Transplantation, Immunosuppression, Infection

Viruses in May 2010

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OUTLINE

- Transplant infections donor and recipient
  - Types
  - Pathogenesis
- Diagnosis of transplant infections
  - Laboratory diagnosis
  - Utility of diagnosis
- Emerging issues
  - New agents
  - Donor screening

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SOT – Recipients

- ~1800 Australians on wait list
  - 78% NSW/ACT and Victoria/Tasmania
  - Most kidney, liver
- Hospitalisation post transplant
  - Major reason infection
  - Resistant organism colonization
  - Continuing long term immunosuppression

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SOT Infections Occurrence

- Epidemiologic exposure
  - Donor organ
  - Self
  - Hospital environment
  - Community
- Net state of immunosuppression

General Concepts - Recipients

- Increasingly potent immunosuppressive agents reduce rejection
- Increasing patient susceptibility to opportunistic infections and cancer
- Recognition of clinical syndromes (BK nephropathy, Adenovirus, Arenavirus)
- Routine antimicrobial prophylaxis
- Infections due to organisms with antimicrobial resistance

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SOT Recipient Infection Types

- BBV
  - Herpesviruses (CMV, HSV, EBV, HHV6, HHV8)
  - HIV
  - HCV
  - HBV
  - HTLVI, II
  - Parvovirus
  - BK/JC
- STI
  - HPV
- Emerging
  - WNV
  - Lyssavirus
  - Arenavirus
  - Antibiotic resistant
  - Antiviral resistant CMV, HCV

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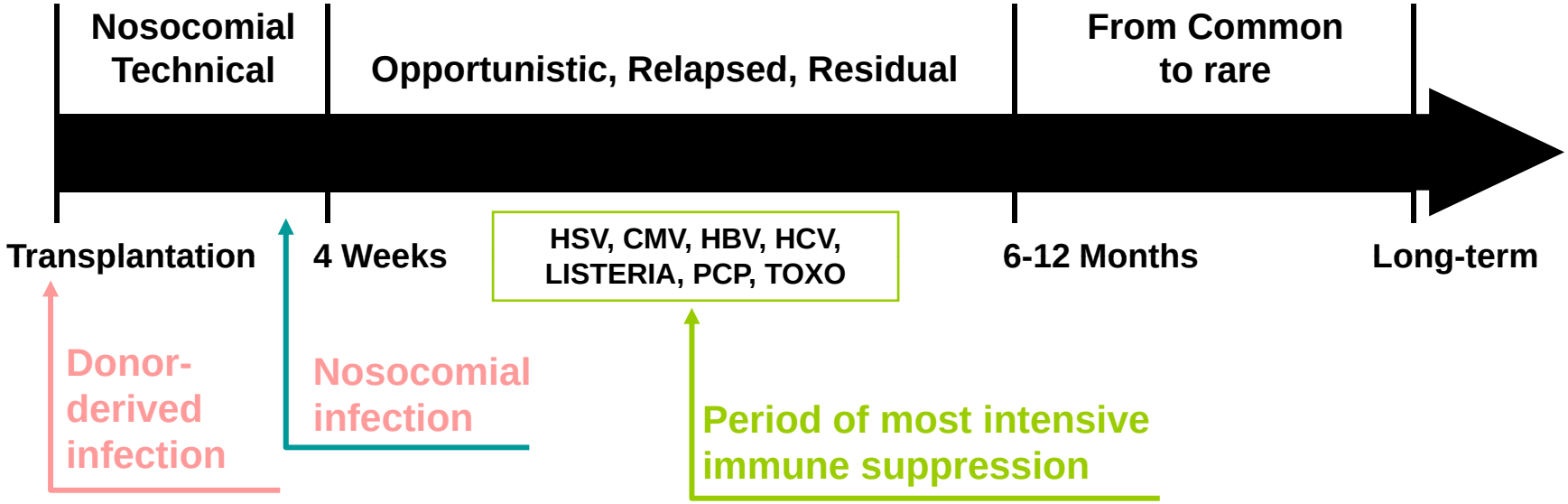
The Timeline of Post-transplant Infections



Common Variables in Immune Suppression

- Rejection, anti rejection therapy, new agents
- Neutropaenia, lymphopaenia
- Viral coinfection (CMV, HCV, EBV)

[Fishman 2005]

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Estimated Number of Persons with Chronic Blood-borne Virus Infections 2000

Region	Population millions	Chronic infections (millions)		
		HIV	HCV	HBV
Africa	749	22.7	22.5	59.3
Asia	3,585	7.3	107.5	286.8
Latin America	504	1.7	15.1	10.3
Europe	729	0.8	21.8	10.9
Oceania	30	0.0	0.9	2.4
North America	305	0.9	9.1	1.9
Total	5,902	33.4	176.9	371.6

[Margolis CDC]

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Main Issues

- High-Risk donors
- Prospective/Retrospective testing
- Ideally universal prospective screening
- False Positives/Negatives

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Transplant costs

- Transplant
  - $65,000-$75,000
  - $11,000 ongoing pa
- Post-transplant infection
  - Additional $5,000-$10,000 pa
  - Graft loss
  - Long-term damage
  - Cumulative (CMV →bacteria)

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"…they belonged, at any rate, to the lowest and smallest but also to the most fruitful beings known…"

J. Henle 1833

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Pathogenesis
Mechanisms of chronic damage

- Up regulation growth factors
- Growth
  - MHC II upregulation
  - MHC II molecules ↑
  - Adhesion molecules ↑
- Chemokines
  - ↑ IL-2 ↑IL-2R
  - ↑ TNF
  - ↑ IL-6
  - ↑ PDGF + ↑ TGF β smooth
  - Muscle proliferation

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CMV Pathogenesis

- Duration of treatment to reduce VL to O depends upon initial VL
- GCV
  - ➢10mg/kg/d IV 92% efficacy
  - ➢1g tds po 47% efficacy

[Emery 1999, 2000]

