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Chronic Granulomatous Disease: Overview and Hematopoietic Stem Cell Transplant

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Abstract

Chronic Granulomatous Disease (CGD) still causes significant morbidity and mortality. The difficulty in considering high-risk yet curative treatments, such as allogeneic bone marrow transplantation, lies in the unpredictable courses of both CGD and bone marrow transplantation in different patients. Some CGD patients may have frequent infections and/or suffer from granulomatous or autoimmune disorders necessitating immunosuppressive therapy, but also experience long periods of relative good health. However, the risk of death is clearly higher in CGD of all types, and the complications of CGD short of death can still cause significant morbidity. Therefore, with recent developments and improvements, bone marrow transplantation, previously considered an experimental or high-risk procedure, has emerged as an important option for patients with CGD. We will discuss the complications of CGD that result in significant morbidity and mortality, in particular the most common infections and autoimmune/inflammatory complications as well as their typical management. We will then discuss the status of bone marrow transplantation.

Keywords

Chronic Granulomatous Disease; Infection; Inflammation; Autoimmune; Allogeneic Hematopoietic Transplantation

Introduction

Chronic Granulomatous Disease results from defects in the NADPH oxidase complex resulting in an inability to produce the superoxide anion necessary for normal killing of bacterial and fungal microorganisms. In addition, this defect predisposes to granulomatous complications and autoimmune diseases. Mutations in at least five different genes involved in the assembly and activation of the NADPH oxidase can lead to CGD. [1] The gene encoding the enzymatic center of the NADPH oxidase, $gp91^{phox}$, is on the X-chromosome and accounts of about 2/3 of the cases. Autosomal forms occur from mutations in $p47^{phox}$,

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p67^{phox} p22^{phox} or p40^{phox}, with the latter being the most recently described.[2] In general, gp91phox deficient patients (X-linked CGD) are the most severely affected whereas patients with mutations in p47^{phox} seem to have the best outcomes overall. Deficiency in p40^{phox} may predispose to more GI disease and fewer infections.[2] Specific mutations affect the severity of disease through the amount of residual NADPH oxidase activity.[3] However, even among patients with similar NADPH oxidase mutations there can be widely different clinical outcomes. Therefore, the genetic type of CGD, the specific mutation, the patient's own infection history, the presence of inflammatory or autoimmune complications and access to appropriate medical care all factor into what to expect from CGD in a particular patient's case.

Infection

Despite the significant progress made in antibiotic and antifungal therapy and prophylaxis, patients with CGD still develop serious infections. Most large studies have shown an infection rate of around 0.15 to 0.3/year.[4, 5, 6] The US National Institutes of Health (NIH) has followed more than 250 patients with CGD over almost 40 years, the majority of whom were diagnosed following infections of skin, lymph node, lung or liver. A small group of patients (~5%) were identified because of inflammatory lesions as their primary clinical event. The diagnosis was usually established early in life (median age of diagnosis 5.4 years), although a small proportion were diagnosed as adults. Notably, the majority of these later diagnoses were due to autosomal recessive forms of CGD.

Isolation of the microorganism causing infection in CGD is essential to rational and appropriate treatment, but it is not always feasible. In the last ten years, 80% of CGD patients at NIH with a pulmonary infection underwent some type of diagnostic procedure, either needle biopsy or bronchial lavage. Of these, 52% were successful in identifying a pathogen. Co-infection, such as fungal with bacterial, was found in less than 10% of biopsies. Viral infections appeared at similar rates as in the general population (unpublished data).

The majority of infections in North American CGD are due to four bacterial organisms (*Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia* complex, and *Nocardia* species) as well as species of the fungus *Aspergillus.* Invasive aspergillosis has been a major cause of morbidity and mortality in CGD, but the advent of the newer azole antifungals has dramatically changed the treatment and outcome of these infections and shifted the intractable fungal infections to non-fumigatus Aspergillus species, dermateacous molds and hyalohyphomycosis such as paecilomyces.[1, 7, 8]

CGD patients may present without symptoms or with low grade fevers and only mild constitutional symptoms inconsistent with the extent of disease seen by imaging studies. Consequently, frequent imaging studies (e.g., CT, MRI), are recommended for clinical monitoring. The paradoxically dampened inflammation in response to some serious infections and the exaggerated responses to some non-infectious stimuli (see below) remains perplexing.

The lung was the most common site of disease in the NIH cohort and *Aspergillus* was responsible for ~40% of the culture positive cases. Chest scans and markers of acute inflammation (e.g., C-reactive protein and erythrocyte sedimentation rate) have proven useful in diagnosis and monitoring of fungal disease (unpublished data). The role for serology such as the β-D glucan and galactomannan assays are undefined in CGD, but when positive may be helpful to follow in some cases. North American studies have identified a much higher incidence of *Burkholderia* and *Nocardia* infections than in European reports,

which in part may reflect the differences in diagnostic approaches and may also reflect environmental differences.[4, 9]

Emerging pathogens in CGD include Gram-negatives (eg. *Granulibacter bethesdensis*[10]), Gram-positives (eg *Actinomyces*[11]), and fungi (eg. *Neosastorya udagawae*[12]). Occurrence of these uncommon pathogens in CGD may provide clues to the critical pathways and functions of the NADPH oxidase.[13–17]

Liver abscesses are common in CGD.[18] Thirty percent of NIH patients have had liver abscesses with 25% of these occurring more than once. *Staphylococcus aureus* was the organism most frequently cultured and surgical resection was the usual treatment. Percutaneous drainage was usually not helpful, as liver abscesses associated with CGD tend to develop multiple loculations. When resected, the lesions are a collection of microabscesses.[18] Corticosteroids have been reported to be helpful in 2 cases of liver abscess.[19] Other staphylococcal infections are typically confined to the skin or lymph nodes.[20]

Patients compliant with prophylaxis still develop skin infections, but these infrequently spread. Skin and soft tissue infections are caused by *S. aureus, Klebsiella* species, *Serratia marcescens, Burkholderia cepacia* complex and some fungi. Lymph node and skin infections have decreased overall and constitute only about 20% of the infections seen in NIH patients.

Use of long term prophylaxis

Antibacterial (trimethoprim/sulfamethoxazole) and antifungal (itraconazole) prophylaxis have significantly reduced the rates and severity of infections in CGD, but breakthrough infections still occur.[21–23] Prophylactic antibiotics were used in 93% of NIH CGD patients, with trimethoprim/sulfamethoxazole the most frequent. Intolerance to sulfamethoxazole or other adverse events typically led to use of trimethoprim alone, cephalosporins, or quinolones.

