General Overview of FA BMT Process and Risks

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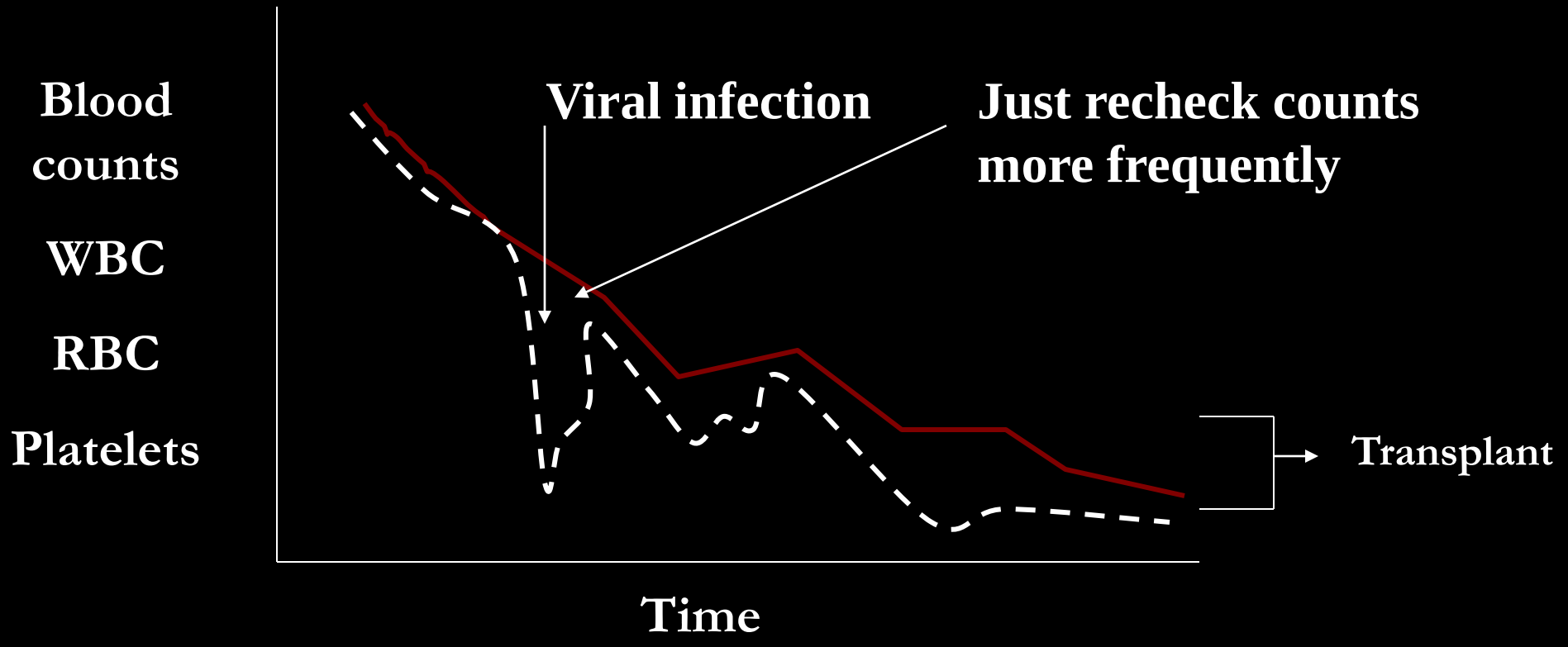
Principal Questions

When to transplant?

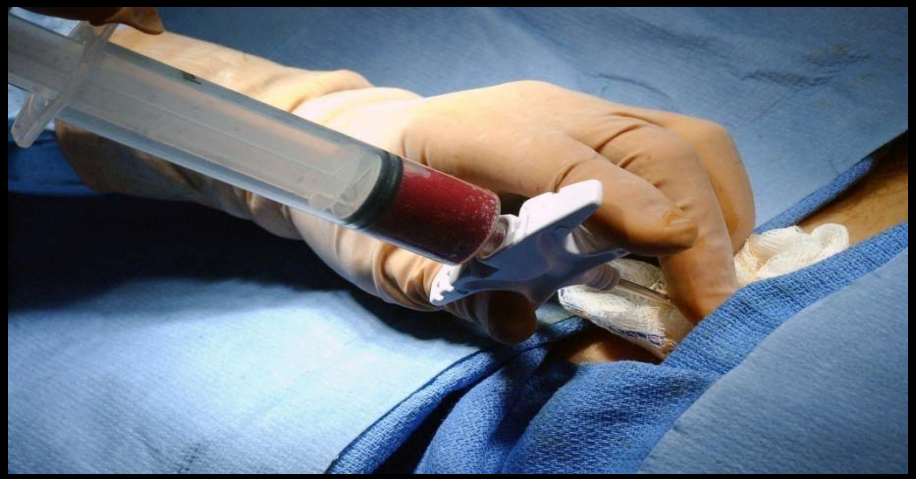
What to expect?

