**IMMUNOLOGY 4**

# Transplantation

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**OBJECTIVES**

To understand which organs can be transplanted, why, and where the transplanted organs come from

To understand some of the ethical and structural/organisational issues surrounding organ transplantation

To understand the immunological issues in transplantation and their impact on organ allocation and rejection after transplantation (including the main types of transplant rejection)

To understand the risks and complications associated with transplantation and transplant immunosuppression

**STRUCTURE OF THE LECTURE**

* Which organs can we transplant?
* Why do we transplant them?
* Where do the organs come from?
* Clinical practice of transplantation
  + Transplantation programme
  + Transplant immunology and immunosuppression
  + Complications of transplantation

**Which organs can we transplant?**

* Autografts
  + within the same individual
* Isografts
  + between genetically identical individuals of the same species
* Allografts
  + between different individuals of the same species
* Xenografts
  + between individuals of different species

Autografts

* Hair
* Skin
* Teeth
* Arteries and veins
* Pericardium and fascia
* Bone and cartilage
* Tendons
* Nerves
* Bowel
* Parathyroid
* Bone marrow
* ?Stem cell derived organs

Xenografts

* Skin
* Heart valves
* Bone and cartilage

Allografts

Solid organ

* + kidney
  + liver
  + heart
  + lung
  + pancreas
  + small bowel
* Free cellular grafts
  + bone marrow stem cells
  + pancreatic islets
* Privileged sites
  + cornea
* Temporary
  + blood transfusion
  + skin
* Framework for new host tissue
  + bone and cartilage
  + tendon and fascia
  + nerve

Transplantation in the UK, 2008-09

|  |  |  |
| --- | --- | --- |
|  | Deceased donor | Live donor |
| Kidney | 1570 | 927 |
| Liver | 667 | 34 |
| Heart | 130 |  |
| Lung | 143 |  |
| Heart and lung | 3 |  |
| Pancreas | 216 |  |
| TOTAL | 2552 | 961 |

**Why do we transplant them?**

**Organ failure**

Organ vital for survival, no long-term replacement therapy: lung, heart, liver

Organ transplantation has benefits over other replacement therapy, including prolonged survival: kidney, bone marrow, pancreas

Organ not vital but improved quality of life: cornea, reconstructive surgery

For example: Kidney transplantation

* Quality of life on renal replacement therapy
* “Time trade-off” method

0 = death; 1 = perfect health

* + dialysis patients average score: 0.41
  + transplant patient average score: 0.74
  + 27% increase in employment rate (38% in males)

**Where do the organs come from?**

The deceased donor

Heart-beating (donor after brain death DBD) – brain dead (usually intracranial haemorrage or head injury), organs perfused until last minute by life support (ventilation)

* + Stringent criteria
    - irremediable structural brain damage - KNOWN cause
    - apnoeic coma NOT due to

depressant drugs

metabolic or endocrine disturbance

hypothermia

neuromuscular blockers

* + - demonstrate lack of brain stem function

pupils both fixed to light

corneal reflex absent

no eye movements with cold caloric test

no cranial nerve motor responses

no gag reflex

no respiratory movements on disconnection (with PaCO2>50 mmHg)

Non-heart beating (donor after cardiac death DCD) – in addition to brain, heart has also stopped for variable length of time before organs are harvested (leads to delayed graft function after transplantation related to ischaemic acute tubular injury)

Removed organs rapidly cooled and perfused

* absolute maximum cold ischaemia time for kidney 60h (ideally <24h)
* much shorter for other organs
* except cornea 96hr (longer with cryopreservation)

Exclude:

* viral infection (HIV, HBV, HCV)
* malignancy
* drug abuse, overdose or poison
* disease of the transplanted organ

“Supply” of organs for transplantation

* The increasing shortage of organs relative to need: mainly a problem for kidney, lungs, and combined heart/lungs
* Cadaveric donor rate (pmp) differs by country

Strategies for reducing the shortfall

* Decrease the demand for organs (improve preventative and interventional therapy)
* Increase cadaveric donation – Organ Donation Tackforce 2008
  + - Review of the role of the transplant co-ordinator
    - donor card campaigns
    - public information
    - “presumed consent”?
* Look for other sources of organs (“marginal donors” (>60, hypertension, smokers,…), high immunological risk transplantation, develop paired exchange programmes, xenotransplantation?stem cell biology?)
* Optimise use of currently available organs
* improve the half-life of an allograft = decrease need for re-transplantation
  + improved surgical preparation/storage
  + improved organ sharing
  + improved immunological work-up
  + improved immunosuppression
    - recent burgeoning of number of drugs available

Live organ donation (kidney and liver)

* Live-related
* Live-unrelated/emotionally related
* Altruistic donation

Risks of Live Donation (figures for kidney donation)

* Risk of perioperative mortality - 0.03% - 0.06%
  + Comparable with the risk in USA of dying in a road traffic accident in one year (0.02%)
  + There have been at least 2 perioperative donor deaths in the UK
* Perioperative morbidity
  + major perioperative complication rate: c.2%
* Late mortality - unilateral nephrectomy in healthy individuals does not have an adverse affect (up to 45 years of follow-up)
* Associated with asymptomatic, non-progressive proteinuria in 25-35% cases
* No convincing evidence of increased risk of hypertension
* Long term renal function – c 75% of normal.

