



**ITALIAN PRIMARY IMMUNODEFICIENCIES STRATEGIC SCIENTIFIC  
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# **COMMON VARIABLE IMMUNODEFICIENCY**

## Recommendations for Diagnosis and Treatment

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## **Aim**

The recommendations for the diagnosis and treatment of Common Variable Immunodeficiency (CVID) have been devised to optimize the approach to the diagnosis and treatment of “orphan diseases” like primary immunodeficiencies.

Establishing a nationwide diagnostic and therapeutic protocol and analysing patient outcome will allow ongoing adjustments and updates designed to offer all patients uniform standards of care.

The aim of these recommendations is to:

- Establish standard diagnostic criteria
- Define therapeutic recommendations
- Record the natural history of the disease, the efficacy of replacement therapy and any side effects of treatment
- Record any complications and devise treatment protocols.

The first part of these diagnostic and therapeutic recommendations presents the clinical and pathogenetic state-of-the-art of CVID. The second part outlines the diagnostic and therapeutic recommendations. The third part offer suggestions for the management of infections, autoimmune complications and malabsorption in CVID patients. This last section is not part of the recommendations as such, but aims to offer updated indications on the diagnosis and treatment of complications arising in CVID.

## 1. INTRODUCTION

### 1.1 What is Common Variable Immunodeficiency?

Common Variable Immunodeficiency (CVID) is a primary immunodeficiency disorder characterised by low immunoglobulin levels and deficient antibody production. CVID is the commonest symptomatic humoral immunodeficiency with an estimated incidence of between 1:10.000 and 1:100.000 individuals. CVID affects men and women in equal measure with an age at onset between the second and third decade of life. The widely variable clinical course and immune changes encountered in CVID patients makes it a syndrome which has yet to be completely defined. Different classifications of CVID patients have been devised but none has met with universal consensus to date.

### 1.2 Biochemistry and genetics of CVID

Most patients with CVID are sporadic cases. Around 25% of patients have a family history positive for a selective IgA defect. The region housing the possible mutation(s) predisposing to CVID and the IgG defect has yet to be identified. This region (locus IGAD1) is probably located in the MHC loci in the telomeric part of the genes coding for class II or the centromeric part of the genes coding for class III.

The mechanism responsible for the maturation defect of B cells and the resulting deficient antibody production has not yet been identified. B cells are usually present, sometimes fewer in number but unable to differentiate correctly into plasma cells producing immunoglobulins. However, some patients do produce antibodies, mainly IgM, both *in vivo* and *in vitro*. Why B cells in CVID patients fail to differentiate correctly into plasma cells producing immunoglobulins remains unsettled. The defect has been attributed to a number of causes: an intrinsic B cell defect, a numeric or functional defect of T cells preventing them sending the appropriate plasma cell differentiation signals to B cells. The functional T cell defect has been ascribed to an impaired production of cytokines or an impaired activation of T cells, pathogenetic mechanisms which are not necessarily mutually exclusive. In some patients, the pathogenetic defect consists in an intrinsic defect in the B cell immunoglobulin switch mechanism and the antibody affinity maturation process. In others the somatic hypermutation process is normal but the B cell molecules involved in the interaction with T cells are reduced or functionally impaired. Half of CVID patients present a T cell defect with diminished proliferative response to mitogens and antigens and an impaired production of cytokines IL-2, IL-4, IL-5 and IFN gamma and TNF. An increase in monocytes producing IL-12 was recently reported. All of the above changes have been found only in subgroups of patients, offering further evidence of the wide heterogeneity of CVID.

### 1.3 What are the symptoms of CVID?

Disease **onset** usually occurs in the second or third decade of life with an enhanced susceptibility to infections. Age at onset of symptoms may be earlier (but not later than the second decade of life) or much later (adulthood). Presenting symptoms in most patients are due to a deficient antibody response to pyogens and are characterised by recurrent bacterial infections of the airways and gastrointestinal tract. Other patients may have a more atypical onset with clinical manifestations often associated with CVID, such as splenomegaly, lymphadenopathy, non caseous granulomata, malabsorption with weight loss and diarrhoea, chronic inflammatory bowel disease or autoimmune

disease (pernicious anaemia, haemolytic anaemia, thrombocytopenia, neutropenia). A review of leading series of CVID patients shows that the diagnosis is established on average five to six years after clinical onset. Patients in whom diagnosis was only reached after a long clinical history of recurrent bacterial infections show permanent sequelae like bronchoectasias, features of chronic bronchopneumonia disease up to respiratory insufficiency or malabsorption which will hinder subsequent clinical and therapeutic control.

