Vesalius SCALpel™ : Transplant (see also: VID 125, 606)

Immunology

general
- TNF stimulated by endotoxin
- NK cells large granular lymphocytes, non-A or B
- interferons antiproliferative, block viruses
- chemokines (30 known) = LMW cytokines: recruit immune cells

hypersensitivity
- 4 types of hypersensitivity
  - 1 immediate: IgE (food, hay fever, anaphylaxis)
  - 2 cytotoxic: IgG, IgM + cell-bound antigen (ABO, Rh, Graves, myasthenia)
  - 3 immune complex: IgG, IgM (serum sickness, RA, glomerulonephritis)
  - 4 delayed: previous sensitized T cell (CD4 + helpers) (contact dermatitis)

3 major components:
- 1 antigen presenting cell (APC): dendritic cells, macrophages
  - phagocytizes antigen
  - antigen broken down in lysosomal system
  - peptide fragments presented on cell surface as major histocompaitbility complex (MHC) class II
    - HLA = a major histocompatibility complex (MHC) antigen
  - also secretes Il-1
- 2 humoral: B lymphocytes, antibody mediated
  - B cells mature to plasma cells, present preformed/existing antibodies
  - responsible for early/hypreracute rejection
  - ABO, HLA incompatibility
- 3 cellular: T lymphocytes (thymus), cell mediated
  - T cell + CD3 surface marker/receptor = T cell-receptor (TCR) complex
  - recognizes and binds to antigen (MHC) on antigen presenting cell
  - requires 2nd co-stimulatory signal
  - T cell stimulated to produce cytokine Il-2
  - drives clonal expansion of that T cell subset to recognize that specific antigen
  - Il-2 also stimulates B cell humoral response
  - T-cells direct further immune response, infiltrate graft and destroy target cells
  - primary mediator of transplant rejection
    - TARGET OF MOST IMMUNOSUPRESSION

immune mediators/cytokines
- soluble messengers, communicate between cells, regulate immune responses
- interleukin 1 & 2: primary regulators of initial immune response

Clinical immunosupression

- 1 deplete lymphocyte population/destroy lymphocytes
  - e.g. thymoglobulin, alemtuzumab

2 inhibit/supress lymphocyte activity, prevent stimulation signals
    e.g. tacrolimus, cyclosporine
3 block lymphocyte proliferation
    interfere with nucleic acid synthesis
    block metabolic pathway
    e.g. mycophenalate mofetil

Pre-transplant matching

two major matches: ABO compatibility and HLA antibodies
ABO
    human immune competence based primarily on preformed humoral antibodies
    compatibility necessary for orgs that express ABO antigens (kidney, heart)
    ABO antibodies attack target antigen in endothelium, thrombosis, necrosis,
        hyperacute rejection
acquired antibodies against human leukocyte antigens (HLA system)
    humoral and cell immunity loci on chromosome 6
    elicited by: transfusion, pregnancy, previous transplant
    complement dependent
    cytotoxic to tissues with corresponding surface antigens
    microcytotoxicity test on lymphocytes
        if antibody present lymphocytes die
    flow cytometry for antibodies more sensitive
    if positive, higher rate of early rejection
    circulating preformed antibodies may be neutralized
        remove with plasmapheresis & IgG
hyperacute rejection now rare because of this testing

Rejection

hyperacute
    mediated by pre-formed B-cell antibodies to ABO, HLA 1
    complement activation
    rare now with screening
    positive X-match (PRA panel) absolute contraindication to kidney transplant
    liver relatively resistant v kidney, heart, lung, pancreas
    immediate as soon as flow restored, minutes to hours
        vascular endothelial damage, leakage, thrombosis, organ turns black
    remove organ promptly
acute
    30% of transplants experience acute rejection
    most common 1st 3-6mo
    most clinical immunosupression directed at acute rejection
    cytotoxic T-cell subset
    can begin 1-3w after transplant

