Transplant Infectious Diseases
An overview

DR NICOLE GILROY
SENIOR STAFF SPECIALIST
INFECTIONOUS DISEASES
WESTMEAD HOSPITAL NSW SYDNEY
Outline

- Transplant populations
  - Solid Organ Transplants (SOT)
  - Haematopoietic Stem Cell Transplants (HSCT)

- Infection-risk assessment
  - Donor, recipient, timing, exposures, immunosuppression
  - Syndromal approach

- Prevention
>33,000 SOT since 1963

>26,000 HSCT since 1992

~1700/yr SOT (yr 2015)

~ 2000/yr HSCT (yr 2015)
Solid Organ Transplants
Australia/NZ 2015 (n=1757*)

- Kidney: 62%
- Heart: 6%
- Heart-Lung: <1%
- Lung: 12%
- Liver: 17%
- Pancreas: 3%
- Intestine: <1%

ANZ Organ Donor Registry (organs transplanted from deceased donors Australia/NZ Jan 1-Dec 31 2015) & ANZDATA 2015
*Includes living donor renal allografts
Solid Organ Transplants

Post transplant survival

Adapted from ANZ Cardiothoracic Organ Transplant Registry, Annual Report 2016

Haematopoietic Stem Cell Transplants (HSCT)

Australia/NZ 2015 (n=2023)

- Autologous: 67%
- Allogeneic - related donor: 13%
- Allogeneic - unrelated donor: 20%

Adapted from ABMTRR Annual Data Summary 2015
Haematopoietic Stem Cell Transplants (HSCT)

Post transplant survival

Adapted from ABMTRR Annual Data Summary 2015
Types of transplant infections

- **Donor-derived infections**
  - Tissue or stem cell product

- **Pathogens from human/animal contact, food, water, blood products**

- **Invasive infections** from endogenous/colonising microflora
  - MROs, Candida, Enterobacteriaceae

- **Accelerated progression** of chronic infection
  - Hepatitis B, Hepatitis C, Human papillomavirus (HPV)

- **Reactivation** of latent infections
  - Viruses (eg CMV), bacteria (eg TB), protozoa (toxoplasma), parasites (strongyloides)

- **Infection from organisms** (usually from the environment) of **low intrinsic pathogenicity**
  - Opportunistic infections eg Fungi (yeasts & moulds) & bacteria (nocardia, atypical mycobacteria)
Infection risk (1)

Donor and recipient

- Donor-derived infection
  - Clinical history (questionnaire) & laboratory screening
    - HIV, HBV, HCV, HTLV I/II, Syphilis, CMV, EBV
    - Sputum gram stain (lung Tx) Toxoplasmosis (Heart Tx)
    - +/- MTB, Chagas, Strongyloides, West Nile, Malaria, Zika

- Recipient-derived infection
  - Clinical history (questionnaire) & laboratory screening
    - HIV, HBV, HCV, HTLV I/II, Syphilis, CMV, EBV, HSV, VZV, toxoplasmosis
    - +/- MTB, Chagas, Strongyloides, West Nile, Malaria, Zika
Unexpected Donor-Acquired infections

- Early atypical transplant infections
- Esp Unexplained neurological syndrome in 20-60 days post Tx

  - **West Nile Virus**
    - 2002: WNV in transplants from infected donor or blood products

  - **Rabies**
    - 2004: 3 deaths (liver, 2 kidneys)
    - Rabies-infected donor
    - Infection from bat, raccoon bite?

  - **Lymphocytic choriomeningitis**
    - 5 clusters in transplant recipients
    - 14 cases, 11 deaths
    - Linked to donor acquisition from pet hamsters

  - **Novel arenavirus**
    - 3 SOT deaths Australia (donor in Europe in weeks before)

  - **Balamuthia mandrillaris (free living amoeba)**
    - 2 clusters 2009 & 2010 related to donors
    - 3 transplant deaths from granulomatous amoebic encephalitis

Infection risk (2)

Exogenous exposures

- **Nosocomial risk factors**
  - Environmental (air /water quality, environmental cleanliness)
  - Sick HCW, other patients, visitors
  - Contaminated devices, blood products, food
  - Antibiotic selection pressure

- **Community risk factors**
  - Occupational exposures
  - Travel
  - Pets
  - Household/close contacts or sexual contacts
Infection risk (3)

