Chronic granulomatous disorder
A guide for medical professionals

Written by medical professionals for medical professionals
www.cgdsoociety.org
**Chronic granulomatous disorder (CGD)** is a rare, inherited disorder of the immune system. The basic defect lies in phagocytic cells (neutrophils and monocytes) which fail to effectively destroy invading bacteria and fungi (see Box 1). Affected individuals are therefore susceptible to serious, potentially life-threatening, bacterial and fungal infection but have normal immunity to viruses. They also experience symptoms associated with chronic inflammation, often granulomatous in nature.

**Incidence and prevalence of CGD**
The exact incidence of CGD is unknown. The birth prevalence of CGD in the United Kingdom and Ireland is approximately 8.5 per million. Despite antibiotic and antifungal prophylaxis, morbidity remains significant, with severe infectious complications common. However, with advances in earlier diagnosis and better treatments, survival rates are likely to be improving year by year.

**Diagnosis**
The functional diagnosis of CGD is made by the demonstration of the inability of phagocytes from affected individuals to produce superoxides (see Box 2). If CGD is suspected it is important that referral is made to a specialist centre and diagnostic tests carried out in a laboratory that is familiar with doing these tests on a regular basis. Genetic testing and counselling of the extended family is recommended. For immigrants, family testing should be done in the new country and in the country of origin.

**Inheritance and types of CGD**
In the Western world the majority of CGD cases are of X-linked inheritance (see Box 3) but the autosomal form of CGD is more common in the Middle East.

**Clinical manifestations**
The hallmark of the clinical presentation of CGD is recurrent infections occurring at epithelial surfaces in direct contact with the environment, such as the skin, lungs and gut. Diagnosis is based on clinical suspicion and confirmed by demonstrating the inability of phagocytes from affected individuals to produce superoxides, by NBT test or flow cytometry (see Box 2).

Infections at these sites which recur, are difficult to treat or otherwise unusual should arouse a suspicion of an immune deficiency, including CGD. Signs and symptoms will be as per normal infections. Infections may present initially as relatively minor (e.g. a cough or cervical lymphadenitis) but they may not easily respond to conventional therapy or may progress. Carriers of X-linked CGD may also experience health problems (see Box 4).
The biochemical basis of CGD

Neutrophils from CGD patients fail to exhibit a ‘respiratory burst’, the increase in oxidative metabolism associated with phagocytosis. This is due to the absence of one of the components of NADPH oxidase, found in phagocytic cells. NADPH oxidase catalyses the formation of superoxide, the precursor to the generation of potent oxidant compounds, by transmembrane passage of electrons from NADPH oxidase to molecular oxygen.

Testing for CGD

Nitroblue tetrazolium test (NBT):
Neutrophils are stimulated with phorbol myristate acetate and incubated with the yellow dye nitroblue tetrazolium. Normal phagocytes reduce this to the dark blue pigment, formazan. Cells are analysed by microscopy, which requires an experienced observer. Carrier mothers of the X-linked type of CGD are identified by a mixed population of NBT+ve and NBT-ve cells.

Flow cytometric reduction of dihydrorhodamine:
The principles are the same as the NBT test, but using a different dye. X-linked carrier status can also be detected.
The majority of affected individuals are diagnosed before the age of 2 years although patients may remain undiagnosed until adult life despite the early onset of symptoms.

**Common presenting features:**
- Skin abscesses
- Perianal abscesses
- Pneumonia
- Liver abscess
- Osteomyelitis
- Septicaemia
- Diarrhoea (may be misdiagnosed as Crohn’s disease)
- Lymphadenitis

### Preventing infection

The most commonly described infectious complications are pneumonia, lymphadenitis, subcutaneous abscess, liver abscess, osteomyelitis and sepsis. The pathogens responsible for the majority of infections in CGD are catalase positive bacteria and various fungi (see Box 5).

_Taking daily antibacterial and antifungal prophylaxis is the single most important factor in keeping CGD patients well._

Whilst these medicines do not provide an absolute guarantee against infections, they are key to reducing the number and severity of infections that people with CGD encounter.