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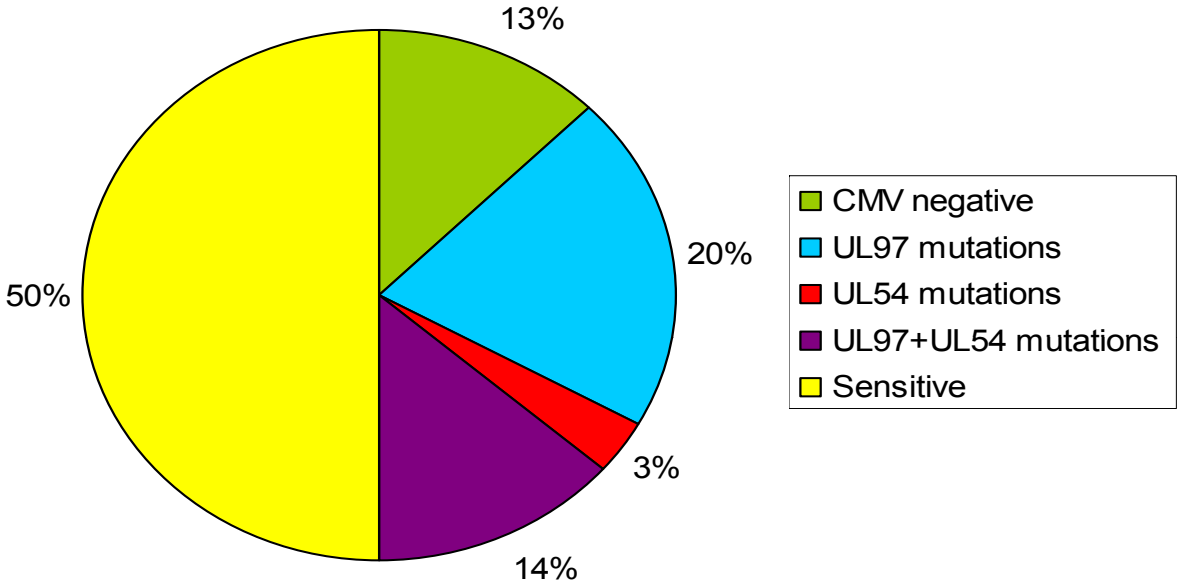
CMV antiviral resistance



- 37% of specimens contain antiviral resistant CMV sequences
- 14% have dual UL97+UL54 mutations
  - Confer multidrug resistance

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Diagnosis

- **Optimal methods vary with population**
- **Serology**
  - ELISA IgG, IgM
  - IgG avidity
- Direct detection
  - direct immunofluorescence
  - NAT
  - Q-NAT
  - Quantitative antigenaemia
  - Viral culture

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HV Infection

- Isolation of the virus from any site or serological evidence
- Primary or Secondary

HV Disease

- Invasive or symptomatic infection with histologic viral cytopathic effect
- Evidence of recent infection + clinical

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Limitations of Serological Tests

- Longer window period than NAT
- Do not distinguish between HCV present or past infection
- HBV escape mutants are not detected
- Occult HCV and HBV infections are not detected

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Summary of BBV testing at SEALS since October 2009

Sample type	No. of donors tested by NAT	No. of organs retrieved
Routine	26	89
Urgent (High-Risk donor)	10	21*
Total	**36**	**110**

*****_Two donors were rejected: one was HBV NAT Positive, and other was deemed not medically suitable_

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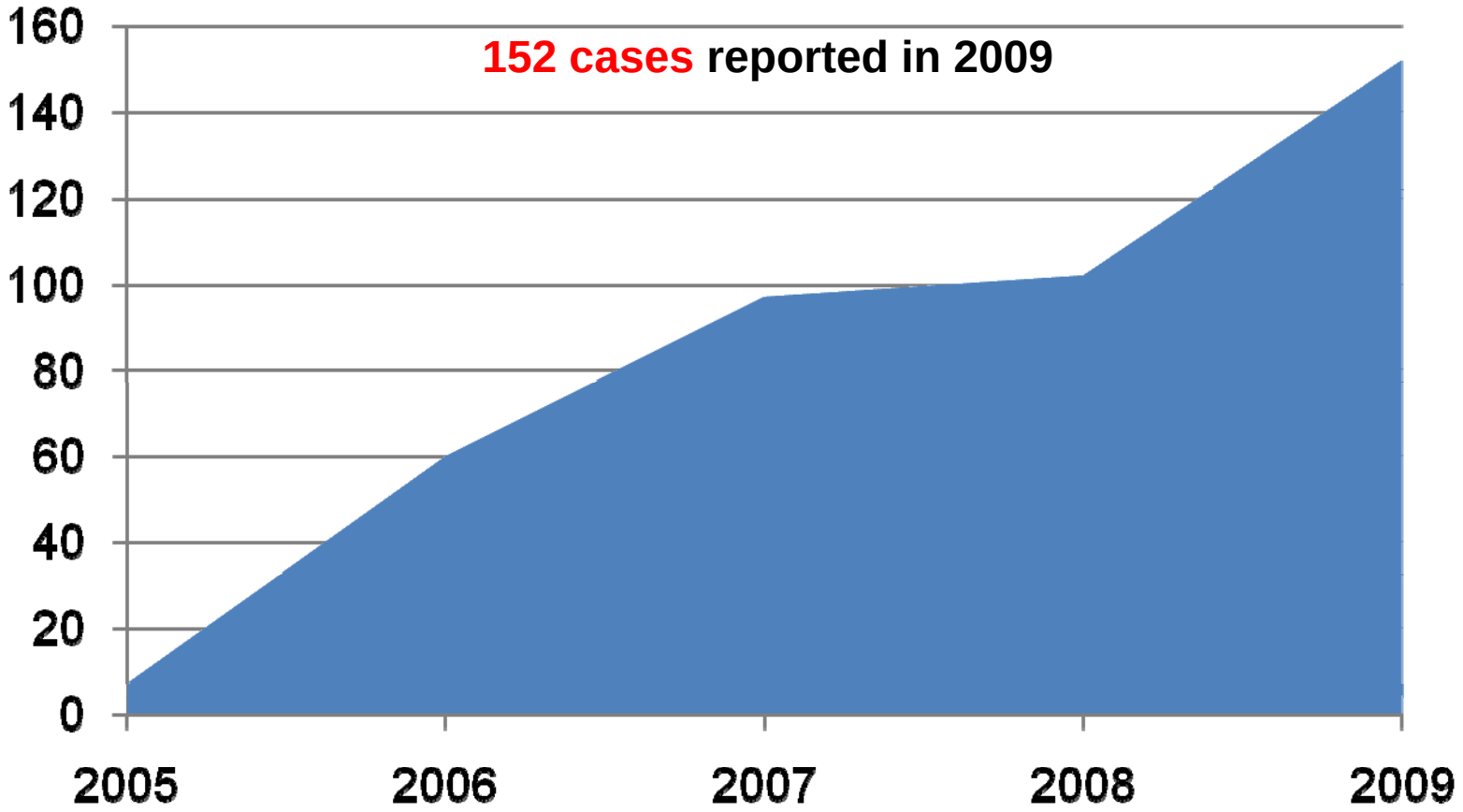
Current DDD Transmission Data