Fungal prophylaxis was used by only 68% of the patients, though recommended for all CGD patients. Of these, 55% were on itraconazole, 30% on posaconazole and 15% on voriconazole. Typically patients on the latter two were receiving them after having been treated for an invasive fungal infection. There are no data in patients with CGD comparing voriconazole, posaconazole or itraconazole. A single center transplant study did show better outcomes with posaconazole as compared to itraconazole; however direct extrapolation to CGD patients may not be appropriate.[24]

Mild toxicity related to drugs was recorded in 36% of the overall NIH cohort, 15% of whom had photosensitivity, most likely due to voriconazole or trimethoprim/sulfamethoxazole. Severe photosensitivity leading to squamous cell carcinoma and melanoma has been reported with long-term voriconazole.[25, 26] Patients receiving voriconazole should use aggressive sun protection. For patients with severe voriconazole-induced photosensitivity, despite sun avoidance, posaconazole causes less photoreactivity.

Interferon gamma (IFN) was shown in 1991 to be effective prophylaxis for CGD.[27] However, use in Europe has been less than in the United States as non-randomized European data suggested less benefit from IFN use.[28] Even in our own cohort, with the advent of better antifungals and more active oral antibiotics, the percentage on INF is only 36% due to intolerance or lack of access. Fevers, myalgias and irritability were reported as reasons for stopping the IFN in 13% of patients in one study. [29]

Renal failure or severe dysfunction occurred in 3.5% of our patients, probably due to long-term amphotericin exposure before the advent of newer agents.

Inflammatory Complications and Autoimmunity in CGD

Dysregulated inflammation in CGD typically occurs in response to a trigger and may be due to either elevated pro-inflammatory or decreased anti-inflammatory mediators. Patients with CGD frequently experience inflammatory complications and some may develop autoimmune problems.[30]

Other than infection, a characteristic feature of CGD is granulomatous inflammation. CGD granulomas are typically non-caseating, composed of multinucleated giant cells, and can be found in multiple tissues, including brain, lungs, liver, spleen and gastrointestinal tract. When present in hollow viscera they can lead obstruction, such as the gastric outlet or ureteral obstruction that are relatively common in X-linked CGD. For most of these granulomas no pathogen is identified and they respond rapidly to steroids, suggesting that the inciting event is not an invasive infectious one. Surgical intervention should be avoided and corticosteroids, when used, are usually started at doses of 1 mg/kg/d and then tapered after one week. In many patients, the symptoms recur when the steroid dose is reduced, thus our current practice is to taper the corticosteroid dose gradually to around 0.1mg/kg/day on alternate days. Patients with recurring problems may be kept on low dose prednisone for years, which does not appear to increase infection rates or impair growth.[6]

A unique presentation in CGD is an acute pneumonitis due to the inhalation of mulch or other decayed organic matter (e.g., potting soil, hay, leaves). Exposure to a large burden of fungal elements and spores triggers an acute inflammatory response leading to fever, hypoxia, and diffuse infiltrates, usually beginning within one week of the exposure.[31] Similar responses are seen in CGD mice exposed to live or even dead fungi, [32] indicating that some of this pathology is due to dysregulated inflammation rather than infection *per se*. Bronchoscopies and lung biopsies may yield one or more fungal pathogens, especially *Aspergillus*. In addition to rapid institution of antifungals, moderately high doses of prednisone (1 mg/kg/day), help prevent respiratory failure and may facilitate more successful healing.[31, 33]

Inflammatory lesions without demonstrated pathogens have also been noted in the lungs of CGD patients, and are characterized by discrete infiltrates on chest CT that wax and wane without intervention. In some patients diffuse pulmonary inflammation can progress to hypoxia and functional limitation.[34] It is difficult to exclude infection despite negative cultures, cytology, nucleic acid testing and the lack of improvement in response to antibacterial or antifungal agents. However, in some cases empiric treatment beyond corticosteroids has included methotrexate. Progressive lung inflammation with augmented NF-kB activation and elevated pro-inflammatory cytokines has been recently demonstrated in CGD mice (p47- and gp91^{phox}-deficient) following intratracheal challenge with zymosan or LPS.[35]

Inflammatory bowel disease characterized by granulomatous involvement of the bowel especially in the perirectal area is hard to distinguish pathologically from Crohn's disease. However, the inflammatory bowel disease of CGD is typically limited to the bowel and unassociated with any of the extra-intestinal manifestations often seen in Crohn's. In the NIH series 43% of X-linked and 11% of p47phox deficient patients had biopsy-proven symptomatic bowel disease.[6] How many had active subclinical disease remains unknown. Other autoimmune diseases in CGD patients and carriers have included IgA nephropathy, anti-phospholipid syndrome, systemic lupus erythematosus, idiopathic thrombocytopenic purpura and juvenile idiopathic arthritis.[7] An estimated 10% of the CGD patients followed

at NIH have some autoimmune manifestation other than inflammatory bowel disease. The underlying etiology for this predisposition to autoimmunity remains unknown. Polymorphisms in a few genes have been loosely associated with inflammatory complications in CGD (MPO, mannose binding lectin, Fc receptors IIa, IIIa and IIIb, TNFa and IL-1 receptor).[36]

Dysregulated inflammation may play a role in the development of autoimmune complications in CGD. For example, normal NADPH oxidase activity plays regulatory roles in apoptosis [37–39] and macrophage clearance of apoptotic cells.[40–42] Altered NADPH oxidase function may therefore lead to aberrant macrophage programming, impaired clearance of antigen and intracellular elements with further recruitment of neutrophils and prolonged production of IL-8, IL-1b, caspases and other pro-inflammatory cytokines. [43, 44] Persistence of CGD phagocytes during induced inflammation was reported in human X-CGD[45] and in CGD mouse peritonitis.[46, 47] These diverse studies suggest that the role of the NADPH oxidase in CGD extends far beyond the simple predisposition to infection.

Treatment for inflammatory and autoimmune complications in CGD is problematic since most agents are immune suppressive and immunity is already impaired in CGD. Many patients respond well to corticosteroids, but they may require prolonged courses. Sulphasalazine and azathioprine are useful steroid sparing agents. TNFa inhibitors such as infliximab are effective anti-inflammatories but may significantly increase the risk of severe and even fatal infections. [48] The risk of infection needs to be weighed carefully against the risks of uncontrolled mucosal inflammation or surgery that may be further complicated by persistent inflammation, abscesses, and fistulae formation at surgical sites. If TNF inhibitors are used, augmented prophylaxis and enhanced vigilance regarding exposures are mandatory. Methotrexate and plaquenil can be effective in those with arthritides or lupus-like problems.

