

**Towards standards
for organ and tissue
transplantation
in the United
Kingdom**

These Standards have been compiled by the British Transplantation Society as representing the best of current or the most desirable practice, following wide consultation among its members, members of the Renal Association and the Royal Colleges of Surgeons and Pathologists.

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1.0 INTRODUCTION

1.1 THE NEED FOR STANDARDS

Each branch of medicine has features which tend to set it apart from others. Transplantation is unique in that it is totally reliant on human tissue and organ donation and unfortunately, that there are insufficient donors 1.1 to meet the increasing demands for organ replacement. As the success of transplantation as a treatment for organ failure increases, more patients are deemed suitable for such treatment and the criteria by which they are judged suitable have evolved. In this context, the setting of standards is very important; responsibilities extend beyond those relating to the patient receiving the organ and reach out to those who donate their organs for transplant. Whilst every opportunity must be taken to increase organ donation within accepted legal, moral and ethical guidelines, it is equally important that no effort is spared to avoid wastage. This process demands the highest standards, if public and professional confidence is to be maintained. Donated organs should be placed where they are most likely to improve quality of life and to be of lasting benefit. However this may present a conflict on occasion in that an organ transplant could improve quality of life but not be of lasting benefit. Avoidable technical and immunological failures must be minimised and the probability of benefit to individual patients calculated in advance. In the present climate of resource constraints three strategies need to be employed to maximise the outcome of transplantation. Firstly the quantity and quality of organs retrieved needs to be improved. Secondly strategies need to be employed in the clinic not only to maximise patient and graft survival but also improve the quality of life of the recipient. Thirdly the allocation of organs must be organised in an equitable manner.

1.2 THE ROLE OF THE BRITISH TRANSPLANTATION SOCIETY (BTS)

The British Transplantation Society, in line with international opinion, has encouraged and kept registry data since its inception. In 1974, that responsibility was passed to the National Organ Matching Service based in Bristol which subsequently became the UK Transplant Service, and finally the UK Transplant Support Service Authority (UKTSSA). Each transplant unit has accepted the obligation to return outcome data to the national registry and, indeed, to many other national and international registries.

In 1981 the British Transplantation Society became aware of a significant centre variation effect for patient and graft survival across the United Kingdom. This centre variation was enthusiastically investigated, but no clear-cut guidelines emerged. Fifteen years later, despite significant improvements in outcome following transplantation throughout the United Kingdom, centre variation is still apparent.

Maxwell's essay on quality of healthcare published in the BMJ in the late 1980's, 1.2 clearly outlined equal access to equal quality of service as being an important parameter for quality of healthcare delivery. For these reasons, and also because the clinical management of a transplant is now much less serendipitous, the Council of the British Transplantation Society feels that the time has come to establish, where possible, national standards for all forms of organ transplantation. As a first step the initiative has been taken to produce this document, in conjunction with the Royal College of Surgeons.

1.3 THE NATURE AND PURPOSE OF THIS DOCUMENT

This document describes the current situation in organ transplantation and embodies contributions from leading figures in each organ speciality area. As the first attempt of its kind, it cannot expect to be fully comprehensive. It is intended as the first in a series which will subsequently facilitate a steady and focused improvement, gradually coming to define the accepted standards for all UK transplantation programmes.

Inevitably the discrepancies in the level of provision and the variation between different provider units are highlighted. This document does not comment on those differences, rather, it aims to generate questions and debate within the profession and the commissioning community.

Although there is much speculation about possible alternatives to human organ donation in the future, including mechanical devices and xenotransplants, this document concentrates primarily on the speciality as it is today and as it is likely to remain for the next few years.

Throughout this document, the principles of organ transplantation are taken to encompass all tissue transplantation including cornea and bone marrow and skin grafting. Transplant procedures for solid organs and corneas are discussed from first assessment, through successful operation and follow-up. It has to be recognised that transplant follow-up continues for a patient's lifetime; that span is steadily increasing.

Best Practice: Throughout the document the endorsements of "best practice", as perceived by the BTS are highlighted in this manner.

2.0 TRANSPLANTATION IN GENERAL

2.1 THE NATURE OF END STAGE ORGAN FAILURE

When a "vital organ" fails death is inevitable except in the case of kidney failure where an alternative exists to prolong life, i.e. maintenance dialysis. It follows, therefore, that if patients with end stage liver, heart or lung failure do not receive an organ transplant, death will ensue. Similarly, when the bone marrow fails as a result of disease, irradiation or drugs, life cannot be sustained. Irreversible damage to the cornea results in blindness. Transplantation of the kidney, liver, heart, lung and bone marrow can save life and restore normal health. In the case of the cornea, vision can be restored.

In the relatively short history of transplantation, graft survival has improved significantly. Today, 85% of patients receiving a kidney, 77% of patients receiving a heart and 65% of patients receiving a liver will have a functioning graft one year after the operation. This success has lowered the threshold for acceptance of patients for transplantation and resulted in an increased demand. Indeed in the renal area, transplantation has in a sense become a victim of its own success. More patients are being accepted for transplantation and need dialysis while they are waiting for a graft. The increasing demand for dialysis constantly exceeds provision, which in turn puts further pressure on the need to speed the flow of renal transplants.

Reducing transplant waiting time by increasing throughput is almost entirely dependent upon the availability of donor organs. This feature, which is peculiar to the transplant speciality, has to be understood by the commissioners of transplant services.

This unique situation means that transplant teams must be committed to national organ sharing schemes, to the development of organ donation, education and organ retrieval methods and to the principle of national protocols and policy development.

The general areas in which standards must be set are:

- * Ethics related to organ donation, and distribution, including alternative sources.

- * Retrieval and sharing of organs for the UK-wide scheme.

- * Selection and continuous reassessment of patients waiting for a transplant.

- * Equity of access to donor organs for all patients.

- * Clinical excellence in transplant surgery and medicine.

- * Management of immunosuppression and long term patient surveillance and support following transplantation.

- * Laboratory standards including quality assurance.

- * Commitment to research and development.

- * Teaching and training.

- * Clinical audit (local and national).

2.2 ETHICAL ISSUES IN TRANSPLANTATION

The foundation for an ethical basis for transplantation was laid with the publication in 1983 of "Cadaveric Organs for Transplantation - A Code of Practice including the diagnosis of Brain Death". This document was drawn up and revised by a Working Party on behalf of the UK Health Departments and refers to the Human Tissue Act 1961. 2.2 In addition, the Human Organ Transplants Act 1989 2.3 provides that a person is guilty of an offence if he or she makes or receives payment for supplying or agreeing to supply organs for transplantation. This Act also limits live donor transplantation to genetically-related individuals and those non-genetically related donors given prior approval by the Unrelated Live Transplant Regulatory Authority (ULTRA).

Where specific guidelines do not exist the burden may fall on the individual clinician to ensure that all aspects of his/her practice conform to accepted ethical standards and particular attention is directed to the following areas:

2.2.1 Cadaver Transplantation

2.2.1.1 Organ allocation

With the existing imbalance between organ donors and potential recipients, organ allocation becomes an important issue especially in situations where individuals may die while waiting for an organ to become available.

Best Practice: Each Transplant Centre should have a written policy which defines its allocation process in a form which can be presented to patients and to society in general. There must be demonstrable equity of access to donor organs irrespective of gender, race or district of residence.

2.2.1.2 Requests for donors

At times, the need to find a cadaveric donor for a life-saving transplant may become an urgent matter. Publicity for the plight of the potential recipient has sometimes been sought in an understandable attempt to maximise the opportunities for identifying a suitable donor. Nevertheless,

such publicity may put undue pressure on the relatives of potential donors.

In general, society does not extend to donors the right to say to whom the organs should go. In contrast to live donation where it is only permitted to donate to close relatives, for cadaveric donors the organ goes to the best matched patient, according to nationally agreed protocols (See 4.2.4 below) This limitation reflects the principle in society of not permitting discrimination on the basis of gender, ethnicity or age. It is recommended that one should be guarded in agreeing preconditions when obtaining permission from donor families, although it would be acceptable to say to the parents of a child donor that if possible the recipient would also be a child.

Best Practice: Identifying the potential recipient for a transplanted organ should be avoided in discussions with the family of a potential donor. Making a definite promise as to the allocation of organs must be avoided.

2.2.1.3 Consent to donation

Under current legislation, it is necessary to ascertain whenever possible from relatives whether the potential donor had expressed a wish to donate or otherwise. In case of sudden death the permission of the coroner must be sought. In practice where relatives strongly object to donation, their views are normally respected. However, it is well established that when the potential donor is known to have wished to donate, relatives rarely refuse. In the absence of the next of kin or other relative of the deceased, and after due search, agreement to donation can be obtained from the "responsible officer" (usually the duty manager) of the hospital in which the body rests. The hospital management have legal responsibility for the body in the absence of relatives.

A signed donor card is a valid document but it does not override the declared wishes of the next of kin. The next of kin are not required to sign a consent form but, rather, to indicate that there is no objection to organ donation. Clearly, the relatives must be given adequate time to consider the request and appropriate support during this difficult time should be provided. It is advisable that medical and nursing staff and transplant co-ordinators (Chapter 3) should undergo training in bereavement counselling before undertaking responsibility for such interviews with the relatives of the donor.

2.2.1.4 Respect for the dead

Multi-organ retrieval procedures are now routine for transplant teams. They can, however, cause distress to theatre staff not familiar with this type of surgery. Although the focus of attention is directed at removing the organs in the best possible condition, it is nonetheless important to show consideration for the feelings of everyone present and to explain the procedures. There is also a requirement to restore the body to as near normal appearance as possible, particularly in the case of corneal or bone donation.

Best Practice: it is important to treat the Donor's body with due respect, restoring normal appearance, with sensitivity to the feelings of the operating theatre staff.

2.2.1.5 Consent for transplantation

All patients should receive a full explanation of the risks and benefits of the proposed transplant. Discussion of all the common complications, any additional risk factors for the particular recipient, and any potentially serious complications (even if they are relatively rare) should take place and should be documented.

Where the procedure is in any way experimental or where the treatment is part of a trial this must be made explicit and the potential recipient given the right to refuse to take part without prejudice to their treatment.

Future problems such as risk of infection and of malignancy should be discussed and if the risk of infection is greater than average, e.g. following the use of anti-lymphocyte agents or when a CMV negative recipient is offered an organ from a CMV positive donor, this should be discussed with the patient.

Best Practice: All patients should be given a full explanation of the risks and benefits of the proposed transplant.

2.2.1.6 Confidentiality

On occasions the recipients of a transplanted cadaveric organ may wish to express their thanks or even make personal contact with the family of the donor. In this situation the wishes of the donor family should take precedence and communication should be organised anonymously through the transplant co-ordinator.

Best Practice: The identity of the donor must be protected.

2.2.1.7 Contraindications to Donation

Clearly, not all patients who die can become organ donors. Those whose death occurs too far from intensive care facilities and/or specialised staff would provide organs that would not be conducive to successful transplantation. Those whose relatives cannot be traced or where there is no knowledge of the patient's recent health or lifestyle, may be suffering from a latent disease and it would be unacceptable to risk transfer to a recipient.

There are now a number of contraindications to donation aimed at ensuring (as far as possible) the safety of the retrieved organs. These are reviewed from time to time by the Committee on Microbiological Safety of Blood and Tissues for Transplantation (MSBT). The Guidance on the microbiological safety of human tissues and organs used in transplantation, issued by the NHS Executive in 1996. 2.4

Best Practice: The ultimate responsibility for deciding the suitability of an organ for transplant is that of the transplanting surgeon, who must satisfy himself that he has all the known facts about the donor and that the organ is safe to transplant. (See Chapter 9.0)

2.2.1.8 Obtaining further advice

It is the duty of each transplant unit to ensure their practice accords to the highest of ethical standards. Difficult issues arise not infrequently and it may be helpful to obtain additional advice from the Ethics Committee of the British Transplantation Society.

2.2.2 Live Donors

The donation of a single kidney by a living relative or in some cases by a non-related donor such as a spouse has proved to be a successful method of increasing organ availability. Donors rarely suffer long term ill effects and the survival rate of grafts from living donors is usually better than those of cadaver origin. (See also 4.2.5 below) Success has also been achieved with segments of liver from live donors and similarly with lung lobes.

The agreement of the donor to any aspect of live donation is governed by the Human Organ Transplants Act 1989 (see 2.5 below).

In seeking to expand the possibilities for live donor transplantation, strenuous efforts should be made to ensure that no element of coercion exists, either overtly or in the more subtle context of family or peer pressure.

In general, it is recommended that the first contact between the transplant team and the potential living donor should be initiated by the latter. The option for a potential donor to withdraw with dignity at any stage in the preparation for donation must be made clear. It is good practice to refer the potential donor for additional assessment to an appropriately experienced clinician who is independent of the transplant team.

Best Practice: Counselling of the donor should focus on the risks to the donor and not on benefits to the recipient.

2.2.3 Regulation of cell and tissue transplantation and related therapies

The new therapeutic possibilities which have arisen from advances in cell biology are beginning to lead to the supplanting of some transplantation techniques by the manipulation of blood cells. A recent Scientific Review commissioned by the UK National Biological Standards Board 2.5 and published by the WHO points to the fact that such developments are beginning to impinge on the regulatory framework for biological materials.

The Board endorses the logic of treating cells and tissues for transplantation - apart from clinical organ transplants - within the

regulatory framework for biologicals. They suggest that the level of regulatory oversight should be graduated according to the amount of manipulation the cells and tissues for transplantation undergo. These new developments, they believe, including both cellular therapy and ultimately xenotransplantation, raise questions of 'product' safety and efficacy that need the expertise of professionals in biological standards and control. These issues are already being addressed in the US and in France and the Board points to the advanced regulatory system employed in Australia under their Therapeutic Goods Act of 1989.

Cellular therapy is a fast moving field where the scientific basis of therapy is changing, raising questions about the behaviour of cells post-manipulation and risks of contamination while *ex vivo*. The potential benefits are enormous and the hazards largely unknown and unquantified. (See also Chapter 8 and 9 below)

Best Practice: There is a need for clarification and adaptation of the regulatory framework, informed by a fast, flexible, expert and fully up to date response from all participants in the field.

