

# A Short Guide to Chronic Granulomatous Disorder - written by medical professionals for medical professionals

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 Box1). Affected individuals are therefore susceptible to serious, potentially life-threatening, bacterial and fungal infection. They also experience symptoms associated with chronic inflammation, often granulomatous in nature.

## 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.

## Inheritance

The majority of CGD cases, approximately two thirds, are of X-linked inheritance (see Box 3). The remainder are autosomal recessive.

## 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)

### Box 1

Neutrophils from CGD patients fail to exhibit a 'respiratory burst', the increase in oxidative metabolism associated with phagocytosis. This is due to 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.

### Box2

**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. X-linked carrier status can be determined by the observation of 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.

### Box 3

Carriers of XL-CGD

In general carriers of XL-CGD are healthy, although in some cases may get recurrent mouth ulcers or even regular skin infections. Occasionally carrier mothers may present with lupus-like symptoms of photosensitivity, skin rash, joint pain and fatigue. Serology may be negative or only weakly positive. Mothers with significant symptoms should be referred to a rheumatologist for further assessment

## A Short Guide to CGD – continued

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:

Lymphadenitis	Skin abscesses	Perianal abscesses
Pneumonia	Liver abscess	Osteomyelitis
Septicaemia	Diarrhoea (may be misdiagnosed as Crohn's disease)	

## Management of CGD

### Preventing infection

The most commonly described infectious complications are pneumonia, lymphadenitis, subcutaneous abscess, liver abscess, osteomyelitis, sepsis

The pathogens responsible for the majority of infections in CGD are catalase positive bacteria and various fungi (see Box 4)

***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.

### Box 4

**Bacteria** - the most commonly implicated bacteria include *Staphylococcus aureus* and the gram negative enterobacteriaceae including *Salmonella*, *Klebsiella*, *Aerobacter* and *Serratia*. *Pseudomonas (Burkholderia) cepacia* is increasingly being recognised as an important pathogen in CGD. Catalase –ve bacteria such as Streptococci rarely cause problems in CGD.

**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 *Chyrosporium zonatum* are increasing.

### Box 5

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)	

## A Short Guide to CGD – continued

### *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 does not affect anaerobic gut flora.

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

### *Antifungal 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.

CGD patients can mount a normal immune response to viruses eg 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 5)

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. A full list of recommended precautions can be found in the CGD Research Trust patient information: [www.cgd.org.uk](http://www.cgd.org.uk). 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 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 etc, 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

## A Short Guide to CGD – continued

### 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.

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 eg clindamycin, 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 anti-bacterial therapy is not obtained, consideration

should be given to commencing empirical antifungal treatment (in discussion with a specialist centre)

### Inflammatory Complications

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. 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.

*Inflammatory complications of CGD include: gingivitis, colitis, pericardial effusion, chronic lung disease, chorioretinitis*

*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).

## A Short Guide to CGD – continued

5-ASA agents (eg. Sulphasalazine, Mesalazine) are useful first line agents in the treatment of CGD-colitis. Steroids, and other immunosuppressive agents, such as Azathioprine, may be indicated where 5ASA 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-ASA's are used in conjunction with Co-trimoxazole a full blood count, should be monitored monthly for the first three 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

## 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 (approx 6 monthly) full blood count and liver function tests are recommended (prophylactic medication may be toxic to bone marrow/associated with altered LFT's). 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 one to two years to monitor progression. Those without lesions at diagnosis should nevertheless 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 emphasized. 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.

## A Short Guide to CGD – continued

### 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 the 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.

## Further Reading/Information

1. Chin TW, Stiehm ER, Falloon J, Gallin JI. Corticosteroids in treatment of obstructive lesions of chronic granulomatous disease. *J Pediatr* 1987; 111:349-52.
2. Goldblatt D, Butcher J, Thrasher AJ, Russell-Eggitt I. Chorioretinal lesions in patients and carriers of chronic granulomatous disease. *J Pediatr* 1999; 134:780-3.
3. Goldblatt D, Thrasher AJ. Chronic granulomatous disease. *Clin Exp Immunol* 2000; 122: 1-9
4. Mouy R, Fischer A, Vilmer E, Seger R, Griscelli C. Incidence, severity, and prevention of infections in chronic granulomatous disease. *J Pediatr* 1989; 114:555-60
5. Mouy R, Veber F, Blanche S *et al.* Long-term itraconazole prophylaxis against *Aspergillus* infections in thirty-two patients with chronic granulomatous disease. *J Pediatr* 1994; 125:998-1003. Schappi M.G., Smith, V.V., Goldblatt D., Lindley K., Milla P.J., Colitis in Chronic Granulomatous Disease, *Arch. Dis. Child* 2001; 84(2):147-151

A patient information booklet for families affected by CGD is available from the CGD Research Trust, Manor Farm, Wimborne St. Giles, Dorset BH21 5NL Tel: 01725 517 977, email: [cgd@cgdrtr.co.uk](mailto:cgd@cgdrtr.co.uk) and can be downloaded from [www.cgd.org.uk](http://www.cgd.org.uk). There are a number of patient information leaflets on other aspects of CGD available on the website.

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