Non-Infectious Complications of Chronic Granulomatous Disease

Knowledge Gaps & Novel Treatment Considerations

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KEYWORDS

• Chronic granulomatous disease • Inflammatory complications
• Inflammatory bowel disease • Hematopoietic stem cell transplant • IFN-gamma

KEY POINTS

- Non-infectious complications of chronic granulomatous disease are common and diverse including granuloma formation, inflammatory bowel disease, pulmonary inflammation, and increased autoimmunity.
- The pathogenesis of inflammatory complications is complex but stems from the underlying defect in NADPH oxidase activity, inability to clear infections, and dysregulated immune response.
- Ideal treatment strategies for patients with inflammatory complications are not standardized and immune modulation and potential for increased risk for infection should be carefully balanced.
- Current treatment strategies include the use of glucocorticoids, steroid-sparing immunosuppressive agents, and antimicrobials.
- Ultimately, curative therapies like allogeneic transplant can induce a long-term remission of the inflammatory complications of the disease.

INTRODUCTION

Chronic granulomatous disease (CGD) comprises a rare group of primary immunodeficiencies of the innate immune system affecting phagocytic cells including neutrophils, monocytes, macrophages, and eosinophils.[1] The estimated prevalence of

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Immunol Allergy Clin N Am 45 (2025) 287–298
https://doi.org/10.1016/j.iac.2025.01.004 **immunology.theclinics.com**
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Abbreviations	
CGD	Chronic granulomatous disease
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplantation
IBD	inflammatory bowel disease
IFN-γ	Interferon-gamma
JAK	Janus kinase
phox	phagocyte oxidase
ROS	reactive oxygen species
SNP	single nucleotide polymorphism
STAT	signal transducer and activator of transcription
Th1	T helper 1
TH17	T helper 17

CGD is around 1 in 200,000 live births.[2] It results from a defect in one of the components of the NADPH oxidase enzyme system involved in generating reactive oxygen species (ROS). The classic X-linked version of the disease, which is usually associated with the least residual oxidase activity, is associated with defects in the catalytic component of the oxidase, gp91phox, while the autosomal recessive forms can result from alterations to other cytosolic components like p47phox, p67phox, or p40 phox, or the other membrane component, p22phox. The hallmark of the ensuing clinical phenotype is increased susceptibility to catalase-positive organisms (eg, Staph aureus, Aspergillus, Candida, Burkholderia, Nocardia, etc.), recurrent and severe infections, and increased mortality during early adulthood especially for patients with the least residual oxidase activity.[3]

While the routine institution of prophylactic antimicrobial therapy has improved infection-related outcomes, the clinical burden of inflammatory and autoimmune complications remains incredibly challenging.[4] Non-infectious complications of CGD have long been recognized ranging from the eponymous granuloma formation to organ-specific uncontrolled inflammatory states and increased autoimmunity. These complications can often mimic other inflammatory or autoimmune disorders and may precede or complicate infectious presentations. These complications may affect a wide range of organ systems including the gastrointestinal and genitourinary tracts, lungs, eyes, and skin.

The focus of this review article will be on these non-infectious complications of CGD, with an emphasis on understanding the clinical spectrum of inflammatory and autoimmune manifestations, underlying pathophysiology, and potential targeted treatment options. Despite improved cognizance of potential mechanisms of inflammation in this disorder, the management inflammation-related morbidity remains challenging due to limited knowledge regarding the optimal therapeutic approach. As such, we will explore current treatment strategies, including glucocorticoids, steroid-sparing immunosuppressive agents, antibiotics, and biologics. Finally, we will examine the status of therapeutic strategies with curative intent including allogeneic hematopoietic stem cell transplantation (HSCT) and autologous gene therapies.

CLINICAL SPECTRUM OF INFLAMMATORY AND AUTOIMMUNE COMPLICATIONS

The inflammatory and autoimmune manifestations of CGD are diverse and may affect a variety of different organ systems. The clinical spectrum includes granuloma formation, gastrointestinal inflammation, pulmonary complications, skin and ocular

manifestations, and a range of autoimmune phenomena. The gastrointestinal system is most affected with prevalence rates exceeding 50% of patients in some series.[5] More severely affected patients with X-linked CGD (CYBB) tend to have higher rates of inflammatory complications than autosomal recessive (CYBA, NCF1, NCF2, NCF4, and CYBC1) patients with more residual oxidase activity.[6] These complications can have varying severity and significantly impact the quality-of-life in patients with CGD, potentially requiring aggressive immunosuppressive therapy to manage.