- treatment
  - increase dose of immunosupressant that the pt is on
  - steroid pulse is first line (more than 80% will respond)
  - if steroids fail, then antibody treatment, graft biopsy, consider antibody-mediated rejection
  - each episode increases the risk of chronic rejection
  - each treatment and duration increases the risk of infection and malignancy
    - infection
      - 1st month common post op infections
      - after 1mo unusual environmental low pathogenicity organisms
        - reactivation latent (usually viral, CMV most) infections
          - highest risk 6-12w post transplant
          - Rx & prophylactic acyclovir, gancyclovir
          - other viral agents: Ebstein-Barr, human herpes virus 6 (HHV-6), hepatitis A, B, C, HIV
        - other prophylaxis: pneumovax, hep B
          - nystatin for oral/esophageal fungus
    - malignancy
      - most lo grade, skin cancers, viral-associated tumors
        - HPV: cervical cancer
        - hep B/C: hepatocellular
        - HSV-8 (herpes): Kaposi's sarcoma
        - EBV (Ebstein-Barr): post transplant lymphoproliferative disorders (PTLD)
          - mimics mono: fever, night sweat, tonsilar enlargement difficult to diagnose
          - transplanted organ involved only 20%
          - 66% one site, 75% extranodal (kidney, bowel, liver, mediastinum, lung, skin)
          - lymphomas make up 22% of cancers in transplant pts
            - most (90%) B-cell, most 1st & 2nd y
            - 30% regress w treatment, 50% mortality
          - CD20 widely expressed on B lymphocytes
            - Rx: rituximab = anti CD20 antibody
      - Rx: decrease dose of immunosupressive, usual cancer Rx (intensive chemo with CHOP)

- chronic rejection
  - months to years
  - B & T-cell mediated
  - most common cause of graft loss after 1st year
- cardiovascular disease
  - immunosupression drugs exacerbate cardiovascular disease, atherosclerosis
  - frequent cause of death after 1st year (less than graft loss, infection)
  - steroids, cyclosporin

Immunosupression agents

induction: deplete lymphocytes or inhibit IL-2
- antithymocyte globulin (ALG)
  - depletes lymphocytes, mainly T-cells, polyclonal antibody
  - profound and prolonged depletion, well tolerated
  - may be used for steroid resistant acute rejection
- alemtuzamab
  - depletes T-cells, monoclonal antibody (CD52)
  - profound and prolonged depletion, well tolerated
  - may be used for steroid resistant acute rejection
- OKT3
  - monoclonal (mouse) antibody to T/CD3+ immune complex
    - binds CD3, blocks activation of cytotoxic t-cell subset
  - lymphocytes then destroyed like ALG
    - profound immunosupression, similar problems
    - decreases T-cells in 30-60m
  - used for induction (rarely) and acute rejection
  - serum sickness, anaphylaxis, rare (5%) flash pulmonary edema
- Il-2 antibodies block IL-2 receptors
  - specific to activated T-cell subset (major activity)
  - also block subset of B-cells with Il-2 receptors and some APC cells
  - humanized and chimeric antibodies
    - e.g. Daclizimab, Balixamab
    - less immunogenic than ALG and OKT3
    - eliminates allergy and serum sickness, infection, malignancy

Maintenance immunosupression

steroids
- mechanism:
  - steroid enters cell, binds to cytosolic receptors
  - complex migrates into nucleus, retards gene transcription
  - decrease T-cell cytokine production (Il-1,2)
  - decrease number of circulating lymphocytes
- supress chronic and acute inflammation

azothioprine/immuran
- maintenance, was most widely used until cyclosporine and tacrolimus
- precursor of 6MP converted in liver, nucleoside analogue
- incorporated into purine biosynthetic pathway
- blocks DNA/RNA synthesis which decreases lyphocyte proliferation and clonal expansion
- complications due to purine biosynthetic block
  - bone marrow suppression, profound leukopenia, major side effect, dose related
  - pancreatitis

heptotoxicity: small vessel veno-occlusive disease
arthralgia

mycophenolate mofetil/Cellcept/inosine monophosphate dehydrogenase
- safe, easy, has replaced azothioprine
- competitive reversible inhibitor of purine synthesis enzyme necessary for guanosine monophosphate (GMP) prosuction
- lymphocytes are the only cells that require GMP synthesis
- lymphocyte specific, limited toxicity
- inhibits both B and T-cell populations
- few side effects allow higher long-term dosing regimens
- complications: GI intolerance, nausea, vomiting, diarrhea
  marrow supression at hi dose

cyclosporine (CSA)/sandimmune, neoral
- fungal metabolite
- metabolized in liver by cytochrome P-450 system
  caution drug/drug interaction: many drugs impair P-450 metabolism
- binds cyclophilin (CyP, intracellular molecule), complex binds and inhibits calcinurin
  inhibiting calcinurin phosphatase enzyme which inhibits cytokine gene transcription blocking synthesis of Il-1 and 2 which inhibits lymphocyte activity and proliferation
- complications
  nephrotoxicity: limiting side effect, dose related
  hepatotoxicity, occasional severe hypertension, hyperlipidemia
  hyperkalemia, hirsuitism, gingival hyperplasia, breast fibroadenoma, tremor/neurotoxicity (aphonia), diabetes