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Ison et *al*. ***Am J Transplant.*** 2009; 9: 1929-1935.

Reports to DTAC: 2006-2009*

Malignancies	# of Donor Reports	# of Recipients w/ Confirmed Tx	# of Attributable Recipient Deaths
Renal Cell Carcinoma	60	6	0
Lung – Adenocarcinoma	9	2	3
Non-Hodgkins Lymphoma	6	4	0
Thyroid Cancer	6	0	0
Prostate Cancer	5	1	0
Melanoma	4	1	1
Glioblastoma Multiforme	3	0	0
Hepatocellular Cancer	3	0	0
Leukemia (AML, CLL)	2	1	0
Ovarian Carcinoma	2	1	0
Breast	2	0	0
Colon Cancer	2	0	0
Neuroendocrine	2	0	0
Pancreatic Adenocarcinoma	2	0	0
Renal Papillary Adenocarcinoma	1	1	1
Liposarcoma	1	1	0
Other	11	0	0
Totals	**121**	**18**	**5**

*Other (Each are single cases with no transmission): Basaloid, Brain – Spindle Cell, Cholangiocarcinoma, Dermatofibrosarcoma Protuberans, GIST, Kaposi's Scarcoma, Lung – Bronchoalverolar, Lung – Small Cell, Lymphoma, Myeloid Sarcoma, Urothelial Cell

Reports to DTAC: 2006-2009*

Virus	# of Donor Reports	# of Recipients w/ Confirmed Tx	# of Attributable Recipient Deaths
HCV∞	26	8	1
HIV†	13	4	2
HBV	15	0	0
West Nile – UPDATE Outcome	12	1	0
Parvovirus	3	1	0
Influenza (2 Pandemic)	3	0	0
HTLV	2	0	1
LCMV	1	2	2
PIV-3	1	0	0
Rabies	1	0	0
Viral Encephalitis	1	0	0
Viral Illness – Unidentified	1	1	0

∞ All but 3 cases non-reproducible NAT results:

- Donor not high risk, Sero -/NAT+ with 3 transmissions
- Donor high risk, Sero -/NAT + with 4 transmissions (HIV/HCV) and 1 death
- Donor HCV + vessel with 1 transmission

†All but 2 cases non-reproducible NAT results:

- 1 Case with 4 transmissions of HCV/HIV and 1 death
- 1 patient with HIV infection post-transplantation

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Reports to DTAC: 2006-2009

Bacteria	# of Donor Reports	# of Recipients w/ Confirmed Tx	# of Attributable Recipient Deaths
Bacteria •*Acinetobacter (2* cases) •Brucella •*Enterococcus* (3 Cases (1 VRE)) •*E. coli* •Gram Positive Bacteria • *Klebsiella* •*Pseudomonas* (4 cases) •*Serratia* •*S. aureus* (2 cases, 1 MRSA) •Streptococcus •*Veillonella* •1 case of bacterial meningitis •1 case of bacterial emboli	25	9	6
Ehrlichia	2	0	0
Legionella	1	0	0
Listeria	1	0	0
Lyme Disease	1	2	0
Nocardia	1	0	0
Syphilis	7	2	0
Rocky Mountain Spotted Fever	1	0	0

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Reports to DTAC: 2006-2009

Other Infections	# of Donor Reports	# of Recipients w/ Confirmed Tx	# of Attributable Recipient Deaths
Mycobacterial Infections			
TB	24	5	1
Mycobacteria avium-complex	1	0	0
Mycobacteria kansasii	1	1	0
Fungal Infections			
Coccidiodomycosis	6	4	4
Histoplasmosis	6	0	0
Zygomycetes	4	2	1
Candida spp	3	2	0
Cryptococcus	3	1	0
Aspergillus	2	2	2
Mycotic Aneurysm	1	0	0
Parasitic Infections			
Chagas	7	4	2
Strongyloides	4	2	1
Schistosomiasis	3	1	0
Babesiosis	2	2	0
Total	**196 + 18§**	**54**	**22**

§Expected Transmissions: 10 Toxoplasmosis, 7, EBV, 4 CMV.
Data 1/1/06 – 10/31/09.

Human Cytomegalovirus

- Morbidity and mortality in immunocompromised
  - HIV-AIDS
  - transplant recipients
  - neonates
- SOT infections

  lung > liver > heart > bowel > kidney
- Allograft injury best evidence linked
  - Heart CAD
  - Lung transplants Bronchiolitis obliterans

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CMV risk factors

- CMV serostatus
  - D+/R-
  - D+/R+
- Patient factors
  - HLA mismatch
  - T cell depletion
  - GVHD
- Coinfection
  - HHV6
  - HHV7
- Therapy
  - High dose steroids
  - OKT3
  - Mycophenolate
  - CNI

