for liver transplantation in Wilson’s disease include cirrhosis with decompensation, progression of hepatic dysfunction despite treatment, exacerbation after discontinuation of therapy, fulminant hepatic failure and progressive and irreversible neurologic disease.

Tyrosinemia type 1 is an autosomal recessive disorder of tyrosine metabolism, with a clinical presentation that includes both acute and chronic liver disease and multiorgan failure with cardiac, renal and neurologic involvement. The management of this disorder has changed dramatically since the introduction of 2 (2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexenedione (NTBC), which prevents the formation of toxic metabolites and produces rapid clinical and biochemical improvement. Liver transplant is now indicated only for those children who have a poor quality of life, do not respond to NTBC or in whom hepatic malignancy is thought to have developed.

Liver transplant in cystic fibrosis is indicated if there is evidence of hepatic decompensation. Fortunately incidence of cystic fibrosis is much less in India as compared to West though it definitely exists.

In Glycogen storage disease type 1 transplant is indicated only for children who develop multiple hepatic adenomas or in whom metabolic control has affected the quality of life. Children with glycogen storage disease types III and IV are more likely to progress to cirrhosis with portal hypertension and require transplant because of hepatic dysfunction.

(C) Chronic hepatitis

Autoimmune liver disease type I and II: Liver transplant is indicated for those children who have not responded to immunosuppression despite alternative therapy such as cyclosporine A, mycophenolate mofetil or tacrolimus and those children who present with fulminant hepatic failure. Fulminant hepatic failure is more likely in children with type II autoimmune hepatitis (LKM1 positive), who have a worse prognosis and an increased requirement for liver transplant.

Chronic hepatitis B and C: Although chronic hepatitis B or C is a major indication for transplant in adults, it is less common in children, many of whom will not develop symptomatic liver disease in childhood. Recurrence of hepatitis B or C is likely in 90% of patients transplanted for chronic disease but not for fulminant hepatitis. Prevention of recurrence of hepatitis B is less likely with prophylactic treatment with hepatitis B immunoglobulin and / or lamivudine.

(D) Cryptogenic cirrhosis

The term cryptogenic cirrhosis is used when despite all investigations the underlying cause of cirrhosis can not be identified.

(E) Fibropolycystic liver disease

Liver transplant is indicated for those children in whom hepatic decompensation occurs secondary to recurrent cholangitis or portal hypertension or if hepatic enlargement affects the quality of life. Because the disease may be associated with infantile polycystic kidney disease in some children, both liver and kidney replacement may be required.
(F) Primary immunodeficiency

In this group of children, it is important to consider bone marrow transplant before the development of significant liver disease or to consider combined liver and bone marrow transplant if necessary.4

Criteria for listing for liver transplantation in chronic liver disease: The major functions of the liver are (a) synthetic functions (b) formation and excretion of bile, (c) metabolic functions like glucose homeostasis and metabolism of nitrogenous wastes and drugs, (d) immunological functions and (e) hemodynamic functions. Any patient with chronic liver disease who has clinically significant abnormalities in 2 or more areas will likely to be benefited from liver transplantation.

Timing of transplant for Chronic Liver Failure: The timing of liver transplantation for children with chronic liver failure may be difficult. It must be remembered that a patient of chronic liver disease must be referred early to a liver transplant centre so that optimum timing for transplant can be decided before the complications of liver disease adversely impair the quality of child’s life and before growth and development are irreversibly retarded. There are certain parameters which are taken as a guide for listing for liver transplantation.

Lab parameters: The most useful guide to the timing of liver transplant is provided by a variety of parameters that include: 1) a persistent rise in total bilirubin > 150 µmol/L (> 9 mg/dL), 2) prolongation of the prothrombin ratio international normalized ratio [INR] > 1.4), and 3) persistent fall in serum albumin to < 35 g/L.5 Serial evaluation of nutritional parameters is a useful guide to early hepatic decompensation.

Clinical parameters: (a) Nutritional assessment: Among the clinical parameters, one of the most important indication for liver transplantation is nutritional assessment. Serial evaluation of nutritional parameters is a useful guide to early hepatic decompensation. Progressive reduction of fat stores (measured by triceps skinfold or subscapular skinfold) or protein stores (measured by midarm circumference or midarm muscle area) despite intensive nutritional support is a good guide to hepatic decompensation.6 Recently, the development of the PELD score (PELD = pediatric end-stage liver disease) has confirmed these observations.7

(b) Psychosocial development: Children with chronic liver disease may have both social and motor developmental delays that increase with time unless reversed following early liver transplant.8,9,10

(c) Hepatic complications: Children with severe hepatic complications such as chronic hepatic encephalopathy, refractory ascites, intractable pruritus and recurrent variceal bleeding despite medical management should be referred immediately for transplant. In some patients hepatopulmonary syndrome develops secondary to pulmonary shunting and this is an important indication for liver transplantation.

II. Acute liver failure

Acute liver failure could result from a wide variety of etiology (Table. 2).

Table 2. Acute liver failure requiring liver transplantation in children

<table>
<thead>
<tr>
<th>Fulminant hepatitis</th>
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<tbody>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Viral hepatitis (A, B, C, or NA-G)</td>
</tr>
<tr>
<td>Metabolic liver disease</td>
</tr>
<tr>
<td>Fatty acid oxidation defects</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
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<tr>
<td>Tyrosinemia type I</td>
</tr>
<tr>
<td>Wilson disease</td>
</tr>
<tr>
<td>Halothane anesthesia</td>
</tr>
<tr>
<td>Acetaminophen poisoning</td>
</tr>
</tbody>
</table>
King’s college (London) have provided certain criteria in acute liver failure which are suggestive of poor prognosis and when present indicate the need for liver transplantation (Table. 3).

Table 3. Kings College criteria for liver transplantation

<table>
<thead>
<tr>
<th>(A) For acetoaminophen poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH &lt; 7.3</td>
</tr>
<tr>
<td>Or the following 3 factors</td>
</tr>
<tr>
<td>PT &gt; 100 sec</td>
</tr>
<tr>
<td>Creatinine &gt; 3.5 mg%</td>
</tr>
<tr>
<td>Grade III or IV encephalopathy</td>
</tr>
<tr>
<td>(B) For other causes</td>
</tr>
<tr>
<td>P.T &gt; 100 sec</td>
</tr>
<tr>
<td>Or any 3 of the following</td>
</tr>
<tr>
<td>PT &gt;50 sec</td>
</tr>
<tr>
<td>Bilirubin&gt;17.5 mg%</td>
</tr>
<tr>
<td>Age&lt;10 years</td>
</tr>
<tr>
<td>Cryptogenic or drug induced liver failure</td>
</tr>
<tr>
<td>Jaundice for more than 7 days before onset of encephalopathy</td>
</tr>
</tbody>
</table>

The outcome of liver transplantation in acute liver failure is less than in cases of non emergent liver transplantation. In most centres in West the 1 year outcome varies from 70% - 80% as compared to other indications where it is more than 90%. Its important to refer patients of acute liver failure to a liver transplant centre when the patient is in grade II encephalopathy or above or when coagulopathy exists so that the patient can be followed up well for the need of liver transplant as transporting a patient late during the course of disease is associated with its own problems.

III. Inborn errors of metabolism

A number of inborn errors of metabolism are secondary to hepatic enzyme deficiencies that do not lead to liver disease. Liver function is normal, but the enzyme deficiency leads to severe extrahepatic disease (Table. 4). The purpose of liver transplant in this group of diseases is to replace the missing hepatic enzyme to prevent or reverse extrahepatic disease.

Table 4. Common causes of inborn errors of metabolism requiring liver transplantation

| Crigler-Najjar syndrome type I |
| Familial hypercholesterolemia |
| Organic acidemia |
| Urea cycle defects |
| Primary oxalosis |
| Maple syrup urine disease |

The timing of transplant depends on the rate of progression of the disease, the quality of life of the affected child and the development of severe irreversible extrahepatic disease.

IV. Hepatic tumors

Benign tumors occupying large part of the liver with no extrahepatic metastasis. Benign tumors are selected for liver transplant only if they cause hepatic dysfunction or are associated with an unacceptable increase in liver size and hepatic resection is impractical. Benign tumor listed for liver transplantation include hemangiomas or hemangioendotheliomas, adenomas and focal nodular hyperplasia.

Malignant hepatic tumors which are unresectable such as hepatoblastoma or hepatocellular carcinoma that are either unresectable or refractory to chemotherapy are considered for liver transplantation as long as there are no extrahepatic metastases.

Contraindications for liver transplant

With increasing experience, there are fewer contraindications to transplant. Although
historically considered difficult, age more than 1 year and size more than 10 kg are no longer contraindications for transplant. Portal vein thrombosis increases the technical risk of the surgery, but it can now be managed with venous or prosthetic grafts. Vascular abnormalities such as the hypovascular syndrome are no longer considered contraindications. Although infection with human immunodeficiency virus (HIV) was a contraindication, the improvement in long-term prognosis with antiviral drugs means that this disease can be controlled before transplant. The following contraindications still remain:

1. **Severe systemic sepsis** (in particular, fungal sepsis) at the time of operation. It is important that the operation be deferred until the infection has been appropriately treated.

2. **Malignant hepatic tumors with confirmed extrahepatic metastases**.

3. **Severe extrahepatic disease** that is not considered reversible following liver transplant. This includes severe cardiopulmonary disease for which there is no possibility of corrective surgery or severe structural brain damage with a poor prognosis.

4. **Multiorgan failure**, especially owing to mitochondrial cytopathy, because it has been shown that unless the mitochondrial defect is confined to the liver, liver transplant is not curative.

5. In the **respiratory chain defects** like Alper’s disease liver transplantation is contraindicated because of the progression of neurodegeneration despite transplant.

6. **Autoimmune and hemolytic anemia** in association with giant cell hepatitis is a rare and fatal disease in which there is a 100% recurrence rate post-transplant and transplant is not recommended.

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**Pre transplant evaluation**

The pre transplantation evaluation of the patient is particularly important and should include the following: (1) Assessment of the severity of the liver disease and the possibility for medical management, (2) Assessment of the technical feasibility of the operation, (3) Consideration of any contraindications, (4) Psychological preparation of the family and child.

