Transplantation, Immunosuppression and Infection

Martin Iversen MD, DMSc
Medical Director Danish National Lung Transplant Programme
Rigshospitalet
Solid Organ Transplantation patients is the largest group of patients with life-long immunosuppression

Immunosuppression is empirical and the degree of immunosuppression cannot be measured directly

Treatment effect (suppression of organ rejection) is always balanced against infection
Long term problems in SOT

Chronic rejection

Infections

Toxicity

PTLD
Figure 4: Cumulative graft failure yearly attrition rates of all transplant types for liver, lung, heart and intestine. Attrition for 0-1 year post-transplant shown in yellow, 1-3 year post-transplant in red, 3-5 year post-transplant in green and 5-10 year post-transplant in purple.
44 year old Dltx female with NSIP. One episode with severe drop in lung function caused by acute cellular rejection. After treatment, regained lung function. Still alive after 4,7 years.
53 year old Dltx woman with Alpha-1-antitrypsin deficiency. Died after 8 years because of BOS

FEV1
21 year old Dltx male with CF. Severe acute onset of BOS after 27 months. No AMR or cellular rejection. Azithromycin non-responder. Died after 33 months.
A typical example of Immunosuppression

One Calcineurin inhibitor leading to suppression of T-cells

One anti-metabolite leading to general suppression of cell replication and activity

Prednisolone in low doses
Increasing degree of Immunosuppression

- Liver transplantation
- Kidney transplantation
- Heart transplantation
- Lung transplantation
Consequences of Immunosuppression

Increased susceptibility to common and opportunistic Infections

Post Transplant Lympho-proliferative Disorders (PTLD)

Toxic effects of treatment
How to titrate Immunosuppression

In the last 20 years doses of immunosuppressive drugs have been reduced by approximately 50%

Was this change in practice evidence-based?
General principles in immunosuppression

Immunosuppression alters the patients response to acute disease

Patients have a suppressed reaction to infection and do not appear as ill as they are
Duration of drug effect

Conventional drugs (steroids, antimetabolites, and CNI’s) have short term effect (days to weeks)

Biological drugs (ATG, rituximab, alemtuzumab) have long term effects (months to years)
Monitoring immunosuppression

Measure concentrations of drugs

Evaluate indirectly by rejection and infection
The current practice in SOT

If the patient has repeated rejections immunosuppression is too low

If the patient has repeated infections or opportunistic infections immunosuppression is too high
Opportunistic infections in SOT

Viral infections; EBV, CMV

Fungal infections; Aspergillus sp. And others

Infections with low virulence bacteria
Fungal invasive infection in solid organ transplantation (increasing order)

Kidney transplantation: 0.5%

Liver transplantation: 2%

Heart transplantation: 3%

Lung transplantation: 8%

Lung transplantation non invasive: 30-40%
Kidney transplant recipients
(Risk factors for invasive aspergillosis)

Graft failure with hemodialysis

High and prolonged use of steroids

Heart transplant recipients
(Risk factors for invasive aspergillosis)

Pretransplant *Aspergillus* in respiratory tract

Reoperation

CMV disease

Posttransplant renal failure with dialysis

Liver transplant recipients (Risk factors for invasive aspergillosis)

Retransplantation

Renal failure

Transplantation for fulminant hepatic failure

Reoperation

Lung transplant recipients
(Risk factors for invasive aspergillosis)

Single lung transplant
Early airway ischemia
Repeated rejections
Posttransplant *Aspergillus* colonization
Pretransplant *Aspergillus* colonization
Early posttransplant *Aspergillus* colonization
Acquired hypohammaglobulinemia

Aspergillus fumigatus in lung: Disease categories

Colonization
Allergic asthma
Allergic broncho-pulmonary aspergillosis (ABPA)
Chronic necrotizing aspergillosis
Toxic pneumonitis
Aspergilloma
Invasive aspergillosis
Aspergillosis: Bronchitis in anastomosis
Chronic necrotising aspergillosis
Aspergillus: Case 1

Woman, 60 year old, single lung transplantation 18 months earlier

Presenting with a small lesion apically in Native lung
Aspergillus: Case 1
Aspergillus: Case 1
Aspergillus: Case 1
Aspergillus: Case 1