Hematopoietic Stem Cell Transplantation for Chronic Granulomatous Disease

Currently the only known cure for CGD is allogeneic hematopoietic cell transplantation. Historically this has only been reluctantly offered due to risks of procedure related morbidity and mortality. Additionally, unrelated donor transplants were riskier than sibling transplants, and the pool of donors was limited. From 1973, when the first CGD bone marrow transplant was performed, until now, 99 transplants, not including cord blood recipients, have been published, with the majority being single case reports. [49–70] However, of the 99 patients transplanted, 50 have occurred in the last 10 years compared to 49 in the prior 27 years. With the advent of non-myeloablative regimens, the risks surrounding transplant have decreased and have permitted transplantation in patients with ongoing infections. Additionally, more transplants are being performed using unrelated donors. Notably, the first transplant ever performed for CGD used an unrelated donor and to date 22 patients have been transplanted using unrelated donors with the majority being performed within the last ten years.

Hematopoietic stem cell transplant has been more frequently offered to European patients with CGD than in North America. The first large report of bone marrow transplantation for CGD was from a group of European centres describing the results in 27 patients transplanted from 1985 to 2000 (7 of whom were described previously in single case reports).[65] HLA matched sibling donors were used for 25 of these cases and the majority received a myeloablative, busulfan-based regimen. In nine patients transplanted during a refractory infection, there were 2 graft failures and severe Graft versus Host Disease (GvHD) in 3, with one patient dying as a result.

In the largest North American study published to date, Horwitz et al. reported the outcomes of 10 patients who received a fully matched sibling donor transplant with a non-myeloablative conditioning regimen of fludarabine, cyclophosphamide, and antithymocyte globulin (ATG).[69] Stem cell products were T-cell depleted and donor lymphocyte infusions were given post transplant to augment engraftment. Eight patients engrafted, but one had significant GvHD resulting in death, with one additional patient dying 18 months post transplant with pneumococcal sepsis despite full myeloid engraftment. Of the non-engrafted patients, both survived and went on to re-transplant with one dying subsequently. Long term follow up in the engrafted patients show stable mixed chimerism in two, including donor lymphoid engraftment of less than 50% in one patient but continued myeloid engraftment, with more than 10 years follow up. All surviving patients with engraftment remain phenotypically well with no evidence of CGD related autoimmune complications or infections.

In 2009, a survey of North American centers treating patients with CGD performed in conjunction with the Center for International Blood and Marrow Transplant Research (CIBMTR) found 59 patients had undergone allogeneic transplant for CGD with 71% survival overall. Three of these patients had survived beyond 10 years, but outcome data are not published. As transplant methods have changed, efforts are underway to comprehensively compile the North American CGD transplant experience both retrospectively and prospectively.

Two other large single-centre studies were recently published, both from European centres. Soncini *et al.* described the results in 20 patients transplanted from 1998 to 2007, one of whom was previously reported as a single case study. Patients ranged in age from 15 months to 21 years. Ten of those were with matched sibling donors, nine using bone marrow and one receiving cord blood. The remainder received transplants from matched and single mismatched unrelated donors, including one cord blood transplant. The follow up ranged from 4 to 117 months; 18 patients survived with continued normal neutrophil function (90%) and two died from pretransplant fungal infections. The majority of the patients received a busulphan/cyclophosphamide conditioning regimen with alemtuzumab added for those receiving unrelated donor products.[70] Schuetz *et al.* also reported 12 patients, 9 of whom received grafts from unrelated donors. The majority received busulfan/ cyclophosphamide with or without either ATG or alemtuzumab. Two patients had graft failure and 5 patients had Grade 1 or 2 acute GvHD. At a mean follow up of 53 months, 9 of the 12 were alive including 7 of the 9 recipients of matched unrelated transplants, all with stable engraftment, including one patient with mixed chimerism. [62]

Most recently a European consortium reported good engraftment rates and minimal GvHD using a non-myeloablative busulfan and fludarabine based regimen for both matched related and matched unrelated donors. The intravenous busulfan dose was targeted to achieve an AUC between 45–65mg/h and either ATG or alemtuzumab was added along with mycophenolate mofetil for graft versus host disease prophylaxis. Of their 24 patients, 9 had matched unrelated donors. Eight patients developed grade 1 acute GvHD, one patient had Grade 2 and one patient had chronic GvHD of the skin only, which responded to treatment. Their only death post transplant was due to pneumonia giving an overall survival to date of 96%. [71]

Preliminary data from the NIH, also suggest that intravenous busulfan may be an integral part of transplant conditioning for patients with CGD. The doses we used were lower than used by Gungor et al., at least based upon the AUCs measured. Fludarabine was not a part of the regimen but alemtuzumab was. 300cGy of total body irradiation(TBI) was also administered to patients receiving unrelated donor grafts. Eleven patients were described by

NIH, 9 received unrelated donor products and patients ranged in age from 3 to 32. There was one failure to engraft using an unrelated cord blood product, and late graft rejection occurred in one patient who received an unrelated donor product. The remainder had almost one hundred percent myeloid engraftment with excellent NADPH oxidase function. There were only two patients with GvHD, both in the skin (one grade 1 and one grade 2). One patient died from renal dysfunction unrelated to transplant, the rest are alive and well, including both patients with graft failure, giving an overall survival of 10/11 or 91%. Notably 9 of the 11 patients had ongoing infection at the time of transplant, and 4 received granulocyte transfusions during the peritransplant neutropenia period.[72]

Cord Blood

The first cord blood transplant for CGD was an 8 year old male transplanted with an unrelated donor matching at 5 of 6 loci published in 1999 by Nakano et al.[73] He was conditioned with 10 Gy TBI, ATG, and cyclophosphamide, but died at day 51 due to infection. Seven subsequent patients have been reported as having received cord blood products, either from related or unrelated donors.[54, 64, 70, 74–77] Three of the patients have required second transplants. One patient received his initial cord blood product for his re-transplant. All appear to have done well, even when a cord product was used for both transplants. More recently with advanced genetic and fertility techniques, three cases of preimplantation selection have resulted in live births of siblings who have provided either cord blood and/or bone marrow. The patients who received these products appear to be doing well.[78, 79]

Discussion

Allogeneic stem cell transplantation for CGD is becoming more common and reflects increased overall transplant success. Survival has increased from approximately 85% prior to 2000 to 90–95%, based on recently reported outcomes and our own results, even with the use of unrelated donors. In fact, outcomes with perfectly HLA matched unrelated donors appear to approach if not equal those using HLA sibling donors. This suggests that donor availability should not be limiting for transplant of CGD patients.