The assessment has been tabulated in Table. 5.

**Preparation for liver transplantation**

**Immunizations**

Most units consider live vaccines to be contraindicated after liver transplant because of the risk of dissemination, secondary to immunosuppression. It is therefore better to complete normal immunizations before transplant.

**Management of hepatic complications**

It is important to ensure that specific hepatic complications are appropriately managed while the patient waits for transplant.

Recurrent variceal bleeding should be managed preferably with esophageal varix ligation than sclerotherapy. Intractable variceal bleeding may require the insertion of a transjugular intrahepatic portal systemic shunt.

Sepsis that includes ascending cholangitis and spontaneous bacterial peritonitis should be treated with broad-spectrum antibiotics, whereas in children awaiting transplant for acute liver failure, prophylactic antifungal therapy is essential.

Ascites should be managed with diuretics and restriction of salt. Intervention with hemodialysis and hemofiltration should be considered if acute renal failure or hepatorenal failure develops.
Nutritional support

It has been demonstrated with several studies that nutritional status at liver transplant is an important prognostic factor in survival.16,17 A high calorie protein feed (150 to 200% of estimated average requirement) is required with high calorie supplements given orally or by nocturnal nasogastric enteral feeding or continuous enteral feeding.

Psychological preparation

Liver transplant is a major undertaking for the child and family; thus, psychological counseling, information giving and preparation of the child and family are paramount using a skilled multidisciplinary team with play therapists, psychologists and school teachers.

Liver transplant surgery

The graft is from either a cadaveric liver or a living related donor.

In cadaveric liver transplantation, the liver of a brain dead person is used for transplantation. Cadaveric transplants could be:

a) Whole graft: The entire graft is transplanted in the recipient.

b) Reduced graft: When only a part of the cadaveric liver (i.e. right/ left/left lateral part) is used for the recipient.

c) Split graft: The shortage of suitable organs for young children led to development of split livers. The liver of the cadaveric donor is divided and used for two patients usually the right lobe for adults and left lobe for children.

Table 5. Pretransplantation assessment

<table>
<thead>
<tr>
<th>Nutritional status</th>
<th>Height, weight, triceps skinfold, midarm muscle area, midarm circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of hepatic complications</td>
<td>Ascites, varices</td>
</tr>
<tr>
<td>Cardiac assessment</td>
<td>Electrocardiography, echocardiography, chest radiography, cardiac catheterization</td>
</tr>
<tr>
<td>Respiratory function</td>
<td>Oxygen saturation, ventilation-perfusion scan, lung function tests</td>
</tr>
<tr>
<td>Neurologic and developmental assessment</td>
<td>Electroencephalography, Bailey developmental scales, Stanford-Binet intelligence scales</td>
</tr>
<tr>
<td>Renal function</td>
<td>Urea, creatinine, electrolytes, urinary protein-to-creatinine ratio, chromium EDTA</td>
</tr>
<tr>
<td>Serology</td>
<td>Cytomegalovirus; Epstein-Barr virus; varicella-zoster virus; herpes simplex virus; hepatitis A, B, and C; HIV; measles</td>
</tr>
<tr>
<td>Hematology</td>
<td>Full blood count, platelets, blood group</td>
</tr>
<tr>
<td>Radiology</td>
<td>Ultrasonography of liver and spleen for vascular anatomy, wrist radiography for bone age and rickets</td>
</tr>
<tr>
<td>Dental assessment</td>
<td></td>
</tr>
</tbody>
</table>
is more popular in Eastern countries like Japan and Korea where cadaveric liver transplantation has not been possible until recently. To carry out living related liver transplants, 2 transplant surgeons team is required as simultaneously surgery is being carried out on the donor and the recipient.

**Auxiliary liver transplant** : The term auxiliary liver transplant is referred when a part of the donor liver (usually segments 2+3) is implanted beside or in continuity with the native liver. The main purpose of this form of liver transplant is to ensure that the native liver is retained in the event of graft failure or for the future development of gene therapy. Auxiliary transplant is now accepted therapy for Crigler-Najjar syndrome type I and also for propionic acidemia and ornithine transcarbamylase deficiency.

The role of auxiliary liver transplant in the management of fulminant hepatic failure is more controversial. The rationale for using this technique in this condition is that, with time, the native liver may regenerate. Two recent studies in adults demonstrated that the native liver regenerates in approximately half of the patients.

**Immunosuppression**

Following liver transplant the patient requires immunosuppression usually life long according to the present consensus. The various immunosuppressive drugs used following liver transplantation are cyclosporine, tacrolimus, mycophenolate mofetil and steroids. Newer drugs like OKT3, sirolimus and basiliximab are used in few patients.

**Post-operative complications**

**Early post-operative complications**

(a) Primary graft nonfunction : Primary nonfunctioning of the transplanted liver occurs within 48 hours. The cause is unknown and may be related to donor factor. The only appropriate management is retransplant.

(b) Surgical complications of intra-abdominal hemorrhage

(c) Vascular thrombosis and venous outflow obstruction.

Hepatic artery thrombosis occurs in approximately 10% of pediatric liver grafts and its frequency has decreased considerably following the introduction of reduction hepatectomy or living related transplant because of the increased size of the donor vessel.

Portal vein thrombosis is less common complication.

(d) Rejection : Acute cellular rejection may occur between 7 and 10 days postoperatively. The incidence of acute rejection varies. It is less common in infants (20%) but increases to 50 to 60% in older children and adults.

In majority of the cases it responds with increase in immunosuppression and high dose of steroids. It has been shown the acute rejection does not affect the long term outcome.

(e) Biliary complications : These include biliary leaks and structures and is usually managed by interventional radiology with requirement of surgical reconstruction in only few cases.

(f) Sepsis : Infection is still the most common complication following liver transplant. Bacterial infections are most common immediately after transplant and are related to the high doses of immunosuppressive drugs and central line infections. The mortality of patients with systemic infection is high but has improved with new agents such as quinupristin and linezolide.

**Late complications post transplant**

These fall into two general categories :

(1) Complication related to allograft itself and
those related to immunosuppressive drugs. They include chronic rejection, CMV and EBV infection, late biliary strictures, hepatic artery or portal vein thrombosis, post – transplant lymphoproliferative disease (PTLD), De novo auto immune hepatitis, nephrotoxicity and hyperlipidemia secondary to immunosuppressive drugs. Other side effects of immunosuppressive drugs include like hypertension, hirsuitism, etc.

Scenario in India

It’s heartening to see that liver transplantation programme in India has eventually picked up well. It has been slow to start with but the pace in the last couple of years has been good. There are several (more than a dozen) centres in the country which are now doing liver transplantation. The adult numbers are far more than the pediatric numbers. Internationally the pediatric liver transplant constitute around 20% of the total transplants. However, in India they are still less than 10% of the total transplants.

Recently in November 2008 a consensus conference was held in New Delhi on liver transplantation and data was collected from various liver transplant centres and compiled. This is provided in Table 6.

One of the major problems that we are facing in the country is lack of cadaveric donation - therefore, most of the transplants whether renal or liver carried out are living related. The human organ donation act was passed in 1984 in India. The donor has to be spouse or first degree relative or emotionally related to the patient. The importance and safety of cadaveric liver transplantation cannot be undermined and all must work in the direction of promoting cadaveric organ donation in our country to benefit several people from various organs harvested. In fact following the promotion of cadaveric organ donation there will be a significant impetus to the liver transplant programme in the country.

Another issue is lack of central registry and availability of little published data on liver transplantation in India.

Author’s centre experience

Sir Ganga Ram Hospital, Delhi is one of major centre of liver transplantation in India where presently more than 12 liver transplants are carried out monthly. They are mostly living related liver transplants due to the shortage of cadaveric organs. In fact it is among the top 3 living related liver centres in the world having performed more than 130 liver transplants annually and it has completed 350 living related liver transplants.

The results have been excellent with more than 92%, 1 year survival. Pediatric transplantation results have been very encouraging with more than 95%, 1 year and 3 year survival.

The indications of pediatric liver transplants at Sir Ganga Ram Hospital are given in Table 7.

Outcome of pediatric liver transplantation has shown incremental improvements from the 1980s to late 1990s. Studies of pediatric liver transplantation (SPLIT) registry 2002, which was initiated in 1995, gives an overview of the results of pediatric liver transplantation in the last 7 years in North America and Canada. Of 1092 pediatric liver transplanted children, the Kaplan – Meier probability of patient survival at 1 and 3 years was 86.3% and 83.3%, respectively, with corresponding graft survival rates of 80.2% and 75.3% respectively.

The Kyoto series, the largest in the world, driven by virtually nonexistent cadaveric supply is based on living related transplantation. The Kyoto comparable series shows excellent and comparable patient and graft survival rates, 81% and 79% at 5 years, to the overall results of cadaveric pediatric liver transplantation.
Table 6. Details of liver transplantation at liver transplant centres, India

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of the Hospital</th>
<th>Total Liver Transplants</th>
<th>Pediatric Liver Transplants</th>
<th>Data Provided by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sir Ganga Ram Hospital, Delhi</td>
<td>306</td>
<td>28</td>
<td>Dr. Soin</td>
</tr>
<tr>
<td>2.</td>
<td>Apollo Hospital, Delhi</td>
<td>199</td>
<td>12</td>
<td>Dr. Subhash Gupta</td>
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<td>Amrita Institute of Medical Sciences</td>
<td>24</td>
<td>-</td>
<td>Dr. Supriya Sharma</td>
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<tr>
<td>4.</td>
<td>Narayana Hrudayalaya</td>
<td>17</td>
<td>12</td>
<td>Dr. Sanjay Govil</td>
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<tr>
<td>5.</td>
<td>Jaslok Hospital, Mumbai</td>
<td>16</td>
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<td>Dr. Sanjay Nagral</td>
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<tr>
<td>6.</td>
<td>Army Research and Referral Hospital, Delhi</td>
<td>23</td>
<td>3</td>
<td>Dr. C. S. Naidu</td>
</tr>
<tr>
<td>7.</td>
<td>Lakeshore Hospital</td>
<td>8</td>
<td>3</td>
<td>Dr. H. Ramesh</td>
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<tr>
<td>8.</td>
<td>Wockhardt Hospital, Mumbai</td>
<td>5</td>
<td>1</td>
<td>Dr. Mahesh Govil</td>
</tr>
<tr>
<td>9.</td>
<td>Manipal Hospital</td>
<td>3</td>
<td>1</td>
<td>Dr. Sadiq Sikora</td>
</tr>
</tbody>
</table>

No data was available from few centres like Global hospital, Hyderabad, SGPGI Lucknow and CMC, Vellore.