See also Bibliographic References 2.7, 2.8, 2.9, 2.10, 2.11 2.12 and 2.13

2.3 ENTRY TO THE TRANSPLANT LIST

Approximately 48 new patients per million population (pmp) are referred to renal transplant units each year for assessment and most are accepted. For cardiothoracic and liver transplantation the proportion accepted after assessment is much lower and the nature of the treatment is much more emergency-based. Selection of patients prior to their being placed on the waiting list and the need for continuous assessment before transplantation is becoming more demanding as more patients are being put forward for treatment. Patients may subsequently be suspended or removed from the waiting list for medical or social reasons and similarly a number of those patients assessed as satisfactory will die, from a variety of causes, on the waiting list prior to receiving a transplant. In the case of renal transplantation most patients are already on dialysis although this is not a prerequisite. There is a school of thought that if sufficient organs were available the ideal would be to transplant patients before dialysis becomes necessary. There are substantial centre variations reported throughout the UK in terms of the percentage of renal patients waiting who are on dialysis, the rate at which patients are added to the waiting list and the length of waiting times for transplants. 2.6

Best Practice: Every local transplant service should agree

criteria with its commissioners for acceptance of patients with particular conditions onto the Transplant list.

2.4 AVAILABILITY AND IDENTIFICATION OF DONOR ORGANS

The Department of Health supports transplantation as an essential component of the treatment of end organ failure. As part of this process transplant centres have a responsibility to support efforts which encourage local hospitals to identify potential donors. All transplant units have a responsibility to take part in the assessment of potential donors and to set up suitably trained teams for the retrieval of donated organs. This process is greatly facilitated by the employment of skilled Transplant Co-ordinators, many of whom have background knowledge of intensive care processes. Most centres employ co-ordinators, part or all of whose function is to facilitate and improve organ recovery, but their deployment and achievements vary widely. (See also 3 below)

The rapid increase in the number of patients deemed suitable for transplantation has not been matched by the supply of donor organs which has reached a plateau in recent years. Strenuous efforts are currently being made to increase organ donor availability, but wide variations in organ availability still occur throughout the UK. 2.14 There is a need to improve understanding of why these variations occur and to make greater efforts both to increase organ availability and also equity of access across the UK.

Best Practice: All centres should take steps to increase the number of donor organs within their region.

2.5 ORGAN RETRIEVAL, MATCHING AND SHARING

Zonal arrangements have been created in the United Kingdom to facilitate the retrieval of hearts, lungs and livers from multi-organ donors. The geographical area of each zone is determined by the nationally established target activity for the liver and cardiothoracic transplant centres. The retrieval of donor kidneys and of corneas is carried out by local centres within the zone in accordance with long established practice. The rules governing zonal arrangements have been set out by the Royal College of Surgeons of England working through the UKTSSA Users' Advisory Groups. They are operated through the UKTSSA 24 hour Duty Office, which also co-ordinates transport arrangements for retrieval teams and organs, and monitored on Users' behalf through the UKTSSA Users' Multi Organ Audit Group.

The Human Organ Transplants Act 1989 regulates the practice of all organ removal, use and transplantation. Compliance with this legislation is mandatory. The names and identities of each donor and all donated organs and the name of each recipient of a donated organ must be registered on the

Human Organ Transplants Act Register which is administered on the UK Health Departments' behalf by UKTSSA. As donor organs are a national resource, identified and retrieved through the National Health Service, the profession has agreed sharing schemes to ensure equitable access to this scarce resource. National Organ Sharing Schemes have been developed for each organ type. The sharing protocols which have been agreed by the profession apply UK-wide and ensure that a patient on any waiting list in the UK has equal access to donor material. The nationally agreed rules for sharing cadaver donor kidneys stipulate that non-compliance with the agreed schemes will be notified to UKTSSA Users' Kidney Advisory Group without recourse to anonymity. Organ matching and allocation criteria for all organs are regularly reviewed at professional meetings, formal committees and in the UKTSSA Users' Advisory Group forum. Reference to National Transplant Database material enables UK specific procedures to be modelled, confirmed using historic data and monitored after implementation.

Best Practice: All centres must participate in the sharing schemes which are designed to produce the best possible outcome for every donated organ which is available for transplantation.

3.0 CO-ORDINATOR SERVICES

The role of transplant co-ordinators has developed differently within individual transplant centres. Despite general acceptance of the need for such posts as part of the centres' operational requirements, and the efforts of the co-ordinators' own professional group, the United Kingdom Transplant Co-ordinators' Association (UKTCA), there is a lack of uniformity between centres on matters such as duties, responsibilities and authority. As a result, recruitment, training and career development for co-ordinators within the NHS has yet to achieve a national pattern. This lack of uniformity could be a contributory factor in the variability of donation rates nationally.

The activities of transplant co-ordinators cover two distinct areas, one related to the procurement of donor organs and the other related to the care of the recipient patients. Procurement co-ordinators most often have a nursing background with ITU and/or renal experience. Recipient co-ordinators have tended to come from senior nursing posts within the cardiothoracic and liver transplant services. For the most part recipient co-ordinators confine their activities to the liver and cardiothoracic recipients, but there are some who also have a role in procurement. There are responsibilities common to both roles but in general terms their duties differ in that the recipient co-ordinator is primarily concerned with the clinical care of the recipient whereas the procurement co-ordinator's priority is promoting organ donation (mainly within the intensive care community) and providing support during the donation process. Standards of Practice for Procurement Co-ordinators and for Recipient Co-ordinators are published by the United Kingdom Transplant Co-ordinators' Association; 3.1 the following briefly summarises those documents and sets the co-ordinator roles in context.

There are considerable regional variations in the way in which both organ procurement and recipient care are organised. A survey undertaken for the Department of Health in 1995 of a sample 55 co-ordinators in the UK showed that, whereas many procurement co-ordinators had no role in recipient management, in some parts of the country procurement co-ordinators spent at

least 20% of their time on recipient work. There is debate within the transplant community about whether or not the two roles should be seen as separate entities; it is nonetheless of paramount importance that there are sufficient personnel in post to meet the needs of both organ procurement and transplantation of the recipient.

3.1 THE PROCUREMENT CO-ORDINATOR

Organ procurement has to be supported on a 24-hour basis throughout the year. It is essential that sufficient personnel should be in post to allow for full 24-hour cover. Co-ordination duties include in-service education of those nursing and medical staff most likely to be involved with potential donors, whether in intensive care units, in operating theatres and/or in Accident & Emergency departments. A teaching service is also offered to medical students and nurses in training. On-site support throughout the referral and retrieval process is an essential part of the care and support necessary for both donor families and donor hospital staff. Contact after the donation process is important in providing a positive outcome for the donor family and feedback for the donor unit and donor hospital theatre staff. Co-ordinators are often involved in obtaining the necessary consent for donation from relatives. Co-ordinators take responsibility for gathering and recording information throughout the donation and transplant procedure including the crucial measurements of warm and cold ischaemia time. They also collect follow-up information and facilitate donor family/recipient communications.

For all co-ordinators, there is also a role in educating the public, whether through local voluntary organisations, in schools or on planned courses. Successfully transplanted patients are sometimes involved in this educational process.

3.2 THE RECIPIENT CO-ORDINATOR

Recipient co-ordinators, some of whom may be styled 'nurse practitioner' or 'clinical nurse specialist', play an important part in maintaining contact between units caring for potential recipients, where the patient is maintained at a hospital other than the hospital in which the Transplant Unit is based. In some areas the concept of 'shared care' has been developed between the transplant team and the recipient's general practitioner.

In some renal units, recipient co-ordinators participate in the pre-operative assessment clinics for prospective live donors and for patients awaiting a cadaveric transplant. They also take part in health education and screening of patients after transplantation. They are commonly responsible for maintenance of the transplant waiting list,

registration of patients onto the National Transplant Database at UKTSSA, and collating offers of donor kidneys.

Recipient co-ordinators working in liver and cardiothoracic units have a more specialised role and are therefore usually full-time recipient co-ordinators supporting individual patients through the pre-operative, post-operative, convalescence and rehabilitation periods.

Best Practice: All centres should employ a sufficient number of well-trained co-ordinators to ensure that the duties detailed above are carried out efficiently.

ORGAN SPECIFIC TRANSPLANTATION

4.0 RENAL TRANSPLANTATION

4.1 INTRODUCTION

Renal transplantation is the most cost-effective form of treatment for patients in end stage renal failure (ESRF). Unfortunately, the supply of donor organs, which averages only 30 pmp per year in the United Kingdom, is greatly outstripped by demand which is 48 pmp per year, or higher 4.1

depending upon the criteria used for selection of patients for this form of treatment (see 4.2 below).

Donor organs are an extremely valuable resource which must be used optimally. It is also important that equity of access to transplantation be achieved both in geographical terms and for those with common HLA types. However, these two goals may conflict

Table 4.1 Transplant activity in the UK and Republic of Ireland, 1995 - 1996

Cadaver Live

Transplants Transplants

Age <13yrs 13-60yrs >60yrs All TOTAL

Year

1995 90(5%) 1483(83%) 223(12%) 156 1954

1996 59(4%) 1366(83%) 218(13%) 183 1826

1997 57(4%) 1349(83%) 226(14%) 175 1807

Note: Figures in brackets give the percentage of cadaver kidney transplants

4.2 DEMAND versus SUPPLY

4.2.1 Suitability for Renal transplantation

Not all patients receiving dialysis are suitable candidates for transplantation. There is evidence 4.2 that selection criteria for the transplant waiting list vary widely throughout the United Kingdom. The proportion of patients maintained on dialysis who are registered with the National Transplant Database for renal transplantation varies from 20% in

some units to over 70% in others, with a UK mean of 30%. In addition, some units place patients on the transplant list before they need dialysis, whilst others do not. Further a number of units do not accept patients with major co-morbid disease on to their transplant list on the grounds that such recipients have poorer survival rates.

In the United States, practice guidelines have been formulated on the basis of consensus and literature review. 4.3 In the United Kingdom definitive criteria for acceptance on to the transplant waiting list have yet to be accepted.

Although standards for investigation of potential transplant recipients have not yet been agreed, it is essential that appropriate data are collected during pre-transplant investigation to allow definitive criteria to be drawn up in the future. This applies particularly to cardiovascular disease where some investigators 4.3 have argued the case for intensive investigation of the cardiovascular system in all potential transplant recipients.

Chronological age by itself, at least up to 70 years, is not a major factor in determining the short term (5 years) survival of grafts. 4.4, 4.5, 4.6 There is a strong case to be made for the early transplantation of pre-pubertal children, regardless of tissue match, in order to maximise opportunities for growth.

An increase in deaths in elderly patients with a functioning graft is counterbalanced by a lower rejection rate in the elderly. However, it is obvious that the outlook for older recipients must be poorer in the long term. To deal with these uncertainties, regular meetings between transplant and dialysis staff need to be held to review patients aged over 55 years possibly annually and those aged over 65 years 6-monthly. Changes in suitability for transplantation may take place without warning.

The median waiting time on transplant waiting lists is 500 days. There are differences relating to age, ABO blood group and HLA specific antibody status. Of all the patients on the UK renal transplant waiting list 13.5% have been waiting more than five years and 18% of these patients are not sensitised to HLA antigens.

Best Practice: All patients who wish to be considered for renal transplantation should be formally assessed by a transplant surgeon and a nephrologist and if found to be suitable have their names placed on the transplant list.

At least 40% of dialysis patients in most units will be suitable for transplantation.

Patients who are placed on the transplant list prior to commencing a maintenance dialysis programme should only receive a well-matched kidney.

Pre pubertal patients may be considered for a pre-dialysis transplant regardless of HLA matching in order to maximise opportunities for growth.

Cardiovascular disease, diabetes, previous malignant disease and other comorbidity should be assessed and recorded. Assessment should be repeated annually, while on the waiting list.

Patients should be placed on or removed from transplant lists only after discussion and with the agreement of transplant surgeons, nephrologists and the patients themselves. The decision should be recorded in the patient's notes.

Not more than 2% of non-sensitised patients should have to wait more than five years for a graft.

4.2.2 Availability of Donor kidneys

Organ supply is central to provision of renal transplantation. The kidney donation rate (cadaver and live donor) in the UK is 30pmp per year. This rate is exceeded consistently in some major European countries such as Austria and Spain. 4.7, 4.7A In Spain in 1997, the organ donor rate was twice that of the UK. Data are available to suggest that the supply of organs from within intensive care units could be increased in the UK by approximately 20%. 4.8, 4.9 The topic has been discussed extensively in the King's fund report 4.10, by Wight and Cohen 4.11 and in a report of the British Transplantation Society working party. 4.9 This report concluded that if all donor sources e.g., including live donors and non-heart beating donors, were considered, the kidney donor rate in the UK could be substantially increased. It is important that awareness of the need for organ donation within intensive care units in the hospitals served by the transplant centre should be developed and sustained by educational programmes led by transplant co-ordinators. Liaison with and full co-operation from intensive care specialists and other staff in the units is crucial.

These arrangements are essential to ensure that all organs offered for transplantation are retrieved. There is some evidence 4.12 that retrieval arrangements are underfunded. It is therefore important that funds are

provided to expand and improve the service.

Best Practice: Organ retrieval services must not be jeopardised by lack of funding.

Each renal transplant unit should be expected to achieve the current national mean retrieval rate of 15 donors per million population per year.

4.2.3 The quality of retrieved kidneys

The quality of retrieved organs is particularly important and takes on special dimensions and creates additional responsibility when one centre is retrieving for another. Improving the quality of organs retrieved pays dividends in the transplant programme overall.

Most kidneys are now retrieved from heart beating donors as part of a multi-organ donor procurement procedure. The minimisation of ischaemic injury optimises the subsequent performance of the transplanted kidney. Some centres in Europe are attempting to increase the number of organs available by retrieving from non-heart beating donors. An increasing number of reports indicate that kidneys from this source can function adequately. 4.14 There is an increase in post-operative dialysis requirements and the retrieval process is more difficult to carry through smoothly than is the case with donors on ventilators. In all cases, the time between retrieval of kidneys and transplantation needs to be kept to a minimum. Connolly et al 4.15 have reported that prolonged cold ischaemia is associated with reduced five-year graft survival. The report of Cecka et al 4.16 and unpublished data from the UK National Transplant Database and Eurotransplant databases also support the association of lengthy cold ischaemia time with inferior graft survival.

The presence of multiple renal arteries in the donor kidney can lead to technical complications and thus adversely affect the outcome of transplantation. It is imperative that a full description of the vascular anatomy and in particular of any injury to a vessel accompanies donor kidneys when transferred between centres.

It is a common perception that kidney damage at retrieval is an increasing problem which is not always reported. Such under-reporting significantly undermines efforts to improve the quality of kidneys procured. Recent studies 4.17 have shown that damage is more likely to occur with elderly donors where only the kidneys and not other organs are retrieved. Such damaged kidneys are anecdotally more likely to be exchanged than to be kept

locally. Provided the damage is accurately reported, it is often possible to perform a repair prior to transplantation and to obtain good kidney function.