- **short term – first 100 days**
- **long term**

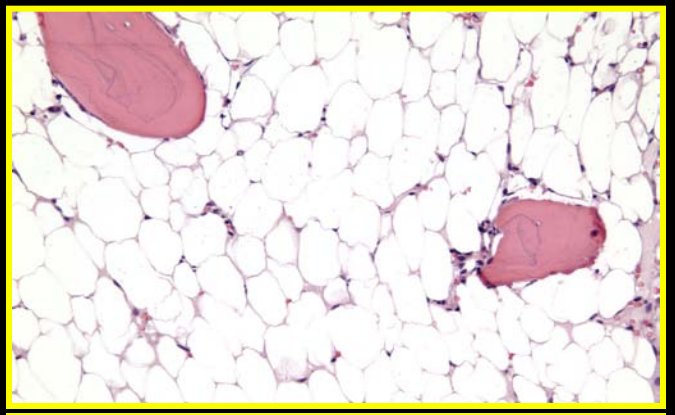
General Pattern of Bone Marrow Failure



Annual marrow testing

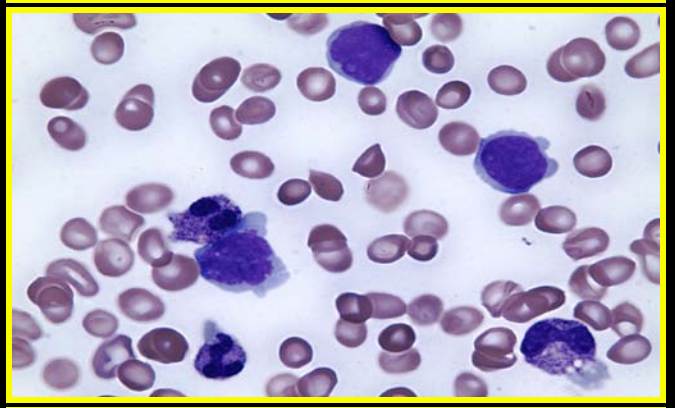


- morphology
- cellularity
- cytogenetics



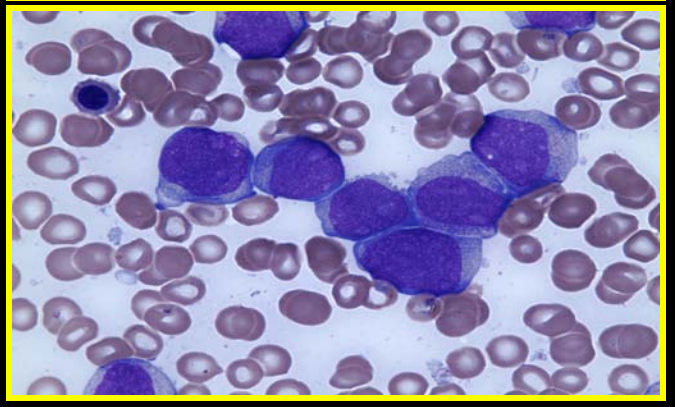
SAA

Aplastic Anemia



MDS

Myelodysplastic syndrome



AML

Acute myeloid leukemia

Best time to transplant

When?

- Before infections
- Before transfusions
- Before MDS/AML

Diagnosis of FA

- q2 month CBC
- annual BM asp + bx
- genotype
- genetic counselor - PGD
- referral to FA center

BM Failure MDS/AML

HGB <9 g/dL
ANC <750/uL
PLT <40,000/uL

HGB <8 g/dL
ANC <500/uL
PLT <20,000/uL

Matched Sibling HCT

Standard Risk Patient

FLU/CY/↓TBI

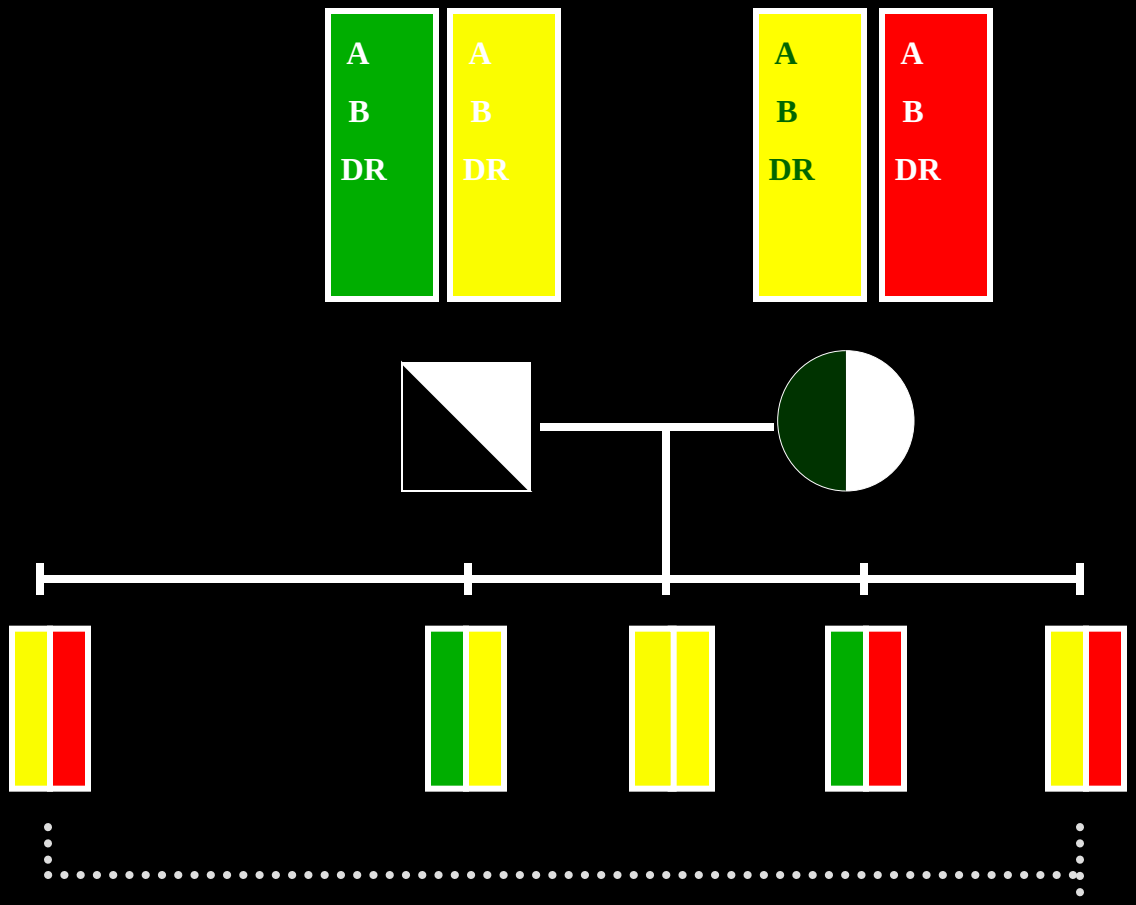
High Risk Patient

Androgen Failure

HCT Principles

- Donor selection
- Preparative therapy
- Engraftment
- Regimen related toxicity
- Acute and chronic GVHD
- Opportunistic infections
- Late Effects
- Survival