### Pathogens responsible for infection in CGD

**Bacteria** – the most commonly implicated bacteria include *Staphylococcus aureus* and the gram negative *Enterobacteriaceae*, including *Salmonella*, *Klebsiella*, *Aerobacter* and *Serratia*. *Pseudomonas (Burkholderia) cepacia*, *Actinomyces* and *Nocardia* are increasingly being recognised as important pathogens in CGD. Catalase negative bacteria, such as *Streptococci*, rarely cause problems in CGD.

These catalase positive bacteria break down hydrogen peroxide, which the host’s immune system uses to fight infection. As a consequence, catalase negative bacteria, such as *Streptococci*, rarely cause problems in CGD because hydrogen peroxide can accumulate to protect against infection.

**Fungi** – *Aspergillus fumigatus* is the most common cause of fungal infection in CGD although reports of infections with other members of the *Aspergillus* family, such as *A. nidulans*, and other fungi, such as *Scedosporium apiospermum* and *Chrysosporium zonatum*, are increasing.

Fungal infections may be difficult to distinguish from bacterial infections on initial presentation (e.g. a cough) but should always be considered in this patient group if they do not respond as expected to empirical antibiotic therapy.
Anti-bacterial prophylaxis
All patients should be commenced on Co-trimoxazole. Although Stevens-Johnson syndrome has been associated with Co-trimoxazole use, it is generally well tolerated in CGD patients and has been shown to reduce the incidence of severe infection. It has broad activity against the pathogens encountered in CGD, is lipophilic and is thus concentrated inside cells and does not affect anaerobic gut flora.

Recommended doses of Co-trimoxazole

<table>
<thead>
<tr>
<th>Age range</th>
<th>Co-trimoxazole prophylaxis (all as a single daily dose)</th>
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<tr>
<td>0–6 months</td>
<td>120mg</td>
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<tr>
<td>6 months–5 years</td>
<td>240mg</td>
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<tr>
<td>6–12 years</td>
<td>480mg</td>
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<td>over 12 years</td>
<td>960mg</td>
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Anti-fungal prophylaxis
All patients should be commenced on Itraconazole (5mg/kg daily), as this has good activity against *Aspergillus* species.

Reported side effects include raised liver enzymes, peripheral neuropathy and Stevens-Johnson syndrome, but Itraconazole is generally well tolerated in CGD patients and studies suggest it is effective in reducing the incidence of fungal infection. Liver enzymes should be checked prior to commencing treatment and subsequently every 6 months.

Acting on significant symptoms
CGD patients can mount a normal immune response to viruses (e.g. colds and flu) and will continue to have these infections with the same frequency as the general population. It can be difficult for families to distinguish those infections that are ‘normal’ from those that are a result of CGD. Families are educated to look out for and act on significant symptoms (see Box 6).

Management of CGD (continued)

The importance of taking daily preventative medication should be emphasised to patients and families. They are advised to take some simple precautions in daily life to minimise the risk of infection. These include not working or playing with or around compost, hay, wood chips, thick grass clippings, other garden waste or firewood that has dry rot or old fungi on it. This will help avoid inhalation of high levels of fungi, as will staying out of barns, caves, sheds and other dusty or damp areas.

A full list of recommended precautions can be found at the CGD Society website www.cgdsociety.org. Advice is aimed at providing a balance between protective precautions and the need to maintain as normal a life as possible.

Immunisations
The only routine immunisation that adults and children with CGD should not have is BCG as it has been associated with disseminated BCG infection. An annual flu vaccine is recommended (over 6 months of age), because of the possible secondary bacterial complications of influenza.

Invasive procedures
Antibiotic cover is recommended for all invasive procedures, including sigmoid/colonoscopy, upper GI endoscopy, bronchoscopy and liver/lung biopsy. Prophylaxis with Ciprofloxacin (and adding Metronidazole if investigation below the diaphragm is involved) should commence prior to procedure and continue for at least 24 hours afterwards. Surgical procedures may require more prolonged courses/different antibiotic combinations and should be discussed with a specialist centre.

