GRAFT vs. HOST DISEASE.

Learning Objectives:

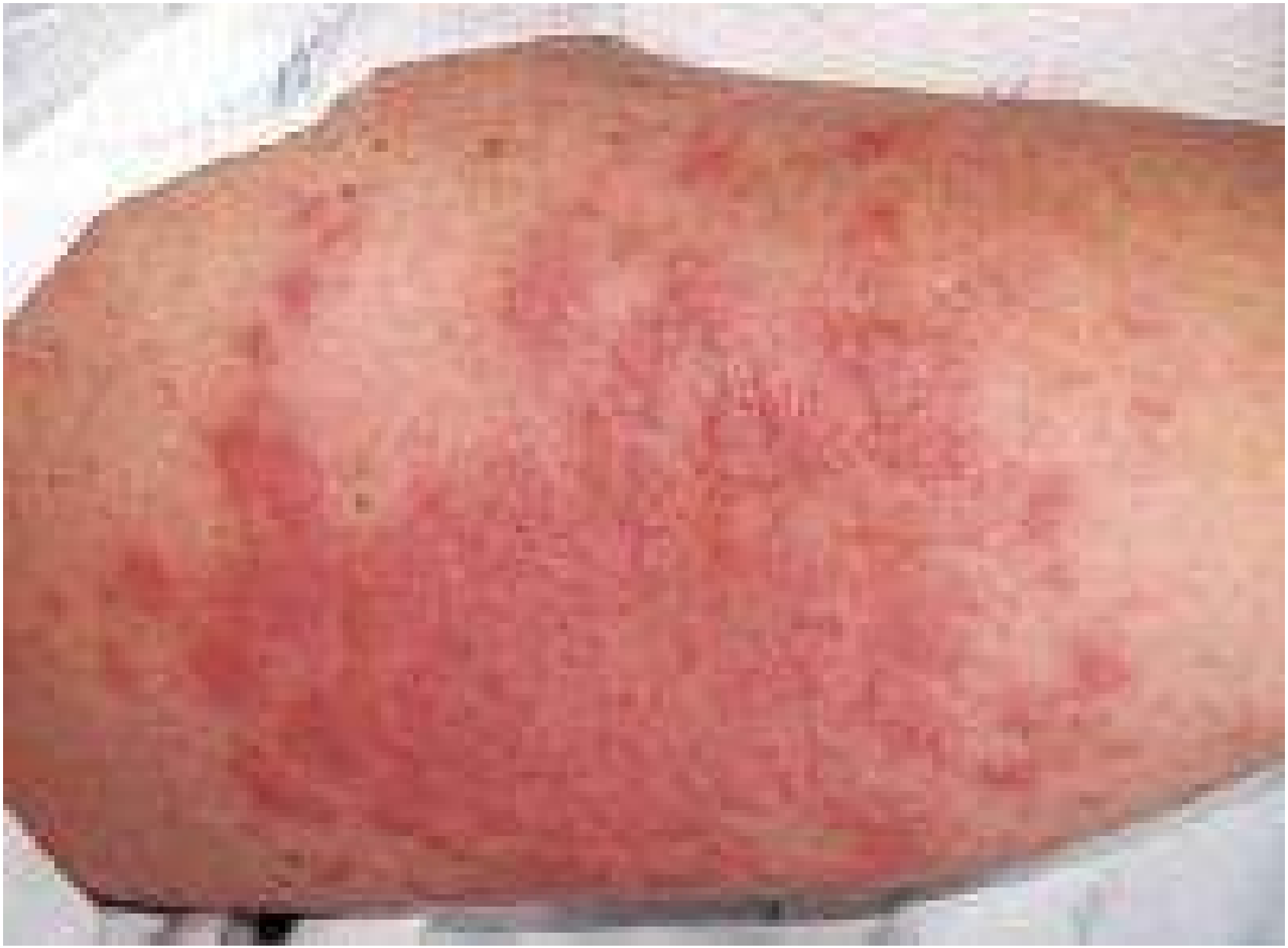
- Be able to define the GVHD.
- Be able to classify the organs most affected.
- Be able to describe manifestations of GVHD in the affected organs.
- Describe the mechanism of GVHD leading to tissue damage.

Introduction to Graft vs. Host Disease.

