Chronic Granulomatous Disease Medical Management

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Disclosures

Horizon Pharma
Speaking and consulting
Medical Management

**Cornerstone of Therapy**
- Prevent infections
- Lifelong antibacterial and antifungal prophylaxis
- Immunomodulatory therapy
- Early identification of infection
- Aggressive treatment of infections
Prevention

Avoidance:
- Swim in pool or salt water
  - Avoid freshwater, pond, brackish water
- Avoid much/potting soil
  - Mulch pneumonitis from Aspergillus
- Avoid other potential mold exposure
  - Compost, potting plans, damp cellar/basement, demolition, digging in dirt, cutting grass, hay rides, raking leaves, smoking marijuana
Identification of Infections

- Early diagnosis of infections critical
- Serious infections can be minimally symptomatic or asymptomatic at presentation
- Monitor for occult infection
  - Personally I check ESR/CRP every visit, elevation prompts aggressive search for infections
- Parents monitor for lymphadenopathy
- Monitor for musculoskeletal changes
Treatment of Infections

**Culture, culture, CULTURE**
- Unless life threatening infections, need cultures before empiric antimicrobials
- Bacterial, mycobacterial, and fungal cultures (hold for nocardia)
- Lymph node—excisional biopsy
- Identification of microbe is critical for treatment

**AGGRESSIVE Treatment**
- Empiric antifungal and antibacterial after cultures obtained
- Steroids sometimes used

**Looooooong Treatment**
- Typically prolonged IV followed by prolonged oral medication for serious infections
Summary

1. Culture—identification of microbe critically important in proper treatment
2. Early treatment—once cultures done
3. Aggressive treatment—IV antifungal and antibiotic after proper cultures
4. Prolonged treatment—required for full eradication
Triple Therapy
Triple Therapy

**Antibacterial**
- *ie trimethoprim/sulfamethoxazole (TMP-SMX)*

**Antifungal**
- *ie itraconazole*

**Immunomodulatory**
- *Interferon gamma-1b*
Antibacterial

**TMP-SMX**

- Bactericidal and effective against most common pathogens
- ~1 Life threatening infection every 10 months without prophylaxis
- With TMP/SMX ~1 life threatening infection every 40 months
- Decreased rate of hospitalizations and surgeries

*Other antimicrobial options available if intolerant to TMP-SMX*
Aspergillus spp account for >35% of all CGD deaths

Antifungal

• i.e. Itraconazole, posaconazole, voriconazole
• Decreased rates of serious invasive fungal infection >50%
• Increased life span
**Interferon gamma-1b**

- *1980s data showed increased phagocyte-mediated killing with IFN-γ*
- *Decreased infections and mortality rate*
  - Most studies done before antifungals
- *Side effects*
  - Flu like symptoms (fever, chills, fatigue) and injection site pain
- *Mechanism*
  - Largely unknown
  - Increased nitric oxide
  - Enhanced macrophage bactericidal activity
- *Least agree upon of triple therapy—used less frequently in Europe than USA*
Effect of Triple Therapy

- Effective when taken
- Survival 90% at 10 years old
- Best current data
  - median age of death 30-40 years old

Bone Marrow Transplant

Should we perform a bone marrow transplant?
Bone Marrow Transplant

https://beyondthedish.wordpress.com/tag/bone-marrow/page/2/
Bone Marrow Transplant

https://cancer.uams.edu/patients-family/treatment/treatment-options/bone-marrow-transplant/allogenic/
Bone Marrow Transplant

**Source**
- Bone marrow
- Peripheral blood stem cells
- Cord blood

**Donors**
- Related
  - Matched sibling
  - Haploidentical (parents)
  - Do not use X-linked carriers
- Matched unrelated
Bone Marrow Transplant

**HLA Typing**
- Cell surface markers recognized by immune cells
- Present on every cell
**Conditioning**
- **Fully Myeloablative Conditioning (MAC)**
  - More toxicity
- **Reduced-Intensity Conditioning (RIC)**
  - Various degrees of myelosuppression
  - Higher rates of mixed chimerism
  - Less toxicity
- **Reduced-Toxicity Conditioning (RTC)**
Bone Marrow Transplant

**Risks**
- Death
- Acute graft vs host disease
- Chronic graft vs host disease
- Veno-occlusive disease
- Loss of future fertility
- Toxicities from conditioning

**Benefits**
- Curative therapy
Who to Transplant?

- Are risks of transplant less than no transplant?
- Consider comorbidities and end organ damage
- Consider HLA matches and cell source
- Consider experience of transplant center
- Avoid active infections
- Steroid dependent inflammatory manifestations
- No universal criteria to transplant
- X-linked—consider genetics
- Residual oxidase activity
- Previous neutrophil transfusions
- Previous blood transfusions (McLeod phenotype)
- Time of year
Bone Marrow Transplant

Current results

- Survival 80-90%
- Graft vs host disease ~10-15%
- Improved quality of life
- Statistics are in studies at experienced centers

Goal

- Transplant patients who the risk of medical management is greater than the risk of transplant
Gene Therapy

- Cell with non-functioning gene
- Functioning gene
- Cell functioning normally
1. Cells are removed from patient.

2. In the laboratory, a virus is altered so that it cannot reproduce.

3. A gene is inserted into the virus.

4. The altered virus is mixed with cells from the patient.

5. The cells from the patient become genetically altered.

6. The altered cells are injected into the patient.

7. The genetically altered cells produce the desired protein or hormone.

Gene Therapy
Gene Therapy

**Gammaretrovirus—previous studies**
- Only can insert into dividing cells
- High rate of insertional oncogenesis (i.e. cancer)

**Lentivirus—current studies**
- Can insert into non-dividing cells
- Self-inactivating vector (SIN)

**CRISPR/Cas9**
- May enable repair at native gene site (very specific)
- Promising pre-clinical data
- Amount of customization required may limit therapy
Gene Therapy

Current Trial

- Boston, Bethesda, and Los Angeles
- >23 months old with no HSCT match and history of serious infections or inflammatory complications
- SIN lentiviral vector
- Currently ongoing
  - No insertional oncogenesis
  - Promising results in other diseases

Prognosis
Questions