Best Practice: Kidneys should always be retrieved by an experienced transplant surgeon.

The retrieval of non-heart beating donor kidneys should be confined to a limited number of pilot studies until there is more evidence that they can be used successfully.

The kidney cold storage time should wherever possible be kept below 24 hours.

Clear documentation relating to issues of anatomy or kidney damage during retrieval should be sent to the transplant unit with the donor kidney. Any damage should be emphasised by telephone in advance of dispatch of the kidney and recorded through the UKTSSA Duty Office.

4.2.4 Allocation and use of cadaver kidneys

Debate continues on the practical and ethical basis for allocation of kidneys. 4.18, 4.19, 4.20 Ten years ago in the United States the United Network for Organ Sharing (UNOS) introduced a formal system of allocating points to potential recipients on the basis of a scoring system. Points were allocated using such criteria as time waited, medical urgency, tissue matching and HLA specific antibody status.

In the UK, during 1997 and early 1998 the UKTSSA Users' Kidney Advisory Group developed and presented revised protocols for the allocation of kidneys to Favourably Matched recipients based on a 3-tier system. This included a requirement that all donor kidneys will be offered to Favourably Matched paediatric recipients and to adults where there is a zero HLA-A, -B, -DR mismatch. These revised protocols were considered and agreed by a meeting of all Renal Transplant Unit Directors and have been put into practice with effect from July 1998.

In the most recent audit undertaken, using 1996 data, a rate of 26 cadaver

transplants per million population was achieved in the UK as a whole. Every transplant centre should aim to achieve at least the national average.

Best Practice: The revised protocols for the allocation of kidneys, developed by the UKTSSA Users' Kidney Advisory Group, should be adopted by all renal transplant centres.

Each unit should aim to transplant at least 26 patients pmp per year with cadaver kidneys.

4.2.5 Live kidney donation

Even a much improved cadaver kidney donation rate is unlikely to satisfy demand and therefore the need for living donors continues.

In the UK live donor transplants currently represent around 10% of all renal transplants, a mean of only three pmp per year. In many European countries the mean exceeds five pmp per year. In Norway 40% (17pmp per year) of all kidneys are obtained from live donors, and as a result a total rate of more than 40 transplants pmp per year has been achieved. 4.10 An important additional justification for living donor transplantation is the superior success rate that can be achieved by comparison with cadaver transplantation. A live donor programme requires built in controls to ensure that donation is altruistic, without coercion or reward and that the risks to the donor are minimised. The requirements of the Human Organ Transplants Act 1989 must be met in every respect. Clearly defined protocols for investigation and management are essential, and such transplants should only be carried out as part of a properly planned programme and not as an occasional event. Guidelines for evaluation of living kidney donors have been drawn up by an ad hoc subcommittee of the American Society of Transplant Physicians. 4.21 Guidelines with a similar purpose are currently being prepared by the British Transplantation Society.

The use of motivated but unrelated living donors, such as spouses, unmarried lifelong partners, step-parents or even close friends, is becoming widely accepted and the graft survival rates obtained are comparable with related living donors and superior to cadaver grafts. 4.22 It is likely that the number of living unrelated donor transplants will increase. The provisions of the Human Organ Transplants Act are specifically designed to prevent abuse in this area. Nonetheless, coercion remains a concern. A particular risk occurs when a potential donor needs a translator in order to understand the questions and issues being put to him/her by clinicians. In this event, the translator should be unknown to both parties concerned and at the same time competent to discuss clearly the implications of major surgery and the recovery process. Unless these criteria are ensured, there is the possibility that the potential donor will either be misled or will not fully comprehend what they are being

asked to undertake.

Best Practice: Encouragement should be given to transplant centres to undertake an ethical expansion of living donor transplantation.

The aim should be to substantially increase the number of live donor transplants from the present figure of three pmp per year.

Every effort should be made to ensure that there are no deaths directly attributed to kidney donation. Complications should occur in less than 1% of live donors. All donors should be followed up on a long-term basis following kidney donation.

4.3 ADULT RENAL TRANSPLANT CENTRES

The provision of renal transplant services for adults together with training and the prospects for future staffing are currently the subject of an enquiry initiated by the Royal College of Surgeons of England. The findings will be included in the next edition of this standards document.

4.3.1 Distribution of renal transplant centres

In England there is a single renal transplant unit serving each of the former regional health authority areas with the exception of West Midlands (2 centres), South West (2 centres) and Trent (3 centres). The Metropolitan regions have 12 transplant centres, 7 in North Thames and 5 in South Thames.

Wales has a single centre in Cardiff (North of Wales is served by Liverpool). There is a single transplant centre in the Republic of Ireland and a single centre in Northern Ireland.

Scotland has 4 transplant centres, one in the West of Scotland, and 3 in the East. There is clearly a considerable variation in the distribution of centres both for population and for geographic reasons. In England the metropolitan transplant centres serve populations of less than 1 million. In the provinces the smallest population served is 1.6 million and the largest 5 million. It seems sensible that some renal transplantation centres should be amalgamated, taking into account geography, population density and communications. This will avoid duplication of specialised and expensive resources, such as organ retrieval teams, and will allow better

training of medical and other staff.

Best Practice: Renal transplant units should generally serve a population of at least 2 million, depending upon geography and communications.

Renal transplant units should usually perform not less than 50 transplants per year and should be capable of achieving 75 transplants per year.

4.3.2 Staffing of renal transplant centres

The Royal College of Surgeons has published guidelines for surgical staffing of renal transplant units. 4.23 It is recommended that there should be one consultant surgeon trained in transplantation per 0.5 million population, with appropriate support staff. Consultant on call rotas should not exceed one in four. Cross-cover by surgeons untrained in transplantation is undesirable and, where such rotas exist, they should be phased out by forming alliances where possible with adjacent transplant units negotiated between Trusts. No service should depend on a single-handed consultant. It seems likely that the requirements for consultant staffing of renal transplant units will of itself lead to rationalisation of services.

Nursing requirements have been dealt with in the "Review of renal services in England". 4.24

Best Practice: Transplant units need to be adequately staffed both medically and surgically, with appropriate training programmes for junior staff. (Full integration with dialysis services and regular contact with physicians in joint care of transplant patients is essential)

Renal transplant centres should function on a 24-hour, 365 days per year basis.

4.4 PAEDIATRIC RENAL TRANSPLANTATION

In 1996, 107 cadaveric and 26 living-related donor (LRD) renal transplants were performed in children and young adults under 18 years of age in the United Kingdom, representing 6.5% and 14.3% of the total number of cadaveric and LRD transplants performed respectively. The recipients in this small but important group are not simply small adults, and have a different set of medical, nursing and psychosocial needs from their adult counterparts. Children and young adults (up to the time of completion of secondary education) should only be transplanted in centres where they can be managed by appropriately trained transplant surgeons, paediatric nephrologists, paediatric surgeons and urologists (in view of the high incidence of urological anomalies amongst the paediatric end stage renal failure population). They should have access to a multidisciplinary team encompassing specialist nursing staff, dieticians, social workers, child psychiatrists/psychologists, teachers, play therapists and, in those centres with a high proportion of children from ethnic minority backgrounds, translators. Such centres would be expected to implement the Department of Health Guidelines: "The welfare of young children in hospital". 4.25

To maintain expertise (in view of the relatively small numbers) and to provide an appropriate standard of care as outlined above, transplantation and post-transplant management should only take place in designated paediatric nephrology centres (Belfast, Birmingham, Bristol, Cardiff, Glasgow, London [Guy's and Great Ormond Street Hospital], Leeds, Liverpool *, Manchester, Newcastle, Nottingham, Southampton *), as previously outlined by the British Association for Paediatric Nephrology (BAPN)

* These designated paediatric nephrology centres are actively involved in the long-term management of children who have undergone transplantation elsewhere (Manchester and Guy's Hospital London).

Centralisation of care has the additional advantage that it facilitates the collection of longitudinal data and hence allows audit of outcome. Where renal transplantation is being performed in hospitals which are geographically distinct from the associated comprehensive paediatric renal unit, arrangements should be developed to allow surgery to occur on the site of these paediatric units; this will require flexibility on the part of both transplant surgeons and surgeons and theatre staff in the paediatric centres. In further recognition that children and adolescents are not simply small adults, transplanting centres should have full access to dedicated paediatric dialysis, intensive care and radiological imaging facilities.

The existing designated paediatric nephrology centres all currently meet the minimum workload necessary to maintain expertise in the general nephrology and acute end stage renal failure as described by the BAPN, though no minimum transplant workload was laid down in this document.

Questions about minimum workloads standards for graft survival and further centralisation of transplantation services should await the forthcoming

publication of centre-specific graft survival data (UKTSSA Users' Kidney Advisory Group).

5. HISTOCOMPATIBILITY MATCHING AND ALLOCATION OF DONOR KIDNEYS

The histocompatibility laboratory should be directed by a medical consultant or consultant clinical scientist who is in charge of the day-to-day laboratory activity and is available for contact outside normal working hours. The laboratory must meet Clinical Pathology Accreditation (UK) Ltd standards, must participate in the UK National External Quality Assessment Scheme (NEQAS) for histocompatibility and immunogenetics, and must be actively involved in research and development.

Staff providing on-call services must be trained at least to the level of the British Society of Histocompatibility and Immunogenetics (BSHI) Certificate of Competence, whilst senior staff should possess the DipRCPath and the director the MRCPPath or FRCPPath or a PhD.

Best Practice: An efficient, high quality histocompatibility service must be seen as an essential part of a successful kidney transplant programme.

4.5.1 Technical Developments

Exciting progress has taken place in the laboratory aspects of kidney transplantation and these are likely to continue. The advent of molecular biological techniques has had a major impact on the quality of HLA matching, and the interpretation of crossmatch results using flow cytometric analysis has prevented patients getting a transplant that would have failed. The BSHI has established standard descriptions of currently available techniques which clinicians should adopt when requesting tests. (See Appendix 11.2)

Best Practice: Cadaver kidneys should be allocated as far as possible on the basis of matching for HLA alloantigens and crossmatching supported by efficient antibody screening.

The regulations incorporated in the Human Organ Transplants Act 1989 specify that, in living donor transplantation, tests are to be carried out by an "approved" Tester, appointed by the Department of Health, to establish a claimed genetic relationship. When there is no claimed genetic relationship or when such a relationship cannot be established, the case must be referred to the Unrelated Live Transplant Regulatory Authority (ULTRA) via the ULTRA Secretariat at the Department of Health. Approved Testers must be fully aware of their responsibility under the regulations and of the penalties of the Act.

Identity or compatibility for ABO blood groups between donor and recipient is essential. The principle of matching the donor kidney tissue type (HLA antigens) to that of the recipient in order to optimise transplant outcome and minimise rejection is well established and has been practised by UK units since 1970. Matching is especially important in determining longer-term (5-15 years) outcomes. 4.26, 4.27 A system for mutual exchange of donated kidneys based on HLA matching is operated on the UK transplant community's behalf through UKTSSA. 4.28 Currently, around 45% of recipients receive a favourably matched kidney.

Best Practice: All renal centres should participate in the agreed UK organ allocation scheme for cadaver kidneys.

All centres should document local allocation criteria.

All potential recipients should be investigated for unacceptable antigens and those identified should be registered with the patient record on the National Transplant Database held at UKTSSA

The definition of "unacceptable" HLA antigens is a priority of the agreed national cadaver kidney allocation scheme.

The aim should be that 45% of recipients receive a favourably matched kidney.

4.5.2 Cross Matching

Immediate i.e. 'hyperacute' rejection of transplanted kidneys can be prevented by performing a crossmatch between the recipient's serum and

donor lymphocytes. Techniques have been available to detect the interaction of recipient antibody and donor target antigen since 1965 and the interpretation of crossmatch results have been greatly extended recently. There are many different techniques used in different centres and different policies on how the outcome of the crossmatch is used. Each centre should establish its own policy based on published data and local experience.

Best Practice: All donor-recipient pairs should be crossmatched before transplantation.

The value of crossmatching by flow cytometry (FC) has become apparent recently, particularly in recipients at high risk of rejection such as children and patients with high levels of circulating antibody due to previous transplantation. Careful standardisation and quantification of the results are necessary. 4.29, 4.30

Best Practice: Flow Cytometric crossmatching should be available for re-transplants, children and highly sensitised recipients.

4.5.3 Screening for antibodies in recipients

Efficient HLA matching and crossmatching procedures should be used together with an advance screening programme to detect pre-existing HLA-specific antibodies.

The definition of sensitisation depends crucially upon the techniques used. The assay most widely used is the complement dependent cytotoxicity assay using a panel of lymphocytes as the target cells. Although the degree of reactivity to the panel is often expressed as a percentage, this is misleading since the panel is chosen to represent a wide range of antigens and not the population as a whole. Recently, tests based on ELISA (enzyme-linked immunosorbent assay) and Flow Cytometry have become available, with the benefits of increased sensitivity and specificity.

Best Practice: All potential recipients should be screened for HLA-specific antibodies 2 weeks after any blood transfusion.

All potential recipients should be screened at least 4 times a year for HLA-specific antibodies.

The tissue types of fathers of children borne by female potential recipients should be determined wherever possible.

Conventionally, highly sensitised patients (HSPs) are defined as those who react with more than 85% of panel cells. To qualify as an HSP, the potential recipient must be shown to have IgG antibodies specific for alloantigens, most often for several HLA-A, -B or -Cw specificities, common in the donor population. Autoreactive IgM antibodies may give the impression of high panel reactivity, but since these antibodies do not prevent successful transplantation their presence must be carefully defined.

All HLA specificities against which the potential recipient may react should be recorded as 'unacceptable antigens' and should be avoided in the transplant kidney.

Best Practice: Highly sensitised recipients should have their sera screened for HLA-specific antibodies, the specificities of which should be defined carefully.

They should receive kidneys that bear only matched antigens (or "acceptable" mismatches)

If antibody screening is carried out regularly after transplantation, accurate crossmatching for re-transplantation can help achieve success rates after re-transplantation as good as those for first transplants.

Best Practice: Following transplantation it is essential that the tissue typing laboratory continues to receive serum samples for antibody screening at each clinic visit.

4.5.4 Interaction between laboratory and clinicians

Transplantation is a multidisciplinary clinical service and the best success rates can be achieved only through a close liaison of laboratory and clinical staff. Highly trained and dedicated staff in a histocompatibility laboratory should meet with clinical colleagues regularly and provide a comprehensive 24-hour service.