HLA Typing



1:4 chance of HLA identity

A 02, 03

B 24, 27

DR 04, 07

A 0201, 0301

B 2402, 2705

DR 0404, 0701

A 0202, 0304

B 2401, 2706

DR 0401, 0701

Estimates

Adult Volunteer Donor Registries

BMT (~14,000,000 donors)

- HLA A (allele level)
- HLA B (allele level)
- HLA C (allele level)
- HLA DR (allele level)
- HLA DQ (not considered)

Chance of finding a donor

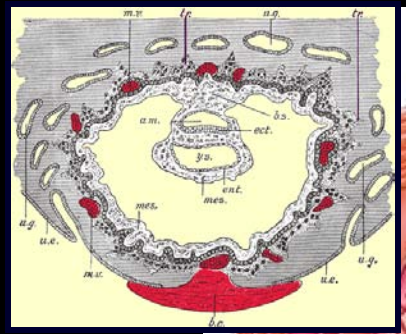
~50% Caucasians
~35% Hispanics
~20% Afr Amer

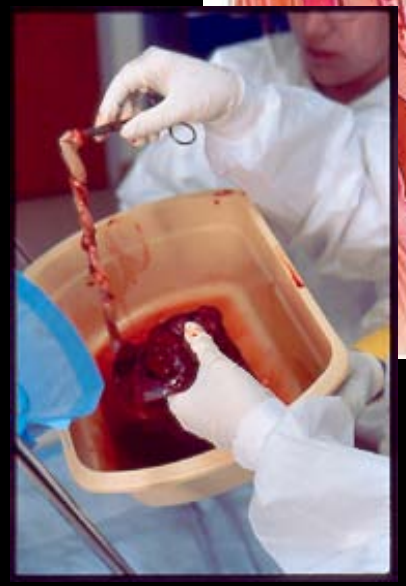
Alternatives
Umbilical Cord Blood

Unique properties of the fetal immune system

- normal proliferative capacity but ↓ cytotoxicity
- highly immunosuppressive
  - T regulatory cells
  - Circulating trophoblasts (IL-10)

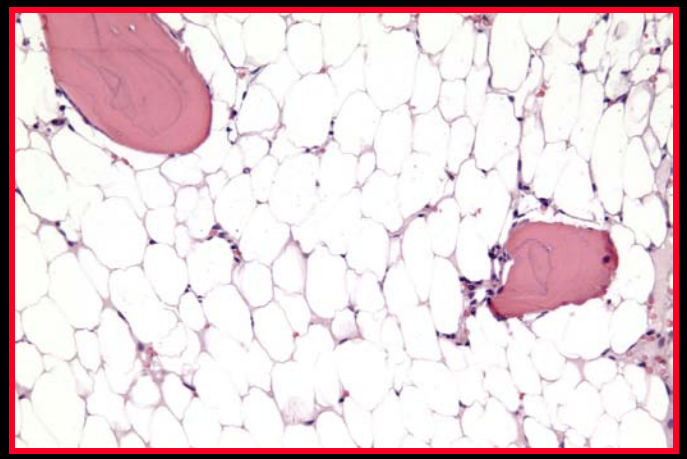
Less HLA restriction
Reduced GVHD





Maternal-Fetal Tolerance
Mechanisms

Hematopoietic Stem Cells



Pluripotent Stem Cell

Self-renewal

Lymphoid Stem Cell

Myeloid Stem Cell

Pre-T cell

Pre-B cell

BFU-E

CFU-E

CFU-Mk

CFU-Mast

CFU-Eos

CFU-GM

CFU-G

CFU-M

CFU-Ost

(?)