Immunosuppression

- **Corticosteroids**
- **Antimetabolites**
  - Mycophenolate mofetil, Azathioprine
- **Calcineurin antagonists**
  - Tacrolimus, cyclosporin
- **mTOR inhibitors**
  - Sirolimus, everolimus
- **Polyclonal Ab**
  - ATG, Thymoglobulin
- **Monoclonal Ab**
  - Daclizumab, basilixumab, Alemtuzumab, OKT3, infliximab, rituximab, etanercept (fusion protein)
Clinical approaches

- Assess infection risks based on:
  - Immune deficits
  - Recipient (R) & donor (D) serostatus (CMV, EBV, VZV, Toxo, Hep B/C, toxoplasma)
  - Likely exposures
  - Time post transplant

- Syndromic approach, examples
  - Febrile neutropenia
  - New pulmonary infiltrate post transplant
  - Encephalitis
SOLID ORGAN TRANSPLANTS
Phase 1: Post Surgery 0-1 month
- Hospitalisation, Surgery +/- ICU
- MROs, C.diff, GNR, GPC
- HSV
- Candida* Liver Tx
- Aspergillus* Lung Tx
- Resp viruses

Phase 2: Opportunistic 1-6 months
- Acute Rejection Intensive IS
- Atypical bacteria - MTB, Nocardia, listeria
- Resp viruses
- CMV
- EBV
- VZV
- BK (renal)
- Pneumocystis
- Cryptococcus
- Toxoplasmosis
- *Heart Tx
- Strongyloides

Phase 3: Community & opportunistic >6 months
- Organ dysfunction, Chronic IS
- CA pneumonia
- Vaccine preventable diseases
- JC (PML)
- EBV (PTLD)
- Late CMV, HSV, VZV
- HPV
- Resp viruses
- Aspergillus and atypical moulds, cryptococcus
HAEMATOPOIETIC STEM CELL TRANSPLANTS
Phase 1: Pre-engraftment
2-6 weeks
Neutropenia
Mucositis

Phase 2: Post-engraftment
To D +100
aGVHD, impaired
cell & humoral immunity

Phase 3: Late phase
>D100
cGVHD
Impaired cell and
humoral immunity

Community Respiratory Viruses
HSV
CMV
BK
VZV
EBV
HHV6

Strep, Staph, GNR
Encapsulated bacteria
PJP
Candidiasis
Aspergillus/moulds
Prevention of transplant infections

- **Primary prevention: prevent exposure**
  - Infection control, donor screening, vaccination

- **Secondary prevention: prevent disease**
  - **Prophylaxis** (CMV, HSV, VZV, PJP +/- Toxoplasmosis, fungi, TB)
  - Pre-emptive therapy- biomarker guided therapy

- **Tertiary prevention: prevent morbidity & mortality**
  - Reliable diagnostics, early empiric or targeted therapy +/- surgery
FEBRILE NEUTROPENIA

SYNDROME 1

Scenario: Pre-neutrophil engraftment post HSCT
Epidemiology (1)

- 60% of febrile neutropenia episodes = infection (microbiological or clinical)

- Bacteraemia in ~ 20% FN episodes

- Mortality from bacteraemia (*IATG-EORTC)
Empiric antibiotics

- Should include broad-spectrum agent that includes activity against *Pseudomonas aeruginosa*
- B-lactam +/- aminoglycoside +/- vancomycin

*Combination empiric regimens should be guided by*

- Local epidemiology
- Known colonisation with MR gram negative or MRSA
- History of antibiotic exposure(s)
- Clinical severity- severe sepsis, septic shock

When temperatures do not go away...

- Non-bacterial infection (eg fungal, viral)
- Bacterial resistance to first-line therapy
  - MRSA, VRE, Stenotrophomonas, ESBL, MR Pseudomonas, MRAB, CRE
- Slow response to drug in use
  - Neutropenia, burden of infection
- Superinfection
- Inadequate dose, suboptimal PK
- Drug fever
- Cell wall deficient bacteria
  - eg mycoplasma, chlamydia
- Infection at an avascular site/ inadequate source control
  - Abscess or catheter
- Disease-related fever
PROLONGED NEUTROPENIC FEVER (>=96hrs), UNRESPONSIVE TO BROAD SPECTRUM ANTIBIOTICS .......