Bronchoscopy with BAL and brushings in Left upper lobe

Cultures with few *Aspergillus* colonies

Brushings with necrotic cells

BAL with neutrophilia
Aspergillus: Case 2

Man, 33 years old, cystic fibrosis

Double lung transplant with good result

After two weeks enteral failure with dependence on intravenous nutrition
Aspergillus: Case 2
Aspergillus: Case 2
Aspergillus: Case 2
PTLD: A Danish Scandiatransplant study

In 4295 Danish solid organ transplant patients 93 PTLD cases were identified from 1995-2013

Male gender and certain HLA types were risk factors

60/77 were EBV positive

Median time to PTLD 2.2 years in EBV pos and 7.2 years in EBV neg

Vase et al. Association of HLA and risk of PTLD in a Danish population-based cohort (in press)
CMV infection in transplantation
Spectrum of disease

Febrile systemic disease with leucopenia and anemia, Mononucleosis type

Pneumonitis

Myocarditis

Gastrointestinal tract disease, hepatitis

Contrary to AIDS retinitis and CNS disease are very rare
Acute CMV infection in transplantation

Leads to decreased cell mediated immunity increasing the risk of bacterial or fungal infection

Increases the expression of MHC class I and II antigens on endothelial cells increasing the risk of acute rejection
CMV infection in transplantation

Reactivation or primary infection

Depends strongly of donor/recipient serostatus

Depends on type of transplantation

Transplanted organ is most susceptible

Occurs when immunosuppression is most intense
<table>
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<tr>
<th>Year of transplantation</th>
<th>2007-2008</th>
<th>2009-2010</th>
<th>2011</th>
<th>Total</th>
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<tbody>
<tr>
<td>Number of transplantations</td>
<td>279</td>
<td>337</td>
<td>193</td>
<td>809</td>
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<tr>
<td>No. males (%)</td>
<td>160 (57%)</td>
<td>204 (61%)</td>
<td>117 (61%)</td>
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<td>Age, median (IQR)</td>
<td>47 (31–57)</td>
<td>48 (35–58)</td>
<td>48 (36–57)</td>
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<td>Transplant type</td>
<td></td>
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<tr>
<td>Heart</td>
<td>25 (9%)</td>
<td>26 (8%)</td>
<td>15 (8%)</td>
<td>66 (8%)</td>
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<tr>
<td>Kidney</td>
<td>123 (44%)</td>
<td>164 (49%)</td>
<td>99 (51%)</td>
<td>386 (48%)</td>
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<tr>
<td>Liver</td>
<td>50 (18%)</td>
<td>60 (18%)</td>
<td>49 (25%)</td>
<td>159 (20%)</td>
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<tr>
<td>Lung</td>
<td>81 (29%)</td>
<td>87 (26%)</td>
<td>30 (16%)</td>
<td>198 (24%)</td>
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<td>Donor / recipient serostatus, No. (%)</td>
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<tr>
<td>D+/R-</td>
<td>45 (16%)</td>
<td>49 (15%)</td>
<td>35 (18%)</td>
<td>129 (16%)</td>
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<tr>
<td>D+/R+</td>
<td>136 (49%)</td>
<td>154 (46%)</td>
<td>87 (45%)</td>
<td>377 (47%)</td>
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<tr>
<td>D-/R+</td>
<td>60 (22%)</td>
<td>79 (23%)</td>
<td>46 (24%)</td>
<td>185 (23%)</td>
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<td>D-/R-</td>
<td>28 (10%)</td>
<td>42 (12%)</td>
<td>25 (13%)</td>
<td>95 (12%)</td>
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<td>9 (3%)</td>
<td>13 (4%)</td>
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</table>

Cunha-Bang et al. Evaluation of a novel program aimed at reducing the risk of severe Viral infection, including CMV, following solid organ transplantation (submitted)
Cunha-Bang et al. Evaluation of a novel program aimed at reducing the risk of severe Viral infection, including CMV, following solid organ transplantation (submitted)
The problem

Immune deficiency does not lead to transplantation
Tolerance

An index of immunodeficiency is probably going to be multidimensional with regard to rejection and infection
What we need in the management of SOT patients

An index to describe the susceptibility to infection

An index to describe the probability of future rejection