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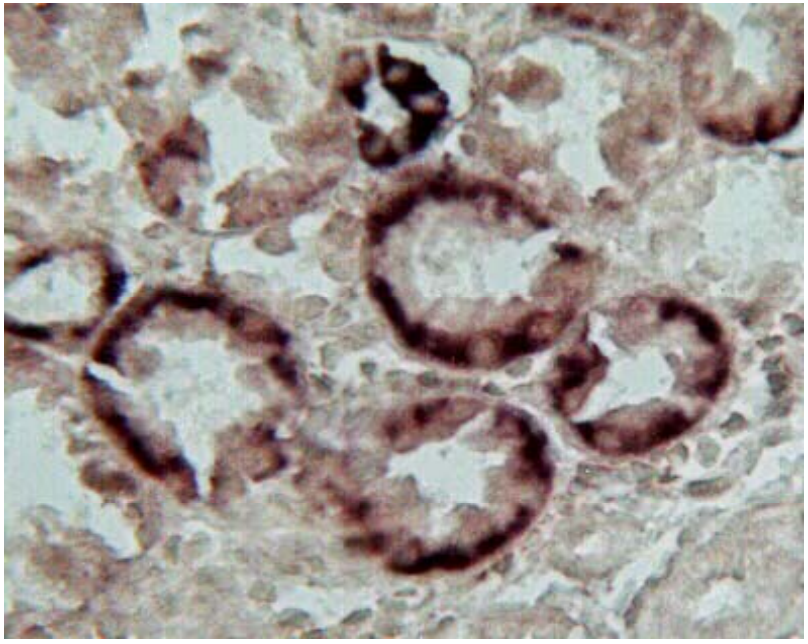
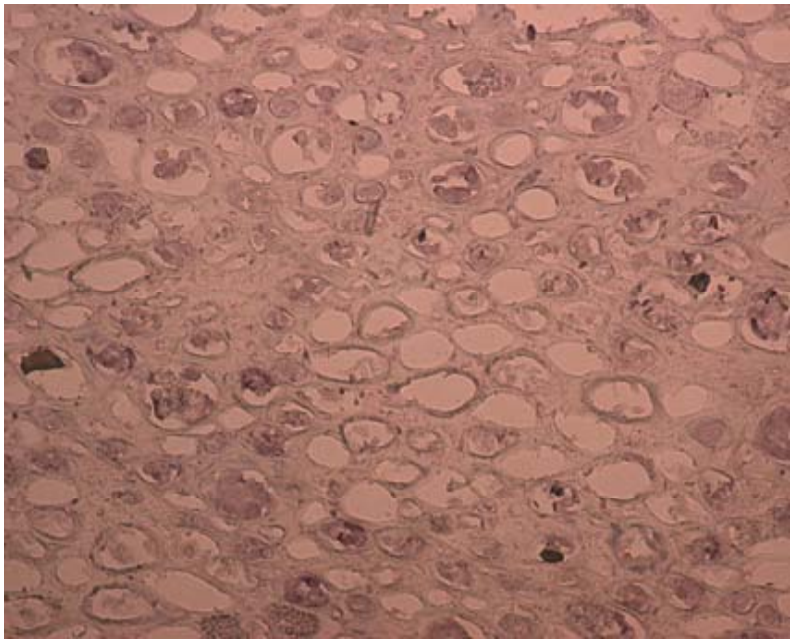
CMV infection of kidney





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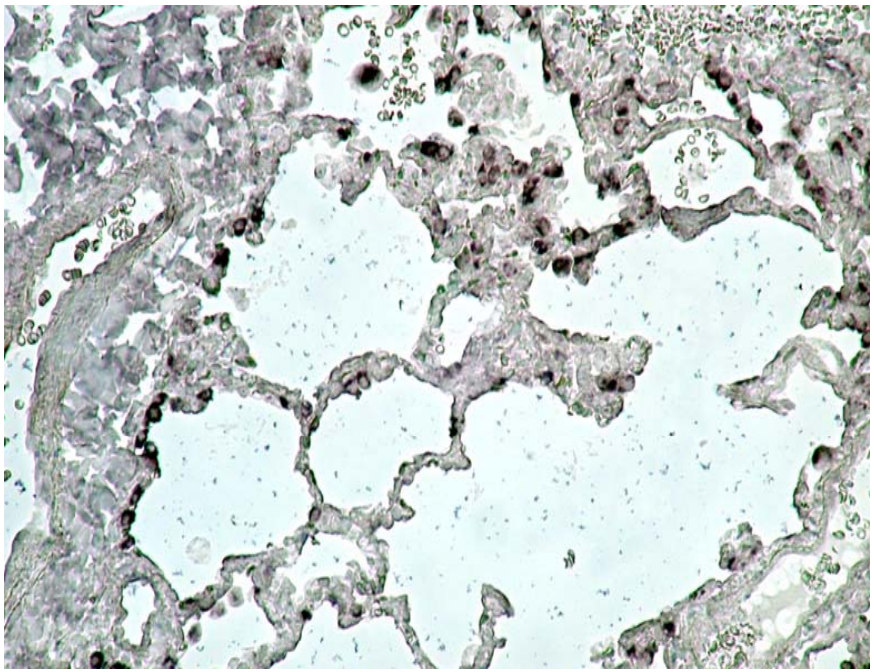
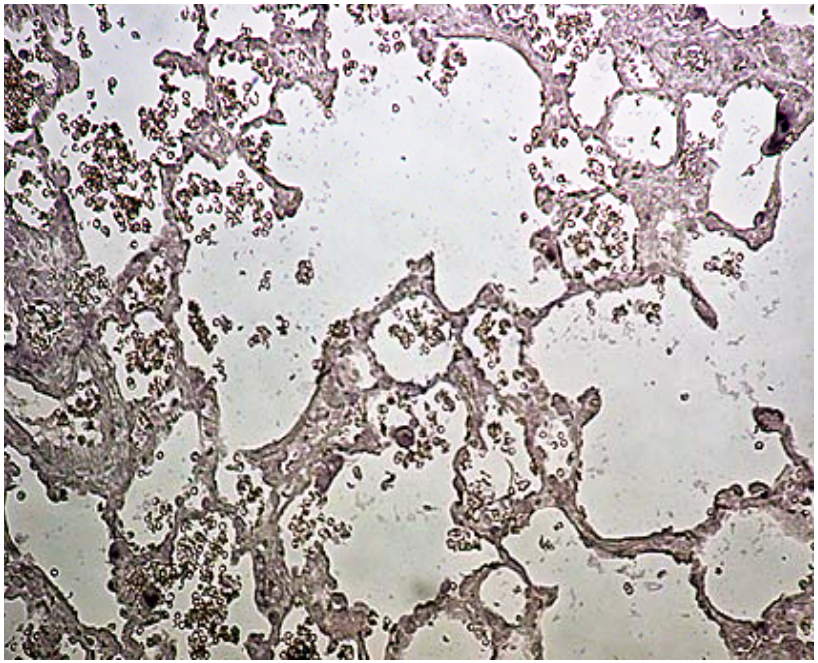
CMV infection of lung