**Table 1.** Frequency of infectious complications in a series of 248 patients with CVID

| <b>Infectious complications</b>              | <b>%</b> |
|--|----------|
| Recurrent bronchitis, sinusitis, otitis      | 98       |
| Pneumonia                                    | 76.6     |
| Viral hepatitis                              | 6.5      |
| <i>Herpes zoster</i>                         | 3.6      |
| Enteritis due to <i>Giardia lamblia</i>      | 3.2      |
| Infection due to <i>Pneumocystis carinii</i> | 2.8      |
| Pneumonia due to mycoplasma                  | 2.4      |
| Chronic mucocutaneous candidiasis            | 1.2      |
| Enteritis due to <i>Salmonella</i>           | 1.2      |
| Sepsis                                       | 1.2      |
| Enteritis due to <i>Campylobacter</i>        | 1.2      |

More recently a high incidence of *H. pylori* infection (41%) has been reported in association with active chronic gastritis and infections of the urogenital apparatus due to *Mycoplasma hominis* and *Ureaplasma urealyticum*.

Less common infectious complications reported in individual patients include: meningitis due to *H. influenzae*, *S. Pneumoniae*, *Listeria*, osteomyelitis, septic arthritis, recurrent parotitis, pyoderma gangrenosum, cerebral abscesses due to *Nocardia*, skin infections due to anaerobes, lung abscess due to *Cryptococcus*, viral myocarditis, bowel infection by *Cytomegalovirus*, pneumonia due to *Mycobacterium avium*, encephalitis due to measles virus, joint infection due to *Mycoplasma*, muscle abscesses due to *E. coli* and *Bacteroides*, erythrocyte aplasia due to *Parvovirus B19* and gastrointestinal infection due to *Histoplasma capsulatum*.

## 1.4 Associated diseases

### Autoimmune diseases

Around 50% of CVID patients present systemic and organ-specific autoimmune manifestations. The table lists the diseases reported in the literature

|                                     |
|-------------------------------------|
| Idiopathic thrombocytopenic purpura |
| Autoimmune haemolytic anaemia       |
| Rheumatoid arthritis                |
| Juvenile rheumatoid arthritis       |
| Sjögren's syndrome                  |
| Primary biliary cirrhosis           |
| Alopecia                            |
| Pernicious anaemia                  |

|                                     |
|-------------------------------------|
| Autoimmune thyroiditis              |
| Autoimmune neutropenia              |
| Nephrosic syndrome                  |
| Systemic lupus erythematosus        |
| Vasculitis                          |
| Dermatomyositis                     |
| Coeliac disease                     |
| Sensory-motor axonal polyneuropathy |
| Insulin dependent diabetes mellitus |
| Addison's disease                   |
| Sarcoidosis                         |

### **Tumours**

Different studies report an increased incidence of tumours, but an exact calculation of the relative risk is not yet available. The increased risk of developing lymphoma varies from 23 to 100% while the risk of gastric carcinoma is around 50%. The table lists the most common tumours in CVID patients.

|   |
|---|
| Non-Hodgkin's lymphomas (namely large B-cell lymphomas) |
| Hodgkin's lymphomas                                     |
| Waldestrom's macroglobulinaemia                         |
| Adenocarcinoma of the stomach                           |
| Adenocarcinoma of the colon                             |

**Gastrointestinal disease.** The commonest disorders affecting the gastrointestinal system are infections and tumours. Other clinically important manifestations are listed in the table. All gastrointestinal complaints can lead to malabsorption and malnutrition.

|                                  |
|----------------------------------|
| Nodular lymphoid hyperplasia     |
| Crohn's disease                  |
| Ulcerative rectocolitis          |
| Protein-losing enteropathy       |
| Malabsorption                    |
| Intestinal lymphangectasia       |
| Intestinal granulomatous disease |

## 1.5 Diagnostic criteria

The European Group for Immunodeficiencies has defined the diagnostic criteria for the different forms of primary immunodeficiencies. According to these criteria a diagnosis can be established with three degrees of accuracy: certain, probable or possible. Identifying a gene mutation is the most reliable means of reaching certain diagnosis. Unfortunately, CVID is one of the few immunodeficiencies in which the gene responsible has not yet been identified so that molecular analysis is not possible and the diagnosis can only be deemed probable or possible.

