CGDSociety

Supporting families affected by chronic granulomatous disorder

Chronic granulomatous disorder

A guide for medical professionals

Written by medical professionals
for medical professionals

www.cgdsociety.org

Chronic granulomatous disorder

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.

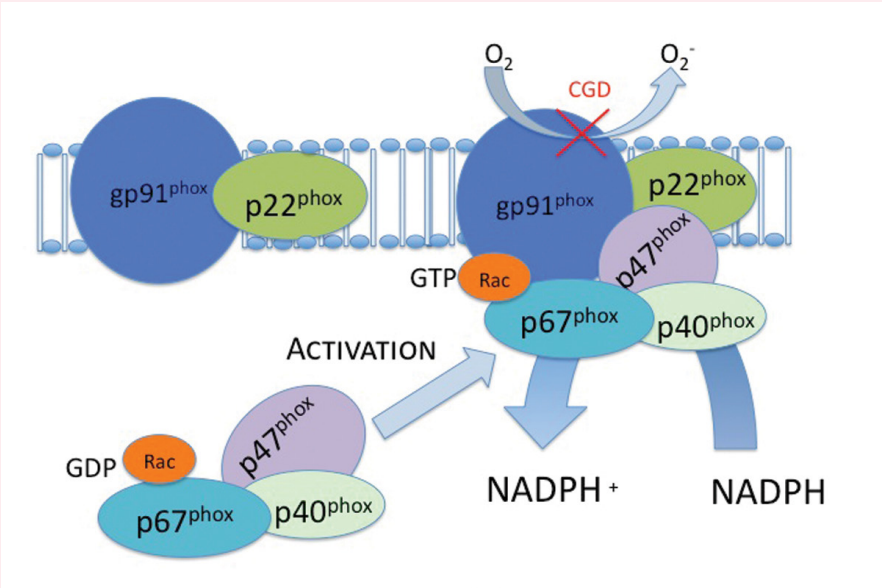
Clinical manifestations

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)*.

1 The biochemical basis of CGD

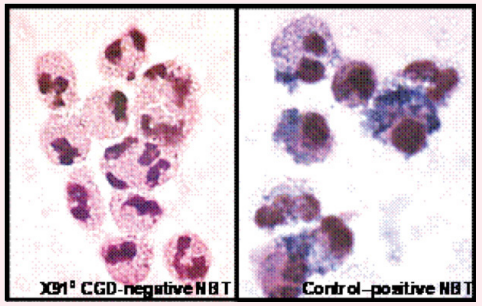
Neutrophils from CGD patients fail to exhibit a 'respiratory burst', the increase in oxidative metabolism associated with phagocytosis. This is due to the absence of one of the components of NADPH oxidase, found in phagocytic cells. NADPH oxidase catalyses the formation of superoxide, the precursor to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



The NADPH oxidase enzyme

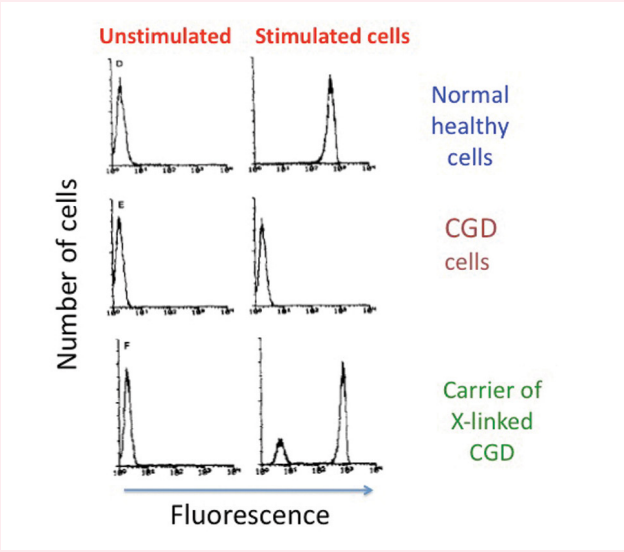
2 Testing for CGD

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.



Diagnosis of CGD by the NBT test

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.



Diagnosis of CGD by flow cytometry

3 Types of CGD

There are five basic types of CGD, grouped according to which of the five subunits is affected by genetic mutation.

Protein	Gene	Genetic inheritance	% of those affected by CGD	Groups affected
gp91phox	CYBB	X-linked inheritance	65%	Males only
p47phox	NCF-1	Autosomal recessive	25%	Both sexes
p67phox	NCF-2	Autosomal recessive	5%	Both sexes
p22phox	CYBA	Autosomal recessive	5%	Both sexes
p40phox	NCF-4	Autosomal recessive	Rare	Both sexes

4 X-linked CGD carrier health issues

Carriers of X-linked CGD are unlikely to have the condition but are known to be at risk from developing a number of symptoms which may resemble lupus (especially the skin features). It is recommended that these CGD carriers presenting with aphthous ulceration, skin rashes, joint pains, fatigue and headaches are considered for referral to a rheumatologist and/or other relevant specialists for treatment of 'lupus-like' symptoms regardless of the results of a test for lupus. In CGD carriers, lupus test results are likely to be negative as supported by published evidence, but symptoms need to be taken seriously.