Granulomas are a characteristic feature of CGD, resulting from the chronic activation of the innate immune system in response to persistent infections or unresolved inflammation. While granulomas can form in any organ, they are most commonly observed in the gastrointestinal tract followed by the lungs, skin, and genitourinary tracts.[5,7] The location and size of the granulomas determine the associated morbidity with some granulomas leading to outlet tract obstruction or strictures.

Gastrointestinal involvement is the most common inflammatory complication seen in patients with CGD. Many patients develop inflammatory bowel disease (IBD)-like symptoms, including abdominal pain, diarrhea, weight loss, persistent elevation of inflammatory markers, and a clinical presentation that can overlap with Crohn's disease, including segmental involvement of the small intestine, fistula formation, and strictures.[8] Endoscopic findings often reveal granulomatous inflammation, ulcerations, and colonic involvement.[9] The management of CGD-associated IBD is challenging, as conventional therapies used in idiopathic IBD may not be as effective in CGD, and the risk of infections complicates the use of certain immunosuppressive agents. While oral 5-aminosalicylates, steroids, immunomodulatory therapies, and biologics like infliximab and vedolizumab have all been used in patients with CGD-IBD, there are no CGD-specific randomized controlled trials available with the best available evidence being small case series to guide treatment selection.

Non-infectious pulmonary manifestations of CGD may include granulomatous inflammation and interstitial lung disease leading to development of bronchiectasis, pulmonary fibrosis, and restrictive lung disease, all of which contribute to high morbidity. These may occur in up to 28% of adult patients and are more common in patients with X-linked CGD.[10] Treatment has largely been focused on aggressive identification, treatment, and clearance of infections. Unfortunately, pulmonary infection and resulting end-organ damage of the lungs and liver remain one of the leading causes of mortality in patients who now have a life expectancy over 40 years.

Inflammatory skin manifestations in CGD may present as granulomatous acneiform eruptions, pustular rashes, or dermatitis.[11] These skin lesions are often refractory to treatment and can become chronic.

Ocular anomalies are seen even in patients without involvement of the neighboring retinitis pigmentosa gene to CYBB. Inflammatory ocular involvement is rare affecting about 5% of patients with CGD.[6] Types of ocular involvement include uveitis, episcleritis, and keratitis, all of which can impair vision if not adequately managed.[5,12]

Autoimmune complications in CGD are increasingly recognized and may affect both patients with CGD and female X-linked carriers of the disease.[13,14] Previously reported autoimmune complications include antiphospholipid antibodies, lupus-like syndromes, and juvenile idiopathic arthritis.[13] At least one study has found that over half of female X-linked carriers reported photosensitivity and about 25% met 4 or more criteria for systemic lupus erythematosus.[14] While skewed X-inactivation leading to functional NADPH oxidase deficiency in a certain subpopulation of cells may contribute to autoimmune dysregulation, these autoimmune findings can be seen in X-linked carriers regardless of lyonization status.[15]

PATHOPHYSIOLOGY OF INFLAMMATORY AND AUTOIMMUNE COMPLICATIONS

The etiology of inflammatory complications in CGD is not completely understood and is likely multifactorial. The fundamental defect is an aberrant NADPH oxidase enzyme complex with impaired ROS production and bactericidal activity. Failure to adequately clear microbial infections likely leads to a sustained chronic inflammatory state and excessive immune activation.[6,7]

The oxidase enzyme system catalyzes the reduction of O_2 to O_2-, through the oxidation of NADPH as the first step in production of antimicrobial oxygen metabolites.[1] The phagocyte oxidase (phox) activity results from the interaction of several components that form an enzyme complex and reside in different compartments of the resting cell. All the components have been identified and their genes have been sequenced. With stimulation of the cell, they assemble in the plasma membrane to express oxidase activity.[1]

The main catalytic component of the oxidase is cytochrome b558 found in membrane fractions. This protein is a heterodimer composed of p22phox (CYBA) and gp91phox (CYBB) subunits. Cytochrome b558 binds NADPH and shuttles electrons to O_2. With stimulation, the cytosolic oxidase components, p47phox (NCF1), p67phox (NCF2), p40phox (NCF4), and a small GTP binding protein, RAC2, translocate to the membrane and cytochrome b558 creating an active oxidase complex that generates ROS and a respiratory burst involved in the microbicidal activity of the cell. Another protein which stabilizes the complex abbreviated EROS (CYBC1) has recently been described.[16] Genetic mutations in the genes for any of these proteins can result in CGD syndromes.