Table 7. Indications for pediatric liver transplantation - Sri Ganga Ram Hospital, New Delhi

1) Acute liver failure (8)
   - Wilson’s disease : 5
   - Hepatitis E (with CLD and Wilson) - 2
   - Hepatitis - A : 2
   - Idiopathic : 1

2) Chronic liver disease (19)
   • Biliary Cirrhosis : 9
     - Biliary atresia - 7
     - Sclerosing cholangitis (LCH*) - 1
     - Choledochal cyst - 1
   • Wilson’s disease : 2
   • Progressive familial intrahepatic cholestasis (PFIC) : 2
   • Cryptogenic cirrhosis : 3
   • Auto immune hepatitis : 1
   • Tyrosinemia : 1
   • Haemangioendothelioma : 1

3) Acute on Chronic liver disease (2)
4) Inborn error metabolism (3)
   • Primary hyperoxaluria type-1 : 2
     (Combined liver-kidney transplantation)
   • Maple syrup urine disease (MSUD) : 1

(*Langerhan cell histiocytosis)
In another large series, Reding, et al reported a 7 year experience with living donor transplants in children, which showed 1 and 5 years survival rates of 92% and 89% for patient and 90% and 86% for graft, respectively. Although biliary complications may be more common in living donor grafts compared with whole organ transplants, these usually do not impact on patient or graft survival.

**Quality of life**

It is now anticipated that children who survive liver transplant will achieve a normal lifestyle despite the necessity for continuous monitoring of immunosuppressive treatment. Children transplanted for certain metabolic liver disease like tyrosinemia type–1 may have both phenotypic and functional recovery. Children with Crigler-Najjar syndrome type 1 have functional recovery of enzyme activity.

An important aspect of long term survival is the development of puberty. A long term study from France has demonstrated that there are no differences between the genders in attaining puberty and developing secondary sexual characteristics. Girls develop menarche and successful pregnancies have been reported for females receiving both cyclosporine and tacrolimus immunosuppression.

**Summary**

Liver transplant for acute or chronic liver failure or for hepatic tumors and certain inborn errors of metabolism is an effective therapy that restores good quality of life to over 80% of recipients. Considerable advances in medical and surgical expertise and immunosuppression have improved not only survival but also quality of life for the majority of liver transplant recipients. It is hoped that advances in molecular genetics will lead to effective gene therapy or hepatocyte transplant. In India, both the infrastructure and expertise for liver transplantation is available and the growth has been satisfactory over the last couple of years in a few centres, and is still far from desirable in many. One major set back is a lack of cadaveric transplant programme in India which needs a big boost.

**Points to Remember**

- **Indications for liver transplantation are chronic liver failure, acute liver failure, certain inborn errors of metabolism and certain hepatic tumors.**
- **Contraindications include from severe systemic sepsis, malignant hepatic tumors with confirmed extra-hepatic metastases, severe extra-hepatic disease, multi-organ failure, respiratory chain defects, autoimmune and hemolytic anemia with giant cell hepatitis.**
- **Nutritional support and immunization constitute a major role in the pre-operative preparations of liver transplantation.**
- **Most studies from large pediatric liver transplant centres show a patient survival of 80%-85% at 5 years post transplantation.**
- **Children who survive liver transplant will usually achieve a normal life style.**

**References**


Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children

Streptococcal throat infection is very common. A 10-day course of penicillin is prescribed mainly to protect against the complication of acute rheumatic fever, which occurs approximately 20 days after streptococcal throat or scarlet fever, and causes damage to the heart valves. Cases of acute rheumatic fever have dropped dramatically in high-income countries, with an annual incidence amongst school-aged children of 0.5 cases per 100,000, compared to 100 to 200 cases per 100,000 in low-income countries. Newer antibiotics, taken for a shorter duration, may have a comparable effect to penicillin taken for 10 days.

We summarized the evidence in the medical literature regarding the effect of two to six days of oral antibiotics (short duration) in treating children with streptococcal throat infection, compared with 10 days of oral penicillin (standard duration).

We searched the literature from 1951 to November 2007. Twenty studies were included with a total of 13,102 cases of streptococcal throat infection. The most common antibiotic studied was azithromycin (n = 6). Compared to standard duration, the short duration treatment had a shorter period of fever (mean difference (MD) -0.30 days, 95% CI -0.45 to -0.14) and sore throat (MD -0.50, 95% CI -0.78 to -0.22), and lower risk of early clinical treatment failure (OR 0.80, 95% CI 0.67 to 0.94), but there was no significant difference in early bacteriological treatment failure (OR 1.08, 95% CI 0.97 to 1.20), or late clinical recurrence (OR 0.95, 95% CI 0.83 to 1.08). The overall risk of late bacteriological recurrence was worse in the short duration treatment (OR 1.31, 95% CI 1.16 to 1.48). However, no significant difference was found when eliminating studies of low-dose azithromycin (10 mg/kg) (OR 1.06, 95% CI 0.92 to 1.22).

The short duration treatment resulted in better compliance (non-compliance OR 0.21, 95% CI 0.16 to 0.29), but more side effects (OR 1.85, 95% CI 1.55 to 2.21). All side effects were self-limiting: mostly mild to moderate diarrhea, vomiting, and abdominal pain. Three studies reported the rate of long duration complications with no statistically significant difference (OR 0.53, 95% CI 0.17 to 1.64).

Three to six days of oral antibiotics for children with streptococcal (strep) throat infection is a safe treatment with a comparable effect to the standard duration of 10 days of penicillin. However, our results must be interpreted with caution in low-income countries where acute rheumatic fever is still a problem.

UPDATE ON RICKETTSIAL INFECTIONS

* Arun Shah

Abstract: Rickettsial infections are reemerging infection like dengue and leptospirosis in India. If not diagnosed and treated properly the severe cases could be fatal especially Indian tick typhus and scrub typhus. It should be considered in differential diagnosis of fever, malaise, myalgia and rash against geographical background and history of exposure to vectors. There is a dramatic response to anti-microbials. Outcome of treatment is much better in children and worse in elderly persons. Other prognostic factors are sex, race and G6PD deficiency. The most important independent determinant of outcome is early diagnosis and treatment.

Keywords: Vasculitis, Eschar, Indian tick typhus, Weil-Felix test.

Rickettsial infections are re-emerging infection like dengue and leptospirosis in India and a challenge to health care providers.

Rickettsial infection is prevalent world wide except Antartica. In India spotty fever group and typhus are being reported from different parts of country especially Tamilnadu, Maharastra, Himalayan belt and Karnataka.

Throughout history rickettsial diseases have been the scourge of human kind. In the past, epidemics of typhus fever have taken more life than all the wars combined together.

An outbreak of typhus in refugee camp of Burundi in 1988 involving more than 30,000 people is a reminder that these diseases can still reemerge with devastating results.

Pathogenesis

The rickettsiae are obligate intracellular gram negative aerobic rod shaped/spherical microorganisms smaller than bacteria but structurally resembling bacteria. Rickettsiae are a rather diverse collection of organisms with several differences. This prohibits their description as a single homogenous group. A general characteristic of rickettsiae is that mammals and arthropods are natural hosts and they are transmitted to humans by arthropods. An exception is Q-fever which is transmitted by airborne droplets. Rickettsial diseases vary considerably in severity from self limited mild illness to fulminant life threatening infections. Severity of infection depends upon the virulence of the organism and host factors such as age, immune status, alcoholism and G6PD deficiency. If not diagnosed and treated in time, some rickettsial infections could be fatal especially rocky mountain spotted fever, epidemic typhus and scrub typhus.

The rickettsial micro-organisms parasitize the intestinal canal of arthropods. Infection is transmitted to humans by bite/contaminated feces of insects like lice, fleas and ticks. The organisms multiply in capillary endothelial cells producing lesions in the skin, central nervous system, heart,
lungs, kidney and skeletal muscles. In epidemic typhus the brain is the target organ and in scrub typhus the cardiovascular system and lungs are affected. An eschar is often found in tick and mite born typhus. An eschar is a black necrotic area/ crust surrounded by erythema at the site of bite. This is due to vasculitis following immunological recognition of the inoculated organism.

**Pathology**

Proliferation of the organism in endothelial cells causes vasculitis leading to hypoperfusion and ischemia. Vasculitis may cause increase in capillary permeability leading to cerebral oedema and pulmonary oedema. Vasculitis along with perivascular inflammation may cause thrombosis and hemorrhage.

**Classification**

Rickettsial infection can be classified into following groups:

1. Spotted fever group
   - Rocky mountain spotted fever
   - Mediterranean fever (Indian tick typhus)
   - Rickettsial pox
   - African tick bite fever
   - Cat flea typhus (TIBOLA)

2. Typhus
   - Epidemic typhus
   - Brill-Zinsser disease (Relapsing louse born typhus)
   - Endemic typhus
   - Scrub typhus
   - Murine typhus

3. Other rickettsioses
   - Q-Fever
   - Ehrlichiosis

- Tick borne lymphadenopathy (TIBOLA)
- Dermacentor (genus of ticks) borne necrosis – eschar-lymphadenopathy (DEBONEL)

**Rocky mountain spotted fever**

It is the most frequently identified rickettsial disease and second most common vector borne disease in USA. It is caused by Rickettsia rickettsii and transmitted by tick bites. Dogs and rodents are reservoirs. It is wide spread in western hemisphere. It is characterized by fever, headache and typical distribution of maculopapular or petechial rash peripheral than central involving palms and soles also in contrast to epidemic typhus. In severe cases larger cutaneous and subcutaneous hemorrhage may appear along with hepatosplenomegaly (33%).