4.6 MANAGEMENT OF IMMUNOSUPPRESSION

Currently, there is insufficient data to permit specific recommendations on immuno-suppressive therapy. Immunosuppressive drugs are used in a variety of combinations: monotherapy, double or triple therapy using Prednisolone and Azathioprine or Mycophenolate Mofetil together with Cyclosporin microemulsions (Neoral TM), or Tacrolimus. These combinations have been developed empirically and debate continues as to the optimal prophylactic regimen. The role of mono- and poly-clonal antilymphocyte agents (OKT3 and ATG) also requires definition, their role is clearly established in steroid resistant acute rejection but has been seriously questioned as "induction therapy" and this is called into question even more with the introduction of anti CD25 monoclonal antibodies Daclizumab and Basiliximab.

The most commonly used regimen for the first year after transplantation is triple therapy with Prednisolone, Azathioprine and Cyclosporin, but it is likely that Tacrolimus and/or Mycophenolate Mofetil will be used increasingly during the next few years together with other newer drugs such as Rapamycin.

Graft survival appears to be similar with all the regimens in current use and including the newer agents. 4.26 It is likely that a greater diversity of regimens will be used in future to "tailor" therapy more accurately to individual patients' needs.

Despite earlier controlled trials, the role of new agents such as Mycophenolate Mofetil and Tacrolimus is still being evaluated. Further prospective studies should allow clearer recommendations to be made. Outcomes need careful auditing as the choice of an Immunosuppressive regimen has substantial cost implications.

Best Practice: All transplant units should have a written protocol for Immunosuppression. All protocols or changes to protocols should be based on evidence from properly conducted clinical trials.

4.7 STANDARDS OF OUTCOME IN RENAL TRANSPLANTATION

Clinical and medical audit should be an integral part of the work of the transplant unit. Patient survival, morbidity and transplant outcomes depend critically upon a number of casemix factors such as the age and co-morbidity of the population transplanted. This in turn depends upon the criteria for selecting patients as potential transplant recipients and, more remotely, on the criteria for acceptance on to dialysis. Every Transplant Unit in the UK is expected to contribute a minimum data set, agreed by the users, to the UKTSSA database. Each unit can then compare its own performance with national and international data.

Outcome data for transplantation in the UK for 1984-93 are available in the renal transplant audit published by the UKTSSA Users' Kidney Advisory Group. 4.1

The figures detailed below are the minimum acceptable results for cadaveric transplantation. Clearly, if every unit in the UK were to achieve results consistent with the present mean or above, the average standard would rise considerably.

4.7.1 Post operative renal function

Around 68% of transplanted kidneys in the UK function immediately. The immediate function rate is dependent upon a number of factors including the types of kidney accepted for use, the ischaemic times, intra-operative events and recipient factors. Kidneys that function immediately usually lead to a shorter period in hospital and they may survive longer. 5% of cadaver kidneys transplanted in the UK never function.

Best Practice: At least 70% of heart beating cadaver renal transplants should function immediately and at least 95% should function eventually.

4.7.2 Patient survival after first cadaver renal transplant

The following are overall results for first cadaver transplants performed

in the UK between 1984 to 1993 together with the recommended standards

Table 4.2 Recommended Patient Survival Standards

Survival time	Survival	Recommended
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of patient (%)	survival (%)	
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1 year	92	>90
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5 years	80	>80
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10 years	63	>60
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4.7.3 Graft survival after first cadaver transplant

The following are overall results for first cadaver transplants performed in the UK (1984 to 1993) together with the recommended standards

Table 4.3 Recommended Graft Survival Standards

Survival time	Survival	Recommended
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of graft* (%)	survival (%)	
---------------	--------------	--

1 year	81	>80
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5 years	64	>60
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10 years	46	>45
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* Graft failure includes death with a functioning graft.

4.7.4 Graft survival after second and subsequent cadaver transplants

The survival time of second transplants should be virtually the same as that of first grafts and that of third and subsequent grafts only slightly inferior provided that there has been adequate analysis of recipient sensitisation using flow cytometric crossmatching. Thus at least 80% of second grafts and 70% of subsequent grafts should be functioning at the end of the first year.

4.7.5 Patient survival following live donor transplantation

There should be at least 99% patient survival at a 1 year after grafting and 95% at five years.

4.7.6 Graft survival following live donor transplantation

95% of live donated kidney allografts should still be working at 1 year and more than 80% at five years.

It will remain difficult to set targets for transplant recipients with diabetes mellitus and/or significant co-morbidity until reliable methods for risk assessment have been designed.

5.0 LIVER TRANSPLANT SERVICES

5.1 INTRODUCTION

Liver transplantation is the only form of life saving treatment for patients in end-stage liver failure. During 1997, 692-cadaver donor and 4 live donor liver transplants were performed in the United Kingdom and Republic of Ireland. Waiting lists have risen from 195 on 31 December 96, to 196 on 31 December 97. 5.1 During 1997 there were 45 deaths among patients on the liver transplant waiting list. Given a population of 61.2 million for the UK and Ireland, these figures would imply a demand for liver transplantation of 12.3 pmp per year to prevent waiting lists rising further. This figure is an underestimate of the real need because some potential candidates are still not being referred to liver transplant centres and some centres have been reluctant to accept certain categories of patients (e.g. alcohol associated liver disease, liver cancer and hepatitis B infection). New therapies and improved results will increase the demand for liver transplantation, probably to around 20 pmp per year. The supply of cadaveric donor organs, 11.3 pmp per year in the United Kingdom in 1997, is insufficient to meet demand.

5.2 DEMAND VERSUS SUPPLY

5.2.1 Suitability for liver transplantation

Liver patients referred for assessment have a number of conditions including primary biliary cirrhosis, chronic active hepatitis, alcoholic liver disease, cirrhosis resulting from hepatitis B and C, cancer and fulminant hepatic failure (including paracetamol overdose). 5.2

Assessment of patients is conducted over 2-5 days and involves careful

discussion with the patients themselves as well as their immediate family and the transplant recipient co-ordinator. Around 75% of referred patients are likely to be accepted on to a liver transplant waiting list, although there is some variation according to the disease diagnosis. In 1993-95, the median waiting time was 29 days. This is expected to increase as the number of patients waiting continues to rise.

Patients with fulminant hepatic failure, considered to have a prognosis of no more than three days without transplantation, are prioritised through the super urgent registration scheme supervised on behalf of the liver transplant community by UKTSSA. Patients with primary liver graft non-function or early hepatic artery thrombosis are also eligible to be registered as super urgent. For these patients, selection policies are standardised with rapid communication mechanisms available. Liver support therapies are still at a fairly early stage of development and are unlikely to impact much for some years to come. This is an area that requires regular review as new liver support therapies become available. During 1993-1995, 503 cases were registered. 66% (331 patients) received a liver transplant, 10% (53 patients) died whilst awaiting a transplant, 12% (60 patients) recovered sufficiently with supportive therapy to return to the elective waiting list and 12% (59 patients, 11 of whom had died) were removed from the superurgent list. 5.3

Patients who are placed on the waiting list must be registered on the National Transplant Database, held at UKTSSA. Patients on the elective waiting list need to be assessed at regular intervals. Care of patients prior to being called in for a transplant should be the shared responsibility of the referring unit and the transplant centre, with the balance of responsibility being dependent on the clinical and geographical situation of the patient concerned.

Best Practice: Between 70% and 80% of patients on whom resources are expended for assessment should be transplanted eventually.

Patients should not have to wait more than one year for a liver transplant.

Super urgent listing should result in a greater than 80% chance of receiving a liver transplant.

Patients should be selected from the waiting list on the basis of compatible ABO blood group, suitable size match, medical urgency and time on the waiting list.

Paediatric livers (less than 16 years) should be offered preferentially to paediatric recipients.

5.2.2 Availability of Donor Livers

In 1993, the Department of Health and the Royal College of Surgeons issued guidance on the zonal retrieval of organs, which provides the protocol for organ retrieval from multi-organ donors. Each (cardiothoracic and) liver transplant unit has an allocated geographical zone for retrieval purposes with the area being determined by the contracted activity for each transplant unit each year. Responsibility lies with the transplant team, within each zone, for assessing every multi-organ donor's suitability, retrieving all useable organs and, either, transporting them back to the Transplant Unit for use, or, for ensuring that they are packed securely and transported to an extra-zonal unit for use according to the national sharing scheme. In a few cases donor livers are split to provide for two transplants. [Zonal arrangements for retrieving livers are audited by UKTSSA through the National Transplant Database and the results are presented to Liver Transplant Unit Directors at six monthly meetings of the UKTSSA Users' Liver Advisory Group. In 1997, 95% of livers were retrieved by their designated zonal team. 59% were used locally and 41% were used by other centres.]

In 1995/96 the mean cadaver donor rate in the UK was 14.6 per million per year. 5.1 The percentage of donations resulting in a liver transplant rose from 36% in 1990 to 85% in 1997, reflecting the impact of improving results for liver transplantation and the development of zonal organ retrieval services. 5.1 However, there is still regional variation. Retrieval rates range between 9.2 to 16.9 per million population per annum. Between 1995 and 1997 15.6% of cadaveric kidney donors were not liver donors (range 0-36.4%), whilst some cadaveric donors (e.g. non heart beating donors) were unsuitable for liver donation, it is clear that in the past the potential resource has not been fully utilised (data to the UKTSSA Users' Liver Advisory Group, April 1998).

Best Practice: Livers should be retrieved from at least 85% of UK organ donors.

Units should retrieve at least 90% of the livers available from within their own zone.

A retrieval rate of at least 12 livers per million population per annum should be achieved.

5.2.3 Quality of retrieved livers

Livers which are evidently cirrhotic, grossly fatty with rounded edges, together with those that have received severe trauma to both lobes, are unsuitable for transplantation. Subject to a restriction on donors in whom there is a risk of transmission of infectious or malignant disease, all other livers should be offered for transplantation.

Livers should be retrieved by a team including a suitably trained lead surgeon, a surgical assistant, a trained scrub nurse, and a perfusionist. The quality of perfusion, anatomical abnormalities, and any inadvertent injury should be recorded on the Core Donor Data form (and the UKTSSA Duty Office informed by telephone) for the benefit of the recipient team.

Best Practice: Unless there are specific contraindications, livers from every cadaveric donor in the UK must be offered for transplantation through the national allocation scheme operated by UKTSSA

5.2.4 Allocation and use of cadaver livers

It is essential that every available liver is collected. This should usually be carried out by the Zonal Team, even when the liver is not required locally. Livers should be offered preferentially to patients on the super urgent list and to paediatric recipients. If the Liver cannot be used locally, it must be offered on by UKTSSA to other centres following a nationally agreed sharing scheme which is monitored through the UKTSSA Users' Liver Advisory Group.

Best Practice: Livers should be offered preferentially to patients on the super urgent list.

Paediatric livers should be offered preferentially to paediatric recipients.

Livers surplus to the needs of the retrieving unit should be

exchanged freely through the national sharing scheme operated through UKTSSA.

5.2.5 Live Liver Donation

The shortage of suitable cadaveric organs, especially for children, has led to the development of liver lobe transplantation from living donors. Clearly this involves some risk to the donor. World wide there have been two reported donor deaths suggesting a donor mortality rate of 1 in 250. There is also an associated donor morbidity due to both surgical and medical complications. The surgical techniques for live donation are similar to those employed in splitting a cadaver liver for implantation into two recipients, although this latter technique should only be used on good quality livers.

Live donor liver transplantation should only be performed within strict ethical guidelines. Donation should be altruistic and not rewarded. (See also 2.2.2 and 4.2.5) The donor should be carefully counselled and given time to take the decision without coercion. In order to provide the highest quality of care to both the donor and the recipient, whilst ensuring the highest quality of organs for transplantation, the two operations should be performed by separate surgical teams. Post-operatively the donor must receive the highest standard of care with a surgeon available to intervene in the event of any surgical complication.

5.3 ADULT AND PAEDIATRIC LIVER TRANSPLANT CENTRES

5.3.1 Distribution of centres

Liver transplant centres in England may only commence transplant programmes following designation by the National Specialist Commissioning Advisory Group (NSCAG) and are funded on a national basis; in Scotland, central funding is provided for the Edinburgh centre. In addition, there is a liver transplant centre in Dublin at St Vincent's Hospital (Elm Park). There are currently seven designated centres in the UK which are:

Addenbrooke's Hospital, Cambridge

Freeman Hospital, Newcastle-upon-Tyne

King's College Hospital, London

Queen Elizabeth Hospital, Birmingham

Royal Infirmary, Edinburgh

St. James's University Hospital, Leeds

The Royal Free Hospital, London

Centres vary in size of waiting lists, activity levels, staffing and case mix of patients treated. Each centre is expected to provide assessment of patients referred for transplantation, to undertake the surgery and to provide life long follow up and support for those patients deemed suitable for transplantation. Following discharge after liver transplantation, arrangements are required for counselling and for rehabilitation. Patient's return visits are initially on a twice-weekly basis, reducing to monthly by the third month and then to three monthly intervals over the next two years. Subsequent visits will be on a six monthly or annual basis.

Where individual centres are concerned there may be difficulties encountered in measuring rates as centres do not have individually defined population bases. Centres provide a nationally commissioned service; patients can be referred to any of the centres from any locality. Higher rates of liver transplantation are currently achieved in the USA (16 pmp) and in some European countries. [UNOS Registry report 1997]

Best Practice: All liver transplant units should be located on a major hospital site with constant access to a comprehensive range of specialist emergency services.

Each transplant unit should aim to achieve at least 12 pmp per annum, based on their zone size.

5.3.2 Staffing

Liver transplantation requires a multidisciplinary team in order to provide optimum care for the assessment, transplantation and follow up of liver

transplant recipients. The elements of the team include surgeons, hepatologists, anaesthetists, intensivists, radiologists and pathologists from the medical side, as well as a full panoply of support from nursing and allied professions. Each liver unit should have a high commitment to training. There must be sufficient medical cover to provide a 24-hour consultant led service in all of the above disciplines. In addition centres must provide a donor retrieval team that is constantly available 24 hours a day and based upon on-call rotas with prospective cover for a lead surgeon, assistant surgeon, scrub nurse and perfusionist.

5.4 PAEDIATRIC LIVER TRANSPLANTATION

Paediatric liver transplants are carried out at Addenbrooke's Hospital, Cambridge, King's College Hospital, London, and the Queen Elizabeth Hospital, Birmingham. Paediatric transplantation should only be carried out in a centre with a full array of paediatric facilities including paediatric anaesthesia, intensive care and paediatric hepatology. Paediatric patients should be cared for on a children's ward by specialist paediatric nurses.