- Graft vs. Host disease is a syndrome that occurs when immune cells from a donor attack the host's normal cells.
- GVHD is one of the major causes of morbidity and mortality associated with an allogenic stem cell transplant.
- GVHD occurs in 30 to 50% of HLA-matched sibling transplants and 60 to 90% of mismatched.

Introduction to Graft vs. Host Disease.

- Unfortunately at this time, we can not separate GVHD from the beneficial graft vs. leukemia effect.
- GVHD is divided into acute and chronic depending on whether the initial symptoms developed before 100 days following Bone Marrow Transplant (BMT)
- The organ systems primarily affected by acute GVHD are the skin, liver, and GI tract.



Manifestations of Graft vs. Host Disease.

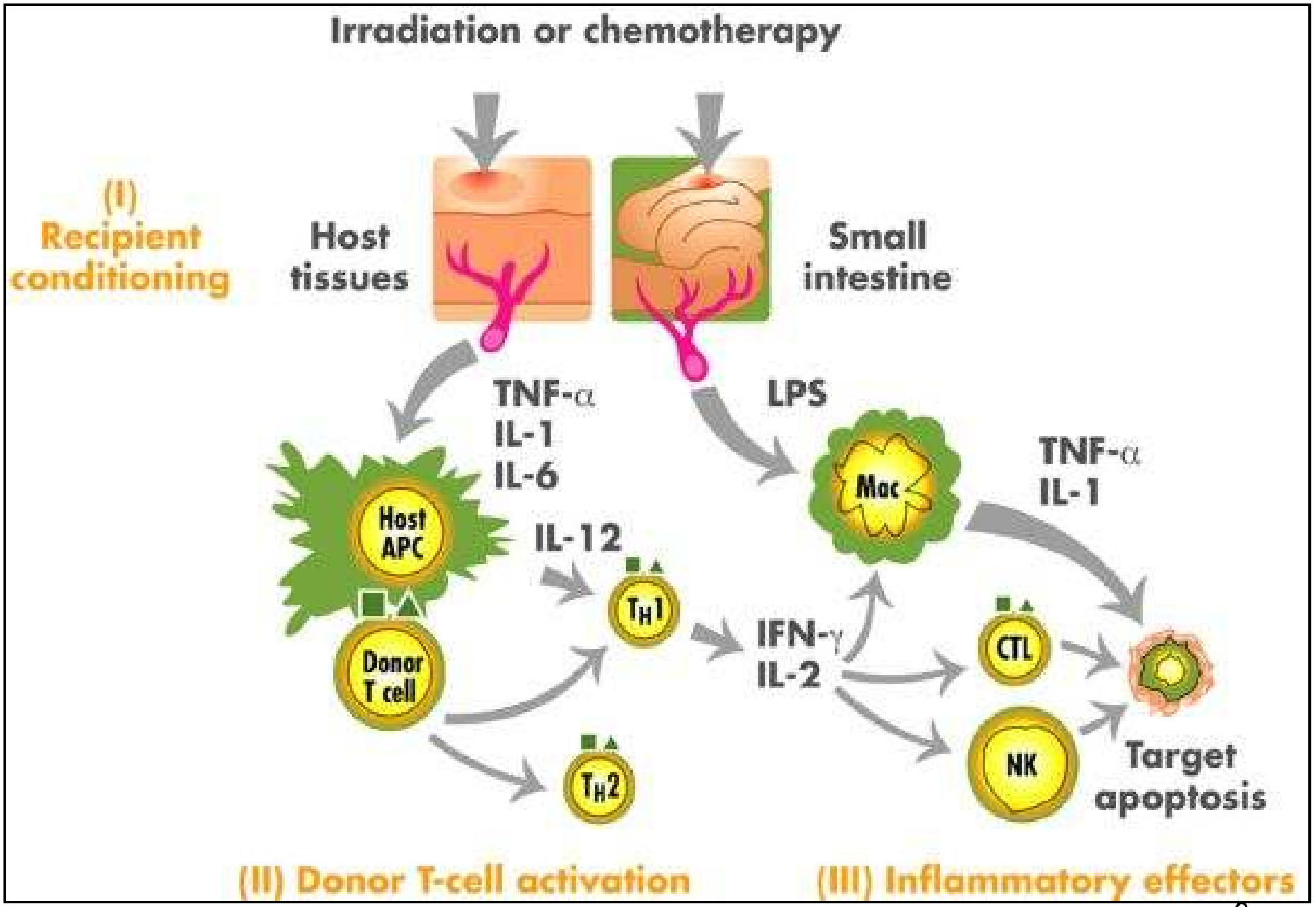
- The liver manifestations are primarily increases in the bilirubin but can also involve transaminitis
- The GI manifestations are diarrhea, nausea, and vomiting.
- The severity of acute GVHD is staged on a I to IV system.