T Lymphocyte

B Lymphocyte

Erythrocyte

Megakaryocyte / Platelets

Basophil / Mast cell

Eosinophil

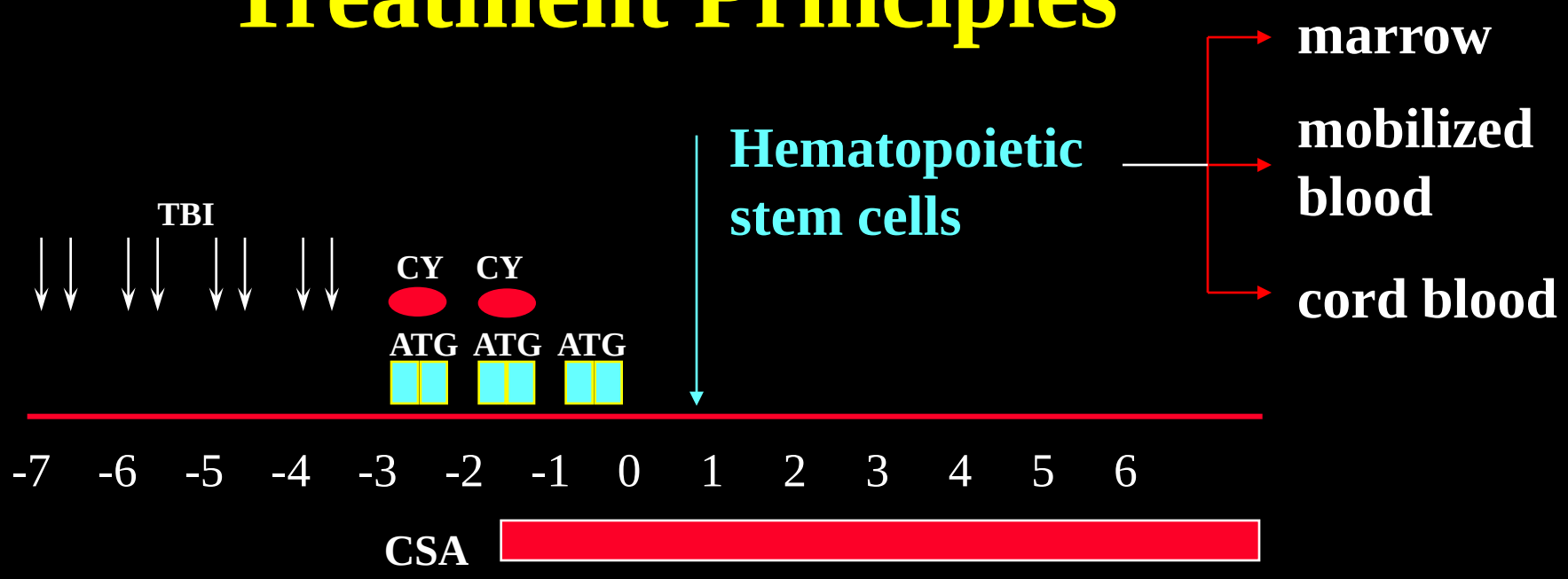
Neutrophil

Monocyte / Macrophage

Osteoclast

Engraftment

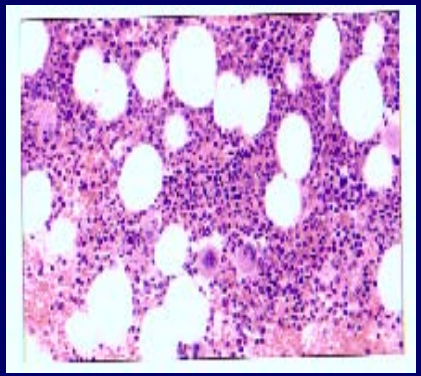
Treatment Principles



Principles

Myeloablation

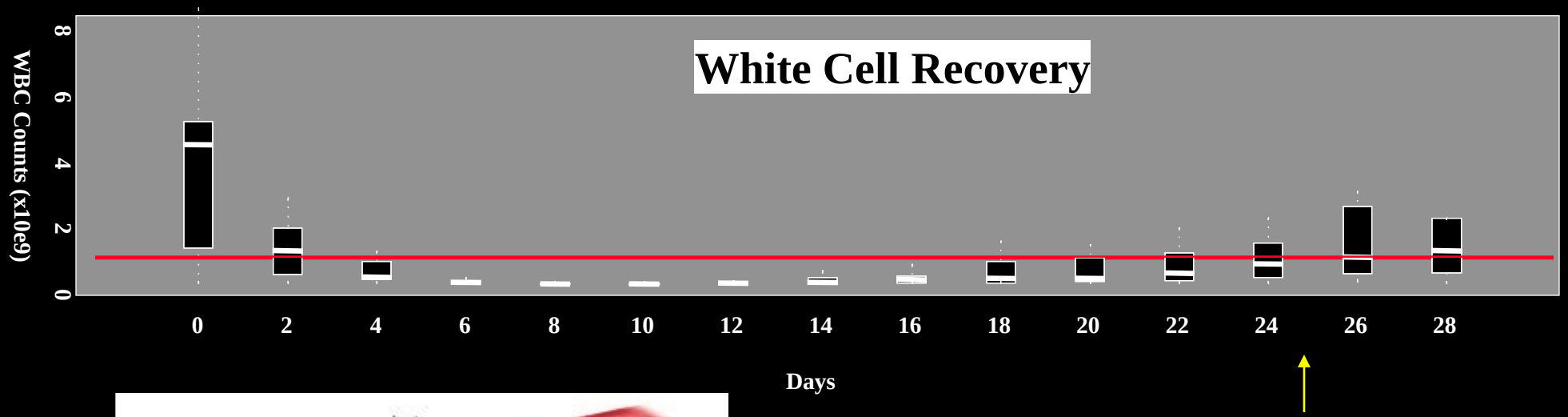
Destroy BM cells and the Host's Immune System