During 1997 82 paediatric liver transplants were carried out in the United Kingdom. 5.1 45 of these patients were less than 5 years old. The majority received a reduced size or split-liver transplant. Survival for paediatric liver transplant is 80% at one year, 70% at five years and 65% at 10 years. 5.3 The results continue to improve.

Best Practice: Paediatric liver transplantation should only take place in centres that are fully equipped and staffed to look after all aspects of paediatric care.

Paediatric liver transplantation should only be performed in centres that are proficient in reduced size and split-liver transplantation.

5.5 STANDARDS OF OUTCOME IN LIVER TRANSPLANTATION

Every Transplant Unit in the United Kingdom is expected to contribute a minimum data set, agreed by the profession, to the National Transplant Database, held at UKTSSA in Bristol, so that they can compare their own

performance with national and international data.

Outcome data for transplantation in the United Kingdom for 1985-95 are available in the liver transplant audit published by the UKTSSA Users' Liver Advisory Group. 5.3

Within the UK there is an ongoing audit, supervised by the Royal College of Surgeons, which is collecting risk and outcome data on all forms of liver transplantation. The data from this audit will, in the future, produce accurate risk stratification for liver transplantation.

The figures suggested below are the minimum acceptable results for emergency and elective cadaveric liver transplantation; clearly, if every unit were to achieve something near the present mean or better, the average standard would rise considerably.

Best Practice: There should be at least 80% patient survival after first elective cadaver liver transplant at one year.

There should be at least 70% patient survival after emergency liver transplant for fulminating liver failure at one year after grafting

There should be at least 70% patient survival after second and subsequent elective liver transplant one year after grafting

There should be at least 70% paediatric Liver Transplantation survival one year after grafting.

5.6 MANAGEMENT OF IMMUNOSUPPRESSION

Post-operative care includes anti-rejection therapy, biopsies and stabilisation of long term immunosuppression regimens. Detailed protocols for post-operative monitoring, drug regimens, mobilisation, biopsy frequency etc., should exist at each centre.

Shared care protocols are not applicable to all units. Communication with referring doctors and GPs must be maintained and encouraged - in

particular, arrangements for the prescription of Immunosuppressive and other life-long medication must be explicit.

6.0 CARDIAC AND PULMONARY TRANSPLANTATION

6.1 INTRODUCTION / HISTORICAL BACKGROUND

Cardiac transplantation began in the UK in 1979, followed in 1984 by combined heart and lung transplantation. The first single lung transplant was performed in 1987 and the first bilateral lung in 1990.

Patients undergoing cardiac transplantation represent a relatively homogeneous population with end stage cardiac failure. Pulmonary transplantation in its various forms (single lung, bilateral lung and heart lung) can be applied to a wide variety of different diseases. The choice of procedure for particular conditions may vary from centre to centre. The problems of donor assessment, peri-operative care and long-term management are however dominated by the lung. Difficulties with the heart in the combined heart and lung transplant are very rare. Thus pulmonary transplantation regardless of the procedure performed or the sort of indication can be regarded as a single entity.

There is a considerable unmet need (see below). In this setting, it is essential to ensure that available organs are used appropriately, that allocation systems are both fair and transparent and that there is equity of access for all potential recipients.

6.2 DESIGNATION OF CENTRES

Centres may only commence transplantation programmes following designation by the National Specialist Commissioning Advisory Group (NSCAG).

There are at present 8 centres designated in England and Wales performing both cardiac and pulmonary transplantation:

Harefield Hospital (in association with the Royal Brompton Hospital)

Northern General Hospital, Sheffield

Papworth Hospital, Cambridge

Wythenshawe Hospital, Manchester

The Hospitals for Sick Children (Great Ormond Street), London

St. George's Hospital, London

Freeman Hospital, Newcastle

Queen Elizabeth Hospital, Birmingham

The Scottish centre in Glasgow at present performs only cardiac transplants.

The designated service provides for:

* The assessment of need and suitability for heart, heart/lung or lung transplant

* The registration of appropriate patients with the UK Transplant Support Service Authority

* Donor organ retrieval

* Transplantation including post-operative assessment, hospital based care and long term follow-up as required.

Until 1995 these centres were funded on a supra-regional basis. At present

contracts are negotiated with lead commissioners acting for commissioning consortia. Individual centre funded activity has remained essentially unchanged since 1995.

6.3 SELECTION CRITERIA FOR RECIPIENTS

6.3.1 Cardiac

At the present the rate of cardiac transplantation in the United Kingdom is approximately 5 pmp, compared with approximately 10 pmp in the USA and France and even higher rates in some European countries. 6.1 It has been estimated that up to 20 patients pmp would be candidates for a heart recipient using current criteria, particularly if hearts were immediately available 6.2 and up to 60 pmp if criteria, particularly with regard to age, were relaxed.

At present only a proportion of potential recipients are accepted on to the waiting list and only a proportion of them will be transplanted. 200-250 individuals are listed at any one time for heart transplant in the UK for approximately 250-280 organs available per year.

Patients listed for cardiac transplantation should have an anticipated survival of less than 80% at one year on optimal medical therapy. The timing of listing for transplant of ambulant patients may be difficult. There are a number of measures of myocardial reserve of which the most useful seems to be the measurement of maximum oxygen uptake (MV02). 6.3

Alternatively there are well validated scoring systems 6.4 which will allow identification of patients who will benefit most from cardiac transplantation.

Broadly accepted absolute and relative contraindications are widely published. 6.5 In general, these contraindications exclude patients likely to have a less good outcome both in terms of absolute survival and potential for rehabilitation. Some relative contraindications will vary from centre to centre depending on local experience. All are tempered by the need to maintain waiting lists at a reasonable size. An example of this is the use of age as a contraindication. Whilst there are centre specific reports of successful outcome in elderly patients 6.6, in practice only 0.2%, of patients transplanted in the United Kingdom are >65 years old. 6.7

[Image]The majority of adults undergoing heart transplant will have endstage ischaemic or idiopathic dilated cardiomyopathy. Those suffering congenital or valvar heart disease are a minority.

6.3.2 Pulmonary

Potential numbers who might benefit from the various forms of pulmonary transplant are not well documented. Approximately 50-60 heart-lung and 100-120 isolated lung transplants are performed annually. The numbers waiting on 31 December 1997 were 126 for heart-lung and 200 for isolated lung.

A comprehensive set of guidelines for the selection of lung transplant recipients has been put together by an international panel and widely endorsed by North American and International Thoracic and Transplant societies. 6.8 This document sets out absolute and relative contraindications as well as acceptance criteria for a range of different pulmonary conditions requiring transplant.

Recommendations with regard to timing, assessment, and decision making in this document should be adopted by centres in the United Kingdom.

6.3.3 Retransplantation

In general, results after retransplantation are consistently inferior to those after first time procedures.

This is particularly so for retransplantation within the first three months 6.9 and for redo heart-lung transplants. 6.10

It is suggested that acute retransplants be avoided. Candidates for late retransplant should fulfil the same criteria as those for first transplants, and in particular should have similar expected outcomes. In general, this implies the application of more stringent selection criteria to this group of patients.

Best Practice:

Cardiac:

The number of transplants carried out in the UK should increase from 5 to 10 pmp.

Units should use one of the well validated scoring systems to identify patient suitability for transplantation.

Elderly patients >60 years should not be excluded from evaluation with a view to transplantation.

Pulmonary:

International guidelines for selection of lung recipients should be followed especially with respect to absolute and relative contraindications.

Retransplantation:

Acute retransplantation should be avoided.

Candidates for late retransplantation should meet the same criteria as for a first transplant.

6.4 PAEDIATRIC TRANSPLANTATION

Cardiac and pulmonary transplantation for patients under the age of 16 years is restricted to three centres - Harefield, Great Ormond Street and Freeman Hospitals. These institutions have appropriate staff and equipment for the assessment, transplantation and follow-up of these patients, and are designated as paediatric centres by NSCAG.

The numbers involved are small: 12 heart and 17 heart-lung patients waiting at 31 December 1997, and 23 heart and 8 heart-lung transplants performed in that year.

Recipients under 16 should not undergo transplantation other than at the designated centres.

Best Practice: Children under 16 years should only undergo transplantation in designated centres.

6.5 ASSESSMENT

Assessment, which should be on an in-patient basis, should be carried out by a transplant team including physicians experienced in the management of endstage cardiac and pulmonary disease. Alternative therapies may well be appropriate. The rapidly evolving management of heart failure in particular demands that potential transplant candidates should be managed by cardiologists with a specific interest in congestive heart failure and ideally in the setting of a heart failure clinic. Potential recipients may have a fluctuating course and they should be followed regularly. A proportion of patients may stabilise such that their one year survival is >80% and therefore they can be suspended from the transplant waiting list.

At acceptance on to the waiting list the patient's family should be informed of the early and late risks of transplantation, of the side effects of immunosuppression and the risk of malignancy.

Best Practice: Assessment should take place as an inpatient.

An integrated team of surgeons and physicians experienced in the management of end stage cardiac and pulmonary failure should carry out the assessment.

Relatives should be informed of both the early and the late risks that accompany Cardio / pulmonary transplantation.

6.6 CRITERIA FOR A TRANSPLANT UNIT

Cardiac and pulmonary transplantation should obviously be performed in a cardiothoracic centre with access to the full range of laboratory and clinical support services. These include 24-hour histopathology, microbiology, haematology and biochemistry laboratories. There should be ready access to nephrology, particularly haemofiltration and dialysis. Advice and management of diabetes, osteoporosis and neutropenia should be

available.

Best Practice: Transplant centres should be reviewed and accredited.

They should have all the necessary support services available to them on a 24-hour basis.

6.7 STAFF

6.7.1 Surgeons

Because of the continuous commitment for donor assessment, organ retrieval and implantation, programmes with one or two surgeons cannot be sustained in the long-term. The programme should have 4 consultant surgeons capable of cardiac and pulmonary transplantation of whom 2 should have transplant as a major clinical interest. The requirements to staff organ retrieval teams on a continuous basis comprises either 5 junior staff capable of at least cardiac retrieval or involvement of consultant staff in removal of donor organs.

Best Practice: a minimum of four consultant surgeons committed to transplantation are required supported by five surgeons in training.

6.7.2 Anaesthesia/Intensive Care

A transplant programme clearly needs all the anaesthetic and Intensive Care facilities of a fully equipped Cardiothoracic Centre. Such a centre will have continuous availability of appropriately skilled anaesthetists, one or two of whom should have a particular interest in the management of the lung transplant patient. Involvement of anaesthetists from the transplant centre in the management of donors, subject to local arrangements and sensitivities, should become widespread.

Best Practice: A supporting team of anaesthetists is essential,

at least one of whom should have a committed interest in lung transplantation.

6.7.3 Physicians

The need for a respiratory physician and heart failure cardiologist has been mentioned under assessment. It is also essential to have a histopathologist experienced in interpretation of endomyocardial and transbronchial biopsies and a microbiologist with experience in the management of immunosuppressed patients.

Non-medical support staff required by the transplant unit include physiotherapists, social workers and dieticians. For many units, they will have a full-time commitment to the programme. There should also be adequate secretarial and most importantly data collection staff.

Best Practice: Physicians experienced in the management of advanced cardiac and pulmonary failure are essential to the service.

Physicians trained in transplant medicine are necessary for the short and long term management of transplant patients

6.7.4 Retrieval Teams

Organ retrieval is reasonably performed by appropriately trained Specialist registrars in Cardiothoracic Surgery. A retrieval team should consist of a Surgeon, with assistant, a theatre nurse, often a perfusionist/technician, and increasingly, an anaesthetist. With the Zonal Retrieval arrangements, some of these personnel may be shared with the relevant liver team, and particularly, duplication of the theatre nurse and the assistant surgeon, except for training purposes, may be avoidable.

Implicit in the Zonal Retrieval System is an undertaking to retrieve, with a suitably trained team, organs not used locally but exported to another centre. This obligation extends up to donors aged 60, and only excludes paediatric donors, where the implanting centre will usually wish to carry out the retrieval.

Best Practice: Retrieval teams including trained surgeons and an anaesthetist, a perfusionist and a co-ordinator need to be available on a 24 hour basis.

6.7.5 Follow-up Clinic

Follow up is part of the designated activity of a transplant programme. Outpatient clinics, with in-patient beds available for the management of more serious problems, form the core of follow up. The problems dealt with at these clinics are "medical" and the clinic is best run by cardiologists and pulmonary physicians with a specific interest in transplantation (often the same individuals involved in assessment.) Initially, follow-up is concentrated in the transplant centre, switching to a formal "Shared Care" arrangement, usually with the original referring team, once the patient is stable. A specific group of late transplant related complications, including chronic rejection and lymphoproliferative disease, may be best managed predominantly at the transplant centre.

Best Practice: Clinics must have beds available for the most difficult problems.

Clinics should be led by physicians trained in transplant medicine.

A shared care arrangement is desirable for long term and long distance follow-up.

6.7.6 Training

Most trainees in cardiothoracic surgery should have some exposure to Cardiopulmonary Transplantation. In the centres, this is achieved by rotation through the transplant programme. The same will be true for Cardiology and Respiratory Medicine. The UK need for surgeons with a specific interest in transplantation is approximately two per year. These individuals should have spent a full year towards the end of their training in one of the larger units. Positions at Papworth and Newcastle are currently recognised for this training.

A small and undefined number of physicians, cardiac and pulmonary, with a specific interest in transplantation, will be needed. Some will be individuals with training in both branches, who specialise in "transplant medicine", although a career structure for such physicians has not yet evolved.

Best Practice: All cardiothoracic trainees should be exposed to cardiac and pulmonary transplantation.

There is a need to train two additional cardio / pulmonary transplant surgeons per year at the present level of activity.

Physicians need to be trained in transplant medicine.

6.7.7 Levels of Activity

Small centres can produce excellent results by dint of careful donor and recipient selection and dedicated attention to detail. In Registry analyses 6.9 activity of less than 9 cardiac transplants and 5 heart and lung transplants is associated with inferior outcome. In practice, given the need to have a minimum of 4 consultant surgeons involved in the transplant programme needed in turn to maintain a level of expertise, together with the commitment to training junior staff it is suggested that the minimum level of activity is 30-40 cardiac transplants and 15-20 pulmonary transplants. These levels are also consistent with the involvement of physicians with specific interests, and the need to staff retrieval teams with appropriately trained surgeons.