**Mediterranean spotted fever (Indian tick typhus)**

It is caused by R.conorii and transmitted by tick bite. It is characterized by high grade fever, malaise, rash and eschar at the site of tick bite. Dogs and rodents are reservoirs and is seen in Mediterranean region, India, middle east and Africa. Recently this rickettsial infection has shown increasing incidence in India. Diagnosis is based on clinical and epidemiological consideration and is confirmed by serology and PCR of skin biopsy.

**Rickettsial pox**

Rickettsial pox is caused by R.akari. It is transmitted by mite bite. Mice is the reservoir. It is spread in North America, Russia, Ukraine, Korea and South Africa. There is high prevalence in urban setting. It is characterized by fever, headache, malaise, chills followed by the characteristic skin rash. Initially eschar with regional adenopathy develops which goes unnoticed. The disease is usually mild and self limiting.
Epidemic typhus

Epidemic typhus is caused by R. prowazekii and is transmitted by infected feces of louse through scratching of skin. Humans are the reservoirs. It is world wide in distribution. It is related to poverty, unhygienic condition, cold weather, war and disaster. Large epidemics have occurred as sequelae to war. It is characterized by high grade fever, severe headache, myalgia, cough (70%) followed by generalized rash sparing face, palm and soles. It is occasionally misdiagnosed as typhoid fever. A mild form of epidemic typhus known as Brill-Zinsser disease occurs years after acute disease due to reactivation especially in old age or immunosuppression.

Endemic typhus

Endemic typhus is caused by R. mooseri and transmitted by feces of infected rat fleas through scratching of skin. It is endemic world wide. The symptoms are usually mild like that of epidemic typhus. The rash may be scanty and transient.

Scrub typhus

Scrub Typhus is caused by Orientia tsutsugamushi and transmitted by mite bite. Approximately one million infections occur every year globally especially affecting Asia-pacific region including India. The disease is characterized by fever, headache (retro orbital), malaise and maculopapular rash. Generalized lymphadenopathy is a common feature (80%). In many cases eschar develops at the site of bite along with regional lymphadenopathy. Severity varies from mild self limiting illness to severe fatal disease in untreated cases (30%).

Q-Fever

Q-Fever is caused by Coxiella burnetti. It results from inhalation of contaminated aerosols or ingestion of contaminated milk. Mammals, birds and ticks are natural reservoirs. Though world wide in distribution it is not yet reported in India. The organism is notorious for its ability to survive for an extended period outside reservoir and vector and for its extreme infectivity. Inhalation of a single microorganism can cause disease. The organisms invade macrophages in lung, endocardium and liver. The clinical manifestations depend on organ involved. Rash is rarely present.

Tibola and Debonel

It is characterized by an eschar associated with painful cervical lymphadenopathy which appears, one week after a tick bite to the occipital scalp. Fever and rash are seldom present. Patients may develop persistent asthenia and alopecia at the site of eschar.

Diagnosis

Early clinical symptoms of these infections are notoriously non-specific and mimic viral illness making the diagnosis more difficult. However certain features that can help in making early diagnosis of rickettsial disease are strong index of suspicion, history of tick bite or exposure, living in endemic area or recent travel to endemic area and similar illness in family members. Rickettsiae are not evident on blood smear and do not stain with most conventional stains. No rapid lab test is available to diagnose infection early in the course of disease. Weil-Felix test available in India has its own limitations. It has low sensitivity but high specificity. It is based on the agglutination of specific somatic antigens of proteus vulgaris OX2, OX19 and OXK with patient’s serum. It becomes positive 2 weeks after onset of disease and thus cannot be relied upon to initiate early therapy. A four fold rise in antibody titre in paired serum or single high titre of more than 1:128 is diagnostic.

Immunoflorescent assay (IFA) is gold standard in confirming the diagnosis.
Unfortunately it is not available in India. Other diagnostic modalities include immunohistological demonstration of rickettsial antigen in punch biopsy of cutaneous lesion, PCR and culture. They are quite expensive and cumbersome.

**Differential diagnosis**

The presenting symptoms mimic many common clinical conditions like influenza, viral exanthematous diseases (measles, rubella) typhoid fever, malaria, dengue fever, leptospirosis, meningococcal septicaemia, kawasaki disease, viral hepatitis and drug hypersensitivity. One should always suspect rickettsial infection with history of tick or mite bite and epidemiological background.

**Management**

**Specific therapy**

Though different rickettsial infections vary greatly in severity, all respond to tetracycline, doxycycline and chloramphenicol. Resistant cases reported from few places respond to quinolones, rifampicin, azithromycin or clarithromycin. There is usually a dramatic response to anti-microbials. Fever usually subsides within 24-72 hours after starting antibiotic therapy. If fever fails to subside, the diagnosis of rickettsial disease should be reconsidered. Doxycycline is the drug of choice and preferred over other tetracyclines. Antibiotics should be continued for at least 3 days after defervescence. Sulfonamides should never be given as they aggravate the disease.

**Supportive therapy**

Supportive care include proper nursing care, adequate hydration, sedation for delirium, blood transfusion for bleeding, control of seizures with anticonvulsants and treatment of intercurrent infection such as pneumonia and typhoid.

**Prevention**

- To avoid exposure to vectors and reservoirs by use of repellents and protective clothing
- Control of vectors and reservoirs by insecticides and rodenticides.
- Vaccine against epidemic typhus and Q-Fever has been shown to be effective and promising.

**Points to Remember**

- **Rickettsial infections are reemerging infections like dengue and leptospirosis and have been reported in several parts of India.**
- Though many rickettsial infections are mild and self limiting, severe cases (less frequent) if not diagnosed and treated properly could be fatal especially Indian tick typhus and scrub typhus.
- **When there is high index of suspicion based on clinical manifestation (non specific), geographical background and history of exposure to vector, it is justified to start empiric anti-microbial therapy awaiting serological report.**
- **There is usually dramatic response to anti-microbials.**

**Bibliography**


NEWS AND NOTES

SOUTH NEOCON 2009, CHENNAI.

III SOUTH ZONE CONFERENCE AND VII ANNUAL CONVENTION OF THE NATIONAL NEONATOLOGY FORUM, TAMILNADU CHAPTER


VENUE: HOTEL SAVERA, CHENNAI

REGISTRATION FEE

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Chair Person : Dr.K.Githa
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FEBRILE SEIZURES

* Kumaresan G

Abstract: Febrile seizure is common in children. It carries a good prognosis. Prolonged and focal seizures are well established risk factors for subsequent epilepsy. Hence treatment should aim to prevent prolonged seizures which can lead to subsequent brain damage. Continuous prophylaxis is indicated only in a select group of children. Recent advances in genetics have shown that febrile seizures can be the initial manifestation of some epileptic syndromes like generalised epilepsy with febrile seizures (GEFS+) and Dravet syndrome, mesial temporal sclerosis can follow prolonged focal seizures. However, in a few cases pre-existing hippocampal malformations can predispose to both febrile seizures and future intractable epilepsies.

Keywords: Febrile seizures, Epilepsy, Continuous, Intermittent therapy.

Febrile seizure is one of the common epileptic syndromes seen in pediatric practice. Its incidence is around 3-4%. The incidence varies and is higher in some parts of world like Japan and developing countries. Recent advances in molecular genetics and neuro-imaging has its impact in our understanding of febrile seizures and pathogenesis of epilepsy.

As per the classification of epilepsies “International league against epilepsy (ILAE)” (1989), febrile seizure has been classified under the category of 4.1 Special syndromes. In the new proposed 2001 classification of epilepsies and epileptic syndromes febrile seizures are included as “Seizures not necessarily requiring a diagnosis of epilepsy”. Febrile seizures are the prototype of occasional epileptic seizures. ILAE guidelines for epidemiological studies in febrile seizures has suggested to include two different groups—one with history of neonatal seizures and those without the history of neonatal seizures. Febrile seizures in the simplest definition are seizures associated with fever of extra-cranial origin. Consensus panel of the National Institute of Health (NIH) in 1980, defined febrile seizures as an event in infancy or childhood, usually occurring between 3 months and five years of age, associated with fever but without evidence of intracranial infection or defined cause.”

Seizures in children who have suffered a previous non-febrile seizures are excluded.

In 1993, the International league against epilepsy modified the definition. The age of onset included after one month as against 3 months in the NIH definition and excluded previous neonatal seizures and other acute symptomatic seizures.

The three important constituents of febrile seizures are age, fever and genetic susceptibility.

Age: 6 months to 5 years is the usual range. In 90% of children seizures occur before 5 years of age. Onset as young as 3 months or occasionally upto 7 years can be seen.
First seizures beyond 7 years should raise the suspicion of epilepsy triggered by fever.

**Fever:** Febrile seizures are precipitated with fever around 38.5°C to 39°C. Rapid rise in temperature is also an important provocative factor. Children who have experienced febrile seizures once may tolerate subsequent high fevers and not have seizures. Seizures may occur in some children with less rise in body temperature or may be the first sign of illness (in about 25%) which makes it difficult to prevent recurrences. Illnesses causing fever include viral infections and bacterial infections like upper respiratory infections. Gastro-intestinal infections are reported to have inverse influence (protective). Immunisation especially with DPT can precipitate febrile seizures. Certain infections like roseola infantum, herpes, and rota virus infection are more prone to cause febrile seizures. Convulsions associated with some infections like shigellosis, salmonellosis, pneumonia and measles may be more due to direct involvement of brain or toxins and hence are not true febrile seizures even though there may not be any changes in CSF. Most of the febrile seizures occur within 24 hours of onset of fever. Seizures occurring late in the febrile illness should raise the suspicion of other causes.