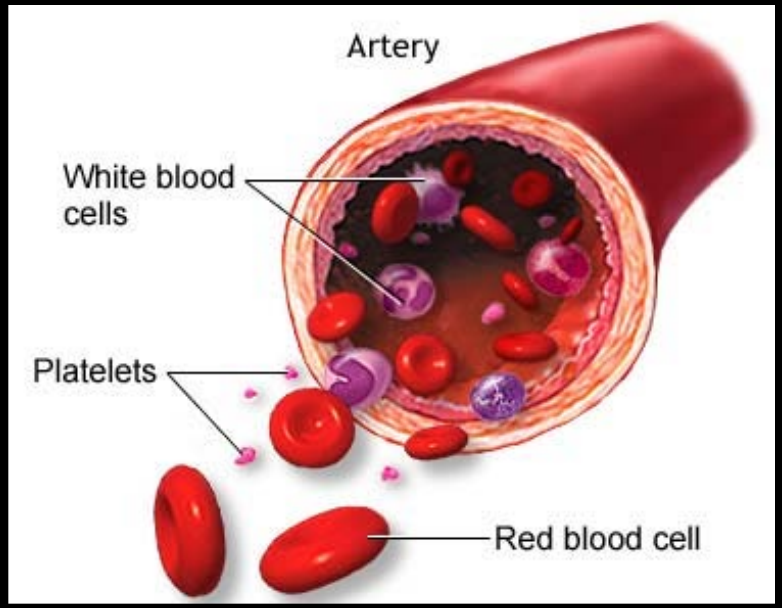


Immunosuppression

Prevention of HVG and GVH reactions

Engraftment



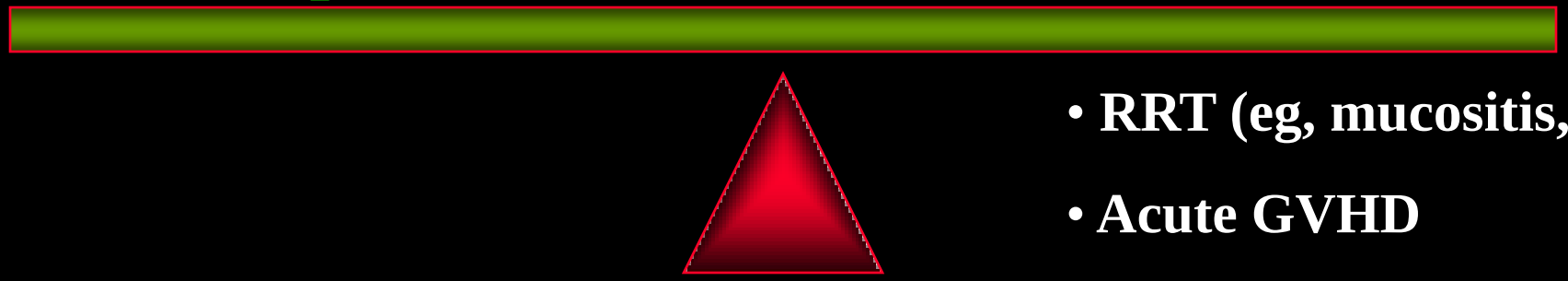


Pace of recovery after marrow infusion

Potential Side Effects
High Risk:Benefit Ratio

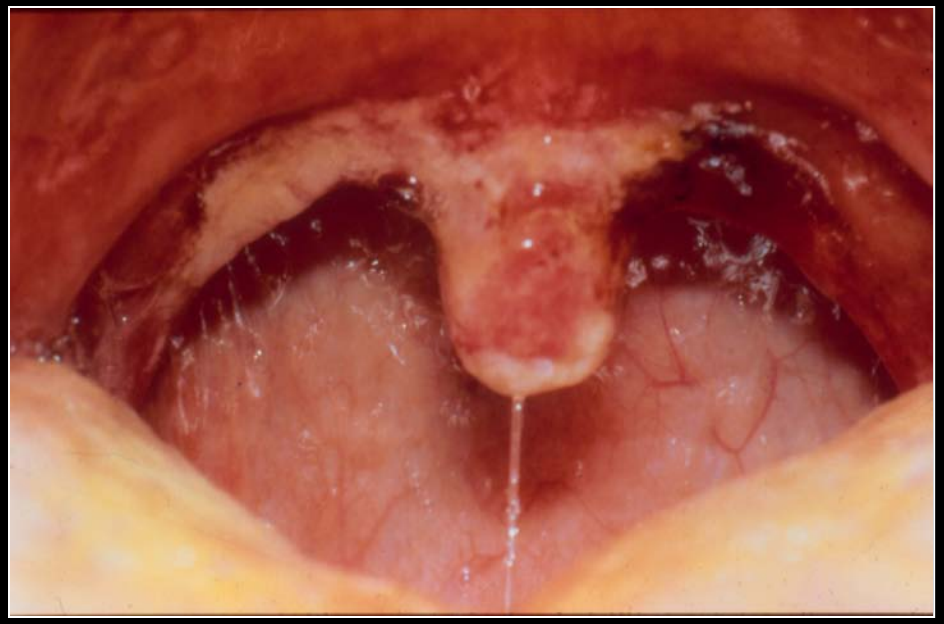
Restoration of Normal Hematopoiesis

Risk of Early and Late Toxicities



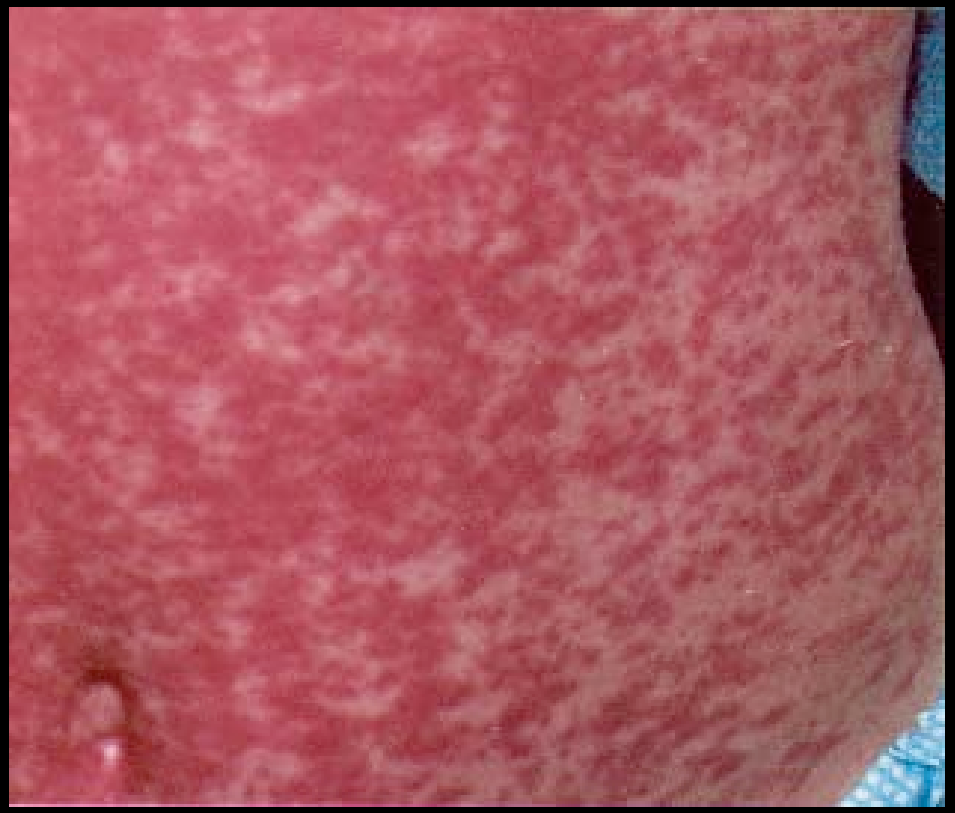
- **RRT (eg, mucositis, VOD)**
- **Acute GVHD**
- **Chronic GVHD**
- **Endocrinopathies**
- **Sterility**
- **Second malignancies**