Stage of Graft-Versus-Host-Disease by Organ System

Organ	Grade	Description
Skin	+1	Maculopapular rash over <25 percent of body area
	+2	Maculopapular rash over 25 to 50 percent of body area
	+3	Generalized erythroderma
	+4	Generalized erythroderma with bullous formation and often with desquamation
Liver	+1	Bilirubin 2.0 to 3.0 mg/dL; SGOT 150 to 750 IU
	+2	Bilirubin 3.1 to 6.0 mg/dL
	+3	Bilirubin 6.1 to 15.0 mg/dL
	+4	Bilirubin >15.0 mg/dL
Gut	+1	Diarrhea >30 mL/kg or >500 mL/day
	+2	Diarrhea >60 mL/kg or >1000 mL/day
	+3	Diarrhea >90 mL/kg or >1500 mL/day
	+4	Diarrhea >90 mL/kg or >2000 mL/day; or severe abdominal pain with or without ileus

Proposed mechanism for acute GVHD.

- There appear to be 3 phases to the development of acute GVHD.
- Damage to host tissues.
- Activation and proliferation of donor lymphocytes.
- Attack on the host cells.

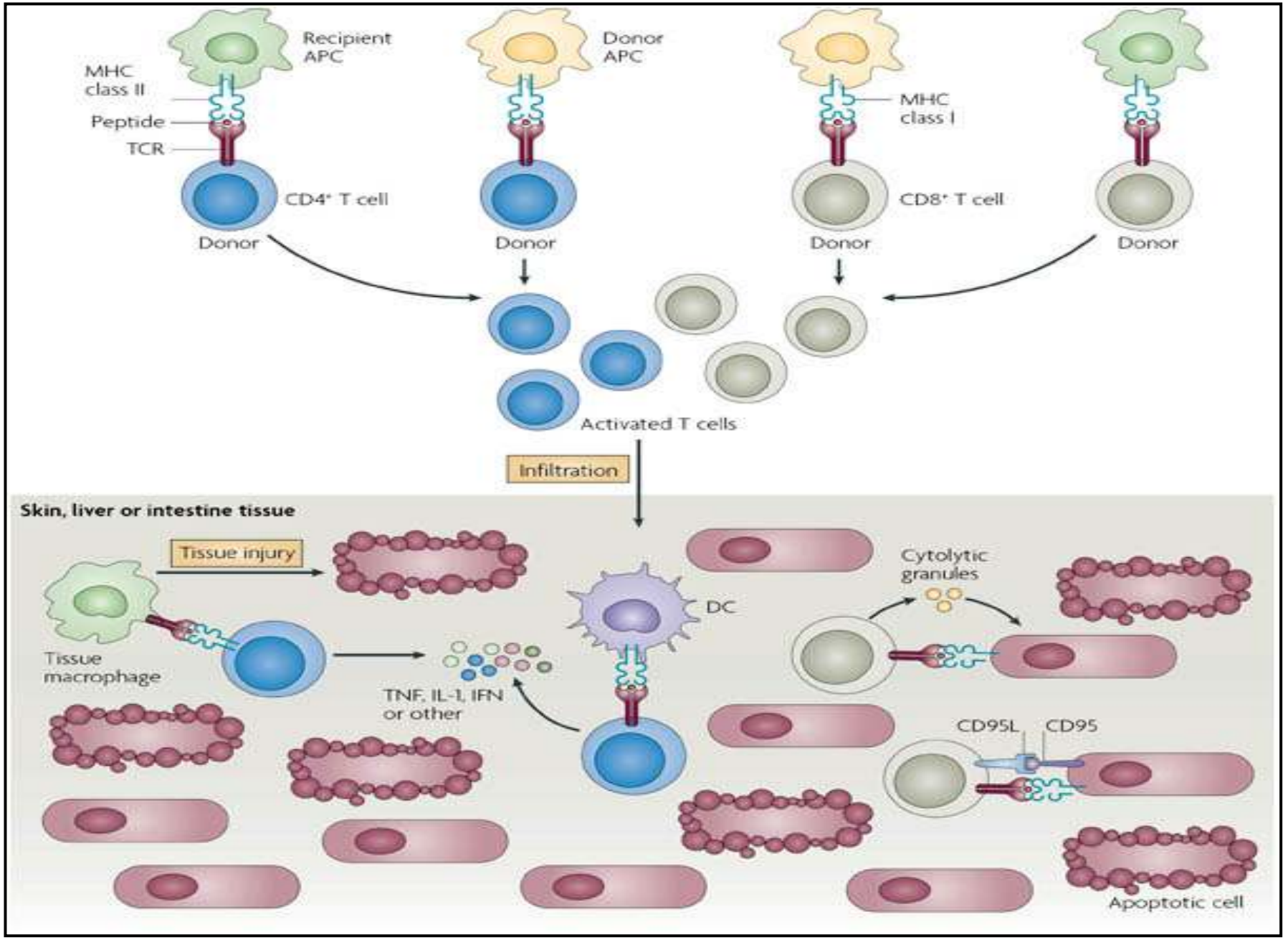

Irradiation or chemotherapy
(I)
Recipient
conditioning
Host
tissues
Small
intestine
TNF-α
IL-1
IL-6
LPS
Host
APC
Mac
TNF-α
IL-1
IL-12
TH1
IFN-γ
IL-2
CTL
Donor
T cell
TH2
NK
Target
apoptosis
(II) Donor T-cell activation
(III) Inflammatory effectors

I. Damage to the Host.

- The damage primarily comes from the conditioning regimen.
- The damage to the host leads to the release of inflammatory cytokines such as TNF-alpha and IL-1.
- In the gut, microbial products such as lipopolysaccharide can enter the circulation.

II. Donor T-cell activation.

- The inflammatory cytokines stimulate antigen presenting cells (APC); followed by activation and proliferation of the donor lymphocytes.
- The APC present host antigens not recognized by the donor lymphocytes.
- The lymphocytes then multiply and differentiate under the influence of IL-2.



ACTIVATION AND PROLIFERATION OF DONOR LYMPHOCYTES

III. Attack of Target Tissues.