Even for those without a matched unrelated donor, cord blood products are proving to be a reasonable alternative, and are being used more frequently. Even in adults, double cord products have had good engraftment rates, at least in the setting of leukemia. [80] In one study, the non-relapse mortality was slightly higher for recipients of double cord products compared to those receiving matched unrelated or matched related donor products. Studies will be needed in CGD to determine if a double cord transplant is preferable to an unrelated donor transplant.[81] Although one published case used a haploidentical donor, the patient rejected requiring a second transplant.[54].

Both peripheral blood stem cells and marrow have been used successfully, and the choice for CGD patients currently depends on donor and center preferences. Data from transplants in aplastic anemia suggest that bone marrow products result in less GvHD; however cell dose can be a limiting factor.[82] Older patients with CGD often have splenomegaly and/or hepatomegaly, thereby requiring a larger cell dose. Although T cell depletion of products has been used in transplants for patients with CGD, the incidence of GvHD with donor lymphocyte infusion is significant, as seen in the first NIH series.[69] *In vivo* or *in vitro* T-cell depletion with alemtuzumab appears to result in less GvHD without significantly affecting engraftment, although the need for viral monitoring is prolonged.

Some transplant centers prefer myeloablative transplant regimens.[65] Although graft rejection is more likely with a reduced intensity conditioning regimen, the risk of GvHD, particularly

acute GvHD, and regimen related toxicity, appears to be reduced with the non-myeloablative regimens. [83–85] This type of conditioning also allows transplantation during ongoing infection, with fewer infection related deaths. Further, those who have rejected after receiving reduced intensity conditioning have for the most part gone on to successful second transplants. On the other hand, patients with McLeod syndrome, (Kell antigen deficiency due to contiguous gene deletion of XK which is found next to the CYBB gene), who have red cell antigen sensitization should be considered for a myeloablative regimen, or at least pretreatment with rituximab, to limit red cell incompatibility as the availability of McLeod matched blood is extremely limited. Elimination of B cells with anti-CD 20 therapy prior to transplant diminishes the risk of transfusion reactions and makes red cell management easier during the transplant period prior to conversion to donor blood type.[51] Those without preexisting red cell antibodies however, have successfully undergone non-myeloablative transplant.[64] Most successful regimens in CGD patients appear to include busulfan. Some consider fludarabine necessary as well; however, the experience at NIH does not support this.

The question remains of which CGD patient to transplant? Given the current success rates, some favour transplanting all CGD patients who have an appropriate donor at the earliest opportunity. The recent data from Kuhns et al, showed that patients with very low superoxide production had worse long term survival than those with higher levels of NADPH oxidase activity suggesting that these patients might be considered appropriate candidates for early transplantation, particularly if a sibling matched donor is available. [3] However, even within this subgroup, there are patients who do relatively well for prolonged periods. Elevated alkaline phosphatase, a history of liver abscesses, and decline in platelet count reflecting portal hypertension are adverse prognostic indicators.[86] These patients may also be considered for early transplantation.

Even with improved survival and longevity due to better infection and inflammation management, complications and their consequences can accumulate over time. However, transplant outcomes are probably better before infectious and inflammatory damage accumulate. Transplant has reversed some of the inflammatory and autoimmune complications associated with CGD and may prevent their development.[65] Therefore, patients with significant inflammatory or autoimmune disease should also be at least evaluated for transplant, preferably at a center with experience in CGD transplantation. Those who have an active infection should not be summarily excluded, as non-myeloablative regimens have been successful even in this setting. Additionally, granulocyte transfusions may be helpful during the transplant period for those with active infections and do not appear to impact on engraftment. [87] For those with a prior history of infections, including fungal infections but no active infection, the necessity to use granulocytes is not clear. Patients who are being considered for transplant should not receive granulocytes prior to transplant (as opposed to during) so as to avoid the development of HLA alloimmunization.

While overall CGD life expectancy is still less than the general population even with the best current care, the strides in infection and inflammation management over the last decades have been significant. Allogeneic hematopoietic transplantation may have unanticipated consequences, and even the reduced intensity regimens may pose unknown long-term risks. Although there has been strong interest and progress in gene based therapies, it has not been shown to be curative at this point and has been reviewed elsewhere.[88] Further, even ex vivo gene therapy appears to require some form of conditioning, so cytoreductive agents may still be needed.[89–91]

However, allogeneic transplantation has also improved dramatically over the last decade, due to improved conditioning regimens and GvHD prophylaxis, high resolution sequence based matching, and improved pre-, peri- and post- transplant management. It has become a successful and sensible option for many patients with CGD, that will likely treat and prevent both infectious and inflammatory complications. While further studies will be required to determine optimal timing, donor selection, and long-term efficacy in these patients, hematopoietic stem cell transplant is finally coming of age as a curative treatment of CGD.

Abbreviations

ATG	Antithymocyte Globulin
AUC	Area under the Curve
CGD	Chronic Granulomatous Disease
CT	Computerized tomography
GvHD	Graft versus Host Disease
IFN	Interferon Gamma
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health

References

1. Segal BH, DeCarlo ES, Kwon-Chung KJ, Malech HL, Gallin JI, Holland SM. Aspergillus nidulans infection in chronic granulomatous disease. Medicine (Baltimore). 1998; 77:345–54. [PubMed: 9772923]
2. Matute JD, Arias AA, Wright NA, Wrobel I, Waterhouse CC, Li XJ, et al. A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40 phox and selective defects in neutrophil NADPH oxidase activity. Blood. 2009; 114:3309–15. [PubMed: 19692703]
3. Kuhns DB, Alvord WG, Heller T, Feld JJ, Pike KM, Marciano BE, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010; 363:2600–10. [PubMed: 21190454]
4. Martire B, Rondelli R, Soresina A, Pignata C, Broccoletti T, Finocchi A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. Clin Immunol. 2008; 126:155–64. [PubMed: 18037347]
5. Kobayashi S, Murayama S, Takanashi S, Takahashi K, Miyatsuka S, Fujita T, et al. Clinical features and prognoses of 23 patients with chronic granulomatous disease followed for 21 years by a single hospital in Japan. Eur J Pediatr. 2008; 167:1389–94. [PubMed: 18335239]
6. Marciano BE, Rosenzweig SD, Kleiner DE, Anderson VL, Darnell DN, Anaya- O'Brien S, et al. Gastrointestinal involvement in chronic granulomatous disease. Pediatrics. 2004; 114:462–8. [PubMed: 15286231]
7. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000; 79:155–69. [PubMed: 10844935]
8. Vinh DC, Shea YR, Jones PA, Freeman AF, Zelazny A, Holland SM. Chronic invasive aspergillosis caused by Aspergillus viridinutans. Emerg Infect Dis. 2009; 15:1292–4. [PubMed: 19751595]
9. van den Berg JM, van Koppen E, Ahlin A, Belohradsky BH, Bernatowska E, Corbeel L, et al. Chronic granulomatous disease: the European experience. PLoS One. 2009; 4:e5234. [PubMed: 19381301]
10. Greenberg DE, Ding L, Zelazny AM, Stock F, Wong A, Anderson VL, et al. A novel bacterium associated with lymphadenitis in a patient with chronic granulomatous disease. PLoS Pathog. 2006; 2:e28. [PubMed: 16617373]