Early Toxicities
Preparative Regimen



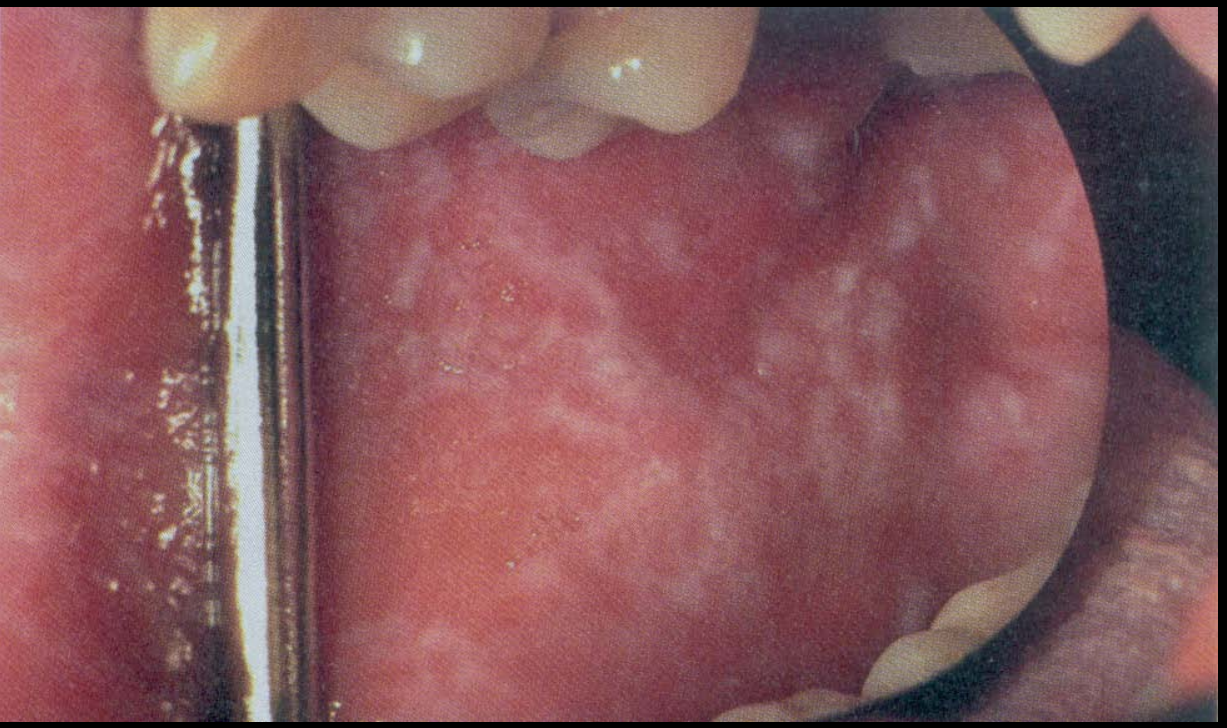
- mucositis (mouth sores)
- nausea, vomiting, diarrhea
- decrease appetite - TPN
- hair loss
- fatigue
- organ toxicity – lungs, liver, kidneys, heart
- increased risk for infection

Acute Graft-Versus-Host Disease



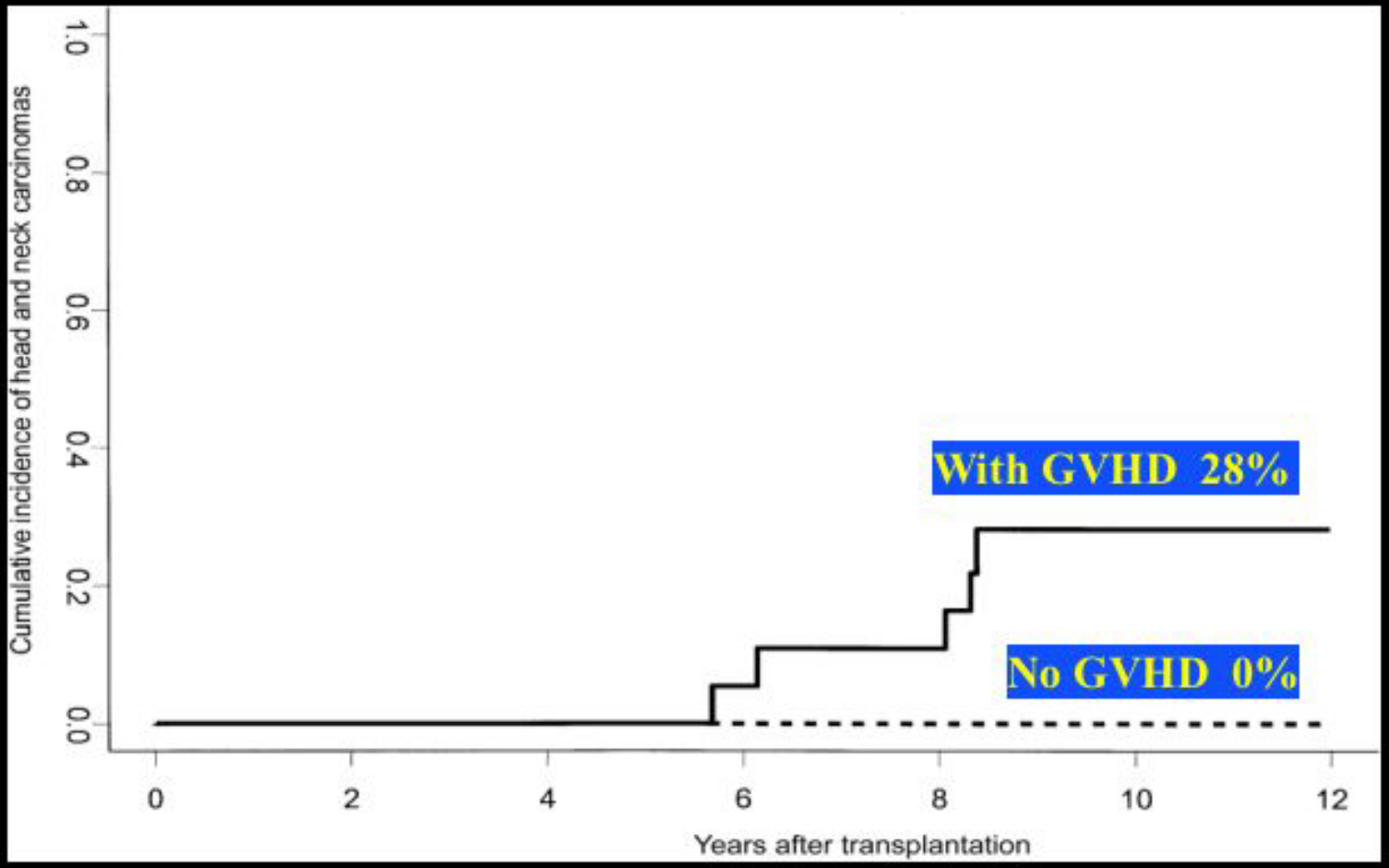
- usually starts first 3 months after BMT
- 50-70% URD BMT recipients
- 30% MSD BMT; UCB recipients
- T cell depletion markedly decrease risk
- fever, rash, nausea, diarrhea, liver