CGD phagocytes move to sites of infection, ingest offending organisms, but cannot kill catalase-positive organisms leading to a vicious cycle of accumulation of immune cells including neutrophils, lymphocytes, monocytes, and macrophages and to persistent activation and an exaggerated inflammatory response. The non-neutrophil immune components including T-cells, B-cells, activated monocytes and macrophages add to the inflammatory nature of the mix,[17] and associated hypergammaglobulinemia and elevated acute phase reactants have been noted for many years.[6] This failure to clear microbes or cellular debris along with inflammatory cells generates the hallmark of infectious or non-infectious complications in CGD: granuloma formation. One clinical study presented data that the onset of inflammatory episodes in CGD patients followed the presentation of initial infections.[5] The relationship between infection and non-infectious inflammatory complications is further complicated by difficulties in identifying microbes in infected sites limiting the diagnosis of infections, as well as smoldering infections, and persistence of antigens.[5,6,18] Some inflammatory complications, particularly in the gastrointestinal and genitourinary tracts have no association with infection. In any case, alterations in key pathways including the inflammasome,[6] changes in CD4 + T helper cell subsets,[4,19] and impaired clearance of chemotactic factors all contribute to inflammation.[20]

The absence of ROS generation by neutrophils from most patients with CGD may create profound alterations in signaling. Oxidant changes can lead to abnormalities in cysteine residues on phosphates and transcription factors, regulating intracellular signaling, for example,[21] CGD neutrophils produce increased levels of TNF-α and CXCL8 through activation of NF kappa beta favoring inflammation.[22] In CGD patients, pro-inflammatory macrophages secreting IL-18 may also contribute to chronic inflammation.[23]

Several studies in murine models and humans have provided insight into development of inflammatory complications in CGD. A murine knock out model of p47phox

deficiency demonstrated post-infectious inflammatory lung damage associated with altered tryptophan catabolism and inhibited indoleamine-2,3-dioxygenase function.[24] Also, in p47phox deficient mice, a particular microbiome signature was associated with colitis.[25] In a p22phox murine model, disruption of intestinal mucous barrier potentiated bacterial growth and increased intestinal inflammation.[26] In some patients, barrier disruption may play a role in gastrointestinal inflammation. Finally, murine models of CGD with a deficiency in ROS generation were associated with an exuberant inflammatory response, T-helper 17 (Th17) pathology, and arthritis.[27]

In humans, genetic background may play a role in the risk of inflammation in IBD. CGD patients with colitis had a higher IBD genetic risk score based on presence of combinations of high risk single nucleotide polymorphisms (SNPs) than those without colitis.[28] The exact interaction of these SNPs with the NADPH oxidase is not well-understood and it would be too premature to consider incorporating this information into screening or treatment protocols for patients with CGD. The intestinal microbiome and metabolomic profile in patients with CGD associated IBD demonstrates a distinctive pattern different than is seen in patients without colitis and healthy control subjects and may play a role in susceptibility.[29] CGD-IBD patients had enrichment of Erysipelatoclostridium, Sellimonas, and Lachnoclostridium species compared to patients with CGD without IBD. This microbiome may overlap but is not identical patients with IBD without CGD. The exact cause is not clear.

Defective autophagy may be observed in patients with CGD and murine models. This is related to ROS-independent activation of the inflammasome and increased release of IL-1β.[30] Blocking the IL-1 receptor decreases inflammasome activation, restores autophagy, and reduces chronic inflammation in mice and patients with CGD.