Investigate for fungal disease, consider empiric antifungal therapy
Invasive Fungal Infection

**Yeasts**
- *Candida* sp
- *Cryptococcus* sp
- *Malassezia* sp
- *Trichosporon* sp
- *Rhodotorula* sp
- *Saccharomyces* sp

**Moulds**
- *Aspergillus* sp
- *Scedosporium* sp
- *Fusarium* sp
- Dematiaceous (black) moulds
- *Zygomycetes*

**Endemic dimorphic fungi**
- *Histoplasma* sp
- *Coccidioides* sp
- *Paracoccidioides* sp
- *Blastomyces* sp
- Penicillium marneffii

**Budding**

**Branching**

**Both**
Invasive Fungal Infection: HSCT

n=983

- Candida sp: 28%
- Aspergillus sp: 43%
- Zygomycetes: 8%
- Fusariosis: 2%
- Other mould: 12%
- Other yeast: 3%
- Pneumocystis: 3%
- Endemic fungi: 1%

Kontoyiannis et al (“TRANSNET”) CID 2010
OTHER EMERGING MYCOSES
Fusariosis

- Blood, skin (paronychia, cellulitis, sinus), catheters
- L-AMB, Voriconazole, posaconazole, +/- surgery

Mucormycosis

- Risk factors: Diabetes, Iron overload, desferox-iron chelation, voriconazole selection pressure, neutropenia
- LAMB 5-10 mg/kg, oral posaconazole, isavuconazole, surgery

Scedosporium (*apiospermum, prolificans*)

- Voriconazole (*apiospermum*)
- Voriconazole + terbinafine (*prolificans*)

Dematiaceous Moulds (Black Fungi)

- Many isolates resistant to AMB
- L-AMB, voriconazole
PULMONARY INFILTRATES IN THE TRANSPLANT RECIPIENT

SYNDROME 2

Scenario: Abnormalities on chest imaging in a transplant recipient +/- fever or respiratory symptoms or hypoxia
Radiological patterns of disease

- Acute focal or multifocal consolidation
  - Esp bacteria

- Subacute, chronic multifocal consolidation
  - Esp fungi, nocardia, mycobacteria

- Large nodules, subacute onset
  - Esp fungi, nocardia

- Micronodules (< 10mm) in a peribronchovascular distribution
  - Esp viral pneumonitis – eg CMV, other herpes viruses, community respiratory viruses
  - Toxoplasma, pneumocystis
Nodular lesions

- Pulmonary aspergillosis
- Pulmonary cryptococcosis
- Nocardiosis
Interstitial disease

CMV

Parainfluenza type 3 (PIV3)

Pneumocystis jirovecii pneumonia (PJP)
Viral pneumonitis

- **Community Respiratory Viruses**
  - RSV, parainfluenza (1-4), influenza A/B, hMPV & ....
    - adenovirus, bocavirus, rhinovirus, coronaviruses

- **Human herpes viruses**
  - CMV, HSV, VZV, EBV, HHV6
Viral pneumonitis

- Community Respiratory Viruses
  - RSV, parainfluenza (1-4), influenza A/B, hMPV & ...... adenovirus, bocavirus, rhinovirus, coronaviruses

  **Nose/throat swabs** - multiplex PCR, DFA or culture
  **BAL** - multiplex PCR, culture, cytology

- Human herpes viruses
  - CMV, HSV, VZV, EBV, HHV6
Viral pneumonitis

- Community Respiratory Viruses
  - RSV, parainfluenza (1-4), influenza A/B, hMPV & ...... adenovirus, bocavirus, rhinovirus, coronaviruses

  **Nose/throat swabs** - multiplex PCR, DFA or culture
  **BAL** - multiplex PCR, culture, cytology

- Human herpes viruses
  - CMV, HSV, VZV, EBV, HHV6

  **Blood** - QPCR (CMV, EBV)
  **BAL** - PCR, +/-culture, cytology
Pneumocystis jirovecii pneumonia

Risk factors

- Esp first 6 months post Tx
- Level of immunosuppression
  - $\geq 20\text{mg}$ prednisone for $> 3$ weeks
- Impaired Cell Mediated Immunity
  - fludarabine, ATG, Campath, TNF$\alpha$ blockers
- No prophylaxis
  - off bactrim
- Less effective prophylaxis
  - Eg pentamidine, atovaquone, dapsone
- Diseases cluster (person-person spread, institutional outbreaks)
ENCEPHALITIS

SYNDROME 3

Scenario: Decreased or altered level of consciousness
OR lethargy OR personality change ≥ 24hrs
+/- fevers, seizures, localizing neurological signs
HHV6 in HSCT