Chronic Graft-Versus-Host Disease

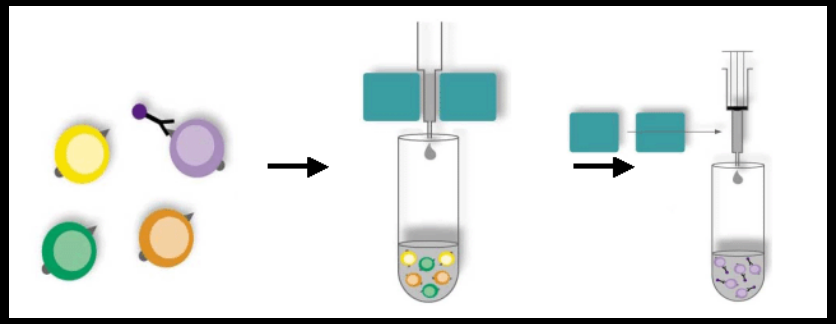


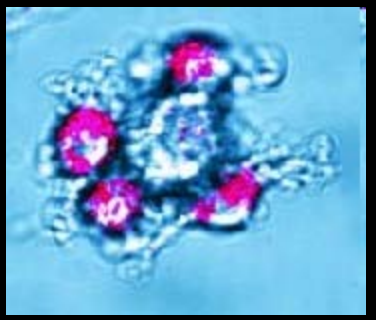
- Occurs after day 100
- Insidious onset
- Dry eyes, dry mouth, loss of appetite, weight loss, rash, poor lung function, liver abnormalities, weakness, contractures, decreasing blood counts

Cumulative incidence of head and neck carcinomas in Fanconi anemia patients according to the occurrence of grades II to IV AGvHD



Guardiola, P. et al. Blood 2004;103:73-77

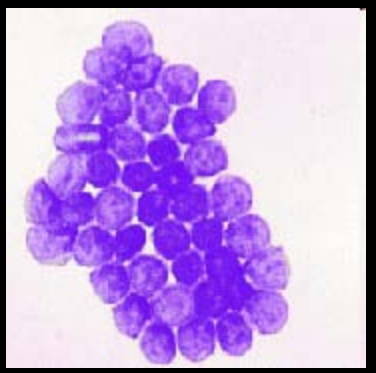




Prevention of GVHD

T cell depletion

Cleave the bead from the cells



CD34+ cells

Graft-versus-Host Disease

Risks

- MM donor
- Age
- TBI

Prevention

- TCD
- CSA/steroids

Is a balance - more immunosuppression = greater risk for infection

Immune Function in FA Patients

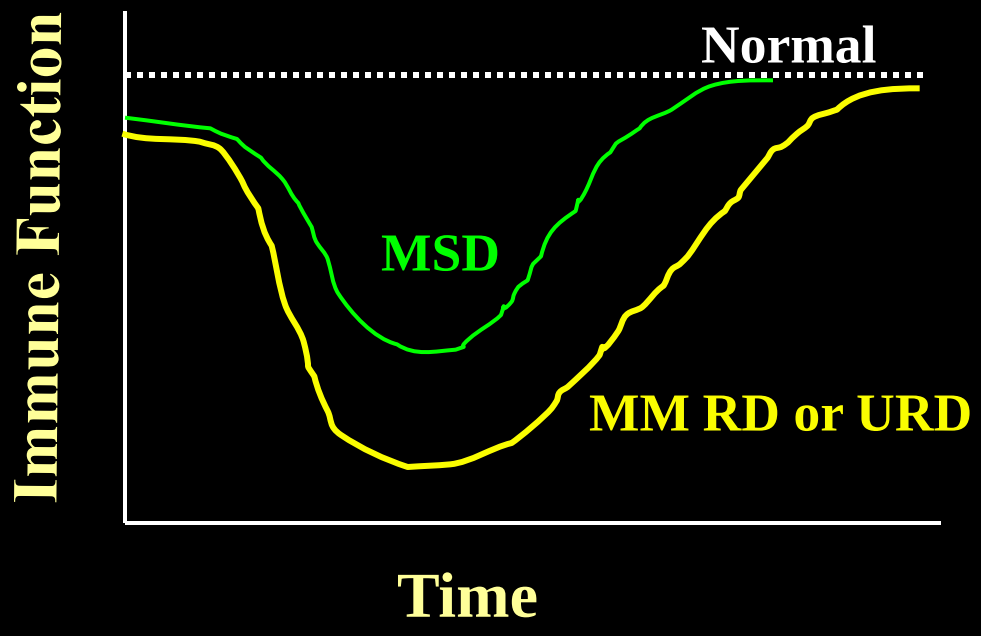
Abnormal immune function prior to transplant

- high incidence infections, esp. opportunistic
- role of androgens, prednisone
- low neutrophil counts

