Pathogenesis/Etiology
- CGD: abnormalities in NADPH oxidase leading to defective phagocyte respiratory burst leading to infection susceptibility and granulomatous inflammation complications.
- Increased susceptibility to infections by certain bacteria and fungi.
- Genetic etiologies: x-linked (gp91phox; about 65% of cases) and autosomal recessive (p22phox, p47phox, p67phox, p40phox).
- Highly lysonized females (less than 5-10% normal neutrophils) may have clinical picture and infection rates similar to x-linked (male) presentation.

Diagnostic Tests
- Dihydrorhodamine oxidation (DHR): Flow cytometry to detect DHR oxidation in PMA stimulated neutrophils.
  - Pattern on flow cytometry can distinguish X-linked and AR forms. Two populations seen in X-linked carriers.
  - Abnormal results possible with myeloperoxidase deficiency and SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis)- these can be diagnosed accurately with NBT tests and superoxide production assays.
- Nitroblue tetrazolium reduction test (NBT): largely qualitative assay to detect NBT reduction by superoxide.
  - Can be falsely normal with residual superoxide production and in X-linked female carriers.
  - Less frequently used now.
- Screen family members with DHR.
- Superoxide production: research assay. Can be helpful in prognosis as higher risk for earlier mortality with little or no superoxide production.
- Genetic testing- necessary for genetic and prenatal counseling. Also can help in prognosis and detection of deletion can lead to contiguous gene diagnoses, such as the Kell blood antigen in McLeod syndrome, retinitis pigmentosa, duchenne muscular dystrophy, and ornithine transcarbamylase deficiency (OTC).

Infections
- Microbiologic diagnosis important to guide therapy.
- Less common but pathognomonic: Granulibacter bethesdensis, Francisella philomiragia, Chromobacterium violaceum, and Paeclomyces infections.
- Infections typically pneumonia, lymphadenitis, liver abscesses, osteomyelitis. Sepsis more common with certain Gram negative infections such as Chromobacterium and Francisella philomiragia.
- Unique infections/Therapies.
  - Mulch pneumonitis: diffuse pneumonitis after large inhalation event. This can be the initial presentation and can be fatal. Treatment requires corticosteroids and antifungals so early diagnosis essential.
  - Granulibacter bethesdensis: infection that has only been identified in CGD. This typically causes necrotizing lymphadenitis and the bacteria can be difficult to grow with typical microbiologic methods.
  - Nocardia pneumonia: intense inflammatory response may result in worsening despite appropriate antimicrobials. If infection controlled, corticosteroids may be helpful to treat pulmonary inflammation. Molds can co-infect with Nocardia and should be covered.
  - Addition of corticosteroids to appropriate antimicrobials can also be helpful in difficult to treat S. aureus liver abscesses.
- Prophylaxis:
  - Trimethoprim/sulfamethoxazole and itraconazole are mainstays of prophylaxis.
  - Voriconazole long-term therapy can be problematic with photosensitivity as well as long-term potential of fluoride toxicity.
  - Itraconazole and corticosteroids can interact leading to higher “seen” levels of steroids.
If sulfa allergic, consider desensitization. Alternatives include trimethoprim alone, 2nd or third generation cephalosporin, and fluoroquinolones (although caution if steroids needed for granulomatous complications).

Interferon-gamma with decrease in number of infections - studies less clear with both TMP/SMX and itraconazole prophylaxis.

### Drug Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
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<tbody>
<tr>
<td><strong>Antibacterial</strong>*</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-</td>
<td>5mg (up to 6-8) mg/kg/day up to 320 mg (divided bid)</td>
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<tr>
<td>sulfamethoxazole</td>
<td></td>
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<tr>
<td><strong>Antifungal</strong></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>100 mg/day &lt;13y or &lt;50 kg or 5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>200 mg/day &gt; 13y or &gt; 50 kg</td>
</tr>
<tr>
<td><strong>Immunomodulatory</strong></td>
<td></td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>50 mcg/m2 SQ 3x/wk</td>
</tr>
</tbody>
</table>

*Alternatives to TMP-SMX if unable to tolerate sulfonamides: trimethoprim as single agent, dicloxacillin, cephalosporins or fluoroquinolones. Above table from reference 5.

### Inflammatory Complications

- Inflammatory bowel disease, gastric outlet obstruction, inflammatory bladder disease may be more prominent initially than infections. Corticosteroids are mainstays of therapy. Increased infection complications have been noted with TNFalpha blockers.
- Surgical wound healing may be complicated by exuberant granulomatous inflammation, and in the absence of infection, steroids may improve healing.

### Bone Marrow Transplantation

- Allogeneic HSCT (hematopoietic stem cell transplant) – only known cure for CGD.
- Procedure related morbidity and mortality greatly reduced, and outcomes improved in recent years.
- Myeloablative vs Non-myeloablative SCT options
  - Myeloablative – lower risk of graft rejection
  - Non-myeloablative SCT – preferred option in many centers due to lower risk of drug/TBI related toxicity, lower risk of sterility, may transplant with active infection, fewer infection-related deaths.
- Transplant survival improved to 90-95% based on recent data (2011), vs 85% before 2000 with allogeneic SCT.
  - 100% survival in 11 children age 1-13 years (4 MRD, 7 MUD [10/10]) 1-8 years s/p SCT, with grade 1 GVHD of skin, no grade II-IV.
  - 93% survival (52 of 56 patients) (16 centers, 10 countries) (21 MRD, 35 9/10 or 10/10 HLA match) median f/u 21 months, GVHD grade III-IV 4% (2 of 56), chronic GVHD 7% (4 of 56), graft failure 5% (3 of 56).
- Another study compared 62 children with CGD ages 0-16 years in Britain & Ireland, 30(48%) underwent HSCT, 32 conservative management with TMP/SMX & 87% itraconazole, survival 90% in each group (median follow-up almost 4 years, but 0.71 episodes of infection/admission/surgery in conservative group vs 0.15 episodes in HSCT.
- Managed conservatively, CGD annual death rate in U.S. 2-5%, 50% survival at age 30 years [registry of 368 published in 2000]. Morbidity/mortality since 2000 improved.
- Preferred transplant considerations: age < 13 years, MRD or 9/10 or 10/10 MUD, lower ROS (reactive oxygen species/NADPH oxidase activity due to more severe phenotype / higher mortality with conservative management (specific X-lined mutation can also be used to predict superoxide production and stratify mortality risk).
- Gene therapy using lentivectors to begin in US and Europe - not curative.

### References