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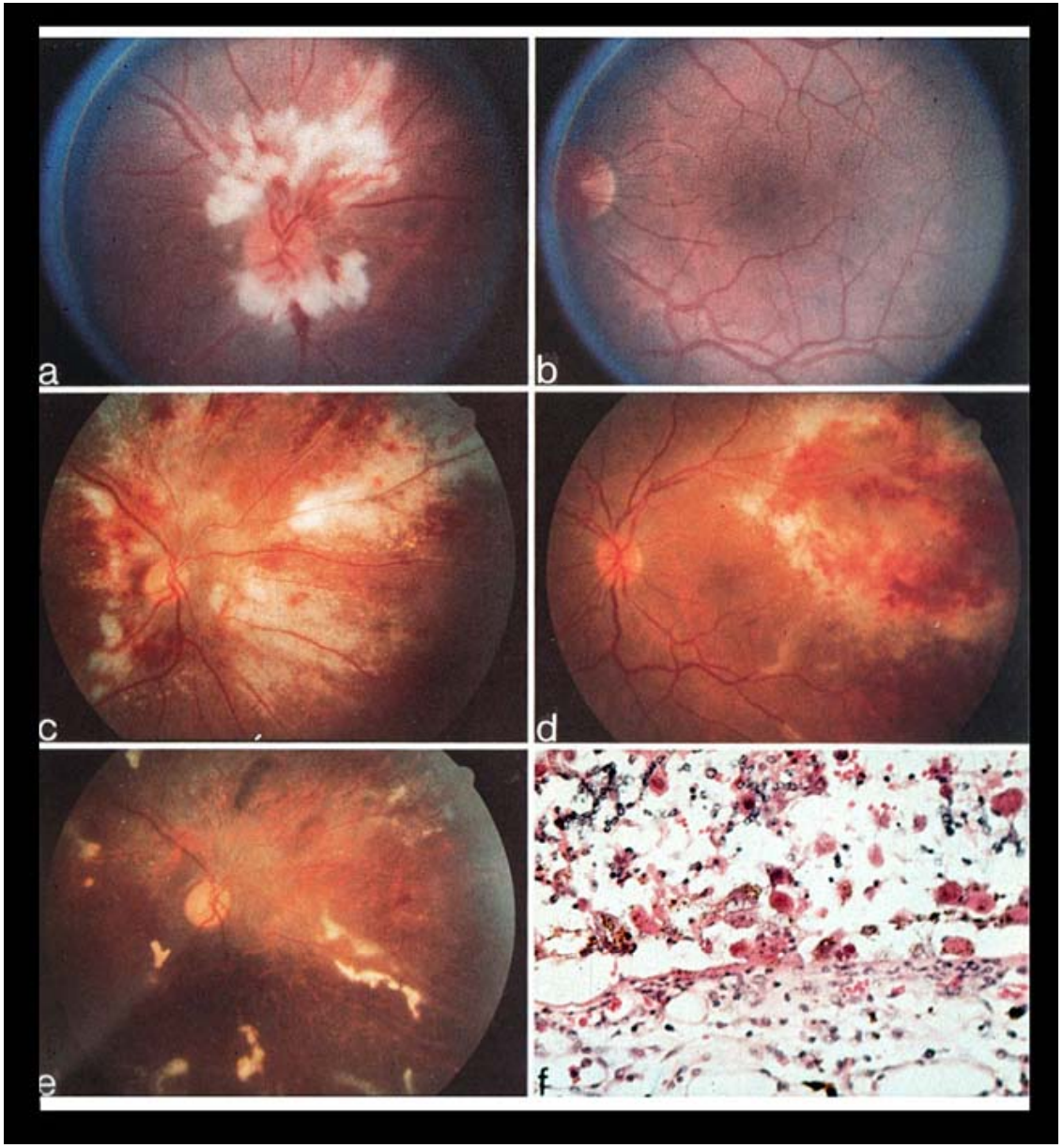

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Quantitation of CMV

- Benefits
  - Surrogate measure of resistance
  - Better correlation with disease
  - Measure of viral load in blood vs other tissue
  - Association with prognosis in some diseases
  - Simplified sample
- Problems
  - Cost
  - Lack of correlation with some disease
  - Lower sensitivity than qualitative
  - Availability
  - Sample size for testing

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QPCR use in transplant recipients

- Initiation of therapy in SCT
  - High risk allogeneic SCT 10,000 c/ml whole blood
  - Pre emptive therapy with GCV 5mg/kg/dy
  - Dose escalation of GCV if no response of VL
- Initiation of therapy in renal transplants
  - Lower risk SOT 30,000 c/ml plasma
- Initiation of therapy in liver transplants
  - Moderate risk SOT 1,000 c/ml plasma, PPV 47%, NPV 83%
  - Moderate risk SOT 5,000 c/5x106 cells, PPV 40%, NPV 90%

[Martin-Davila 2005; Rayes 2005; Verkruyse 2006]

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Emerging issues

- Zoonoses
  - WNV
  - Bat lyssavirus
  - Hendra/Menangle/Nipah
- Long-term immunosuppression + cancer
  - EBV
  - Endogenous retrovirus
  - HHV-8

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New agents

- Imported infections
  - Dengue
  - New variant CJD
- Unexpected infections
  - Arenavirus
  - Seronegative HIV
  - Seronegative HCV
- Respiratory
  - Negative on routine testing
- Gastrointestinal
  - Negative on routine testing

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Proposals

- Develop and institute pre-transplantation testing guidelines similar to those developed for US and expand those being developed for Australia
- Analysis of sensitivity, specificity and cost-effectiveness of different testing algorithms
- Develop and institute cadaver donor screening protocols