The lifespan of the neutrophil is determined by apoptosis. Because CGD neutrophils have a defective NADPH oxidase and fail to produce oxidants, they are resistant to apoptosis and have longer survival. These cells produce fewer anti-inflammatory mediators after phagocytosing apoptotic targets.[31] Furthermore, these neutrophils are less likely to engage in DNA damage and repair and produce more inflammatory cytokines.[17] Ingestion of gp91phox deficient cells by murine models can lead to autoantibody formation.[32]

Apoptotic neutrophils are cleared by macrophages in a process termed efferocytosis.[33,34] This process is also abnormal *in vitro* and in CGD patients. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, restores efferocytosis *in vitro*. Two patients with CGD received this drug for a non-CGD related issue, and it resulted in improved efferocytosis and ROS generation *in vivo*.[34]

Continued investigations in humans and animal models in the future have the potential to increase our understanding of the pathogenesis of inflammatory complications in CGD and provide therapeutic strategies to reduce or eliminate them.

TREATMENT OF NON-INFECTIOUS COMPLICATIONS

Despite increasing understanding of potential contributory pathogenic mechanisms underlying non-infectious complications of CGD, there is limited evidence to guide the management of these inflammatory conditions. Current treatment strategies are primarily extrapolated from the management of other inflammatory and autoimmune disorders, but they may have suboptimal efficacy or increased risks in patients with CGD. The treatment of inflammatory complications in CGD often relies on immunosuppressive therapies, which can exacerbate the underlying susceptibility to infections, creating a delicate balance between controlling inflammation and avoiding infectious complications.

Glucocorticoids are commonly used as first-line therapy for controlling acute inflammation in CGD, particularly in cases of obstructive granulomatous disease or CGD-associated IBD.[35] A commonly reported dosing regimen uses prednisone 1 mg/kg/day for 2 weeks gradually weaning off over 8 to 12 weeks. Steroids may also need to be utilized concurrently with antibiotics in the setting of certain types of infection like hepatic abscesses or disseminated Nocardia to address the dysregulated hyperinflammation seen in CGD. While effective in rapidly reducing inflammation, the prolonged or repeated courses of steroids can be associated with intolerable side effects including increased susceptibility to infections, hyperglycemia, hypertension, growth impairment, and bone disease. Given these risks, there is a need for steroid-sparing strategies in the management of CGD-related inflammation. Several steroid-sparing immunosuppressive agents have been used in small case series, including azathioprine, sulfasalazine,[36] cyclosporine, and thalidomide.[37] These can be associated with significant toxicities and several patients taking thalidomide had to discontinue therapy due to neurotoxicity.[37] While, these agents are commonly used in the treatment of IBD and other autoimmune disorders, their efficacy in CGD is not well-established.[38]

Given the role of IL-1β in driving inflammation in CGD, IL-1 inhibition has emerged as a potential therapeutic strategy. Anakinra, an IL-1 receptor antagonist, has been used with mixed results.[30,39] Prolonged treatment is likely necessary, and it is not clear which subset of patients might benefit the most, so further investigation in a larger cohort of patients is required.

TNF-α inhibitors, such as infliximab and adalimumab, are widely used in the treatment of idiopathic IBD and other autoimmune conditions. However, their use in CGD is controversial due to the increased risk of severe and even fatal infections, usually with typical CGD pathogens like Burkholderia, Candida, and Staph aureus and not mycobacterial infections typically-associated with this infliximab. While TNF-α blockade can be effective in reducing inflammation, its use must be carefully weighed against the heighted risk of infections in CGD patients.[36] While we typically avoid use of TNF-α blockade, if it is used, we could consider an augmented antimicrobial prophylaxis regimen (eg, voriconazole or posaconazole in lieu of itraconazole) and enhanced clinical monitoring protocol for infections.[40]

Vedolizumab is a biologic agent that binds to α4β7 integrin and blocks its interaction with MAdCAM-1. Because α4β7 is expressed primarily on gut endothelial cells, the immunomodulatory effect is more localized with less systemic off target effects. Thus far, only a small number of patients with CGD-related IBD have been treated with vedolizumab. While a single case report showed improvement in fistulizing colitis,[41] a larger series of 11 patient showed more mild improvements without significant reduction in systemic steroid exposure.[42]

Antibiotics, especially metronidazole or ciprofloxacin, used as either monotherapy or in combination, have been used in pediatric patients to treat IBD.[43] These agents can help decrease bacterial overgrowth and alter the intestinal microbiome in favor of more advantageous bacteria. Ciprofloxacin has good activity against gram negative enteric bacteria, while metronidazole is efficacious against potentially detrimental anaerobic pathogens. However, long-term use of antibiotics raises concerns about development of antibiotic resistance and for potential disruption of the microbiome.