11. Reichenbach J, Lopatin U, Mahlaoui N, Beovic B, Siler U, Zbinden R, et al. Actinomyces in chronic granulomatous disease: an emerging and unanticipated pathogen. Clin Infect Dis. 2009; 49:1703–10. [PubMed: 19874205]
12. Vinh DC, Shea YR, Sugui JA, Parrilla-Castellar ER, Freeman AF, Campbell JW, et al. Invasive aspergillosis due to Neosartorya udagawae. Clin Infect Dis. 2009; 49:102–11. [PubMed: 19489714]
13. Messina CG, Reeves EP, Roes J, Segal AW. Catalase negative Staphylococcus aureus retain virulence in mouse model of chronic granulomatous disease. FEBS Lett. 2002; 518:107–10. [PubMed: 11997027]
14. Dorman SE, Guide SV, Conville PS, DeCarlo ES, Malech HL, Gallin JI, et al. Nocardia infection in chronic granulomatous disease. Clin Infect Dis. 2002; 35:390–4. [PubMed: 12145721]
15. Segal BH, Barnhart LA, Anderson VL, Walsh TJ, Malech HL, Holland SM. Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. Clin Infect Dis. 2005; 40:1684–8. [PubMed: 15889369]
16. Huang YF, Liu SY, Yen CL, Yang PW, Shieh CC. Thapsigargin and flavin adenine dinucleotide ex vivo treatment rescues trafficking-defective gp91phox in chronic granulomatous disease leukocytes. Free Radic Biol Med. 2009; 47:932–40. [PubMed: 19631269]
17. Brechard S, Tschirhart EJ. Regulation of superoxide production in neutrophils: role of calcium influx. J Leukoc Biol. 2008; 84:1223–37. [PubMed: 18519744]
18. Lublin M, Bartlett DL, Danforth DN, Kauffman H, Gallin JI, Malech HL, et al. Hepatic abscess in patients with chronic granulomatous disease. Ann Surg. 2002; 235:383–91. [PubMed: 11882760]
19. Yamazaki-Nakashimada MA, Stiehm ER, Pietropaolo-Cienfuegos D, Hernandez-Bautista V, Espinosa-Rosales F. Corticosteroid therapy for refractory infections in chronic granulomatous disease: case reports and review of the literature. Annals of Allergy, Asthma & Immunology. 2006; 97:257–61.
20. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM. Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore). 2000; 79:170–200. [PubMed: 10844936]
21. Gallin JI, Alling DW, Malech HL, Wesley R, Koziol D, Marciano B, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med. 2003; 348:2416–22. [PubMed: 12802027]
22. Beaute J, Obenga G, Le Mignot L, Mahlaoui N, Bougnoux ME, Mouy R, et al. Epidemiology and Outcome of Invasive Fungal Diseases in Patients With Chronic Granulomatous Disease: A Multicenter Study in France. Pediatr Infect Dis J. 2010
23. Mouy R, Veber F, Blanche S, Donadieu J, Brauner R, Levron JC, et al. Long-term itraconazole prophylaxis against Aspergillus infections in thirty-two patients with chronic granulomatous disease. J Pediatr. 1994; 125:998–1003. [PubMed: 7996377]
24. Sanchez-Ortega I, Patino B, Arnan M, Peralta T, Parody R, Gudiol C, et al. Clinical efficacy and safety of primary antifungal prophylaxis with posaconazole vs itraconazole in allogeneic blood and marrow transplantation. Bone Marrow Transplant. 2010
25. Cowen EW, Nguyen JC, Miller DD, McShane D, Arron ST, Prose NS, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. J Am Acad Dermatol. 2010; 62:31–7. [PubMed: 19896749]
26. Miller DD, Cowen EW, Nguyen JC, McCalmont TH, Fox LP. Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. Arch Dermatol. 2010; 146:300–4. [PubMed: 20083676]
27. The International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. N Engl J Med. 1991; 324:509–16. [PubMed: 1846940]
28. Mouy R, Seger R, Bourquin JP, Veber F, Blanche S, Griscelli C, et al. Interferon gamma for chronic granulomatous disease. N Engl J Med. 1991; 325:1516–7. [PubMed: 1944433]
29. Marciano BE, Wesley R, De Carlo ES, Anderson VL, Barnhart LA, Darnell D, et al. Long-term interferon-gamma therapy for patients with chronic granulomatous disease. Clin Infect Dis. 2004; 39:692–9. [PubMed: 15356785]

30. De Ravin SS, Naumann N, Cowen EW, Friend J, Hilligoss D, Marquesen M, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. J Allergy Clin Immunol. 2008; 122:1097–103. [PubMed: 18823651]

31. Ameratunga R, Woon ST, Vyas J, Roberts S. Fulminant mulch pneumonitis in undiagnosed chronic granulomatous disease: a medical emergency. Clin Pediatr (Phila). 2010; 49:1143–6. [PubMed: 20724349]

32. Morgenstern DE, Gifford MA, Li LL, Doerschuk CM, Dinauer MC. Absence of respiratory burst in X-linked chronic granulomatous disease mice leads to abnormalities in both host defense and inflammatory response to Aspergillus fumigatus. J Exp Med. 1997; 185:207–18. [PubMed: 9016870]

33. Siddiqui S, Anderson VL, Hilligoss DM, Abinun M, Kuijpers TW, Masur H, et al. Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. Clin Infect Dis. 2007; 45:673–81. [PubMed: 17712749]

34. Brown KL, Bylund J, MacDonald KL, Song-Zhao GX, Elliott MR, Falsafi R, et al. ROS-deficient monocytes have aberrant gene expression that correlates with inflammatory disorders of chronic granulomatous disease. Clin Immunol. 2008; 129:90–102. [PubMed: 18676204]