Additional immune compromise after transplant

- chemotherapy, irradiation
- CSA, steroids
- GVHD

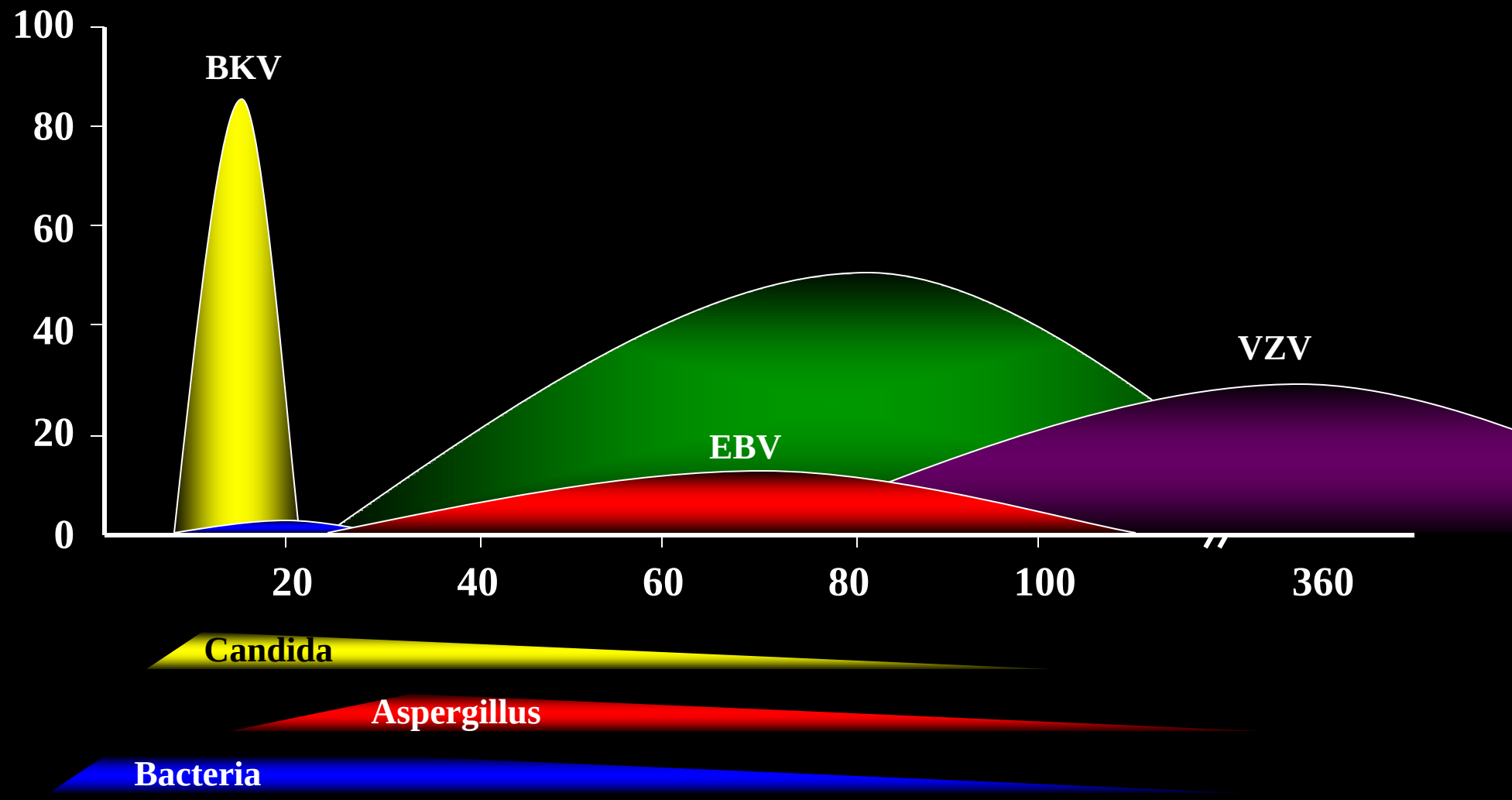
Immune Reconstitution After BMT



Delayed if

- older recipient
- unrelated donor
- mismatched related donor
- acute GVHD
- chronic GVHD

Risk of Infections after Allogeneic HCT



Transitions after BMT

Day 100 after BMT

- if stable, may go home to referring MD
- no longer need to wear mask outside all the time if immune system strong enough
- often readmissions for fevers, viral infections
- keep central line in as long as needed

School/Work

- if no active GVHD or infection, earliest return
  - 3 months if matched sibling donor
  - 6 months if unrelated donor

Immunizations After BMT

- Start at 1 year after BMT
  - later if chronic GVHD
- No live virus vaccines until at least 2 years after BMT
- Patient and all family members should receive influenza vaccine once past day 60

What is known about survivorship/late effects issues in patients with Fanconi anemia?

- Almost nothing
- No publications in medical literature address this specifically
- Important to follow all FA patients systematically
  - prevention
  - close monitoring and early intervention
  - long term follow-up

Fanconi Anemia
Survivorship/Late Effects Clinic

- Margaret MacMillan, MD
- John Wagner, MD
- Pat Fidler, RN
- Heather Zierhut, MS
- Daniel Mulrooney, MD - internal medicine
- Anna Petryk, MD - endocrinology
- Lynda Polgreen, MD - endocrinology
- Frank Ondrey, MD - ENT
- Rahel Ghebre, MD - gynecology
- Sarah Jane Schwarzenberg, MD - gastroenterology
- Jo-Anne Young, MD - infectious diseases

-- neuropsychologists, ophthalmology, audiology, cardiology, pulmonology, nephrology, dentistry

Care for the Whole Person to Optimize Quality of Life

- Neurocognitive deficits
- Anxiety
- Depression
- Social Withdrawal
- Loss
- School/work
- Insurance

Conclusions

- HCT offers the only proven cure for bone marrow failure in patients with Fanconi anemia
- FA patients have unique challenges for successful HCT
- FA patients should undergo HCT at a center specializing in HCT for FA
- All FA patients need to be followed carefully for life to optimize quality of life
- Research is important part of HCT and late effects clinical care