### **Common Variable Immunodeficiency (CVID)**

#### Probable diagnosis:

- Male or female patients with markedly decreased levels (2 SD below normal values for age) of at least two classes of serum immunoglobulins (IgG, IgA, IgM) and all of the following:
- Onset of symptoms after two years of age;
- Absent isohaemoagglutinins;
- Poor response to immunization
- Exclusion of other causes of hypogammaglobulinaemia

#### Possible diagnosis:

- Male or female patients with markedly decreased levels (2 SD below normal values for age) of at least one class of serum immunoglobulins (IgG, IgA, IgM) and all of the following:
- Onset of symptoms after two years of age;
- Absent isohaemoagglutinins;
- Poor response to immunization
- Exclusion of other causes of hypogammaglobulinaemia

Since diagnosis cannot be confirmed by molecular analysis, it is important to rule out all other causes of hypogammaglobulinaemia (table)

| <b>Differential diagnosis of hypogammaglobulinaemias</b>   |
|--|
| <p>Drug-induced:</p> <ul style="list-style-type: none"> <li>- antimalarials</li> <li>- captopril</li> <li>- carbamazepine</li> <li>- glucocorticoids</li> <li>- fenclofenac</li> <li>- gold salts</li> <li>- penicillamine</li> <li>- phenytoin</li> <li>- sulfasalazine</li> </ul>      |
| <p>Genetic disorders:</p> <ul style="list-style-type: none"> <li>- hyper-IgM syndrome</li> <li>- transcobalamin II deficiency and hypogammaglobulinaemia</li> <li>- X-linked agammaglobulinaemia</li> <li>- X-linked (EBV-associated) lymphoproliferative syndrome</li> </ul>            |
| <p>Chromosome abnormalities:</p> <ul style="list-style-type: none"> <li>- chromosome 18q syndrome</li> <li>- monosomy 22</li> <li>- trisomy 8</li> <li>- trisomy 21</li> </ul>   |
| <p>Infectious diseases:</p> <ul style="list-style-type: none"> <li>- HIV</li> <li>- congenital rubella</li> <li>- congenital CMV infection</li> <li>- congenital Toxoplasma infection</li> <li>- mononucleosis</li> </ul>  |
| <p>Tumours:</p> <ul style="list-style-type: none"> <li>- chronic lymphoid leukaemia</li> <li>- hypogammaglobulinaemia with thymoma (Good's syndrome)</li> <li>- non Hodgkin's lymphoma</li> <li>- B-cell tumours</li> </ul>  |
| <p>Systemic diseases:</p> <ul style="list-style-type: none"> <li>- immunoglobulin hypercatabolism immunodeficiency</li> <li>- immunodeficiency due to excessive immunoglobulin loss (nephrosis, severe burns, lymphangectasia, severe diarrhoea)</li> <li>- cryoglobulinaemia</li> </ul> |

## **1.6 Immunoglobulin replacement therapy**

Immunoglobulin replacement therapy was proved effective in the Sixties. It is now clear that all immunodeficient patients with low levels of serum IgG and a deficient antibody response must be given gamma globulin treatment by intramuscular, subcutaneous or intravenous infusion. The current treatment of choice is intravenous infusion (IVIg) at doses of 400 mg/kg/month to reach IgG serum levels >500 mg/dl, the concentration required to prevent major infections. The treatment protocol, i.e. the dose of IgG to administer and the interval between one treatment and the next, must be tailored to each individual as some patients have an accelerated catabolism requiring higher doses of IgG or a shorter interval between treatments. More than twenty years' experience of IVIg therapy have proved it a life-saving treatment. The side effects of IVIg may be immediate (rash, fever, muscle pain, urticaria, headache, bronchospasm, hypotension, and rarely anaphylaxis) and long-term (the transmission of infectious agents like hepatitis C virus is well documented). Immediate adverse effects can be controlled by suspending the infusion and giving steroids or adrenalin, whereas the regulations governing the use of blood products should be strictly applied to prevent the risk of infection.