6.8 OUTCOME MEASURES

There is in the UK an ongoing audit, supervised by the Royal College of Surgeons, which is collecting risk and outcome data on all thoracic organ transplants. The data from this audit will, in the future, provide accurate risk stratification for all forms of thoracic transplantation.

Survival, at various time points, is available for the UK and from International Registries, for the various procedures:

United Kingdom 1995-97

30 day + 1 year* 2 year*

Heart 91(87-95) 79(76-82) 76(72-79)

Heart-Lung 82(70-93) 72(64-80) 61(50-72)

Lung 81(73-88) 69(64-75) 58(50-65)

+UK Cardiothoracic Transplant Audit, reproduced from UK Cardiac Surgical Register 1996-97

*NSCAG Annual Report 1997-98. 6.1

International**

1 year 2 year

Heart 79 75

Heart-Lung 60 54

Lung 71 60

**Registry of the ISHLT. 6.9

Best Practice: In the light of these figures, and in order to secure the optimal use of the limited donor pool already alluded to in the introduction, high standards for the UK are appropriate. Whilst there may well be short-term fluctuations, the following percentage survival figures are the minimum target.

30 Day 1 Year

survival survival

Heart 85 80

Heart Lung 80 70

Lung 80 70

7.0 CORNEAL TRANSPLANTATION SERVICES

7.1 INTRODUCTION

Several features of corneal transplantation deserve mention in the context of the establishment of standards:

- a. The majority of ophthalmic units in the United Kingdom and Republic of Ireland (more than 250) carry out some corneal transplantation.
- b. Storage of corneas for varying lengths of time involve different laboratory techniques in Eye Banks
- c. Not all corneal transplants are registered on the National Transplant Database.
- d. Although full thickness (penetrating) corneal transplants account for the majority of ocular tissue transplantation other operations are also carried out. i.e. partial thickness corneal transplant (lamellar keratoplasty, epikeratoplasty) scleral grafts and transplantation of limbal stem cells.

7.2 SOURCES OF ORGAN

a) Cause of death - principle causes of death for corneal donors are:-

1. Cardiovascular

2. Cancer

3. Trauma

Multiorgan donors account for 18% of corneal donors. Contraindications to donation are published (see Appendix 11.1)

b) Regional variations

In 1994 retrieval rates according to UK region varied from 18 to 74 per million of population.

7.3 EYE BANKING

The Eye Banks in the United Kingdom are:

Bristol and Manchester (Corneal Transplant Service)

East Grinstead*

Norwich* (East Anglian Eye Bank)

Moorfields Eye Hospital *, London

St George's Hospital, London

* These Banks which use cold storage (up to 10 days) send surplus corneal scleral discs to the Corneal Transplant Service, which uses organ culture (up to 30 days).

7.4 SCREENING OF DONORS

In line with the majority of European Countries all donors are screened for HIV, Hepatitis B and Hepatitis C (and discarded if positive.)

7.5 INDICATIONS FOR TRANSPLANTATION

Principle indications for surgery are:

1 keratoconus (21%)

2 endothelial failure from previous eye surgery (13%)

3 primary endothelial failure (9%)

Diagnostic data on many patients is unclear, particularly patients undergoing surgery for previous graft failure.

7.6 TRANSPLANT ACTIVITY

Approximately 3000 penetrating corneal grafts are carried out each year in the UK.

Centre activity varies from 130 per annum to 1 per annum

7.7 TISSUE MATCHING

World wide there is no absolute consensus as to the value of tissue matching in corneal transplantation. However, in the United Kingdom surgeons are able to identify those recipients who are at enhanced risk of rejection i.e. those with previous immunological graft failure and or, two or more quadrants of stromal vascularisation. They may then request HLA

matching. Matching criteria for antigens is currently under discussion

7.8 REGISTRATION

Most surgeons, who use tissue provided by the Corneal Transplant Service, register their patients on the National Transplant Database. This is a prerequisite for requesting matched material. However, many grafts are only notified at the time of surgery or afterwards, and as indicated above it is believed that some are not reported at all.

7.9 SURGERY

The development of eye banking has converted transplantation to a largely elective procedure. Although many consultant surgeons and surgeons in training are involved with corneal transplantation there has been a progressive move to dedicated surgeons undertaking the majority of operations in the larger centres.

7.10 POST OPERATIVE TREATMENT

Most surgeons employ routine topical immunosuppression in the form of steroids for at least one year following surgery. Some surgeons use minimum amounts of steroids indefinitely.

Rejection episodes - all surgeons use intensive potent topical steroids for rejection episodes; some surgeons use oral steroids as supplementation, others intravenous methyl Prednisolone.

There are no published guidelines on the treatment of rejection episodes.

7.11 FOLLOW UP

The Corneal Transplant Follow up Study 7.1 which followed around 3,000 patients recruited between 1987 and 1991 for up to one year revealed a great deal of information about activity in the United Kingdom. Since that time surgeons have been requested to provide follow up data for up to three

years. The UKTSSA Users' Ocular Tissue Audit Group is in the process of revising the data collection mechanism with a view to improving quality of data and the proportion of cases on which this is available.

COMMENT: Action on the following is current, pending or would be desirable:

1. Availability of accurate data on all patients waiting for surgery.
2. Improved data collection on ocular tissue transplantation other than penetrating keratoplasty.
3. Guidelines for retrieval including permission to use tissue for research.
4. Criteria for tissue matching.
5. Post operative treatment regimes and for graft rejection episodes.
6. Improved follow up data
7. Establishment of an inspectorate of eye banks by a suitable body.

8. STANDARDS IN HAEMOPOIETIC STEM

CELL TRANSPLANTATION

The clinical use of bone marrow transplantation has progressed greatly in the last twenty years. Whereas in 1980 bone marrow transplants were carried out sporadically in just two or three specialist centres in the UK, today more than 300 allografts and 600 autografts are performed annually in more than 50 hospitals. Recently peripheral blood has largely replaced marrow as source of stem cells for autografting and may assume a similar role in allografting. Important numbers of stem cells are present in the umbilical cord blood of neonates and this source of stem cells has also proved valuable, especially when the recipient is a child. Thus the technology is currently more correctly referred to as haemopoietic stem cell (HSC) transplantation to cover all three stem cell sources.

Various efforts have been made by differing agencies to define desirable standards for HSC transplants. It is hoped that the recommendations will eventually become the basis for formal accreditation.

8.1 TRANSPLANT CENTRES

In 1995 Link and colleagues on behalf of the European Group for Blood and Marrow Transplantation (EBMT) published a series of recommendations for standards to be achieved in hospitals undertaking HSC transplant procedures. 8.1

2. INDICATIONS FOR ALLOGRAFT AND AUTOGRAFT PROCEDURES

Schmitz and colleagues on behalf of the EBMT summarised current practice in Europe for the year 1996. 8.2 Transplant procedures were categorised by patient age, by disease, by stage of disease and by donor type and classified into three categories: 'routine', 'to be performed in the context of a clinical research protocol' or 'developmental'. This report will be up-dated annually.

8.3 UNRELATED DONOR TRANSPLANTS

HSC transplants that involve the use of unrelated donors pose special problems. The standard of care for the volunteer must be especially high and he or she must be carefully counselled before donation. Issues of consent, donor/recipient anonymity, methods for stem cell collection and transportation, insurance and reimbursement need to be considered very carefully. 8.3 Further issues may arise if the donor resides in one country and the patient is undergoing treatment in another country. The World Marrow Donor Association (WMDA) was established in order to co-ordinate guidelines for such 'international' transplants; a series of recommendations were published in 1994 8.4 but many of the sections in this paper could apply as well to 'local' transplants as to international transplants.

8.4 STEM CELL COLLECTION, MANIPULATION AND TRANSFUSION

In the United States the Internal Society for Hematotherapy and Graft Engineering (ISHAGE) has now produced a comprehensive series of recommendations specifying the standards for transplant centres and the optimal practice for collection, manipulation and transportation of haemopoietic stem cells. 8.5 ISHAGE has supported the establishment of an independent organisation, designated the Foundation for the Accreditation of Hematopoietic Cell Therapy (FACHT), whose function is to ensure that the ISHAGE standards are accepted and observed by transplant centres in North

America. The Accreditation Sub-Committee of the EBMT is currently scrutinising the ISHAGE document with the intention of adapting it for use in Europe. A similar document was produced by the National Health Service Executive in the UK in 1997. 8.4

9.0 THE TRANSMISSION OF INFECTIONS AS A RESULT OF SOLID ORGAN TRANSPLANTATION

9.1 TESTING

Every effort must be made to minimise the risk of transmission of infections between donor and recipient. To this end it is important to have a careful and detailed history of potential exposure and "at risk" behaviour, together with a precise diagnosis as to the cause of death and full documentation of any micro-organism that might be either the cause of death or complicating the agonal phase of the donor's disease.

These would normally be obtained by the transplant co-ordinator and their value can not be overestimated. A good clinical history can never be adequately replaced by serological assays. 9.1 The relevant screening for occult infection in potential organ donors are listed in Table 9.1

TABLE 9.1: CURRENT AND RECOMMENDED TESTING

Current serological testing Recommended additional tests

HIV 1 & 2 p24 Ag

H BV Sag HTLV I & 11 Ab

HCV Ab H BVc Ab

CMV DELTA Agent

Toxoplasma Ab HCV RNA (in HCV Ab + recipients)

Syphilis EBV Ab

Culture of preservation / perfusion fluid

Liver enzymes: ALT

Serum and DNA bank

Best Practice: The organisms which constitute an absolute contraindication to organ donation by virtue either of the virulence of the organism and / or the lack of reliably efficacious antimicrobial therapy are listed in Table 9.2.

TABLE 9.2: ABSOLUTE CONTRAINDICATIONS TO ORGAN DONATION

HIV I & II

HTLV I & II

SYSTEMIC VIRAL INFECTIONS:

measles

enterovirus

parvo virus B 19

adenovirus

rabies

DEEP OR SYSTEMIC FUNGAL INFECTIONS

MENINGO-ENCEPHALITIC SYNDROMES OF UNKNOWN AETIOLOGY

PRION DISEASE (PROVEN OR RISK)

RESISTANT ORGANISMS (e.g. MRSA, VRE)

SEPSIS SYNDROME OF UNKNOWN AETIOLOGY

9.2 HIV 1 & 2

Infection with or the risk of infection with the HIV virus remains an absolute contraindication to organ donation. In view of the time lapse after infection and before antibody appears, a history of possible exposure remains a vital part of the screening process. Testing for the p24 antigen would reduce but not eliminate false negative results.

9.3 HTLV 1 & 2

Donation of organs from donors infected with the HTLV virus are also excluded. Routine testing is not currently recommended in the UK, as the prevalence is so low. However, in certain parts of the United Kingdom where there are a significant number of donors from areas where the infection is endemic, testing should be included.

9.4 HEPATITIS B

Infection with hepatitis B frequently results in life long persistence of the virus with incorporation of the viral geneome in the liver. Liver donation is absolutely contraindicated from patients with serological evidence of past hepatitis B infection. 9.5 As with HIV there is a prolonged period of time during which potential donors with HBV are not HBV surface antigen positive. Testing for HBV core antibody reduces this window, but does not close it. The tests for HBV core antibody are not robust and false positives occur leading to the loss of otherwise suitable donors. 9.6 A core antibody positive result is likely to be a true positive in the presence of surface antibody or e antigen although negative results for these two tests are not helpful in deciding true or false positive core antibody result. Mutant hepatitis B virus exist in which the usual excessive production of free surface antigen does not occur. Low levels of surface antigen occur more commonly in-patients co-infected with the delta agent. HBV surface antigen positive renal donors have been used successfully and safely for HBV surface antigen negative recipients where the recipient has been effectively vaccinated and the transplant covered by HBV immunoglobulin. 9.7

Increasing numbers of HBV positive recipients are being transplanted, but they do need to receive a careful pre transplant assessment including a

liver biopsy if liver function tests are not entirely normal. A recipient, who is HBV positive with normal liver function and/or a normal liver biopsy, can be safely transplanted at least in the medium to short term. As with HCV positive donors, consideration needs to be given to the use of solid organs other than the liver from HBV positive donors to HBV positive recipients. 9.8 At present HBV positive donors are not used even for HBV positive recipients. Interpretation of HBV serology is complex. HBV seropositivity can be a marker for other hazardous organisms and at risk behaviour. The presence of HBV surface antibody may be due to vaccination, recent administration of hepatitis B immunoglobulin or blood transfusion.

9.5 HEPATITIS C

Hepatitis C is transmitted to recipients by donor tissue in about 50% of HCV antibody positive donors, but in a much higher percentage of those who are HCV RNA positive, perhaps approaching 100%. The risk of liver disease developing in an HCV negative recipient of an HCV positive transplant is about 35% (relative risk of 4). 9.9 To date no statistical effect on patient survival or graft survival has been noted, but little long term data is available. 9.10 It should be noted that 14% (4 patients) of 29 seronegative recipients of seropositive organs died of or with liver failure. 9.9 Increasing experience with HCV after solid organ transplantation indicates that the incidence and severity of progressive liver disease is considerably less than with HBV. 9.11, 9.12 The use of organs from HCV positive donors is being considered for recipients in need of life saving transplants and those with co-morbid conditions likely to limit life expectancy. 9.13, 9.14 Clearly, the use of HCV positive donors requires the informed consent of the potential recipient.

The exclusion of all HCV positive donors as currently recommended is estimated to cause the loss of 4.2% of donor organs in the USA. In the UK it is estimated that 1 % of the donor pool is HCV antibody positive.

There is clear evidence of superinfection and reinfection by donor virus. 9.15, 9.16 Even though this may occur, significant liver disease seems to be very uncommon. 9.17

9.6 CMV

CMV can be transmitted by the organ donor. The recipients at greatest risk are those who are seronegative for CMV antibody (R-) and so are at risk of a primary infection (D+/R-). Reinfection with donor strain of virus (D+/R+) is more common than reactivation of recipient virus and is likely to produce more severe disease and more frequent infection than reactivation (D-/R+). The risk of CMV after transplantation is dependent on several factors which permit a prophylactic strategy. The risk of serious CMV disease depends not only on the serological status of donor and recipient, but also on the total burden of immunosuppression and the organ being transplanted.

9.7 EBV

Transmission of EBV occurs to seronegative recipients. A primary EBV infection in a recipient of a solid organ transplant greatly increases the risk of post transplant lymphoproliferative disorder by in some cases as much as 20-30 fold. There is some evidence to suggest that prophylactic Acyclovir or Ganciclovir may help reduce this risk by reducing viral replication and the infectious load of organism.