**Genetics:** High rates of familial clustering of febrile seizures are seen. However, despite common occurrence no definite mode of inheritance is established. The rate of recurrence is 1 in 5 with family history of febrile seizures in siblings and 1 in 3 if the both the parents had febrile seizures. Although an acquired condition, pre-existing inherited factors for determining lower seizure threshold exist. Polygenic mode of inheritance and autosomal dominant inheritance with incomplete penetrance and variable expression are the possible explanations. Studies in families with large number of affected children have shown mutations involving sodium channel or GABA receptors (SCNA1A, SCNA1B) which have been linked to at least to four chromosomal sites 8q13-21, 19p13.3, 19q and 2q23-24.

Many epileptic syndromes are known to present initially as febrile seizures and may be mistaken for non-specific familial clustering. Generalised epilepsy with febrile seizures (GEFS PLUS) and severe myoclonic epilepsy in infancy (Dravet syndrome) are the classical examples. Despite being a common condition, genetic studies are positive only in 17% of cases and hence more genetic studies are awaited.

**Clinical features**

Simple febrile seizure is characterized by brief generalized seizures, lasting for a few minutes and recovery without any sequelae. Febrile seizure is considered to be complex if one of the three factors are present: 1) prolonged for more than 15 minutes, 2) focal and 3) multiple episodes in one febrile illness.

About one third of children show at least one of these features. Wallace has reported the occurrence of prolonged seizures in 7.6% and focal in 4% and multiple in 16% in her series. Others have reported 16-35% showing prolonged febrile seizures.

The following are risk factors for first febrile seizures: 1) patient age (6 months-3 years), 2) degree of temperature elevation, 3) febrile seizures in first or second degree relative, 4) family history of afebrile seizures, 5) neonatal discharge at 28 days or later, 6) developmental delay in the child, 7) attendance at day care and 8) maternal smoking and drinking during pregnancy.

The differential diagnosis of febrile seizures includes events like rigors, reflex anoxic seizures (14 out of 100 children in a series), head trauma, hypoglycemia, phacomatosis and seizures.
produced by toxins and drugs. Acute bacterial infections of central nervous system is an important differential diagnosis especially in very young infants and signs of meningitis may not be obvious at the early stage. In about 15% of children with bacterial meningitis seizures may be the presenting symptom. However the seizures are usually complex and disturbances in the level of alertness is seen on careful examination. Febrile seizures may be the initial presentation of some epileptic encephalopathies like GEFS+ syndrome and Dravet syndrome (severe myoclonic epilepsy). However seizures in these conditions are usually prolonged, focal and have frequent recurrences within a few months. Family history of afebrile seizures including multiple types and developmental delay will be warning signs.

**Investigations**

In the absence of specific signs the yield from routine investigations like electrolytes and blood sugar is very low. The indications for CSF analysis are clearly established. 1) febrile seizures for the first time in children below one year of age, 2) complex febrile seizures, 3) above 12 months of age if signs and symptoms of infection elsewhere or prolonged drowsiness or if meningeal signs are present and 4) prior use of antibiotics a few days earlier, as this may mask early signs of CNS infection. EEG studies have a very limited value in the evaluation and are not routinely indicated. They may be used if the clinical description raises doubt about the diagnosis of seizures. Non-specific changes may be seen and the observed changes do not provide information regarding the risk of recurrence of febrile seizures or subsequent epilepsy. Some parents expect or even demand an EEG. But the yield is more troublesome than its worth.

**Natural course**

Earlier studies in 1980 thought “They don’t do very well”. This was based mainly from the data from tertiary care centers and data from adult patients referred for surgery for intractable epilepsy. However many population based prospective studies have helped change this view. The different results from various studies are due to differences in inclusion criteria. Seizures with fever may occur in three circumstances: 1) febrile seizures the typical type, which account for the majority of cases, 2) fever and seizures may be the manifestation of febrile encephalopathy, which may exist with normal CSF findings and may have sequelae, 3) febrile seizures may be the initial manifestation of a future epileptic syndrome due to the low seizure threshold. Excluding 2 and 3, the true febrile seizures carry excellent prognosis. This is the reason for the change in concept regarding long term usage of anti-convulsant drugs as the adverse effects of drugs is more than their benefits in a benign condition.

Two aspects have to be analysed in the course of febrile seizures 1) risk of recurrence of febrile seizures and 2) risk of subsequent afebrile seizures and epilepsy.

**Recurrence of febrile seizures:** In about one third of children febrile seizures do not recur. In others it may recur two to three times. Repeated recurrences even upto 10 times or persisting beyond 7 years of age have been seen occasionally. Well established risk factors for recurrence include: 1) first febrile seizures before 12-18 months of age, 2) complex febrile seizures and 3) family history of febrile seizures. Following is the frequency of recurrence rate with no risk factors 15%, with only one risk factor 30%, with two risk factors 40% and with all three factors it is 65%. Less well established risk factors include occurrence of seizures with low-grade fever (more likely) and family history of febrile seizures (recurrence rate about twice than the usual
A family history of febrile seizures does not seem to predict recurrent febrile seizures.\textsuperscript{23}

**Febrile seizures and risk of later epilepsy**

Unquestionably there is a relationship between early febrile seizures and later development of epilepsy.\textsuperscript{12} Three factors have been recognized as major risk factors for later epilepsy: 1) complex first febrile seizures, 2) abnormal neurological state before the first febrile seizures, 3) history of febrile seizures in the child’s parents/siblings.\textsuperscript{24} The incidence of epilepsy in the population is around 0.5%. In children who have none of the above 3 risk factors the risk is double (1%). In children with one risk factor the risk is 4 times (2%) and with two or more risk factors the risk is around 10%. Simple febrile seizures were associated with generalized epilepsies and complex febrile seizures (especially prolonged) with temporal lobe epilepsy.\textsuperscript{25}

The time interval between febrile seizures and later afebrile seizures was between one year (40-70%) to four years in 85%. About one third may have one afebrile seizure whereas other two third may go on to have recurrent afebrile seizures (epilepsy).

The relationship of febrile seizures to subsequent intractable epilepsies has been controversial. Studies from centers performing surgery for intractable epilepsies found that many patients with medial temporal sclerosis had febrile seizures in their childhood. However this correlation has not been seen in many prospective and population based studies. This may be due to rarity of the condition and hence not picked up by studies not including adequate number of cases and the long interval between febrile seizures and subsequent intractable epilepsies. Animal studies and recently available techniques like MRI have shown changes in hippocampus of temporal lobe following prolonged febrile seizures. In a study, 4 out of 27 cases studied shortly after febrile seizures, showed acute oedema with swelling of hippocampus of one hemisphere which later progressed to hippocampal atrophy, similar to picture seen in temporal lobe epilepsy in adults.\textsuperscript{11} It is now clear that prolonged seizure of any etiology could cause similar changes and the duration of seizures is more important than the etiology. However the etiology of mesial temporal sclerosis could be varied.\textsuperscript{26} Some children without history of febrile seizures (6 out of 23) and 2 out of 27 with history of febrile seizures showed evidence of pre-existing abnormalities. These pre-existing abnormalities can predispose to prolonged and focal febrile seizures. Febrile seizures in turn aggravate damage to already vulnerable structure.

However it is clear that prolonged seizures of any etiology carry the risk of causing brain damage leading to future epilepsy. Hence before we decide on long term therapy for febrile seizures the following points have to be remembered.

1. The natural history of typical febrile seizures is benign, hence the emphasis is on avoiding long term anti-convulsants. Long term studies on intelligence, behaviour and IQ have shown no changes. Some of the earlier studies reported with some bad outcome are due to inclusion of febrile encephalopathies of other etiologies.
2. Prolonged seizures carry the risk of potential brain damage and hence prompt and early control of seizures is of utmost importance.
3. Frequent recurrence of febrile seizures increases parental anxiety and also carries risk of injuries due to seizures. Hence a select group of patients with risk for frequent recurrences or risk of seizure associated brain damage due to lack of immediate access to health facilities may need prophylactic use of anticonvulsants.
**Prompt control of seizures**

Because of the risks associated with prolonged seizures, the definition of status epilepticus duration has been reduced to 15 minutes from initial 30 minutes and any child brought convulsing has to be treated as status epilepticus. Prompt control of seizures in the prehospital setting is done with rectal diazepam 0.5mg/kg and upto a maximum of 5mg is to be used for infants. Parents must be taught the method of therapy. If ready made preparations are not available injectable preparations can be used for rectal use. Other modalities of therapy like intra nasal or buccal midazolam or sublingual lorazepam may replace the cumbersome rectal routes of administration.

Control of seizures in the hospital set up is the same as for status epilepticus of any cause. Prompt treatment to stabilise the vital signs followed by intravenous drugs with any one of the benzodiazepines like diazepam, lorazepam or midazolam as per the protocol of the hospital should be followed. With these the mortality of febrile status is negligible. Deaths are related to the cause for fever than the seizures per se (0.08%). However it is worth remembering that febrile seizures contribute to 25% of causes of status. Only 5% of febrile seizures go into status and if the initial presentation is as status the subsequent episodes are likely to be prolonged. The importance of the need for prompt medical therapy is well reflected in the following statement. “The best technique under present circumstances is to concentrate efforts on establishing an effective emergency treatment of febrile convulsions and to make it readily available to those who need it. It obviates the need for any type of continuous therapy when medical help is at hand or if treatment can be administered by the parents themselves.”

**Intermittent therapy:** American academy of pediatrics says “Potential adverse effects of prophylactic therapy is not commensurate with the benefits”. Initial use of rectal diazepam was replaced by intermittent use of oral diazepam (0.33mg/kg/dose 8th hourly). Drugs which can rapidly build up blood levels can only be effective. These drugs have to be given early in the illness and continued for three to four days.

Of late clobazam has been preferred as it has lesser sedation and longer duration of action. Some children may show hyperactivity or vomiting during therapy. Ataxia is less marked than with diazepam and 12th hourly administration is easier than three times as with diazepam. The dose of clobazam is either as 0.3 mg/kg - 1mg/kg/day or as 5mg/day in two divided doses upto 5kg body weight,10mg/day for body weight 6-10kg, 15mg/day for body weight 11-15 kg and 20 mg/day for weight above 15 kg.

Intermittent therapy may not be effective when seizures are the first sign of the illness or occur with lower degrees of fever. Failure to initiate prompt use by the parent or care giver often leads to failure. Prompt control of fever with anti-pyretics is important. However their use alone is not protective.