Significant symptoms of infection in CGD

- A fever of 38°C or above
- Warm, tender or swollen areas
- Hard lumps
- Sores with pus or rashes
- Persistent diarrhoea
- Persistent cough or chest pain
- Night sweats
- Frequent or persistent headaches
- Loss of appetite
- Weight loss
- Pain or difficulty on urinating
- Difficulty swallowing food
- Vomiting shortly after eating (on a more or less consistent basis)
Treatment of acute infection

Any febrile illness should be treated promptly with antibiotics, proceeding to appropriate intravenous therapy where necessary. Whilst this may raise some concern about inappropriate treatment of viral infections/overuse of antibiotics, a ‘safety-first’ approach should always be adopted for patients with CGD. Patients with CGD may require longer antibiotic courses, sometimes at higher doses, or in combination, because of their poor host response. If a poor response is made to initial treatment, advice should be sought from a specialist centre.

The spectrum of bacteria that cause infection in CGD should always be taken into account when considering the choice of antibiotics. Oral Ciprofloxacin is a useful first line agent because of its spectrum of activity and capacity to penetrate intracellularly. The benefits of using Ciprofloxacin in children in this context outweigh the risks of arthropathy.

Dosage of Ciprofloxacin for treatment of acute infection

**Dose (orally):**

**Child:** 7.5mg/kg 12 hourly

**Adult:** 500mg to 750mg 12 hourly

IV antibiotics

IV Teicoplanin and Ciprofloxacin are a good choice for first line therapy in severe sepsis, with Metronidazole being added if infection below the diaphragm is suspected. If Staphylococcus is isolated, Flucloxacillin and Fucidin (or another antistaphylococcal antibiotic, e.g. Clindamycin and Clarithromycin) may be used.

Fungal infections should always be considered in the differential diagnosis of any sepsis syndrome. If a prompt response (within 7–10 days) to antibacterial therapy is not obtained, consideration should be given to commencing empirical antifungal treatment (in discussion with a specialist centre).

Inflammatory complications

Inflammatory complications of CGD include:

- Chronic lung disease
- Colitis
- Pericardial effusion
- Gingivitis
- Fulminant mulch pneumonitis
- Chorioretinitis

It is important to note that fulminant mulch pneumonitis is a real emergency that requires both antimycotics and steroid treatment.

Colitis is probably the most common significant inflammatory complication of CGD. Histological features include an apparent paucity of neutrophils, increased eosinophilic infiltrate and pigmented macrophages. Granulomas may or may not be present. A CGD associated colitis can be misdiagnosed as Crohn’s disease where symptoms such as diarrhoea, weight loss, failure to thrive and perianal disease constitute the initial findings. Where colitis is suspected, referral should be made to a gastroenterologist for endoscopic investigation and biopsy (as macroscopic appearance can be deceptively normal).

Long-term follow up of CGD has revealed that with improved survival or increasing age, symptoms of obstruction in hollow organs, or inflammation not obviously associated with infection, may become prominent. Although incompletely understood, this is likely to represent an exuberant inflammatory response to a minor stimulus, e.g. a resolved infection. A raised ESR and low Hb can be found even in apparently uninfected patients and probably reflects ongoing, sub-clinical inflammation. The CRP is rarely raised when the patient is apparently infection free and thus remains a better marker of sepsis in the acutely ill patient.
5-ASA agents (e.g. Sulphasalazine and Mesalazine) are useful first line agents in the treatment of CGD-colitis. Steroids, and other immunosuppressive agents, such as Azathioprine, may be indicated where 5-ASA has failed to induce/maintain remission. However, these agents should be used with caution, and in discussion with a specialist centre, particularly where there is concurrent infection or history of fungal infection.

NB: Where 5-ASAs are used in conjunction with Co-trimoxazole, a full blood count should be monitored monthly for the first 3 months and 3 monthly thereafter, due to the potential for blood dyscrasias.

Obstruction of hollow organs
People with CGD are at risk of getting obstruction of the gut or urinary tract due to granulomatous inflammation. This may manifest as a difficulty in swallowing (obstruction of the oesophagus), vomiting (gastric outlet obstruction), abdominal pain (obstruction of the bowel) or difficulty in passing urine (obstruction of the ureter). All of these conditions respond promptly to steroids but it is essential to rule out an infectious cause before starting steroid therapy. Steroids should be used with particular caution, and preferably in discussion with a specialist centre, where there is known concurrent infection or history of fungal infection.

Inflammatory complications (continued)

Monitoring

Clinical
All patients should have an identified local physician/paediatrician and access to advice from an immunologist/physician familiar with CGD. Regular outpatient review (6 monthly if well) is recommended, shared between local/specialist centres.