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Sources of residual risk

- Infectious, window period donations
  - time between infectivity and detection with screening tests may be different from time of exposure to an agent
- Viral variants
  - strains, subtypes
  - Most not detected by current tests
- Infectious chronic antibody negative carriers
- Errors (testing or product release)

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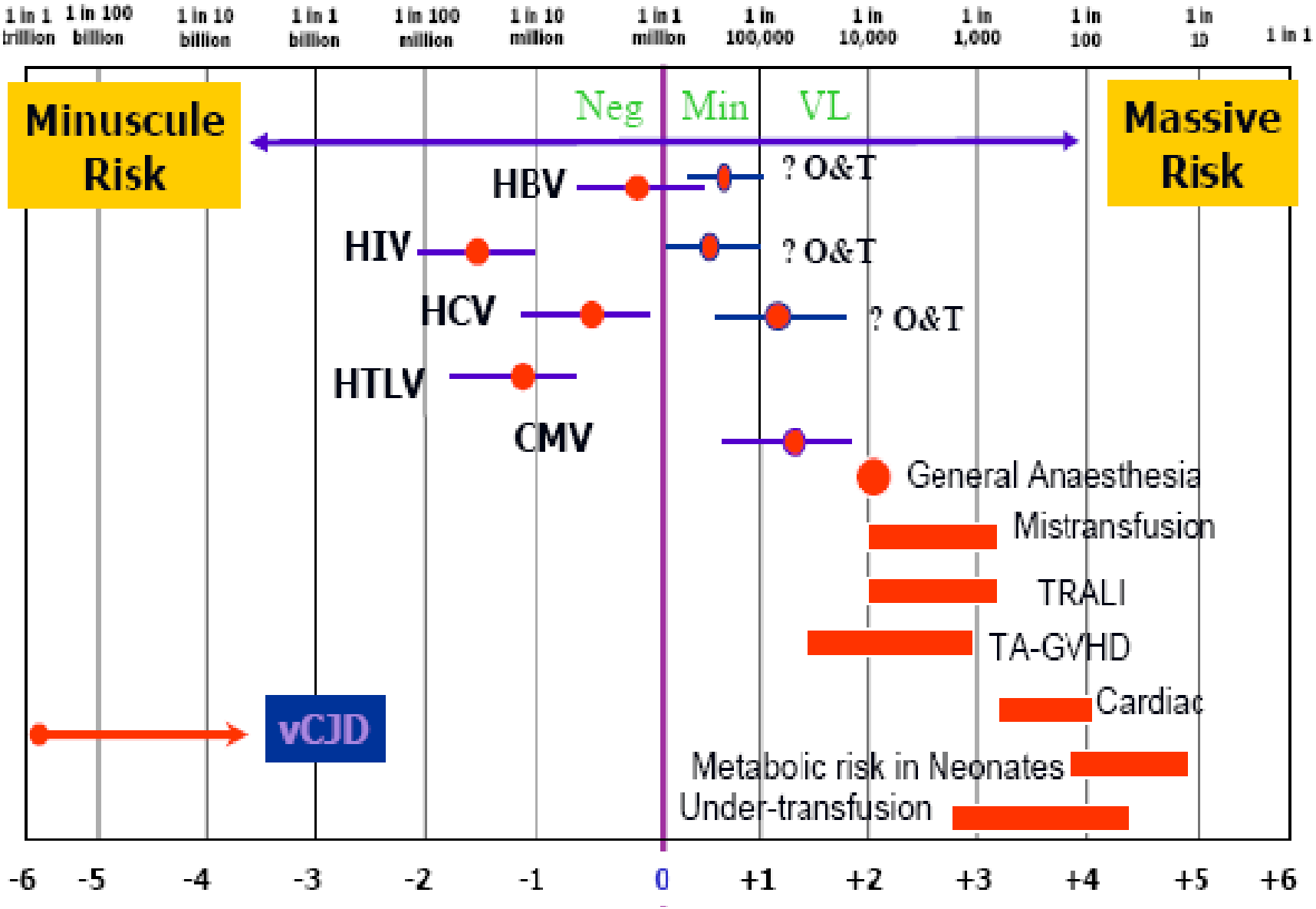
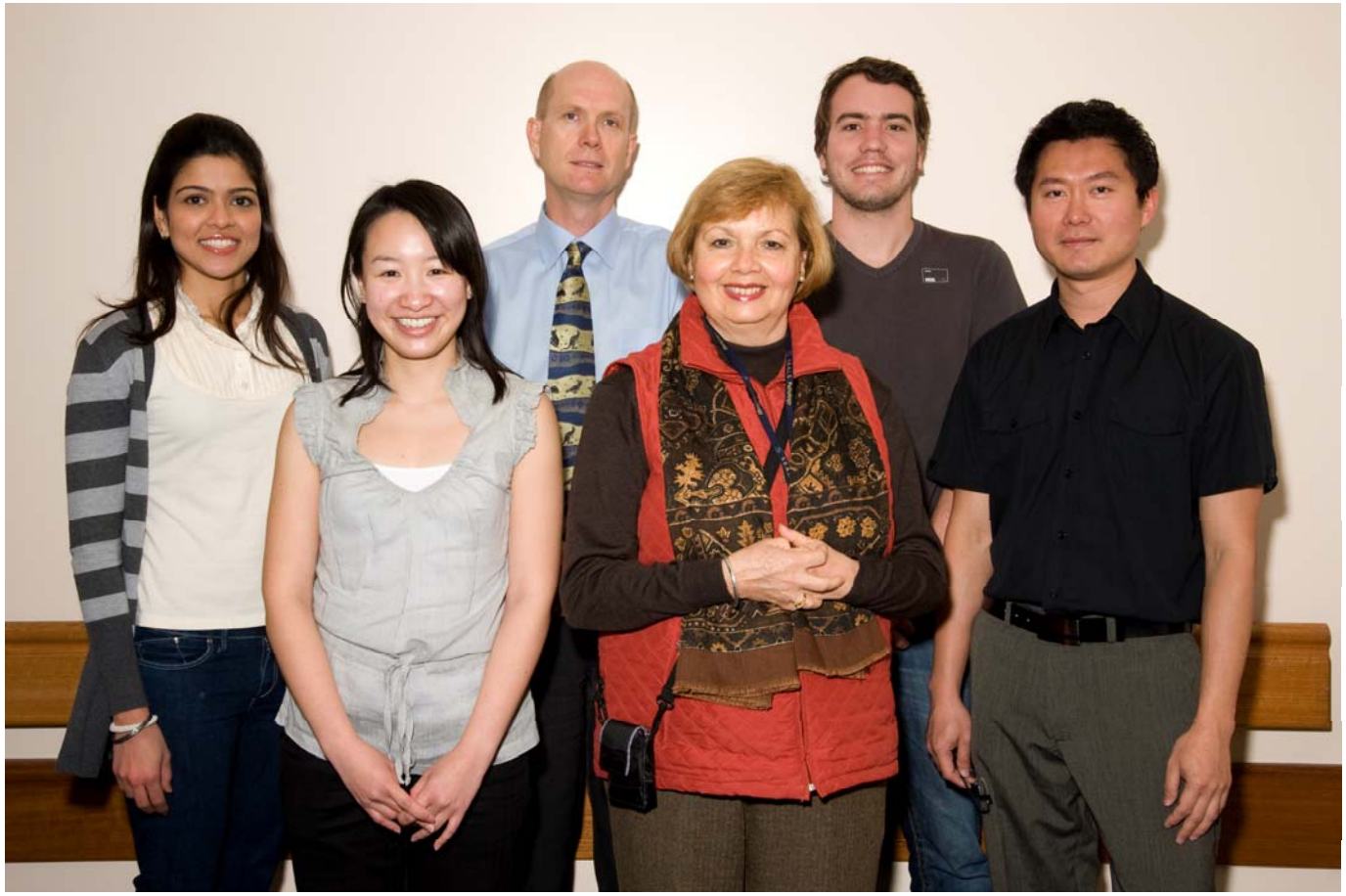
Comparative risk in medical procedures