**Continuous use of drugs:** This is indicated only in a select group of children which include the following: 1.First complex febrile seizures, 2. Prior neurological abnormalities, 3. Family history of afebrile seizures, 4. Failure of intermittent therapy and 5. Situations where doubts exist about availability of emergency medical therapy (which can lead to prolonged seizures with risk of brain damage).

Drugs that are useful are phenobarbitone and sodium valproate. Drugs like phenytoin and carbamazepine are not effective. Phenobarbitone is given in the dose of 3-5 mg/kg/day and sodium valproate 10-20mg/kg/day. Phenobarbitone can cause hyperkinesis, inattention, drowsiness, sleep disturbances and impaired cognition and fall in
IQ on longterm use. Drug compliance is often poor. Abrupt withdrawl can precipitate seizures. Life threatening hepato toxicity at times and pancreatitis are to be watched for while on sodium valproate. These side effects may outweigh the benefits and hence the long term prophylaxis with anti-convulsants has to be used only in selected circumstances.29

However many studies have shown their beneficial effects.

**Incidence of recurrence of febrile seizures**

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An Indian study has also shown the beneficial effects of phenobarbitone.6 Other studies have shown no treatment benefit.26,37 However the risk vs benefit and the benign nature of illness restricts its use to selected situations only. Since 90% of recurrences occur within two years, the therapy is to be continued for two seizure free years or one year from the last seizures whichever is longer. After withdrawing anticonvulsants parents must be advised to use intermittent prophylaxis of benzodiazepine until 7 years of age. ‘Although daily anti convulsants may be appropriate in children with febrile seizures, there are reasons not to treat with daily medication’.15 It is worth remembering that prophylaxis against recurrence of febrile seizures does not minimize the risk of future epilepsy.

Conselling the parents is very important. Witnessing their child convulsing is stressful. Parents have to be taught on how to handle the child like proper positioning and care during seizures with prompt use of rectal or buccal or intranasal medicines and the need for emergency medical care if seizures are prolonged. The long term benign nature of true febrile seizures has to be explained clearly.

**Points to Remember**

- **Febrile seizures generally carry a good prognosis.**
- **Aim of the treatment is to prevent prolonged seizures to avoid brain damage subsequently.**
- **Rarely, febrile seizures may be the initial manifestation of some epileptic syndromes.**

**References**


**CLIPPINGS**

**Cyclosporin (the drug for preventing organ rejection after transplant) as an oral corticosteroid sparing agent in stable asthma**

Some people with asthma need to rely on corticosteroid drugs to control their asthma. Corticosteroids help reduce the inflammation (swelling) of the airways (passages to the lungs) associated with asthma. Long-term use of these drugs may have serious adverse effects, so other ways to try and cut down on the need for corticosteroids are sometimes tried. Cyclosporin is the drug used to prevent organ rejections after transplants, and it can be used for other conditions involving inflammation (such as arthritis). The changes with cyclosporin are small and of questionable clinical significance. Given the side effects of cyclosporin, the evidence available does not recommend routine use of this drug in the treatment of oral corticosteroid dependent asthma.


**Do different types of dressing used to protect the central venous catheter site reduce the chance of developing a catheter related infection?**

A central venous catheter is a small tube inserted into a major vein to allow medications and other fluids to be ‘dripped’ in over a period of time without repeated injections. It is used in preference to a peripheral catheter (e.g. in the hand or arm) when access is required for long periods of time or the fluids that are administered may be damaging to the tissues. However, because central catheters are open to large veins they are associated with a risk of blood infection. Several different kinds of dressing are used for protecting the central venous catheter site, including transparent polyurethane dressings, gauze and tape. These dressings may vary in their durability, ease of use, ability to prevent infections and skin reactions. However, the review of trials found there is not enough evidence to determine whether any of the dressings for central venous catheters are better than any of the others.

CHILDHOOD VITILIGO – AN OVERVIEW

* Jayakar Thomas

Abstract: Vitiligo is a relatively common dermatologic disorder in children and one that has been observed since ancient times. Depigmentation of the skin, with loss of melanocytes on histology characterizes this disorder. A range of clinical phenotypes leads to varying degrees of morbidity. The cause of vitiligo remains unknown, although an autoimmune pathogenesis seems most likely. Treatment also remains difficult. A number of new therapies show significant potential. In this review, we will focus on the classification of childhood vitiligo, hypotheses of pathogenesis and treatment.

Key words: Childhood, Vitiligo, Aetiology, Treatment.

The term vitiligo is thought to come from the Greek vitelius (calf), and thereby to connote the resemblance of the white spots of vitiligo to white patches on a calf. Its initial use is attributed to the Roman physician Celsus in the second century AD.¹ Vitiligo presents as sharply demarcated depigmented macules, that can appear anywhere on the skin. There is a predilection for orifices - eyes, nostrils, mouth, nipples, umbilicus and genitalia.¹ The natural history of the disorder is that it either spreads quite quickly (over months) and then is stable or it relentlessly spreads over the body with time (over years). Sites of trauma (koebnerization), such as the elbows, may develop vitiligo. One percent of the population is affected by vitiligo. Twenty-three to twenty-six percent of these are children under the age of twelve.²⁴ It is the most commonly acquired hypomelanosis.⁵ Vitiligo can be extremely disfiguring, leading to significant patient morbidity. A number of different studies have measured the quality of life for patients with vitiligo. Low self-esteem, poor body image and poor quality of life has been found in patients with vitiligo, including significant psychiatric morbidity (up to 25% in one study).⁵ This is of particular concern for children and adolescents, as they are in their formative years and are developing their sense of self.

Classification

Vitiligo can be divided into essentially two categories - generalized and localized. Under the generalized there are two forms, namely, vitiligo acro-facialis and vitiligo vulgaris. Under the localized version of the disease there is vitiligo areata and vitiligo zosteriformis or the segmental variant, with perihalo nevi as an adjunct. Segmental vitiligo is common in children and is characterized by early onset, rapid progression and then persistence without change. There are no specific precipitating factors. The disease spreads in a linear fashion and may also lead to poliosis.⁶ The first study of childhood vitiligo was conducted by Halder, et al. Previously, the observation had been made that vitiligo was an “acquired, sometimes familial depigmentary
disorder of skin and hair” and that 50% of patients develop vitiligo before age 20. They concluded that childhood vitiligo is a distinct subset of vitiligo, with high incidence of segmental type, family history of autoimmune or endocrine disease, early or premature graying, increased autoantibodies and poor response to topical psoralen plus ultraviolet A (PUVA).³

Aetiopathogenesis

The pathogenesis of vitiligo has long been debated. An autoimmune etiology appears to be the most plausible, with melanocytes destroyed secondary to auto-antibodies. Recent work has shown high numbers of cytotoxic T lymphocytes specific for melanocytic antigens in vitiligo, which supports a direct melanocyte specific attack.⁷ As vitiligo is often seen in the setting of coexisting autoimmune disorders, organ-specific antibodies and aberrations in T and NK cell profiles are seen, a role for cell-mediated immunity is also supported. Autoimmune thyroiditis is the most common association in children with vitiligo. A recent study showed that 16% of patients with nonsegmental vitiligo had thyroid alterations, whereas all patients with segmental subtype had normal thyroid studies.⁸ This suggests thyroid studies in all children with non-segmental vitiligo, so as to find thyroid dysfunction early. This appears to be a rational course of action. Another recent report found four children with Hashimoto’s thyroiditis,⁹ a type of autoimmune thyroiditis. Pernicious anemia, Addison’s disease, and lupus¹⁰ have all been documented in adults with vitiligo. Recently, a report of two children with unilateral poliosis of the eyelashes was described, in association with vitiligo. In one child, the findings occurred simultaneously. In the other, poliosis occurred first.¹¹ A significant association between familial nonsegmental vitiligo and HLA-B46 has been discovered. By contrast, HLA-A31 and CW4 are seen in non-familial patients, who also develop lesions at an older age than those with the segmental subtype.¹²

Treatment

Treatment of vitiligo is often difficult and frustrating, both for the patient as well as the physician. Many modalities have been and continue to be used. The following therapies and their efficacy will be discussed: topical corticosteroids, topical immunomodulators, phototherapy including PUVA, topical PUVA, UVB and monochromatic excimer laser or light, as well as microphototherapy, surgical options including autologous mini-punch grafting; blister roof grafting, and epidermal cell transplantation. The issue of bleaching accomplished by hydroquinone, monobenzone, or Q switched ruby laser will also be addressed. In determining efficacy of treatment, greater than 75% repigmentation is considered a cosmetically acceptable level of repigmentation.¹²

Medical

Topical corticosteroids: Topical corticosteroids are often used as therapy for vitiligo. A meta-analysis in 1998 found that corticosteroids resulted in more than 75% repigmentation of 56% of segmental vitiligo patients and 55% of generalized vitiligo patients.¹³ In 1999, the same group made an attempt to establish evidence based guidelines for treatment of vitiligo in children and adults. Another meta-analysis of the literature was performed, which again showed that corticosteroids are the most effective and safest therapy for segmental vitiligo.¹⁴

Topical immunomodulators: With the introduction of topical immunomodulators (tacrolimus and pimecrolimus), many had hoped they would be a panacea for a number of cutaneous disorders, including vitiligo. A number of studies have shown their efficacy or near-
efficacy to topical corticosteroids, without the attendant adverse effects, such as atrophy.\textsuperscript{15-17} With new concerns regarding their long-term safety, the topical immunomodulators may best be used to treat small and/or difficult areas, such as the eyelids. An interesting report of focal hypertrichosis in a child while using topical tacrolimus for vitiligo was recently described.\textsuperscript{18}

**Systemic PUVA:** Photochemotherapy (PUVA) was originally developed in the 1940’s by an Egyptian physician for the treatment of vitiligo. It has subsequently been used for many different cutaneous disorders. Repigmentation with PUVA is widely variable and rarely is 100\% achieved. In general, dark skin types have better repigmentation than paler skin types. Usually, one to three years of treatment are needed for optimal results, which is one of the drawbacks.\textsuperscript{19} PUVA has the highest rates of adverse effects among nonsurgical treatments, such as nausea, vomiting, phototoxic reactions and a theoretical increased long-term cutaneous malignancy risk. For these reasons, this method is not being used as often for vitiligo.