tacrolimus/FK506
- fungal metabolite
- structurally different from CSA, but similar mechanism of action
  binds to 5FK506 binding protein (FKBP) similar to CyP
  complex inhibits calcinurin, block synth Il-1,2
  inhibits lymphocyte activity and proliferation
- 100X more potent than CSA
- maintenance, refractory rejection, salvage
- complications similar to CSA
  nephrotoxicity: limiting side effect, dose related
  glucose intolerance (more DM than CSA), neurotox, hypomagnesemia, alopecia, (less hyperlipidemia and hypertension)
  no gingival hyperplasia or hirsuitism

sirolimus/rapamycin
- macrolid antibiotic, structurally similar to tacrolimus
  binds FKBP, different mechanism of action than tacrolimus & cyclosporine
  blocks Il-2 signals to nucleus, blocking lymphocyte proliferation
- inhibits growth-factor stimulated lymphocyte proliferation
- effects synergistic with CSA and tacrolimus, can be used in combination
- can be used as single agent for lo risk

side effects:

no nephrotoxicity
increases triglycerides cholesterol and liver enzymes
decreases platelets and WBCs

Drug protocols: 2 components

induction
most regimens include 3 drugs
hi dose steroids, CSA or FK506, azathioprine or mycophenylate, OKT3 or ALG (less common now), lymphocyte depletion or anti-IL-2 antibodies
steroids
maintenance
lo dose steroids; CSA or FK506, azathioprine or mycophenylate
most drugs tapered to lo dose after 6mo to 1y
steroids can often be stopped or only used for rejection episodes

Kidney transplant

transplant increases life expectancy 2X dialysis
diabetics more benefit than non
only 20% 5y survival on dialysis
6 antigen match (0 antigen mismatch) 52% 10y graft survival, no match 37%
living donor 94% 1y v 88% cadaver
continuous pulsatile perfusion preferred preservation method high risk cadaver kidney
early vascular thrombosis renal TP manifested by no urine: reimplant
25% of renal TP reactivate herpes zoster within 6 mo
predictors of long term graft failure: etiology of recipient's renal failure, number of acute rejection episodes, creatinine @ 6mo
BK polyoma virus
90% endemic in donor kidneys, 5% recipient nephropathy, 50% loss of function
two types: BK renopathic, JC leukoencephalopathy
increasing creatinine over weeks, inflammation different from rejection
more common with mycophenalate & tacrolimus, switch to cyclosporine
usually indicative of over-immunosuppression, treat with gradual decrease in immunosuppression
cidofovir a treatment option

Liver transplant

indications: hepatitis C (20%), alcoholic cirrhosis (18%), primary biliary cirrhosis (10%), unspecified/cryptogenic (10%), sclerosing cholangitis (9%), acute hepatic necrosis (6%), hepatocellular carcinoma
end stage liver disease 90% 1y mortality
if alcoholic is abstinent 6mo, good TP candidate
APACHE II best predictor of 1y survival after liver TP
emergency transplant in fulminant liver failure

transplant before irreversible brain damage
sepsis and multiple organ failure contraindications

hepatorenal syndrome: splanchinc vasodilatation, decreased SVR, intense renal arteriolar vasoconstriction (osmolality, lytes mimic hypovolemia)
temporary benefit vasopressin analog (desmopressin/DDAVP) to reverse splanchnic vasodilatation
reversible with liver transplant

hepatocellular cancer in decompensated cirrhotics
3% risk/y of HCC with hepatitis C
contraindications to transplant: >2 tumors, tumor > 5cm, extrahepatic mets
in operative candidates transplant is best chance for long term survival

absolute contraindications: uncorrectable cardiopulmonary disease, irreversible pulmonary hypertension, pressor-dependent hypotension, recent intracranial hemorrhage, HIV/AIDS, uncontrolled sepsis, extrahepatic malignancy, inability to comply with treatment, (age > 60 alone not a contraindication), metastatic colon cancer
pulmonary hypertension hi risk ventilatory failure immediately after reperfusion

eight predictors of liver transplant survival: age of donor and recipient, creatinine, pro time, bili, hx of prior transplant, warm ischemia time (min), cold ischemia time (hrs)
(AST, sex and hepatitis C not predictors)

hepatitis C most common cause of end stage liver disease in US
80% chronic hep C after acute illness
20-30% of all liver transplant pts
universal reinfection of the graft into C+ pts, earlier cirrhosis
C+ donor into C+ recipient same survival as C- donor
CMV exacerbates chance of failure from hepatitis C

hep B transplant rare recurrence of infection, excellent outcome
severe untreated contraindication to liver TP

hepatic artery thrombosis and acute rejection most common causes of early graft loss
4% incidence adults, 6% children: 50% need retransplant
35% incidence acute rejection reactions

pancreatic transplant reverses the early secondary complications of diabetes

Small bowel: large amount of lymphoid tissue
require high dose immunosuppression
high (20%) incidence of lymphoma, fatal CMV infection