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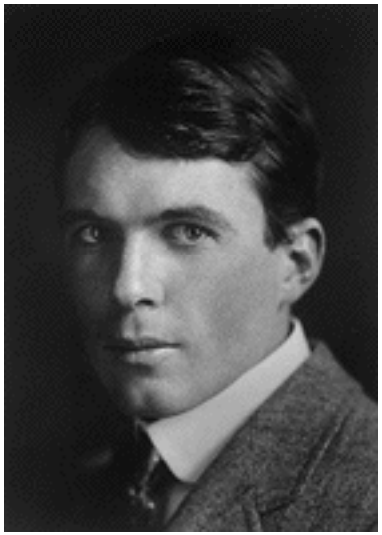

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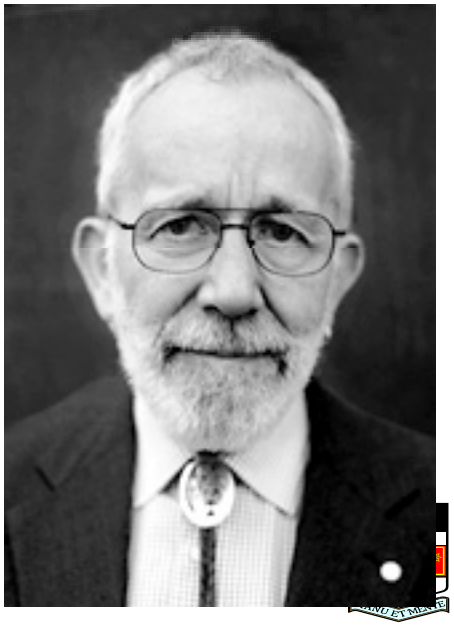