**Topical PUVA:** Topical PUVA is an attempt to limit the area that becomes photosensitized and avoid some of the effects of systemic psoralen. This method also has side effects, including erythema, blistering and hyperpigmentation of normal, adjacent skin. When topical PUVA was compared to narrowband UVB in the treatment of generalized vitiligo, the therapies were found to be comparable, but narrowband UVB had fewer adverse effects and less cumulative UVB dose.\textsuperscript{20}

**Narrowband UVB:** Narrowband UVB for the treatment of generalized vitiligo in children has recently emerged as a promising therapy. A meta-analysis in 1999 found that narrowband UVB was the most effective and safest therapy for generalized vitiligo.\textsuperscript{17} Subsequently a number of open trials in children with generalized vitiligo have been conducted, with the best results on the face and neck and in vitiligo present for a shorter duration. Hands and feet show little response. Treatment three times per week seems to have a somewhat better response than twice per week.\textsuperscript{21-24}

**Microphototherapy - UVB:** A variation of narrowband UVB, microphototherapy has been used to treat both segmental and non-segmental vitiligo. The beam is focused only on areas affected by vitiligo. An open trial of adults and children with both segmental and generalized vitiligo were treated with this modality. Seventy percent achieved normal pigmentation in greater than 75\% of treated areas. This may be the treatment of choice in patients with <30\% BSA (body surface area) involvement and the best treatment for children, as the cumulative dose of radiation is very low and non-affected skin does not become hyperpigmented.\textsuperscript{25}

**Monochromatic excimer light (MEL):** Monochromatic excimer light has been used to treat adults with either segmental or generalized vitiligo. Good results were found, with 95\% of patients showing some repigmentation and approximately 50\% greater than 75\% repigmentation. Significantly, three patients responded to MEL who had not responded to narrowband UVB in the past. The results are similar to those with excimer laser; however, MEL has the advantage of lower power density leading to reduced risk of overexposure, the possibility to treat larger areas at a time, and shorter treatment duration. These advantages may allow this method to be useful in children, however it has unknown efficacy, as no children under 15 years were treated in this study.\textsuperscript{26}

**Surgical**

**Epidermal grafting (autologous mini-punch grafting, blister roof grafting):** Surgical methods offer other options in the treatment of
vitiligo. Segmental vitiligo is the best indication for surgical repigmentation and these patients are good candidates for epidermal grafting. A retrospective case series of 143 patients treated with suction blister epidermal grafting showed the best results in segmental subtypes, and in patients less than 20 years old. However, no children less than 10 years were included in the study. Significantly, localization of the vitiliginous area did not affect treatment outcome, as it often does in medical therapies such as narrowband UVB phototherapy.27 A comparison of mini-punch grafting and split skin grafting in chronic, stable, segmental vitiligo showed better results with split-skin grafting, particularly over the face and extremities. In this study, which included children as young as 10 years, the surgical technique was followed by three months of PUVA.28

Cosmetic cover-ups: If all treatments have failed; the patient does not wish to undergo treatment; or while treatment is ongoing, cosmetic cover-ups can be very useful. A recent study investigated quality of life in vitiligo patients and the effect of using camouflage. Using camouflage, particularly for the face, head and neck improved the patients’ quality of life, especially for “feelings of embarrassment and self consciousness” and “choice of clothing”.29

Points to Remember

• **Childhood vitiligo is unique and different from adult vitiligo.**

• **It is suggested that an autoimmune pathogenesis seems most likely and that thyroid studies should be obtained regularly in children with generalized vitiligo.**

• **Treatment of vitiligo depends on subtype and age, with a number of promising treatments for children on the horizon, including narrow-band UVB phototherapy and surgical techniques.**

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A 5 month old male infant, second born of non consanguineous marriage was referred for progressive abdominal distension with failure to thrive for 1 month. On examination he was alert, with massive hepatosplenomegaly and had no dysmorphism. X-ray abdomen (Fig.1) and liver biopsy (Fig.2) done are shown above.

What is the diagnosis?
In this issue, we will continue our quest to diagnose more disorders of ventral induction. These disorders take place at 5 to 6 months when the primitive brain vesicles have formed and the bulk of neurons are yet to develop. We saw the supratentorial holoprosencephaly. Now we will see the infratentorial Dandy-Walker malformation. The cerebellum, pons and the medulla develop from the rhombencephalon and the fourth ventricle is the remnant of the corresponding primitive vesicle. Failure of this process causes Dandy-Walker malformation (DWM). DWM (Fig.1) consists of a malformation of the roof of the fourth ventricle and of the cerebellum. The enlarged fourth ventricle loses its normal shape, expands and balloons out backwards. It behaves as a cyst and displaces the tentorium and the occipital lobe upwards as you can see in Fig.2. Fig.2 is a midsagittal section where you can see a hypoplastic, thinned out cerebellum lifted upwards. The posterior fossa is filled with black fluid. Fig.3 is a basal CT section in DWM. The hypoplastic cerebellar hemispheres are seen only laterally. The upward displacement of the tentorium can cause an internal obstruction of normal CSF flow, with resultant hydrocephalus as is evident in this picture. Fig.1 also shows an associated interhemispheric cyst displacing the lateral ventricles outward.

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The Dandy Walker variant, as the name suggests, is part of the spectrum of the DWM. The degree of cerebellar hypoplasia is mild. Fig.4 is the scan of a 21 year old boy who has mild mental retardation and was unable to complete school but drives cars for the family and relatives. Note the widened vallecula due to vermian hypoplasia. The rest of the cerebellar hemispheres are present. The fourth ventricle is mildly dilated.

The megacisterna magna is the mildest in the Dandy Walker continuum. The patient is clinically normal. The fourth ventricle, vermis and cerebellar hemispheres are normal. In Fig.5, a large cisterna magna is seen communicating with the fourth ventricle. Also note that there is no dilation of the other ventricles. Occasionally the posterior fossa can be enlarged.

In Joubert’s syndrome the fourth ventricle is enlarged with vermian hypoplasia. A section just above the cerebellum shows a molar tooth appearance due to thinned superior cerebellar peduncles.

Fig.6 also shows a large posterior fossa cyst. This is an arachnoid cyst and is not to be mistaken for DWM because the cerebellum is normal and the vermis is intact. The fourth ventricle and the
cerebellum are compressed anteriorly by this large cyst. Arachnoid cysts are classified under disorders of neuronal proliferation, differentiation and histiogenesis- an event that takes place after ventral induction. They are benign cysts that occur in the cerebrospinal axis in relation to the arachnoid membrane and do not communicate with the ventricular system. Posterior fossa arachnoid cysts are rare but it is a differential diagnosis that should be remembered as the treatment is different.

In the past few issues we have seen disorders of dorsal and ventral induction where hypoplasia of the various structures manifest as abnormalities in the cerebro spinal fluid. This is easily identifiable by ultrasound, as long as the fontanelle is open. For older children CT or MRI is essential.

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**Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)**

Typhoid or paratyphoid fevers (known as enteric fever) are infectious diseases caused by *Salmonella* bacteria. There were over 25 million new cases worldwide in 2000. Infections are mostly in the middle- and low-income countries where sanitation and water supplies are poor. The diseases are common in the Indian subcontinent, South-East and Far East Asia, Africa, Central and South America, and the Mediterranean region. Enteric fever occurs mainly in young people between five and 19 years and in some areas it is common among children less than five years’ old. The infection is usually transmitted by ingestion of food or water contaminated with faeces from people who have the infection. Symptoms include intermittent fever, severe headaches, abdominal discomfort, loss of appetite, malaise, vague abdominal tenderness, and enlarged liver and/or spleen. About 10% to 15% of people get complications, which include bleeding, shock, and inflammation of the pancreas, heart muscles, and the brain. For many years, antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole were used for treating enteric fever. However, multiple-drug resistant strains of the bacteria have now emerged. Other antibiotics like the fluoroquinolones, cephalosporins, and azithromycin are used as well. This review of trials looked at azithromycin as a treatment for uncomplicated enteric fever. There were seven trials (from Egypt, Vietman, and India) involving 773 people, all treated in hospital. There was limited evidence showing azithromycin is effective for treating typhoid or paratyphoid fevers. This is especially important where there are multiple-drug resistant strains. Azithromycin was better than some of the other drugs used. However, care will need to be taken to prevent strains becoming resistant to azithromycin too. More large trials, preferably multicentred and involving outpatients in areas endemic for enteric fever, are needed.

STROKE AFTER PRIMARY VARICELLA ZOSTER VIRUS INFECTION

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Neurological complications are known to occur with varicella infection especially during reactivation. But occurrence of intracerebral vasculopathy leading to hemorrhage and monoplegia is unusual with primary varicella. Here we share our experience of managing such a case and discuss the guidelines that should be followed.

Case report

12-year-old male child who had chicken pox 14 days back, presented with history of headache, giddiness and vomiting for 2 days. He had one episode of generalised seizures on the day of admission. He was having chicken pox, which started 14 days prior to the present problems. Skin lesions were in non-infective scab form at admission. There was no history of head trauma. On examination he was drowsy but arousable with stable vitals. He was afebrile. Neurological examination showed no deficits or no signs of cerebral irritation. Fundus was normal. Tendon jerks were normal but plantars were bilateral extensor. After admission he had several episodes of right focal seizures (but had left focal and generalised as well) and he became stuporose. He was given intravenous phenytoin and sodium valproate. Further focal seizures were controlled with intravenous diazepam. The neurological findings changed over the first 3 days with development of weakness of right upper limb. He had grade 2/5 power, hypotonia and all the deep tendon jerks were brisk.