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

Management of CGD

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.

5 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

Age range	**Co-trimoxazole prophylaxis** (all as a single daily dose)
0–6 months	120mg
6 months–5 years	240mg
6–12 years	480mg
over 12 years	960mg

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)*.

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.

6 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

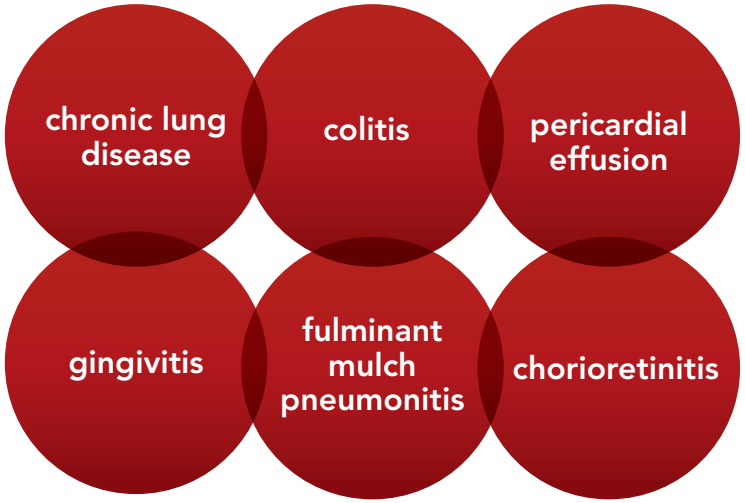
IV antibiotics

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:



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.

People with CGD are at risk of getting obstruction of the gut or urinary tract due to granulomatous inflammation.

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

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.

- HSCT be undertaken in centres specifically recognised for the transplantation of patients with primary immunodeficiency.

- Standard conditioning protocols, as published by the EBMT/ESID Inborn Errors Working Party, are followed, and that reduced intensity conditioning is undertaken in the context of a clinical trial, such as that initiated by Güngör et al.

Gene therapy for CGD

The principle behind bone marrow transplantation is that stem cells can be taken from another individual and grafted into a patient with a blood disorder such as CGD, or even cancer, to provide a lifelong source of normally functioning cells. In principle this is straightforward, but there are some significant challenges. The main problem with transplantation from another individual is that the tissue match (HLA-compatibility) may not be perfect. This means that there is a risk of rejection, and also of an immune reaction against the recipient of the transplant called 'graft-versus-host-disease'. The better the match, the less likely this is to occur, but it is still a significant risk, particularly where patients are ill or have infections at the time of treatment.

Today there are also drugs that can alleviate the risk, but these can lead to a long period of immunosuppression, during which time the patient is quite vulnerable to serious infections. This is compounded by the fact that a transplant for diseases such as CGD will require significant chemotherapy to 'kill off' the existing bone marrow stem cells and allow the new healthy cells to establish themselves in the bone marrow. However, transplant is today very successful if a family donor or unrelated bone marrow donor (including cord blood donors) are closely matched. In the absence of this, risks may be considerable.

For this reason, many groups in the world are developing newer methods for the treatment of CGD. One such strategy is gene therapy. The objective here is to correct the patient's own bone marrow using defective viruses to take a functional gene into the stem cells. This will allow the bone marrow to produce cells, such as neutrophils, that are now able to work properly. Many studies have shown that this actually works in the laboratory and more recently in patients. Even short-term correction of the CGD defect has led to clearance of life-threatening infections that were resistant to other means of treatment.

Gene therapy is a relatively new branch of medicine. Research is ongoing to improve gene therapy for CGD, so that it becomes an alternative, permanent cure when a BMT is not a viable option.

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

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Specialist centres for CGD in the UK

PAEDIATRIC CARE

1. Great North Children's Hospital, Newcastle upon Tyne, United Kingdom
Consultant: Professor Andrew Gennery
Institute of Cellular Medicine
Paediatric Immunology Department
Great North Children's Hospital
Queen Victoria Road
Newcastle upon Tyne NE1 4LP
Telephone: +44 (0)191 282 5234
Fax: +44 (0)191 273 0183

2. Great Ormond Street Hospital for Children, London, United Kingdom
Consultants: Professor David Goldblatt
Clinical Immunology Department
Great Ormond Street Hospital
Great Ormond Street
London WC1N 3JH
Telephone: +44 (0)20 7829 8834

ADULT CARE

The Royal Free London Hospital, London, United Kingdom
Consultant: Dr David Lowe
Clinical Immunology Department
The Royal Free London Hospital
Pond Street
London NW3 2QG
Telephone: +44 (0)20 7794 0500

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

Notes

Notes

CGDSociety

Supporting families affected by chronic granulomatous disorder

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**.