Post transplant acute limbic encephalitis (PALE)

- Viraemia
  - In 50% 2-4 weeks post transplant

- Acute Limbic Encephalitis
  - Median onset 62 days post HSCT
  - Anterograde memory loss, seizures, confusion
  - MRI: hyperintensities of hippocampus & amygdala

- Other—pneumonitis, hepatitis

1. Ogata et al J Infect Dis 2006  
2. Seeley et al Neurology 2007  
3. Mata et al Bone Marrow Transplant 2008  
4. Schmidt-Hieber Haematologica 2011
HHV6
Diagnosis & management

Diagnosis
- Quantitative PCR for HHV6 (plasma, blood, serum)
- Clinical + MRI imaging + CSF PCR
- Antigen detection in tissue

Therapeutic options for HHV6 disease
- Ganciclovir or foscarnet (cidofovir is second line)
- Theoretical advantage of foscarnet
  - Improve activity against HHV6 in vitro
  - Less marrow toxicity
Post transplant lymphoproliferative disease
PTLD

- Uncontrolled proliferation/expansion of EBV-infected B cells (donor or recipient origin) in the absence of an effective EBV-specific cytotoxic T cell response

- Cause of lymphoid malignancies incl multifocal CNS

- Incidence
  - Intestinal transplant (11-33%)
  - Lung (7%)
  - HSCT (~1%)

  - ~80% occurring within 1 yr of Tx
EBV
Post Transplant Lymphoproliferative Disease

- Presentation
  - Headache
  - Seizures
  - Focal neurology

- Risk factors
  - T cell depleted graft
  - HLA mismatch
  - ATG or Alemtuzumab
    - Splenectomy
    - Primary EBV infection (D+/R-)

Biopsy - Day+130 post BMT
Diffuse Large B Cell Lymphoma

EBV QPCR - $10^4$-$10^5$ copies/ml
Polyomaviruses

Disease spectrum

- **BK virus**
  - Polyomavirus-associated nephropathy (Renal Tx)
  - Haemorrhagic cystitis (HSCT)
  - Disseminated endothelial injury
  - Neuroblastoma

- **JC virus**
  - Haemorrhagic cystitis (BK coinfection)
  - Progressive multifocal leukoencephalopathy (PML)
  - Medulloblastoma

- **SV40**
  - Ependymomas, Choroid plexus tumours
  - Mesothelioma, Osteosarcoma, NHL?

Petrogiannis-Paliotis NEJM 2001
Polyomaviruses

Disease spectrum

- **BK virus**
  - Polyomavirus-associated nephropathy (Renal Tx)
  - Haemorrhagic cystitis (HSCT)
  - Disseminated endothelial injury
  - Neuroblastoma

- **JC virus**
  - Haemorrhagic cystitis (BK coinfection)
  - **Progressive multifocal leukoencephalopathy (PML)**
  - Medulloblastoma

- **SV40**
  - Ependymomas, Choroid plexus tumours
  - Mesothelioma, Osteosarcoma, NHL?
Progressive multifocal leukoencephalopathy
PML

- HIV, transplantation, malignancies & monoclonal therapies (natalizumab, rituximab)

- Rapidly progressive focal neurology
  - Ataxia, visual fields, paraesthesia, paresis, cognitive decline

- MRI
  - Asymmetric demyelination typical
  - No contrast enhancement

- CSF
  - PCR JCV

- Brain Biopsy
  - Viral inclusions in oligodendrocytes
  - Immunoperoxidase +ve
  - EM+ve

Bag AK et al Am J Neuroradiol 2010;31:1564
Toxoplasmosis Encephalitis

- In allogeneic HSCT
  - Asymptomatic reactivation in ~16%
  - Disease in 2-6%
- In heart/ heart-lung (D+/R-)
  - Donor-acquired infection
- Median time to onset ~60 days post-transplant
- Single or multiple ring enhancing abscesses
- +/-Disseminated disease- pneumonitis, hepatitis, myocarditis
- Co-trimoxazole for prevention

Summary

- **Risk assessment**
  - Type of transplant, donor characteristics, immune deficits, immunosuppression, exposures, time from transplantation

- **Modify risk**
  - Prevention: immunisation, prophylaxis, preemptive therapy, empiric therapy and targeted therapy

- **Syndromic approach**
  - Broad differential diagnosis in setting of immunosuppression
  - Empiric therapy against likely pathogens pending results of definitive diagnostics tests
  - Keep an open mind...