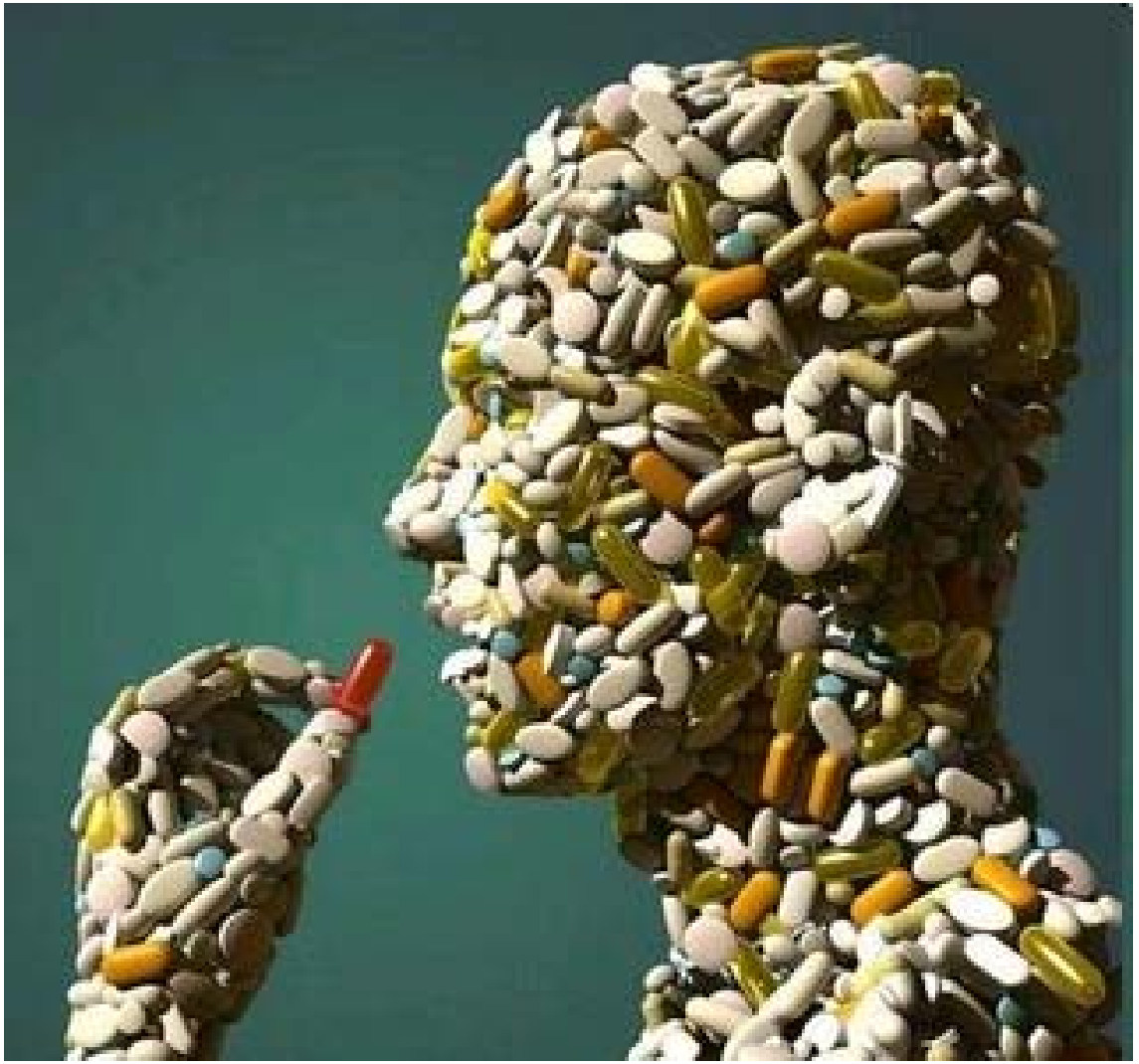

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Therapy

- Antivirals
  - ganciclovir (bone marrow toxicity)
  - foscarnet (renal toxicity)
  - adefovir
  - prophylaxis with ValGCV, ValACV, GCV, ValGCV
- Pre-emptive therapy
- Primary prophylaxis
- No effective vaccine

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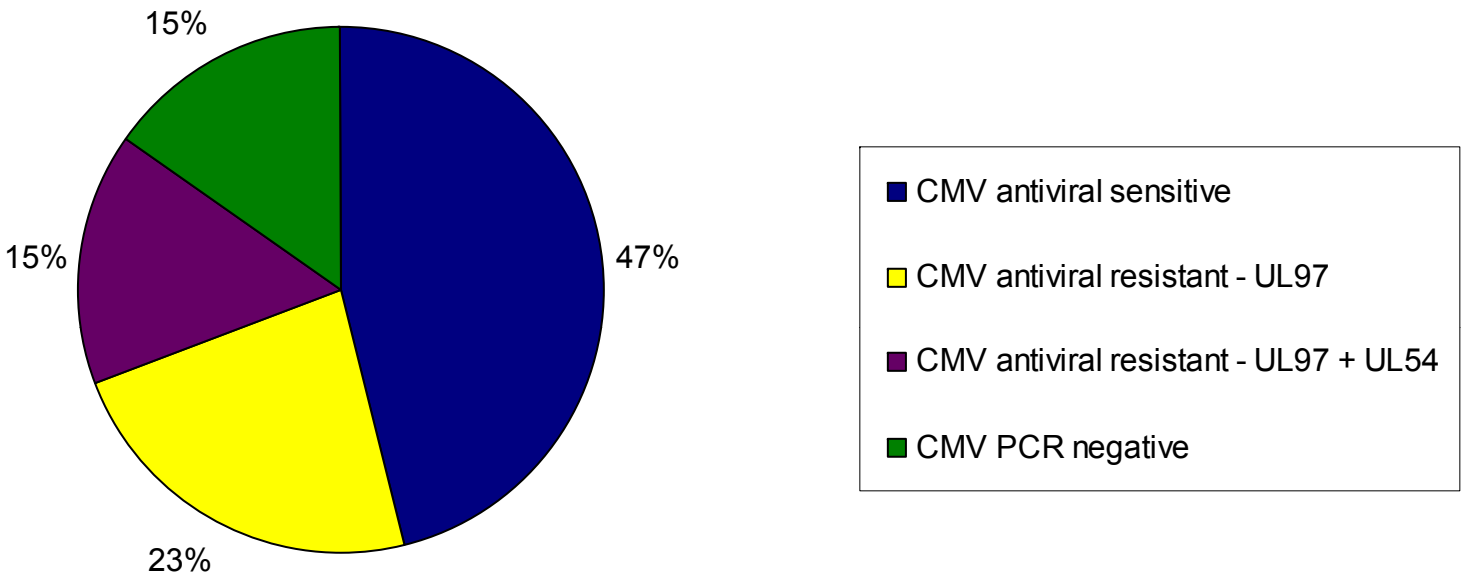
CMV antiviral resistance



- 38% of patients harbour antiviral resistant CMV
- 15% have dual UL97+UL54 mutations

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Antivirals for resistant CMV

- Foscarnet
- Cidofivir
- Combination therapy
  - ➢GCV 0.5 dose + PFA escalating to 125 mg/kg
  - ➢GCV 0.5 dose + PFA 0.5 dose 90 mg/kg
  - ➢GCV 1.0 dose + CMV IVIG
  - ➢?more toxic

[Mylonakis 2002; Mattes 2004]

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Donor-Derived Infections

- Most are latent (CMV, TB, *T. gondii)*
- Rarely can be acute (Bacteremia/viremia at time of procurement i.e. West Nile, rabies, HIV, hepatitis, LCV)
- The majority of these are subclinical in healthy patients, but can be catastrophic when transplanted into an Immunosuppressed patient
- At present, routine evaluations of donors for infectious diseases relies upon serologic antibody testing, and thus sensitivity is not 100% for those that may not have had time to seroconvert

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Donor Screening

- Epidemiologic history
- Serologic testing for VDRL, HIV, CMV, EBV, HSV, VZV, HBV (HBsAg, anti-HBsAg), and HCV
- Microbiologic testing of blood and urine
- Chest radiography
- Known infections (appropriate therapy?)
- Possible infections (e.g., encephalitis, sepsis)
- Special serologic testing, nucleic acid assays, or antigen detection based on epidemiologic factors and recent exposures (e.g., toxoplasma, West Nile virus, HIV, HCV)

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NAT testing

- HCV
  - LOD 15 IU/ml (10 cp/ml)
- HIV-1
  - LOD 68 IU/ml (40 cp/ml)
- HBV
  - LOD 12 IU/ml (5 cp/ml)
- 3 Molecular tests run in parallel
- TAT 6-8 hrs

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HIV markers during early infection