Blood tests
Regular (approximately 6 monthly) full blood count and liver function tests are recommended (prophylactic medication may be toxic to bone marrow/associated with altered LFTs). A CRP and ESR should also be performed routinely and whenever the patient is unwell. A microcytic, hypochromic anaemia is often detected although it often remains refractory to iron therapy.

Ophthalmology
Patients and carriers of CGD may have chorioretinal lesions and thus should be assessed at diagnosis. The aetiology of these lesions is unclear and they do not appear to interfere with vision in the majority of patients. However, it is recommended that those with lesions should be assessed every 1–2 years to monitor progression. Those without lesions at diagnosis should be assessed every 2–3 years using dilated fundoscopy.

Dental
The importance of good dental hygiene and mouth care for people with CGD should be emphasised. Patients are advised to brush their teeth twice daily and seek regular dental care. A number of patients do have problems with persistent gingivitis and mouth ulcers. Antibiotic prophylaxis should be prescribed for any dental treatment likely to cause bleeding: Ciprofloxacin (7.5mg/kg for a child, 500mg for an adult, oral prep.) should be given before the procedure followed by 2 doses, 12 hours apart, in the 24 hours following the procedure.

Nutrition/growth and development
Some children with CGD grow and develop more slowly than their peer group. They may also experience some delay in reaching puberty. The causes of growth failure in CGD are not yet fully understood and are likely to involve a number of different factors. It would appear that a number
Monitoring (continued)

of CGD children achieve ‘catch-up’ growth and go on to achieve reasonable adult height. However, there are some, particularly those who have received prolonged courses of steroids, had repeated infections or major fungal infection, who will demonstrate failure to thrive and growth failure.

Weight and height should therefore be measured and plotted on centile charts at each clinic visit. Failure to thrive is often associated with poor nutritional intake, increased nutritional requirements due to sub-clinical inflammation and colitis symptoms. Children failing to maintain their weight will benefit from specialist nutritional advice and support with nutritional supplements (rarely tube feeding) and should therefore be referred to a dietician. Referral to gastroenterology and endocrinology should be considered, in liaison with the specialist centre.

Adult patients may also experience problems maintaining their weight, for much the same reasons. Patients often report reduced appetite and interest in food. Again, advice from a dietician as to how to increase calorie intake is of benefit. Infection should be suspected with recent, sudden weight loss and consideration given to further referral as symptoms indicate, e.g. gastroenterology.

Emotional impact of CGD
CGD presents a multitude of challenges for patients and their families. These challenges involve managing the physical elements of the condition, as well as the psychological issues involved in coping with a complex condition, whilst, at the same time, trying to maintain a family life. It is sometimes difficult for families to talk about these emotional issues for a variety of reasons, including stigma, fear of being judged and fear of managing their own emotions.

It is important that families are given time and encouragement to talk about their concerns relating to themselves, their child and other family members. This enables not only a close therapeutic alliance to be formed with the family but also enables difficult topics to be brought to the fore in discussion, and appropriate sources of support to be considered.

Cure of CGD

Haematopoietic stem cell transplantation in CGD
Whilst lifelong antibacterial and antifungal prophylaxis with Co-trimoxazole and Itraconazole has improved short- and medium-term survival, and steroids and aminosalicylates may ameliorate colitis and other inflammatory complications, these treatments do not cure the underlying genetic defect. Haematopoietic stem cell transplantation (HSCT) can cure CGD, with resolution of infection and colitis. In those with growth failure, who have remaining growth potential, HSCT can allow catch-up growth to previously normal centiles. In the majority of patients, prophylactic medication can be discontinued post-HSCT. Survival and cure are equivalent with either a matched sibling or well-matched unrelated donor and reach 85–90% in specialist centres designated to transplant patients with primary immunodeficiency.

Specific timing of transplantation is difficult to recommend but should be considered early. Given that worse transplant outcomes are seen in patients with refractory infection or significant inflammation, patients should be considered for transplantation early after diagnosis, or after the development of specific prognostic symptoms, particularly if a well-matched donor is available, so that families can be appropriately counselled. Whilst transplantation is generally best tolerated in childhood, successful outcomes are possible in adults using new transplantation techniques.

