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 histocompatibility 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/hyperacute 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
II-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/suppress lymphocyte activity, prevent stimulation signals
e.g. tacrolimus, cyclosporine
3 block lymphocyte proliferation
   interfere with nucleic acid synthesis
   block metabolic pathway
   e.g. mycophenolate 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 immunosuppression directed at acute rejection
   cytotoxic T-cell subset
   can begin 1-3w after transplant
treatment
increase dose of immunosuppressant 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 immunosuppressive, 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
immunosuppression drugs exacerbate cardiovascular disease, atherosclerosis
frequent cause of death after 1st year (less than graft loss, infection)
steroids, cyclosporin
**Immunosuppression 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

alemtuzumab
- 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 immunosuppression, 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. Daclizumab, Balixamab
- less immunogenic than ALG and OKT3
- eliminates allergy and serum sickness, infection, malignancy

**Maintenance immunosuppression**

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
- suppress chronic and acute inflammation

azathioprine/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 lymphocyte 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 II-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 II-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 II-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 mycophenolate, OKT3 or ALG (less common now), lymphocyte depletion or anti-IL-2 antibodies
teroids

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
ey 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%),
unspecific/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: splanchic vasodilatation, decreased SVR, intense renal arteriolar
vasoconstriction (osmolality, lytes mimic hypovolemia)
temporary benefit vasopressin analog (desmopressin/DDAVP) to reverse splanchic
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