35. Segal BH, Han W, Bushey JJ, Joo M, Bhatti Z, Feminella J, et al. NADPH oxidase limits innate immune responses in the lungs in mice. PLoS One. 2010; 5:e9631. [PubMed: 20300512]

36. Foster MH, Fitzsimons MM. Lupus-like nephrotropic autoantibodies in non-autoimmune mice harboring an anti-basement membrane/anti-DNA Ig heavy chain transgene. Mol Immunol. 1998; 35:83–94. [PubMed: 9683254]

37. Yamamoto A, Taniuchi S, Tsuji S, Hasui M, Kobayashi Y. Role of reactive oxygen species in neutrophil apoptosis following ingestion of heat-killed Staphylococcus aureus. Clin Exp Immunol. 2002; 129:479–84. [PubMed: 12197889]

38. Frasch SC, Berry KZ, Fernandez-Boyanapalli R, Jin HS, Leslie C, Henson PM, et al. NADPH oxidase-dependent generation of lysophosphatidylserine enhances clearance of activated and dying neutrophils via G2A. J Biol Chem. 2008; 283:33736–49. [PubMed: 18824544]

39. Arroyo A, Modriansky M, Serinkan FB, Bello RI, Matsura T, Jiang J, et al. NADPH oxidase-dependent oxidation and externalization of phosphatidylserine during apoptosis in Me2SO-differentiated HL-60 cells. Role in phagocytic clearance. J Biol Chem. 2002; 277:49965–75. [PubMed: 12376550]

40. Fernandez-Boyanapalli R, McPhillips KA, Frasch SC, Janssen WJ, Dinauer MC, Riches DW, et al. Impaired phagocytosis of apoptotic cells by macrophages in chronic granulomatous disease is reversed by IFN-gamma in a nitric oxide-dependent manner. J Immunol. 2010; 185:4030–41. [PubMed: 20805415]

41. Fernandez-Boyanapalli R, Frasch SC, Riches DW, Vandivier RW, Henson PM, Bratton DL. PPAR{gamma} activation normalizes resolution of acute sterile inflammation in murine chronic granulomatous disease. Blood. 2010; 116:4512–22. [PubMed: 20693431]

42. Fernandez-Boyanapalli RF, Frasch SC, McPhillips K, Vandivier RW, Harry BL, Riches DW, et al. Impaired apoptotic cell clearance in CGD due to altered macrophage programming is reversed by phosphatidylserine-dependent production of IL-4. Blood. 2009; 113:2047–55. [PubMed: 18952895]

43. Lekstrom-Himes JA, Kuhns DB, Alvord WG, Gallin JI. Inhibition of human neutrophil IL-8 production by hydrogen peroxide and dysregulation in chronic granulomatous disease. J Immunol. 2005; 174:411–7. [PubMed: 15611265]

44. Fadok VA, Bratton DL, Guthrie L, Henson PM. Differential effects of apoptotic versus lysed cells on macrophage production of cytokines: role of proteases. J Immunol. 2001; 166:6847–54. [PubMed: 11359844]

45. Gallin JI, Buescher ES. Abnormal regulation of inflammatory skin responses in male patients with chronic granulomatous disease. Inflammation. 1983; 7:227–32. [PubMed: 6681319]

46. Jackson SH, Gallin JI, Holland SM. The p47phox mouse knock-out model of chronic granulomatous disease. J Exp Med. 1995; 182:751–8. [PubMed: 7650482]

47. Segal BH, Kuhns DB, Ding L, Gallin JI, Holland SM. Thioglycollate peritonitis in mice lacking C5, 5-lipoxygenase, or p47(phox): complement, leukotrienes, and reactive oxidants in acute inflammation. J Leukoc Biol. 2002; 71:410–6. [PubMed: 11867678]
48. Uzel G, Orange JS, Poliak N, Marciano BE, Heller T, Holland SM. Complications of tumor necrosis factor-alpha blockade in chronic granulomatous disease-related colitis. Clin Infect Dis. 2010; 51:1429–34. [PubMed: 21058909]
49. Gungor T, Halter J, Klink A, Junge S, Stumpe KD, Seger R, et al. Successful low toxicity hematopoietic stem cell transplantation for high-risk adult chronic granulomatous disease patients. Transplantation. 2005; 79:1596–606. [PubMed: 15940051]
50. Klaudel-Dreszler MA, Kalwak K, Kurenko-Deptuch M, Wolska-Kusnierz B, Heropolitanska-Pliszka E, Pietrucha B, et al. Treosulfan-based conditioning regimen in a second matched unrelated peripheral blood stem cell transplantation for a pediatric patient with CGD and invasive aspergillosis, who experienced initial graft failure after RIC. Int J Hematol. 2009; 90:571–5. [PubMed: 19866337]
51. Honig M, Flegel WA, Schwarz K, Freihorst JF, Baumann U, Seltsam A, et al. Successful hematopoietic stem-cell transplantation in a patient with chronic granulomatous disease and McLeod phenotype sensitized to Kx and K antigens. Bone Marrow Transplant. 2010; 45:209–11. [PubMed: 19503108]
52. Horn B, Soni S, Khan S, Petrovic A, Breslin N, Cowan M, et al. Feasibility study of preemptive withdrawal of immunosuppression based on chimerism testing in children undergoing myeloablative allogeneic transplantation for hematologic malignancies. Bone Marrow Transplant. 2009; 43:469–76. [PubMed: 18955982]
53. Kansoy S, Kutukculer N, Aksoylar S, Aksu G, Kantar M, Cetingul N. Successful bone marrow transplantation in an 8-month-old patient with chronic granulomatous disease. Turk J Pediatr. 2006; 48:253–5. [PubMed: 17172071]
54. Kikuta A, Ito M, Mochizuki K, Akaihata M, Nemoto K, Sano H, et al. Nonmyeloablative stem cell transplantation for nonmalignant diseases in children with severe organ dysfunction. Bone Marrow Transplant. 2006; 38:665–9. [PubMed: 17013427]
55. Kordes U, Binder TM, Eiermann TH, Hassenpflug-Diedrich B, Hassan MA, Beutel K, et al. Successful donor-lymphocyte infusion for extreme immune-hemolysis following unrelated BMT in a patient with X-linked chronic granulomatous disease and McLeod phenotype. Bone Marrow Transplant. 2008; 42:219–20. [PubMed: 18560413]
56. Miki M, Ono A, Awaya A, Miyagawa S, Onodera R, Kurita E, et al. Successful bone marrow transplantation in chronic granulomatous disease. Pediatr Int. 2009; 51:838–41. [PubMed: 20158628]
57. Ozyurek E, Cowan MJ, Koerper MA, Baxter-Lowe LA, Dvorak CC, Horn BN. Increasing mixed chimerism and the risk of graft loss in children undergoing allogeneic hematopoietic stem cell transplantation for non-malignant disorders. Bone Marrow Transplant. 2008; 42:83–91. [PubMed: 18391990]
58. Petrovic A, Dorsey M, Miotke J, Shepherd C, Day N. Hematopoietic stem cell transplantation for pediatric patients with primary immunodeficiency diseases at All Children's Hospital/University of South Florida. Immunologic Research. 2009; 44:169–78. [PubMed: 19471860]
59. Rappeport JM, Newburger PE, Goldblum RM, Goldman AS, Nathan DG, Parkman R. Allogeneic bone marrow transplantation for chronic granulomatous disease. J Pediatr. 1982; 101:952–5. [PubMed: 6754900]
60. Ringden O, Remberger M, Svenberg P, Svahn BM, Dahllof G, Gustafsson B, et al. Fludarabine-based disease-specific conditioning or conventional myeloablative conditioning in hematopoietic stem cell transplantation for treatment of non-malignant diseases. Bone Marrow Transplant. 2007; 39:383–8. [PubMed: 17310137]
61. Sastry J, Kakakios A, Tugwell H, Shaw PJ. Allogeneic bone marrow transplantation with reduced intensity conditioning for chronic granulomatous disease complicated by invasive Aspergillus infection. Pediatr Blood Cancer. 2006; 47:327–9. [PubMed: 16628555]
62. Schuetz C, Hoenig M, Gatz S, Speth F, Benninghoff U, Schulz A, et al. Hematopoietic stem cell transplantation from matched unrelated donors in chronic granulomatous disease. Immunologic Research. 2009; 44:35–41. [PubMed: 18846320]