Lumbar puncture performed on day one showed no cells with normal sugar and protein. CT brain done on day 2 showed bilateral intraparenchymal hemorrhage of both cerebral hemispheres, more on left side (Fig.1). Diagnosis of cerebral vasculopathy was made based on 1) clinical picture, 2) temporal association with varicella infection and 3) CT findings. He was treated with intravenous acyclovir for 10 days along with steroids for first 3 days. Other supportive measures were continued. By the end

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Fig. 1. CT Brain showing bilateral intraparenchymal hemorrhage.
of first week he showed good clinical response. He had no further seizures. Sensorium returned to normal. Power in right upper limb gradually improved and was grade 4/5 at discharge. He was discharged on day 11 and had normal neurological examination findings on first follow up after a week.

**Discussion**

Varicella Zoster virus (VZV) is a human alpha herpes virus. Primary infection causes chicken pox or varicella. Subsequently the virus remains latent in cranial, dorsal root and autonomic ganglia, the reactivation of which later on lead on to development of herpes zoster. The neurological complications of varicella are rare in children. Herpes zoster rather being uncommon in pediatric age group, its neurological problems are also not seen in children.

The common neurological syndrome is acute cerebellar ataxia occurring with a frequency of 1/4000 in children. Other presentations are cerebral vasculopathy or encephalitis, aseptic meningitis, myelitis, Reyes syndrome, optic neuritis and Guillain Barre syndrome.

Varicella Zoster encephalitis has a worse prognosis than ataxia. Encephalitis is known to occur in 0.1-0.2% of patients with VZV infection in all age groups. The pathogenesis of VZV encephalitis is said to be due to the spread of virus along the trigeminovascular or cervico vascular connections, CSF pathways and hematogenous spread. The virus is not seen in brain of immunocompetent children-rather it is seen in arteries of both anterior and posterior circulation. Because of this, VZV encephalitis is now recognized as a vasculopathy involving large and small arteries.

Large vessel vasculopathy also known as unifocal vasculopathy or granulomatous arteritis occurs in immunocompetent children and presents acutely whereas small vessel disease or multifocal vasculopathy is almost exclusively seen in the immunocompromised and presents subacutely. Though unifocal vasculopathy is more commonly described in elderly as a part of reactivation it can occur at any age including infants. It is characterized by fever, headache, vomiting, altered mental status and focal abnormalities such as hemiparesis and sensory changes. Seizures are a prominent feature of VZV encephalitis occurring in 29-52% of cases. Symptoms appear approximately 1 week after the rash and may develop acutely or gradually. Neurological sequelae are observed in 10-20% of patients. CSF show lymphocytic predominance. Neurological imaging with CT or MRI reveals infarcts which may be hemorrhagic. Although absolute number of varicella encephalitis is higher in children due to the relative higher incidence of varicella itself, the age specific incidence of encephalitis is higher in adults. In adults encephalitis occurs with a frequency of 1-2 cases per 10,000 whereas in children the incidence is only 1/33000.

In our patient a diagnosis of VZV vasculopathy was made because of clinical features of encephalitis, right monoplegia and CT findings of hemorrhage. But there are some atypical findings here. The presentation is acute but clinical features appeared during primary infection itself rather than with reactivation phase. Also lack of lymphocytes in CSF could not be adequately explained. We could not find similar reports in literature.

Most of the neurological complications of VZV are associated with replication of the virus in CNS. Diagnosis of vasculopathy involves identification of virus DNA with PCR and/ or antibody in CSF (category 1 recommendation). Antiviral therapy is the key in the management. Patients with VZV vasculopathy should be treated with intravenous acyclovir 500mg/m2/day for
7 days in otherwise healthy children and longer in the immunocompromised. (category 1 recommendation). Steroid therapy with prednisolone for 3-5 days should be considered to reduce inflammation in CNS (category 3 recommendation)\(^8\).

**Conclusion**

VZV can cause primary and reactivation infection.

Encephalitis or vasculopathy is common in reactivation phase in elderly but can occur at any age.

Vasculopathy can present as unifocal in immunocompetent and multifocal in immunocompromised children.

Treatment includes acyclovir therapy with short course of steroids.

**References**


**Answer to Picture Quiz:**

Fig. 1 : Bilateral adrenal calcification

Fig. 2 : Liver biopsy showing marked steatosis with small and large fatty vacuoles.

Diagnosis : Wolman disease

Wolman Disease is a rare fatal autosomal recessive disorder due to deficiency of enzyme acid lipase characterized by accumulation of cholesterol esters and triglycerides in histiocytic foam cells of most visceral organs. The clinical features include hepatosplenomegaly, failure to thrive, steatorrhea, etc. Adrenal calcification seen radiologically in abdomen is the hallmark of this disease. There is no specific therapy available. Recently umbilical cord stem cell transplant has been advocated to restore acid lipase levels and if performed early may be curative.
OPEN LIP SCHIZENCEPHALY CAUSING CHILDHOOD HEMIPARESIS - A CASE REPORT

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Schizencephaly is a rare disorder consisting of gray matter lined cleft extending through the full thickness of cerebral hemisphere from the cortex to the ependymal lining of the ventricles. In type 1 (closed lip) the cerebral cortical walls on either side of the cleft are in close contact. In type 2 (open lip), a wide subarachnoid space separates the two walls. The clinical course includes seizures, motor deficit and developmental delay. CT scan demonstrates size and extent of the cleft, whereas MRI is preferred to identify associated intracranial malformations. We report a case of schizencephaly causing childhood hemiparesis.

Case Report

A 2 year old male child born of non-consanguineous parentage, presented with two episodes of generalised tonic clonic seizures (GTCS). There was no history of fever or trauma. He had GTCS at 1 year 8 months of age and was on sodium valproate regularly. Birth history was normal. He had delay only in motor milestones, learned to walk only a few days back. The mother noted left hand preference and paucity of right hand movement of the child since infancy (Fig.1).

Examination revealed normal head circumference, no dysmorphism or organomegaly. Child had hemiparesis right (Fig.1). Power was grade 3/5 in right upper limb and 4/5 in right lower limb. Deep tendon jerks were brisk on right side with extensor plantar response. After control of seizures with injection phenytoin, CT scan of brain was performed. It showed left sided wide open lip schizencephaly with rest of the cerebral hemispheres, ventricles and posterior fossa being normal (Fig.2).

Fig.1. The child with right sided hemiparesis

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Schizencephaly is a rare neuronal migration disorder characterized by a cleft in the cerebral hemisphere lined by gray matter extending from the ventricular surface (ependyma) to the pial surface of the brain. It is often parasylvian, may be unihemispheric or bihemispheric, open lip or closed lip type. The open lip type may communicate with the lateral ventricle. Associated intracranial malformations often include polymicrogyria, gray matter heterotopia, absent septum pellucidum, optic nerve hypoplasia, hydrocephalus and septo-optic dysplasia.

Schizencephaly may be due to failure of normal migration of primitive neuroblasts as evident from microgyri, cortex and large neuronal heterotopias. It may be due to an encephaloclastic disorder resulting from destructive changes after infarction in the middle cerebral artery territory. Studies using single strand conformation polymorphism at times revealed germline mutation in the homebox gene EMX2. However, beside genetic theory, toxic, metabolic and infectious causes are proposed as etiology.

Clinical manifestation varies according to the severity of the lesion. Unilateral type 1 lesion presents with mild hemiparesis, seizures and normal development. Unilateral type 2 lesion patients have mild to moderate developmental delay, hemiparesis and seizures as in our case. Patients with bilateral clefts have severe mental and motor deficit and often blindness. Seizures are often intractable, which include GTCS, partial motor, sensory seizures and infantile spasm.

Investigation like CT scan of brain is diagnostic of open lip schizencephaly, but MRI delineates better the gray matter lining the cleft, differentiates schizencephaly from porencephaly and identifies associated gray and white matter anomalies.

Schizencephaly should be considered as one of the differential diagnosis of childhood hemiplegia/paresis, especially when it is associated with developmental delay and seizures. Neuroimaging is necessary to confirm the lesion, its nature and extent - thus enabling to explain its static nature to the parents. Control of seizures is very important to prevent neurological deterioration. Intractable seizures may require surgical intervention. Associated treatable conditions like hydrocephalus, should be identified and treated early. Physiotherapy of the affected side is the mainstay to preserve functional usefulness.

References


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NEWS AND NOTES

RESPICON – 2009

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Conference : 12th, 13th September 2009
Mammen Mappila Hall, Kottayam

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Q.1. A child of 8 years suffering from acute hepatitis B, I want to know whether this child should be vaccinated with Hepatitis B later on?

Q.2. A male child 10 years old attended my clinic with history of contact with Hepatitis B patient 2 months back. He is not vaccinated with hepatitis B. How should I manage this child?

Dr. Pradyut Kumar Mandal
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A.1. The natural history of acute hepatitis in older children is better than young infants since the incidence of chronicity is inversely proportional to the age of acquisition of the virus. About 10% of children in this age group will not clear the virus by the end of 6 months and continue to be HBsAg positive. This group therefore do not require immunization.

85-90% will naturally seroconvert and will become HBsAg negative by the end of 6 months followed by anti-HBs positivity. However, they will continue to be anti-HBc IgG positive. This group therefore do not require immunization.

So this child with acute hepatitis should be followed up for a period of 6 months to decide whether he/she will not require or will not respond to vaccination. If there is a good clinical and biochemical improvement there is a high chance of natural seroconversion. At the end of 6 months if HBsAg is negative it indicates that the child has cleared the virus and does not require immunization. The detection of anti HBs will confirm the seroconversion. If the child continues to be HBsAg positive after the end of 6 months he/she is considered as a chronic HBV infected individual and needs appropriate follow up and therapy. This child will not respond to the vaccine.

A.2. This child with history of contact with HBV positive patient 2 months ago should be checked for HBsAg status. If he is HBsAg negative then he should receive 3 doses of active immunization with Hepatitis B vaccine 10 microgram at 0,1 and 6 months interval. There is no role for immunoglobulin in this situation.

If he is found to be HBsAg positive then vaccine cannot be given but instead his anti-HBc IgM status should be tested. If found positive then it indicates that he has acquired a recent infection. He is followed up for 6 months to check for clearing. If he becomes HBsAg negative he has naturally seroconverted but if he does not he is considered to have a chronic HBV infection and needs follow up and appropriate therapy as indicated.

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