9.8 BACTERIAL INFECTIONS

The use of organs from donors with bacterial infection is demonstrably safe 9.18 provided certain criteria and precautions are taken. Donors with adequately treated bacterial meningitis 9.19 and even those with a demonstrably positive blood culture (again if adequately treated) have been used safely and without transmission of the infection. It cannot be overstated that the donor with a meningo-encephalitic syndrome of unknown aetiology cannot be used.

9.9 FUNGAL AND PARASITIC INFECTIONS

Systemic or deep seated fungal infections represent an absolute contraindication to organ donation. Seeding of anastomotic suture lines with fungi (or bacteria) is associated with a high risk of rupture and significant morbidity and mortality. Where appropriate, donors should be screened for other organisms including malaria.

9.10 ADDITIONAL CONSIDERATIONS

The recommended screening tests are outlined in Table 9.1 but it needs to be remembered that false negative results can occur either because of the time interval between infection and antibody production or because of the effect that large volume blood transfusions (more than 4 units) will have on the laboratory testing for antibody or antigen titres. Wherever possible a pre transfusion sample should be tested.

The addition of liver enzyme testing, particularly ALT may be of value in identifying patients with occult hepatitis when serological results are difficult to interpret.

With increasing organ sharing and distribution with multi organ procurement the risk of bacterial contamination increases and the need to culture preservation / perfusion fluid needs reemphasis.

It is worth considering that new viruses and new strains of existing organisms continue to be identified. As techniques for diagnosis improve and such tests are being automated and speeded up, consideration should be given to establishing a donor serum and DNA bank for subsequent retrospective analyses.

10.0 XENOTRANSPLANTATION

10.1 INTRODUCTION

Relatively little is known about the nature and extent of physiological problems after xenotransplantation and these may also be a barrier to clinical success. Perhaps the major concern about xenotransplantation is the potential risk of transmission of infectious agents, e.g. viruses such as porcine endogenous retrovirus. These agents pose a potential risk to both the recipient of the graft and to the general public.

A number of leading investigators have argued for a moratorium on clinical xenotransplantation pending further definition of the potential risks and benefits of clinical Xenotransplantation. 10.1

10.2 CURRENT STATUS OF XENOTRANSPLANTATION IN THE UK

There is no clinical xenotransplantation activity in the UK at the present time. The DoH established an advisory group on the ethics of xenotransplantation chaired by Ian Kennedy, which published its report in 1996. 10.2 The report was, in principle, positive towards clinical xenotransplantation and the use of genetically modified pigs as a source of organs for human transplantation was judged ethically acceptable. However the report highlighted the limitations in existing knowledge about the problems of xenograft rejection, functional compatibility of pig organs and, in particular, the risk of transmission of infectious agents. The need for further research in these areas was emphasised, along with the requirements for a full and proper risk benefit analysis.

As a result of the Kennedy report, the U.K. Xenotransplant Interim Regulatory Authority (UKXIRA) was established. This Authority does not have statutory powers currently but exists to advise government on the action

necessary to regulate xenotransplantation.

10.3 FUTURE PROSPECTS FOR XENOTRANSPLANTATION IN THE UK

The introduction of xenotransplantation into clinical practice is unlikely in the foreseeable future. However it is possible that clinical trials of xenotransplantation will, subject to UKXIRA approval, begin within the next ten years.

Detailed clinical guidelines are clearly not possible at present but it is obvious that the introduction of clinical xenotransplantation must occur within a rigorously controlled framework with strict adherence to detailed protocols which define every aspect of transplantation. The International Transplantation Society recently published a series of detailed recommendations which cover the major issues. 10.3 The introduction of xenotransplantation in centres which do not have extensive experience and success with clinical allotransplantation is inconceivable and any multi-disciplinary team envisaging xenotransplantation must include all the key disciplines including physicians with expertise of infectious diseases in the context of transplantation.

Some of the key areas that will need to be addressed by centres planning to undertake xenotransplantation include: selection of suitable recipients, quality of care, management of risk, monitoring of patients and their contacts for infection, setting up of educational programs for patients, their relatives and the general public. Finally the programme must be rigorously evaluated. The approval of the institution's ethical committee and informed consent of the recipient will, of course, be mandatory.

Appropriate arrangements for breeding and care of the donor animals is essential together with protocols for the screening of the animals for pathogens. Finally it will be important to ensure that commercial interests do not prejudice the rigorous application of standards for clinical evaluation of xenotransplantation.

11.0 APPENDICES

11.1 CADAVERIC DONOR ASSURANCES AND DONOR REPORTING

- A protocol prepared by

The British Transplantation Society

UK Transplant Co-ordinators' Association

UK Transplant Support Service Authority

May 1998

INTRODUCTION

1. This protocol identifies clear lines of responsibility for the collection of information about the medical and social history of potential organ donors. It remains the responsibility of the transplant surgeon to discuss with potential recipients the risks associated with transplantation, including those of transmission of infectious agents.

2. 'Guidance on the microbiological safety of human tissues and organs used in transplantation' issued with circular HSG (96) 2.4 by the NHS Executive defines four main categories of absolute exclusion from organ donation. They are:

i. Patients with high risk factors for transmissible diseases

ii. Patients with a history of malignancy

iii. Patients with diseases of unknown aetiology

iv. Patients with other untreated systemic infections

3. The NHS Executive's guidance also makes recommendations (pages 6 and 7) on the selection of donors. It is the responsibility of transplant co-ordinators to ensure that a full social and medical history is obtained and recorded in each case. This may be by means of reference to medical notes, and if possible to the clinician caring for the patient prior to their death, interview with the donor family and, if necessary the GP.

4. No organs may be offered either through UKTSSA or to transplant centres until these enquiries are complete. If any doubt exists then the transplant co-ordinator should seek further medical advice from transplant clinicians.

5. Once donation has been confirmed and the necessary consent(s) obtained, the donor should be examined and an accurate record made of any tattoos, signs of intravenous drug use, skin malignancies or evidence of surgical procedures.

6. The UKTSSA Core Donor Data form must be completed and signed by the transplant co-ordinator.

7. The mechanism for the safe transfer of information about the condition of any organ considered for transplant operates through the use of the UKTSSA organ donor information forms and the routines agreed from time to time with representatives of the UKTSSA Duty Office as representatives of the transplant community. The use of this channel ensures that the information is fully logged but it is nevertheless the responsibility of the retrieving unit to ensure that adequate records are maintained for their own purposes.

8. It is the responsibility of the transplant surgeon to be satisfied as to the safety of the donor material prior to the transplant operation and to make any checks that they feel are appropriate to ascertain the full facts.

RESPONSIBILITY OF DONOR CO-ORDINATOR

9. The donor co-ordinator will assess the eligibility of all potential organ donors with regard to medical and social/behavioural history and current status by completing at least two of the following actions:

- i. contact the potential donor's family or close friend(s);

- ii. contact the potential donor's General Practitioner;

- iii. review the medical notes and discuss eligibility with the clinician caring for the patient.

10. Where there is obvious evidence of tattoos, previous surgical procedures these must be reported. In the case of intravenous drug abuse the donation should not proceed further. In a few exceptional circumstances the family interview may need to be conducted over the telephone. This is not recommended but if it does occur it must be recorded as such. The co-ordinator should document their findings in the medical notes. Having satisfied themselves of the eligibility of the potential donor, the donor co-ordinator will contact the UKTSSA Duty Office to confirm the donation and they will also complete and sign the Core Donor Data form. If in doubt they must discuss the case with a transplant clinician.

RESPONSIBILITIES OF UKTSSA

11. The UKTSSA Duty Office will ensure that for every potential donor, they receive confirmation of eligibility to donate from the donor co-ordinator; and will pass on to the eventual recipient centre(s) any information they receive either from the donor co-ordinator or subsequently from the retrieving surgeon.

12. The Duty Office will ask the donor co-ordinator:

"Do you have remaining doubts about the eligibility of this donor?"

"If so, what are they (and these will be passed on to the recipient unit)? If not, are you satisfied that the donor criteria are met in this case and have you completed the Core Donor Data form?"

RESPONSIBILITY OF RETRIEVING SURGEON

13. The retrieving surgeon(s) will review the eligibility of the potential donor and satisfy themselves that all donation criteria are met prior to removal of organ(s). They will also report any damage or relevant factor found on explanation and record the procedure and findings on the medical notes.

14. The retrieving surgeon will review the medical notes and if necessary discuss with the co-ordinator if there are any areas of difficulty. If further contact with the donor family is needed this should be made via the transplant co-ordinator since the co-ordinator will usually have interviewed the family previously. If further clarification is needed then contact should be made with the GP or clinician caring for the patient immediately prior to referral for donation. The retrieving surgeon(s) will sign the Organ Specific Donation form to confirm absence of contraindications to the donation and to report any relevant damage or physical features.

15. It is the responsibility of the retrieving surgeon(s) to ensure that full information regarding any possible contraindications for the use of any organ(s) reaches the transplant surgeon(s) so that the fullest possible risk assessment can be made in each case.

RESPONSIBILITY OF TRANSPLANT SURGEON

16. The transplant surgeon must ensure that all potential recipients are aware of the risks involved in transplantation. They must also satisfy themselves that adequate checks have been made to discover any contraindications to transplantation in relation to a specific organ donor for an organ for when they will be taking responsibility. In doing so, the transplanting surgeon must have regard to the current published guidance [CMO (87) 5, 2 March 1987; PL/CMO (90)2, 26 April 1990; PL/CMO(93)11, 31 August 1993; CDC(1994); HSG(96)26, 26 March 1996; PL/CMO(96)5, 1 July 1996].

17. The transplanting surgeon will review the Organ Specific Donor form and contact the retrieving surgeon or donor co-ordinator to obtain any clarification they require. It is the responsibility of the clinician to ensure that full information regarding any possible contraindications for the use of any organ has been considered and the risks assessed. The transplant surgeon may request further specific tests to be carried out before transplanting the organ. Final responsibility for the condition of the transplanted organ rests with the transplant surgeon.

11.2 HISTOCOMPATIBILITY TESTING FOR TRANSPLANTATION

The following summary and recommendations have been prepared by the British Society for Histocompatibility and Immunogenetics (BSHI).

11.2.1 Introduction

For successful allogeneic stem cell (peripheral blood, cord blood or bone marrow) and organ transplantation, clinical teams must have access to high quality Histocompatibility and Immunogenetics (H&I) services. In this section BSHI defines what constitutes high quality H&I services. It is recognised that the range of services required may vary between the transplant specialities.

11.2.2 Laboratory Accreditation

Within the UK, laboratory accreditation comes under the auspices of Clinical Pathology Accreditation (UK) Ltd (CPA). To obtain CPA accreditation, laboratories must comply with a broad range of standards covering laboratory facilities, health and safety, management, procedural issues and training. In addition, there are standards which are specific for H&I. Laboratories achieve accreditation following a satisfactory report by CPA inspectors who are experienced in H&I. All laboratories providing H&I services for transplantation should be CPA accredited before the end of the year 2000.

Accreditation of H&I laboratories involving a wide range of standards covering all areas of testing, is provided by two professional bodies: the American Society for Histocompatibility and Immunogenetics (ASHI) and the European Federation for Immunogenetics (EFI). EFI is the recognised accrediting body within Europe and laboratories providing H&I services for transplantation should achieve EFI accreditation.

BSHI has an important input into the ongoing review process of the EFI Standards and has produced an addendum of standards which are recommended for UK laboratories.

ASHI accreditation is also acceptable.

11.2.3 Personnel Qualifications and Training

Crucial to the provision of a quality service and the introduction of future developments are the staffing structures and personnel qualifications within the H&I laboratory.

The Laboratory Director should have Membership of the Royal College of Pathologists in H&I and, if a scientist, have a substantive Grade C Clinical Scientist post or equivalent. Other scientific/technical staff should have successfully completed a recognised training scheme in H&I [BSHI, Council for Professions Supplementary to Medicine (CPSM)] and should participate in relevant CPD or CME schemes. Trainees must participate in a recognised training scheme. It is therefore essential that training opportunities are provided within the laboratory for all personnel.

11.2.4 Service Provision

H&I laboratories will offer different repertoires of tests depending on the services they provide and the transplant programmes that they support. Descriptions of the tests that can be offered are given in the document 'Standard Tests in Histocompatibility and Immunogenetics', which can be obtained from BSHI.

Each laboratory should provide a description of the tests offered and their clinical application.

Laboratories providing services for transplantation must participate in a relevant external quality assurance scheme (e.g. NEQAS for H&I) for each of the services offered and demonstrate an acceptable standard of performance.

11.2.5 Laboratory/Clinical Liaison

It is important that close liaison is maintained between the laboratory and the clinical teams. The Head of Laboratory and other appropriate laboratory staff must therefore establish good professional relationships with the medical and professional staff on the transplant Centre.

Laboratory representation at relevant clinical and audit meetings is essential.

11.2.6 HLA Typing

As a minimum, for solid organ transplantation the products of the HLA-A, -B, -C, -DR and -DQ loci must be determined at the level required for the organ sharing programme. For the allogeneic or unrelated stem cell recipients, the patient and short-listed potential donors should be typed for HLA-A, -B, -C, -DR and -DQ gene products by molecular methods at high resolution to facilitate the final selection process.

11.2.7 Antibody Detection and Definition

HLA specific antibodies present in the recipient and directed against donor antigens are known to cause hyperacute or accelerated renal and thoracic organ transplant rejection.

It is therefore essential to test all patients on the renal and thoracic organ transplant waiting lists for the presence of HLA specific antibodies.

Except in cases of clinical urgency, patients with a history of sensitisation should not be registered on the waiting list unless antibody test results are available.

It is the responsibility of the clinical team to ensure that samples for antibody testing are sent to the laboratory at the agreed frequency and when specifically requested (e.g. following blood transfusion).

Testing should provide information on antibody specificity and panel reactivity and should distinguish HLA specific from autoreactive and other non-HLA antibodies.

Following transplantation, the laboratory should test recipients for the presence of HLA specific antibodies. The policy should stipulate the frequency of testing and testing following a transplant nephrectomy. Serum samples must be stored for use in future crossmatch tests.

11.2.8 Crossmatching

A pre-transplant donor/recipient crossmatch is a vital procedure to prevent hyperacute or accelerated transplant failure. Each centre must therefore have an agreed and documented policy describing the crossmatch tests to be performed prior to transplantation, the selection of samples to be tested and the interpretation of results.

The policy must clearly define those circumstances when pre-transplant crossmatching is not considered mandatory. The policy must be supported by published evidence and documented local data. Relevant sera from all patients on the current waiting lists must be stored and readily available for use in crossmatch tests.