63. Schuetz C, Hoenig M, Schulz A, Lee-Kirsch MA, Roesler J, Friedrich W, et al. Successful unrelated bone marrow transplantation in a child with chronic granulomatous disease complicated by pulmonary and cerebral granuloma formation. Eur J Pediatr. 2007; 166:785–8. [PubMed: 17103189]
64. Suzuki N, Hatakeyama N, Yamamoto M, Mizue N, Kuroiwa Y, Yoda M, et al. Treatment of McLeod phenotype chronic granulomatous disease with reduced-intensity conditioning and unrelated-donor umbilical cord blood transplantation. Int J Hematol. 2007; 85:70–2. [PubMed: 17261504]
65. Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, Di Bartolomeo P, et al. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985–2000. Blood. 2002; 100:4344–50. [PubMed: 12393596]
66. Soncini E, Slatter MA, Jones LBKR, Hughes S, Hodges S, Flood TJ, et al. Unrelated donor and HLA-identical sibling haematopoietic stem cell transplantation cure chronic granulomatous disease with good long-term outcome and growth. British Journal of Haematology. 2009; 145:73–83. [PubMed: 19222467]
67. Del Giudice I, Iori AP, Mengarelli A, Testi AM, Romano A, Cerretti R, et al. Allogeneic stem cell transplant from HLA-identical sibling for chronic granulomatous disease and review of the literature. Ann Hematol. 2003; 82:189–92. [PubMed: 12634956]
68. Yokoyama S, Kasahara M, Fukuda A, Sato S, Mori T, Nakagawa A, et al. Successful living-donor liver transplantation for chronic hepatic graft-versus-host disease after bone marrow transplantation for chronic granulomatous disease. Transplantation. 2008; 86:367–8. [PubMed: 18645505]
69. Horwitz ME, Barrett AJ, Brown MR, Carter CS, Childs R, Gallin JI, et al. Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T-cell-depleted hematopoietic allograft. N Engl J Med. 2001; 344:881–8. [PubMed: 11259721]
70. Soncini E, Slatter M, Jones L, Hughes S, Flood T, Barge D, et al. Haematopoeitic stem cell transplantation for chronic granulomatous disease - a single-centre experience. Bone Marrow Transplantation. 2008; 41:S28–S.
71. Gungor, T.; Albert, M.; Schanz, U.; Slater, M.; Gennery, A.; Waver, A.; Teira, P.; Haddad, e; Ahmad, I.; Lachance, S.; Shaw, P.; Stepensky, P.; Resnik, I.; Seger, R.; Hassan, M. Successful low-dose busulfan/ full-dose fludarabine based reduced intensity conditioning in high risk pediatric and adult chronic ganulomatous disease patients. XIVth Meeting of the European Society for Immunodeficiencies; Istanbul, Turkey. 2010. p. 1
72. Kang EM, Kelly C, Hilligoss D, Marquesen M, DeCastro R, Wilder J, Kwatemaa A, Khuu H, Stroncek D, Malech H. A novel non-myeloablative regimen for related and unrelated allogeneic transplantation of high risk patients with chronic granulomatous disease (CGD). Biology of Blood and Marrow Transplantation. 2011; 17:1. [PubMed: 20685255]
73. Nakano T, Boku E, Yoshioka A, Fukimara Y. A Case of McLeod Phenotype Chronic Granulomatous Disease who Received Unrelated Cord Blood Transplantation. Journal of Pediatric Hematology. 1999; 12:264.
74. Jaing TH, Lee WI, Cheng PJ, Chen SH, Huang JL, Soong YK. Successful unrelated donor cord blood transplantation for chronic granulomatous disease. Int J Hematol. 2010; 91:670–2. [PubMed: 20224873]
75. Mochizuki K, Kikuta A, Ito M, Akaihata M, Sano H, Ohto H, et al. Successful unrelated cord blood transplantation for chronic granulomatous disease: a case report and review of the literature. Pediatr Transplant. 2009; 13:384–9. [PubMed: 18627513]
76. Parikh SH, Szabolcs P, Prasad VK, Lakshminarayanan S, Martin PL, Driscoll TA, et al. Correction of chronic granulomatous disease after second unrelated-donor umbilical cord blood transplantation. Pediatr Blood Cancer. 2007; 49:982–4. [PubMed: 17941061]
77. Bhattacharya A, Slatter M, Curtis A, Chapman CE, Barge D, Jackson A, et al. Successful umbilical cord blood stem cell transplantation for chronic granulomatous disease. Bone Marrow Transplant. 2003; 31:403–5. [PubMed: 12634733]
78. Reichenbach J, Van de Velde H, De Rycke M, Staessen C, Platteau P, Baetens P, et al. First successful bone marrow transplantation for X-linked chronic granulomatous disease by using

preimplantation female gender typing and HLA matching. Pediatrics. 2008; 122:e778–82. [PubMed: 18762514]