Interferon-gamma (IFN-γ) has long been used as an adjunctive immunomodulatory therapy in patients with CGD to enhance immune function and reduce the frequency of infections [PMID: 36385358]. While its primary indication in CGD is to prevent infections, the role of IFN-γ in modulating the inflammatory complications of the disease is murkier.

IFN-γ is a type II interferon and a pleiotropic cytokine produced primarily by T cells, natural killer cells, and macrophages in response to infection or immune activation. Its primary function is to modulate immune responses, particularly in the context of pathogen clearance and regulation of inflammation. IFN-γ exerts its effects by binding to the IFN-γ receptor, a receptor complex expressed on the surface of many immune cells, including macrophages, dendritic cells, neutrophils, and T cells. Upon binding to its receptor, IFN-γ triggers the activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, leading to the transcription of IFN-γ-regulated genes involved in immune responses.[44]

The immunomodulatory effects of IFN-γ include enhancing the microbicidal activity of macrophages and neutrophils, increasing the expression of major histocompatibility complex molecules and thus promoting antigen presentation, stimulating the production of pro-inflammatory cytokines such as IL-12, and regulating the differentiation of T helper 1 (Th1) cells, which are critical for effective defense against intracellularly pathogens.[44]

In CGD, IFN-γ has been shown to enhance the activity of phagocytes and improve microbial killing, despite the inherent defect in NADPH oxidase activity. This is thought to occur through a combination of ROS-independent pathways and the activation of other immune functions that compensate for the ROS deficiency, but exact mechanisms are still under evaluation.

IFN-γ can upregulate the production of various antimicrobial peptides, enzymes, and cytokines that contribute to pathogen clearance. For example, IFN-γ increases the expression of inducible nitric oxide synthase in macrophages, leading to the production of NO, which has antimicrobial properties.[45] Additionally, IFN-γ can enhance phagocytosis and promote maturation of phagolysosomes, improving the ability of cells to kill ingested microorganisms through mechanisms independent of ROS.

Upon binding to its receptor, IFN-γ activates the JAK-STAT signaling pathway, which leads to the transcription of a wide array of immune-related genes. These genes encode for proteins involved in immune activation, such as pro-inflammatory cytokines, chemokines, and antimicrobial peptides. IFN-γ also increases the expression of MHC class I and II molecules on antigen-presenting cells, improving their ability to present microbial antigens to T cells.[46] This promotes the activation of Th1 cells, which secrete IFN-γ and other cytokines that further enhance the immune response. This positive feedback loop amplifies the immune system capacity to recognize and respond to intracellular pathogens.

IFN-γ plays a crucial role in regulating inflammation, and its effects in CGD are particularly relevant given the inflammatory complications of the disease. By promoting a Th1-skewed immune response, IFN-γ enhances the production of pro-inflammatory cytokines, including IL-12 and TNF-α, which is critical for controlling intracellular infections. However, the cytokine balance in CGD is already skewed toward a pro-inflammatory state due to impaired ROS production, and the role of IFN-γ in this context is complex.

While IFN-γ enhances the immune response it can also suppress excessive inflammation through its regulatory effects on macrophages and T cells. IFN-γ can limit the activity of Th17 cells, which are associated with autoimmune and inflammatory diseases, by promoting the differentiation of regulatory T cells (Tregs) and suppressing the production of IL-17, a cytokine implicated in autoimmune pathology.[27]

In CGD, where patients experience heightened inflammatory responses, the ability of IFN-γ to modulate Th1/Th17 balance and regulate pro-inflammatory cytokine production may help mitigate some of the inflammatory complications of the disease, including granuloma formation and IBD-like symptoms.

In CGD, the failure to clear pathogens effectively due to the defective oxidative burst leads to chronic stimulation of the immune system and formation of granulomas in various organs. IFN-γ plays a dual role in granuloma formation. On the one hand, it promotes the activation of macrophages and the recruitment of immune cells to sites of infection, facilitating the formation of granulomas. On the other hand, IFN-γ can also regulate the chronic inflammation associated with granuloma formation by enhancing the resolution of infection and promoting the clearance of pathogens through non-ROS-dependent mechanisms.