**N.B.**

***Unlike the recommendations for XLA and CGD, the current recommendations for CVID do not serve for diagnostic purposes in the sense that they do not specify national reference centres for analysis of blood samples for CVID diagnosis. Whereas certain diagnosis of XLA and CGD is based on genetic/molecular analysis which is not always available in local hospitals, CVID diagnosis is established on the basis of serum immunoglobulin levels, circulating B cells and immunologic tests routinely available nationwide.***

***For this reason, these recommendations serve mainly to assess the natural history of CVID by filling in and collecting forms containing clinical and immunological information before and after diagnosis. The analysis of these forms will yield information on clinical symptoms at onset, at diagnosis and during follow-up. This will serve to devise the most appropriate therapeutic protocols tailored to individual patients given the widely variable clinical course of the disease, thereby better controlling long-term complications and improving the quality of life of CVID patients. In addition, the assessment of immunological parameters during follow-up may disclose a correlation between immunological changes and the onset of certain complications such as autoimmune illnesses which are particularly common in CVID.***

## 2. DIAGNOSTIC PROTOCOL

### 2.1 Inclusion criteria

Males and females more than three years of age with all the following clinical and laboratory characteristics:

- serum IgG levels below 500 mg/dl
- serum IgA levels below:
  - 30 mg/dl in patients less than < 16 years
  - 60 mg/dl in patients more than > 16 years
- Circulating B cells over 2%
- symptoms

#### **and for NEW diagnosis:**

- deficient antibody response to tetanus (<0.01 UI/ml) and/or pneumococcus (response < 2 x 4 after immunization with respect to pre-vaccination values) according to literature reference parameters (Anti-pneumococcal antibody response in normal subjects: a meta-analysis. J Allergy Clin Immunol. 1996; 98:205-15).
- The following tests:
  - bone marrow aspirate (only in children with abnormal blood parameters; in adults always);
  - lung CT scan and abdominal ultrasound or total body CT scan;
  - expression of CD40L, AID\*;
  - genetic analysis for XLP (only males)\*;
  - PCR for CMV, EBV, HIV\*

(\*the reference laboratories are available for these tests)

A registration form (**Form 1.03**) and a diagnosis form (**Form 23.01**) will be filled in for patients meeting these inclusion criteria. Annual follow-up forms (**Form 23.02**) will then be filled and sent to the AIEOP Operation Office in Bologna.

All subjects meeting the inclusion criteria will follow the set therapeutic recommendations.

## 2.2 Tests to be done at onset and during follow-up:

### - At diagnosis:

Haemochrome

Azotaemia, creatininaemia

Transaminase levels

Protein electrophoresis

sideraemia

IgG, IgA, IgM

C3, C4, ANA,

PCR

CD3, CD4, CD8, CD19, CD16

HCV RNA, HIV RNA

Antitransglutaminase Ab

For new diagnosis: T lymphocyte proliferation to mitogens and antigens (prior to vaccination)\*

Liver and spleen ultrasound

EGDS (compulsory > 20 years of age; when clinically indicated < 20 years of age)

Chest and paranasal sinuses CT scan

(\* at reference laboratories if necessary)

### - Every 3 months:

Haemochrome

Preinfusion IgG levels, IgA, IgM

Azotaemia, creatininaemia

Transaminase levels

Protein electrophoresis

sideraemia

### - Every 12 months:

C3, C4, ANA

HCV RNA

Liver and spleen ultrasound

### - Tests to be done when clinically indicated and every 5 years after 10 years of age

High resolution lung CT scan

Chest and paranasal sinuses CT scan

### 3. TREATMENT RECOMMENDATIONS

#### 3.1 Intravenous immunoglobulin replacement therapy

This protocol aims to ascertain the efficacy and tolerability of a replacement therapy based on the administration of polyvalent human immunoglobulins for intravenous infusion at doses designed to maintain **pre-infusion** serum IgG levels constantly above 500 mg/dl. This will allow the therapeutic protocol to be tailored to individual needs.

**Products:** All products currently available in Italy can be deemed equally effective from the therapeutic standpoint. Therefore, if a product is well tolerated the patient should continue the treatment with the same product. Conversely, if a patient has severe adverse reactions or mild side-effects not controlled by the usual measures (reducing the speed of infusion, administration of antipyretics antihistamines or steroids) another IVIG product should be tried.

**Dose:** A dose of 400 mg/kg/month usually maintains serum IgG levels above 500 mg/dl, considered the protective limit for the main infections. If serum IgG levels are < 500 mg/dl after the first six months of infusions (the time usually required to reach a plateau), the interval between IVIG administrations should be shortened or the dose of IVIG increased maintaining the same treatment interval.