**THE CLINICAL PRACTICE OF TRANSPLANTATION**

**Pre-transplantation management**

Waiting list

Immunological investigations

Other investigations

**Transplantation surgery**

**Post-transplantation management**

Immunosuppression

* Induction agents
* Corticosteroids (current tendency for reduction of steroids)  
   PLUS
* Other immunosuppressive drugs

Complications of transplantation

* Rejection
* Infection
  + early period
    - typical post-operative bacterial infection
    - oropharyngeal candidiasis
    - aspergillosis
  + medium term
    - CMV (after 1-2 months) - seronegative recipients should have prophylaxis
    - pneumocystis
    - tuberculosis
* Drug side effects
* Malignancy
  + UV-induced skin cancer
  + post-transplant lymphoproliferative disease (PTCLD; mostly B cell, EBV-driven)

Why a graft fails

* Surgical complications
* Bad quality organ
* Rejection
* Recurrence of original disease
* Others: infection, drug toxicity, bad vascular supply, ureteric obstruction etc.

Rejection

Recognition and destruction by recipient immune system(immune-mediated damage)

Acute cellular rejection (T-cell mediated)

Acute antibody-mediated rejection (antibody-mediated, B cells)

Gold standard for diagnosis of rejection is the biopsy of the transplanted organ (easy for kidneys, more problematic for other organs)

*Hyperacute rejection*

* Caused by pre-existing antibodies
* Historical sensitization: the patient has “seen” the antigen before
  + previous transplant
  + previous transfusion
  + pregnancy
* Bind to graft endothelium in minutes
* Destroys graft in hours
* Every patient screened by direct crossmatch

*Acute rejection*

T or B-cell mediated, or both

*Chronic rejection*

T or B-cell mediated, or both

**RENAL TRANSPLANTATION**

* Matching
  + ABO blood group matching
  + HLA matching
* 60-80% kidneys produce urine “on the table”
  + others have “delayed graft function”
* 10-25% suffer acute rejection
  + usually reversible
* Monitoring for good blood and urine flow and rejection
  + serum creatinine
  + DTPA perfusion scan/ultrasound
  + serial renal biopsy
* Outcome
  + 5-year graft survival rate currently around 89% (living) – 83% (deceased)
  + 10-year survival around 60-70%
  + current “life-expectancy” of first kidney: 11yr
  + in ideal conditions, could be up to 40 yr

**CORNEA TRANSPLANTATION**

* Supply and demand
  + most patients never get on waiting list, but corneas are “ordered”
* Cornea is “immunologically privileged site”
  + immunosuppression not required
  + rejection does occur
* Matching
  + historically not considered important
* Outcome
  + first graft: c75% 5 year survival

**LIVER TRANSPLANTATION**

* Supply and demand
  + relatively well matched
* Options for transplantation
  + Orthotopic transplantation - replacing the diseased liver
  + Heterotopic transplantation - placing a new liver in a different place (right subhepatic region)
  + Live lobe transplantation
* Organ-specific issues
  + surgical technique is very difficult and complications are common
  + thrombosis of hepatic artery or portal vein may occur
  + haemorrhage is very common
* Matching
  + ABO blood group
  + size
  + HLA matching controversial and not practical
* Rejection
  + liver is less aggressively rejected than many other organs
* Outcome

3 year survival: cirrhosis 69%  
 emergency 56%  
 cancer 39%

**HEART TRANSPLANTATION**

* Supply and demand
  + Short-fall of supply
  + predicted demand: 20-60/million population
  + current supply: 6/million in UK
* Matching
  + appropriate blood group
  + size
  + ?HLA matching
* Rejection
  + only reliable way to detect is regular endomyocardial biopsy
* Outcome
  + 85-90% 1 year survival
  + 75% 5 year survival
  + 50% live 10-12 years
  + functional rehabilitation excellent

**LUNG TRANSPLANTATION**

* + - Supply and demand
  + approx 200 suitable donors per year in UK
  + 111 on heart/lung waiting list and 205 on lung waiting list at 31.12.2000
    - Options for transplantation
  + heart-lung transplant
  + single lung transplant
  + sequential double lung transplant
* Matching
  + ABO match
  + size
    - Outcome
  + for heart-lung and single lung transplant
    - 80% 1 year survival
    - 50% 5 year survival
  + less good for double lung transplant

**CONCLUSIONS**

Transplantation is:

* + - highly successful
    - potentially life-saving
    - cost-effective

The major problems are the lack of donor organs and the immunological rejection of transplanted organs.