Both the original prospective IFN-γ prophylaxis trial and a long-term follow-up analysis from one of the National Institutes of Health cohort demonstrated no increase in rates of IBD in patients receiving IFN-γ.[47,48] Additionally, there was some suggestion that rates of non-gastrointestinal granulomatous complications were slightly lower than seen in a contemporary European cohort, which did not receive IFN-γ.[47] It is also unclear whether a specific subset of patients is most likely to respond to IFN-γ therapy.

CURATIVE THERAPY FOR INFLAMMATORY COMPLICATIONS

While the management of CGD-associated inflammatory complications remains challenging, curative therapies that can restore normal NADPH oxidase activity offer the potential for long-term disease control. Allogeneic HSCT is currently the only clinically available curative therapy for CGD, capable of restoring normal NADPH oxidase function and reversing both infectious and inflammatory complications. With a suitable well-matched related or unrelated donor, transplant outcomes are quite good with overall and event free survival exceeding 80% at 2 to 5 years post-transplant.[49,50] However, HSCT carries significant risks, including graft-versus-host disease (GVHD) and transplant-related mortality, particularly in older patients or those with pre-existing organ damage.[50]

HSCT has been shown to improve both the infectious and inflammatory manifestations of CGD, with recent advances in conditioning regimens and donor selection improving outcomes. In one series, all patients with CGD-related IBD experienced resolution of IBD symptoms within 2 years of transplantation.[49] In another series, durable resolution of inflammatory symptoms was noted extending out 5 years from transplant.[51] The presence of inflammatory complications like IBD prior to transplant is not associated with inferior post-transplant outcomes.[49,51]

The development of autologous gene therapy for CGD offers a promising alternative to allogeneic HSCT, particularly for patients without a suitable donor or those at high risk for GVHD. Gene therapy involves correcting the genetic defect in the patient's own hematopoietic stem cells, allowing for the restoration of NADPH oxidase activity without many of the risks associated with allogeneic transplantation.[52] Few patients have been treated with autologous gene therapies to this point and significant issues need to be addressed before this therapy is more widely adopted including the real risk of clonal hematopoiesis, suboptimal NADPH oxidase restoration, and durability of response.

SUMMARY

Non-infectious complications, particularly inflammatory and autoimmune manifestations, represent a significant clinical challenge in the management of CGD. The pathophysiology of these complications is complex, involving impaired NADPH oxidase activity, dysregulated immune pathways, and altered interactions with the microbiome. Despite the improvement in infectious outcomes in CGD, treatment options

remain limited for non-infectious complications, and there is a need for more targeted and effective therapies.

Current management strategies often rely on glucocorticoids and other immunosuppressive agents, but the balance between controlling inflammation and preventing infections remains difficult. Experience with alternative therapies, including IL-1 inhibition and vedolizumab, is limited and further research in larger cohorts of patients is needed to establish their role in CGD. Ultimately, curative therapies such as HSCT and hopefully autologous gene therapy in the future, which restore normal NADPH oxidase activity, are the most definitive methods to provide long-term control of inflammatory and autoimmune manifestations. Continued research into the underlying mechanisms of inflammation in CGD and the development of novel therapies will be essential in improving the quality-of-life for patients with this complex disorder.

CLINICS CARE POINTS

- Inflammatory complications are common in patients with chronic granulomatous disease and should be routinely screened for using a combination of clinical history, physical examination, and laboratory markers of inflammation.
- Glucocorticoids are typically used as first-line therapy for patients with obstructive complications or IBD but may have intolerable long-term side effects if they cannot be weaned to lower doses.
- TNF-α blockade use in patients with CGD-IBD is associated with higher rates of serious infection in patients and is generally avoided or used cautiously.
- Allogeneic stem cell transplant can restore normal NADPH oxidase function leading to long-term resolution of inflammatory complications. The presence of these complications pre-transplant does not affect transplant success.

DISCLOSURES

C. McKinney: No conflicts of interest to disclose. D. Ambruso**:** Received a grant from Horizon Pharmaceuticals, United States for an investigator-initiated trial looking at the mechanism of action of IFN-gamma.

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