It is recommended that:
• HLA-antigen tissue typing is performed soon after the diagnosis is made, so that potential donors can be identified.

• Transplantation be considered early after diagnosis if an HLA-identical sibling or well-matched unrelated donor is available – families and patients should be seen by a specialist with experience of transplanting patients with primary immunodeficiency, who can provide good-quality up-to-date advice about risks and benefits.
Even short-term correction of the CGD defect has led to clearance of life-threatening infections that were resistant to other means of treatment.
Further reading/information

Prevalence, clinical course and complications of CGD

Noninfectious manifestations and complications of chronic granulomatous disease

Chronic granulomatous disease in patients reaching adulthood: a nationwide study in France

Common severe infections in chronic granulomatous disease

Special article: chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry

CGD overview and clinical management of CGD

Recent advances in understanding and treating chronic granulomatous disease

Modern management of phagocyte defects

A comprehensive approach to the management of children and adults with chronic granulomatous disease

Managing inflammatory manifestations in patients with chronic granulomatous disease

CGD and haematopoietic stem cell transplantation

Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency
Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study


Allogeneic reduced-intensity hematopoietic stem cell transplantation for chronic granulomatous disease: a single-center prospective trial


Clinical outcome in children with chronic granulomatous disease managed conservatively or with hematopoietic stem cell transplantation


Treo sulfan-based conditioning for allogeneic HSCT in children with chronic granulomatous disease: a multicenter experience


Gene therapy for CGD

Gene therapy for primary immunodeficiencies: current status and future prospects

Qasim W, Gennery AR. Drugs, 2014 Jun; 74(9): 963–969.

Future of care for patients with chronic granulomatous disease: gene therapy and targeted molecular medicine

Keller MD, Notarangelo LD, Malech HL. Journal of Pediatric Infectious Disease Society, 2018 May 9; 7(Suppl_1):S40–S44.

X-linked carriers of chronic granulomatous disease: illness, lyonization, and stability


Inflammatory and autoimmune manifestations in X-linked carriers of chronic granulomatous disease in the United Kingdom


Clinical manifestations of disease in X-linked carriers of chronic granulomatous disease


Aspergillosis and CGD

Aspergillosis in chronic granulomatous disease

King J, Henriet SSV, Warris A. Journal of Fungi, 2016 May; 26;2(2).

Invasive fungal infections in patients with chronic granulomatous disease

Further reading/information (continued)

Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: a multicenter study in France

Differential diagnosis of CGD in patients presenting with inflammatory bowel disease

Gastrointestinal features of chronic granulomatous disease found during endoscopy

Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn’s disease

Inflammatory bowel complications in CGD

Inflammatory bowel disease in chronic granulomatous disease: an emerging problem over a twenty years’ experience

Diagnosis and treatment of gastrointestinal disorders in patients with primary immunodeficiency

Ophthalmology

Molecular identification of bacterial DNA in the chorioretinal scars of chronic granulomatous disease

Chorioretinal lesions in patients with chronic granulomatous disease

Oral pathology in CGD

The NADPH oxidase NOX2 plays a role in periodontal pathologies

Quality of life issues in CGD

Emotional and behavioural difficulties in chronic granulomatous disease

Health related quality of life and emotional health in children with chronic granulomatous disease: a comparison of those managed conservatively with those that have undergone haematopoietic stem cell transplant

Health-related quality of life and emotional health in X-linked carriers of chronic granulomatous disease in the United Kingdom
Specialist centres for CGD in the UK

PAEDIATRIC CARE

1. Great North Children's Hospital, Newcastle upon Tyne, United Kingdom
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Acknowledgements

This guide is approved by the CGD Society Medical Advisory Panel (February 2019).

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About the CGD Society

The Chronic Granulomatous Disorder Society (CGD Society) is the leading global charity dedicated to promoting an understanding of CGD and providing support to affected individuals and their families.

Our website www.cgdsociety.org provides medical information and practical advice on living with CGD. It is free to become a member of the CGD Society. Please go to www.cgdsociety.org/register/.

If we can be of any help, please contact us at hello@cgdsociety.org or on 0800 987 8988, where you can leave a message.

Our charity is reliant on voluntary donations. To make a donation, please go to www.cgdsociety.org/donate.