- GVHD is primarily mediated by cytoxic T lymphocytes (CD8+) but helper T lymphocytes (CD4+) and NK cells are also involved.
- The host cells are destroyed by either direct cytotoxic activity or inflammatory cytokines.

Decreasing the damage to the host.

- This can be divided into giving less rigorous conditioning regimens or blocking the cytokines or other products that lead to the activation of APC's.
- Antibiotics have been shown to decrease the frequency of acute GVHD.

Decreasing the damage to the host.

- TNF-alpha inhibitors have been tried to decrease GVHD
- Other investigations have shown delay in the development of acute GVHD but not reduction rate with the use of prophylactic TNF-alpha inhibitors.

Stopping activation and proliferation of donor lymphocytes.

- Cyclosporine
- Methotrexate
- Tacrolimus
- Sirolimus
- Mycophenolate mofetil
- Steroids
- Alemtuzamab (Campath)
- Anti-IL2 antibodies

Methotrexate.

- Methotrexate is a folate antimetabolite
- As a single agent significant GVHD develops in 70%
- It has found a significant role in prevention when used in combination with other immune suppressant medications.

Cyclosporine.

- Cyclosporine is a calcineurine inhibitor
- Inhibition of calcineurine prevents the transcription of TNF-alpha and many cytokines (IL-2, IL-3, IL-4) which decreases the proliferation of lymphocytes.
- Notwithstanding, a 40% development rate for acute GVHD (Grade II-IV) in HLA-matched transplants has been reported.

Summary.

- **Graft vs. Host disease is a syndrome that occurs when immune cells from a donor attack the host's normal cells.**
- **GVHD is divided into acute and chronic depending on whether the initial symptoms developed before 100 days following Bone Marrow Transplant (BMT).**
- 3 phases to the development of acute GVHD: Damage to host tissues; activation and proliferation of donor lymphocytes; attack on the host cells.