79. Goussetis E, Konialis CP, Peristeri I, Kitra V, Dimopoulou M, Petropoulou T, et al. Successful hematopoietic stem cell transplantation in 2 children with X-linked chronic granulomatous disease from their unaffected HLA-identical siblings selected using preimplantation genetic diagnosis combined with HLA typing. Biol Blood Marrow Transplant. 2010; 16:344–9. [PubMed: 19835970]
80. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, McGlave PB, Miller JS, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood. 2005; 105:1343–7. [PubMed: 15466923]
81. Brunstein CG, Gutman JA, Weisdorf DJ, Woolfrey AE, Defor TE, Gooley TA, et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. Blood. 2010; 116:4693–9. [PubMed: 20686119]
82. Chu, R.; Brazauskas, R.; Kan, F.; Bashey, A.; Bredeson, C.; Camitta, B., et al. Biology of Blood and Marrow Transplantation. Comparison of Outcomes after Transplantation of G-CSF-Stimulated Bone Marrow Grafts versus Bone Marrow or Peripheral Blood Grafts from HLA-Matched Sibling Donors for Patients with Severe Aplastic Anemia. In Press, Uncorrected Proof
83. Couriel DR, Saliba RM, Giralt S, Khouri I, Andersson B, de Lima M, et al. Acute and chronic graft-versus-host disease after ablative and nonmyeloablative conditioning for allogeneic hematopoietic transplantation. Biol Blood Marrow Transplant. 2004; 10:178–85. [PubMed: 14993883]
84. Diaconescu R, Flowers CR, Storer B, Sorror ML, Maris MB, Maloney DG, et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. Blood. 2004; 104:1550–8. [PubMed: 15150081]
85. Sorror ML, Maris MB, Storer B, Sandmaier BM, Diaconescu R, Flowers C, et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. Blood. 2004; 104:961–8. [PubMed: 15113759]
86. Feld JJ, Hussain N, Wright EC, Kleiner DE, Hoofnagle JH, Ahlawat S, et al. Hepatic involvement and portal hypertension predict mortality in chronic granulomatous disease. Gastroenterology. 2008; 134:1917–26. [PubMed: 18439425]
87. Borge DP, DeCastro R, Theobald N, Malech H, Leitman S, Kang EM. Successful Control of Preexistent Active Infection by Granulocyte Transfusions During Condigioning Induced Cytopenia In Patient with Chronic Granulomatous Disease Undergoing Hematopoietic Stem Cell Transplant. Blood. 2010:116.
88. Grez M, Reichenbach J, Schwable J, Seger R, Dinauer MC, Thrasher AJ. Gene therapy of chronic granulomatous disease: the engraftment dilemma. Mol Ther. 2011; 19:28–35. [PubMed: 21045810]
89. Ott MG, Schmidt M, Schwarzwaelder K, Stein S, Siler U, Koehl U, et al. Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med. 2006; 12:401–9. [PubMed: 16582916]
90. Kang EM, Choi U, Theobald N, Linton G, Long Priel DA, Kuhns D, et al. Retrovirus gene therapy for X-linked chronic granulomatous disease can achieve stable long-term correction of oxidase activity in peripheral blood neutrophils. Blood. 2010; 115:783–91. [PubMed: 19965657]
91. Aiuti A, Slavin S, Aker M, Ficara F, Deola S, Mortellaro A, et al. Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. Science. 2002; 296:2410–3. [PubMed: 12089448]

Table 1

Outcomes of transplant in the largest studies to date.

Author (Reference)	Year[1]	Number of Patients	Unrelated	Related	Conditioning Regimen (number of patients per regimen)	GvHD prophylaxis	Number of patients with aGVHD <2	Number of patients with aGVHD>2	cGVHD	Overall Survival Causes of death[2]	DFS
Seger et al. (65)	2002	27	2	25	MA(17): Bu/Cy MA(1):Bu/Mel/Alemtuzumab MA(1):Bu/Cy/ATG MA(1): Bu/Cy/TNI MA(1):Bu/Cy/TT/ATG MA(1):Bu/Flu/ATG NMA(2):Bu/Flu ATG NMA(1): Flu/Cy/ATG NMA(1): Flu/TBI	Cyclosporine (27) Methotrexate (13) Prednisone(4)	3	4	3	23/27 Multiorgan failure, Pneumonia and GVHD, Pneumonia, Nonengraftment with aspergillus and VOD,	22/27
Horwitz et al. (69)	2001	10	0	10	NMA: Cy/Flu with ATG and Donor lymphocyte Infusions	Cyclosporine	3	1	2	7/10 Graft failure with retransplant, Pneumococcal pneumonia, GVHD with fungal infection	6/10
Soncini et al. (66)	2009	20	10	10	MA(16):Bu/Cy, +/− Alemtuzumab^ MA(1):Bu/Mel/Campath1-G NMA(2):Flu/Mel/Alemtuzumab NMA(1)Bu/Flu/Alemtuzumab	Cyclosporine	5	0	3	18/20 Fungal infection	18/20
Schuetz et al. (62)	2009	12	9	3	MA/MSD: Bu/Cy MA/MUD(6): Bu/Cy/Flu + Alemtuzumab or ATG MA/MUD(2): Flu/Mel/RIT* ?/MUD(1): Flu/TBI	Not reported	5	0	2	9/12 Chronic GvHD, ARDS, BK virus	7/12
Gungor et al. (71)	2010	24	9	15	NMA: Dose adjusted IV Bu, Flu, Alemtuzumab	Mycophenolate	9	0	0	23/24 Pneumonia	22/24
Kang et al. (72)	2011	11	9	2	NMA: IV Bu, Alemtuzumab +/− 300cGy radiation^	Rapamycin	2	0	0	10/11 Refusal to continue dialysis	8/11

GvHD-Graft versus Host Disease, a- acute, c-chronic, DFS-Disease Free Survival, MA-Myeloablative, NMA-Nonmyeloablative, Bu-Busulfan, Cy-Cyclophosphamide, Mel-Melphalan, ATG-Antithymocyte Globulin, TNI-Total Nodal Irradiation, TT-Thiotepa, Flu-Fludarabine, RIT-Radioimmunotherapy, VOD-Venoocclusive disease, MSD-Matched Sibling Donor, MUD: Matched Unrelated Donor, ARDS-Acute Respiratory Distress Syndrome,

[1]-Year published,

[2]-Each cause listed per patient

[^]-for unrelated donor recipients,

[*]-Radionimmunotherapy=anti-CD66 Yttrium-90 labeled antibody (17Gy)