11.2.9 Transplant Donor Testing

Laboratory staff must be available to HLA type and crossmatch organ material on a 24 hours, 365-day basis. More than one person should be available for complex tests or when several donors are under investigation. The contact name and telephone number of the relevant staff must be accurate and up to date and describe the arrangements in place for consultant advice. The laboratory must have a security policy which ensures the safety of staff working in and out of normal working hours.

11.2.10 Information Technology

H&I laboratory staff must validate the HLA phenotype and HLA antibody results on the transplant patient administration system operated by UKTSSA.

Following registration of a patient on the national transplant waiting list or record amendment, laboratory staff should verify UKTSSA records and immediately notify UKTSSA of any errors that would affect organ allocation.

11.2.11 Planning & Costing

H&I laboratories have a major role within the multidisciplinary team involved in the provision of transplantation services. This particularly

applies to stem cell, renal and cardio-thoracic transplantation but also applies to a lesser extent to liver and corneal transplantation.

The planning and development of transplant services requires long term manpower planning and must take into account the full requirements of the laboratory services.

Business Planning estimates must take into account the full cost of provision of a comprehensive H&I laboratory service including on-call services, training, participation in quality assurance schemes and development.

11.2.12 Future Developments

Developments in clinical transplantation and transplantation science are on going (e.g. tolerance induction, new immunosuppressive regimens, xenotransplantation).

As the field of clinical transplantation advances, this must be paralleled by advances in H&I to ensure that relevant H&I services are available to support transplant programmes.

12.0 TERMS, BIBLIOGRAPHY OF REFERENCES

12.1 TERMS

Ab.

Antibody

Accreditation

A process recognising that a service reaches and maintains accepted pre-defined standards and practices.

Acyclovir

An anti viral agent against herpes virus

Ambulant patients

Walking patients

Anastomotic suture lines

Joined by stitches e.g. arteries

Antibody

A chemical produced by the body in response to a specific stimulus e.g. an infection

Anti CD25 antibodies (Daclizumab & Basiliximab)

Monoclonal antibodies which block IL2 receptors and prevent rejection.

Anti-lymphocyte agents

Anti bodies used to destroy human lymphocytes

Antilymphocyte agents (OKT3 and ATG)

Antibodies raised against human lymphocytes in another animal and used to both prevent and treat rejection.

Antimicrobial therapy

Drugs which kill micro-organisms e.g. antibiotics

Azathioprine

The first ever immunosuppressive drug, inhibits purine synthesis

Audit

A process to review service activity against local and national performance measures and action to modify the service on the review evidence.

Best practice

The accepted optimal service procedure based on external audit data.

Bilateral lung

Both lobes of lung

Biopsy

Removal of a small tissue sample from the body for pathological examination.

BMA

British Medical Association.

Brainstem

The brainstem controls respiration and cardiac function, without brainstem function life cannot continue. Tests for destruction of the brainstem form the basis for the diagnosis of death in-patients supported on a ventilator.

Bridging therapies

Short term treatment using temporary procedures prior to use of more preferable longer term treatments.

BSHI

British Society for Histocompatibility and Immunogenetics. The professional organisation for Tissue Typing Laboratory scientists.

BTS

British Transplantation Society.

Cadaveric Organs

Organs from a dead donor

Cardiothoracic

Refers to the surgery of the heart and the contents of the chest

Centre variation

Differential outcome which is observed between UK transplant units. This may reflect case mix variation between recipients or treatment protocols.

Chronic active hepatitis

Slow progressive inflammatory disease of the liver

CMV

Cyto Megalo Virus

CMV negative recipient

A transplant recipient who has no natural immunity to Cyto Megalo Virus

Commissioners

Agencies responsible for developing and funding selected specialist service

Co-morbidity

Other medical conditions affecting the same patient

Cornea

The transparent layer at the front of the eye

Costing process

The procedure of establishing the cost of providing a service in a NHS Trust. Careful definition of the service content must be made to allow meaningful comparisons between costed services.

Crossmatching (antibody screening)

Crossmatch between the recipient's serum and donor lymphocytes testing for the presence of anti bodies against white cells in blood

Cyclosporin (Neoral TM)

Powerful immunosuppressive drug, can be used on its own it inhibits IL2

Double or triple therapy

Immunosuppression using more than one drug

Endothelial

Cells lining the inside of blood vessels

End stage organ failure

The point at which a diseased organ is irreversibly damaged.

Evidence based medicine

Use of a best practice treatment derived from a review of clinical experience of a number of alternative therapies.

Fulminant hepatic failure

Sudden total failure of the liver often caused by poisoning e.g. paracetamol overdose.

Ganciclovir

An anti viral agent against CMV

GMC

General Medical Council

Grafting

Implantation of an organ

Graft survival

A calculation of surviving transplanted organs or tissues expressed as a percentage of the total number of transplanted organs or tissues in the study. Actuarial methods are used to account for the wide range in transplant time experienced. The end point is transplant organ or tissue failure or patient death. Patient survival is a similar calculation with death of the recipient as the sole end point of the study.

Haemopoietic stem cell

Cells from which blood cells originate

HBV

Hepatitis B Virus

HCV

Hepatitis C Virus

Heart and lung

Transplantation of the heart together with both lungs

Heart beating donor

Organs and tissues for transplantation are removed from donors fulfilling the nationally agreed and legally defined criteria of brain stem death having obtained the permission of the donor's relatives. Such donor hearts beat up to the time of organ and tissue removal because of mechanical support mechanisms (ventilators). In some centres, kidneys for transplantation are removed up to one hour after death has been certified in non-ventilated non-heart beating donors who have usually been admitted to the emergency room following traumatic injury. The graft survival of kidneys from non-heart beating donors is poorer than that of kidneys from heart beating donors. Corneas can be removed from donors up to 36 hours after death has been certified.

Hepatic artery thrombosis

Blockage of the main artery to the liver

Hepatologists

Non surgical liver specialists

Histocompatibility

Similar cells

HIV

Human Immunodeficiency Virus

HLA alloantigens

Foreign HLA antigens

HLA types

Markers on the surface of human lymphocytes which allow them to be matched against another humans lymphocytes

HOT Act

The Human Organs Transplant Act (1989) and accompanying Regulations. The Act prohibits removal and transplantation of organs for any form of profitable gain. It also limits transplantation of organs from living donors unless donor and recipient are established to be closely genetically related or the transplant has been authorised by ULTRA. The Act also established the national organ transplant register.

Hyperacute rejection

Very aggressive form of rejection mediated by pre-existing antibodies and occurring within hours of transplantation.

Immunogenetics

The study of the inheritance characteristics of the immune system

Immunological failures

Foreign material destroyed by the immune system e.g. transplant by rejection

Immunosuppression

The depression of an individuals innate biological ability to eliminate foreign organisms (bacteria and viruses). In the context of transplantation the recipient's ability to reject the organ or tissue is controlled by administering drugs for the entire post transplant period. Commonly used drugs are azathioprine, prednisolone, and cyclosporin whilst more recently developed drugs include tacrolimus and mycophenolate. Sometimes, antibody treatments such as anti-thymocyte globulin and anti-T cell immunoglobulins are used; these preparations are manufactured in animals. There are many side effects from these drugs since their immunosuppressive actions are not specific to the transplanted organ so transplant recipients are at increased risk from viral and bacterial infections.

Intensivists

Specialists in Intensive Care

Ischaemic injury

Damage caused by cutting off the blood supply to an organ e.g. the kidney

Keratoconus

Progressive obliteration of the transparent part of the eye

Limited resources

Organs and tissues for transplantation are in limited supply due to the nature of organ and tissue donation being entirely voluntary and limited almost exclusively to heart beating donors from intensive care units.

Living donors

In some instances it is possible to remove organs and tissues from healthy persons for transplantation. The commonest situation is that of bone marrow donation. One kidney may be removed from a healthy person for transplantation provided the terms of the HOTA Act are complied with. The non-diseased heart removed from combined heart and lung transplant recipients may be transplanted into a heart failure patient. Corneas may be grafted when taken from eyes removed from patients undergoing surgery for facial cancer treatment. Evolving strategies include live donor liver and lung lobe transplants.

Lung lobes

Each lung lobe comprises discrete segments each with its own blood supply.

Lymphoproliferative Disease

Cancer of the lymph nodes

Maintenance dialysis

Long term treatment on a kidney machine

Malignancy

A cancer

Mechanical devices

Artificial dialysis machines are used to support kidney failure patients by cleansing the blood outside the body. Artificial liver machines are under development and ventricular assist devices are in restricted use as bridging devices prior to heart transplantation.

Meningo-encephalitic

Relates to the meninges (membranes around the brain) and the brain.

Micro-organism

A life form that can only be seen with a microscope, e.g. a bacterium or a virus etc

Monotherapy

Immunosuppression using only one drug

Multi-organ donor

A donor who donates more than one organ

Mycophenolate Mofetil

The latest and best inhibitor of purine synthesis

National Organ Sharing Scheme

Agreed collaborative rules for equitable allocation of organs to recipients (see annexe). Printed copies are held centrally by UKTSSA and transplant unit directors are required to "sign up" to the schemes which cover all solid organs and corneas. The rules are modified through the UKTSSA organ specific Advisory Groups which may seek the opinion of unit directors.

National resource

All organs donated and removed from heart beating and non-heart beating donors are available to all UK waiting list patients. The agreed allocation rules are set out in the National Organ Sharing Schemes. Similarly, patients have free access to any NHS transplant service in the UK but to only one such service at any given time. Whilst organs and tissues may be transplanted to NHS eligible patients using the facilities of private sector hospitals this rarely happens. Patients not entitled to NHS treatment are eligible for organs only after all NHS entitled patients have first been considered.

Nephrology

The study of kidney disease

Neutropenia

Shortage of white cells

NHS Market

The system which is internal to the NHS, facilitating costing of services and charging of NHS Purchasers for transplant unit services.

Non heart beating donors

Donors from whom the organs are removed after the heart has stopped beating

Non-sensitised patients

Patients who have not yet and therefore have not yet been able to make anti bodies against a particular antigen

Organ allocation

The process by which a recipient is selected to receive a donated organ. The criteria used for organ allocation are agreed in the National Organ Sharing Schemes.

Organ donation

The gift of an organ or tissue from one person (donor) to another (recipient). The donor and recipient may be known to each other as in bone marrow transplantation and live donor organ transplantation or may not know each other, as in cadaver donor kidney, liver or heart transplantation. Organ donation and transplantation is regulated by the HOT Act.

Organs and tissues

An organ is an integrated group of body cells performing specific vital function(s) having its own blood supply. Organs commonly transplanted are the kidney, liver, heart, lung, and pancreas.

A tissue is a group of body cells which is a constituent of an organ or has the ability to regenerate. Tissues commonly transplanted are bone marrow and corneas.

Osteoporosis

Bones deprived of calcium.

Paediatric

Pertaining to children

Patient registration

Potential organ and tissue transplant recipients must be registered for their need for a transplant both in the local transplant unit and with the UKTSSA national waiting list.

Patient survival

A calculation of surviving transplanted patients expressed as a percentage of the total number of transplanted patients in the study. Actuarial methods are used to account for the wide range in transplant time experienced. The end point is patient death. Graft survival is a similar calculation with failure of the transplanted organ or tissue or death of the recipient as the end point of the study.

Patient's Charter

A national statement of the expectations and rights of patients which they should receive during their treatment with NHS services.

Peer review

A review process inviting comment and criticism on a manuscript by one or more professionals considered to have expert knowledge in the relevant field. The outcome is dependent on the reports made by the reviewer(s) who are anonymous to the author.

Porcine endogenous retrovirus

A virus confined to the pig slow growing and hard to find, may be harmless in the pig but action in man is unknown

Prednisolone

Steroid drug with a powerful anti inflammatory action

Primary biliary cirrhosis

Inflammatory disease of the liver

Prophylactic regimen

Preventative programme of treatment usually refers to prevention of rejection or infection

Pulmonary

Lung

Quality assurance

An ongoing process which monitors the quality of procedures. Results from quality assurance exercises detect shortfalls in quality and alert for implementation of repair processes.

National and local process by which the standards in laboratories are compared and maintained

Rapamycin

Powerful immunosuppressive drug

Recipient assessment

The medical check needed to ensure that a patient is fit to enter a transplant waiting list or is fit to undergo the surgery of an organ or tissue transplant.

Renal arteries

Arteries that carry blood to the kidney

Research and development

The search for new information to improve services and the application of that information to services.

Retrieval zone

A geographical area agreed centrally and allocated to an organ retrieval team to become its responsibility for removal of organs and tissues from all referred organ and tissue donors.

Royal Colleges

Institutions assigned Privy Council status and authority over medical procedures. They are based in London and Edinburgh. Those relevant to transplantation are the Royal Colleges of Surgeons, Physicians, Ophthalmologists and Pathologists.

Segments of liver

The liver comprises eight discreet segments each with its own blood supply

Serological

Serum is part of the blood but without cells

Shared care

In the broadly based discipline of organ and tissue transplantation, patients may often be cared for under the responsibility of more than one Medical Consultant.

Single lung

One lobe of lung

Solid organ

E.g. kidney, heart etc. as opposed to cells and tissues

Standards

An agreed defined set of procedures which establish the level which any service must achieve to become accredited.

Tacrolimus

Powerful immunosuppressive drug, can be used on its own it inhibits IL2

Transplantation

The implantation of an organ or tissue to a patient (recipient) having been removed from another person (donor) who may or may not be genetically related.

UK

United Kingdom of England, Scotland, Wales, Northern Ireland and the associated islands. The UKTSSA supports services in the UK and in the Republic of Ireland.

UKTCA

UK Transplant Co-ordinators Association. The national professional body for transplant co-ordinators.

UKTSSA

UK Transplant Support Service Authority. A Special Health Authority of the NHS with specific responsibility for central co-ordination of organ and tissue transplantation in the UK and Ireland. Users interact with UKTSSA via the organ specific Advisory Groups.

ULTRA

Unrelated Live Transplant Regulatory Authority. A Government Authority overseeing organ transplants between unrelated persons where the donor is living. The ULTRA Members are appointed by the Minister for Health.

Vascular anatomy

Structure and disposition of the arterial supply and venous drainage of an organ

Vessel

A loose term for an artery or a vein

Vital organ

An organ without which life is not possible e.g. heart

Waiting list

A register of patients eligible to receive an organ transplant.

Xenotransplantation

Transplantation of organs or tissues using non-human animals as donors.

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