##### 3.1.1 How to start treatment

- 3.1.1.1 Give a detailed explanation and ask for signed informed consent (for treatment with blood products)
- 3.1.1.2 Take a blood sample when required (section 2.2) and when clinically indicated
- 3.1.1.3 Record the type of product, batch number and expiry date in the patient's clinical records
- 3.1.1.4 *(Adults present more side effects of IVIG administration than children so that treatment recommendations differ as reported below. **The infusion protocol is based on the indications drawn up in the guidelines of the Italian Society of Immunology and Clinical Immunology (SIIC Bulletin year XIII, nos.2-3, April-September 1999)***

**For children refer to the recommendations for XLA:**

Start the infusion as follows (child weighing over 20 Kg):

first hour: 30 ml

second hour: 60 ml

third hour: 90 ml

fourth hour: 120 ml

subsequent hours: 120 ml/h

Infusion speed should be gradually increased without hurrying but adapted to each individual patient. If the patient feels unwell during the infusion, especially during the first treatment sessions, the infusion should be slowed down.

If the patient weighs less than 20 kg infusion speed should never exceed 60 ml/h.

**For adults:**

Start the first infusion by two-way administration of saline solution with only two or three drops of the IgG product then suspend the IgG for 15 minutes infusing only saline solution. If there are no adverse reactions IVIG infusion can be continued at a dose of 30 ml in the first hour (around 10 gtt a minute). If there are no adverse reactions increase the infusion speed to 60 ml/h (around 20 gtt a minute). Do not administer more than 2.5g IVIG at the first infusion. In the absence of early and late reactions a second infusion of IVIG can be given on the next day according to the protocol already described for a total dose of 5 g. If there are no early or late adverse reactions another 5g IVIG can be given on the third day (patients weighing more than 40 kg). Subsequent administrations will be scheduled as above at 15 day intervals for the first six months adjusting the interval thereafter (every 10-15-21 days) depending on pre-infusion serum IgG levels.

**3.1.2 What to do before each infusion:**

-Take the history and examine the patient, recording the type, batch number and expiry date of the IgG product in the patient's clinical records.

**3.1.3 Reactions to intravenous immunoglobulin administration**

Intravenous immunoglobulin administration gives rise to two main side-effects:

- 1) Allergic and/or inflammatory reactions which may be vasoactive or anaphylactoid reactions or generalized anaphylaxis;
- 2) Intravenous transmission of infectious agents.

**3.1.3.1 Vasoactive or anaphylactoid reactions** usually appear within the first 30 minutes of infusion and are characterized by abdominal pain, low back pain, nausea and vomiting, fever, headache, muscle pain and weakness lasting up to several hours after the end of infusion. Dyspnoea and hypotension seldom occur.

Reactions usually arise during the first infusions and during multiple chronic episodes of infection since a Herxheimer reaction probably takes place with the massive release of endotoxins by the many bacteria destroyed by immunoglobulin infusion.

**What to do**

- a) Suspend the infusion which can be resumed a few minutes later reducing the speed.
- b) If fever and/or headache and/or muscle pain are present give salicylates (10-20 mg/Kg) or paracetamol (10 mg/Kg) before resuming infusion.
- c) When a patient has presented systemic symptoms corticosteroids (hydrocortisone 10 mg/Kg) and antihistamines (clorphenamine 0.1 mg/Kg) should be administered intravenously about an hour before the start of subsequent infusions. If fever was the only symptom premedication with paracetamol is sufficient.
- d) If the reaction was severe, a product prepared by a different method should be tried. The new product should be infused adopting the same criteria as for the first infusion.

**3.1.3.2 Anaphylactic reactions** presenting the classic symptoms of IgE-mediated anaphylaxis: dyspnea, rash, vomiting, cardiocirculatory collapse and loss of consciousness up to generalized shock are rare and usually arise during the first infusions at the start of infusion.

### **What to do**

- a) Suspend the infusion immediately and send for a resuscitation expert.
- b) Administer adrenaline 1:1000 subcutaneously at a dose of 0.01 ml/Kg to be repeated 15 minutes later. If the patient's general and cardiocirculatory conditions fail to recover administer adrenaline 1:10.000 intravenously at a dose of 1 ml in bolus (irrespective of the patient's weight) followed by continuous intravenous infusion of 1-4 µg/Kg/minute of the same solution until arterial pressure is resumed.
- c) It is essential to keep the venous access used for IgG infusion patent as it may be required in case of shock caused by administration of emergency fluids or drugs (other vasodilators and bronchodilators in addition to adrenalin).
- d) IgG infusion must not be resumed on the same day even if the patient recovers promptly.
- e) After an anaphylactic reaction subsequent intravenous immunoglobulin infusion should be undertaken in a facility with an intensive care physician present adopting the same criteria as for the first infusion and infusing a different product. If the reaction should recur, intravenous immunoglobulin treatment should be suspended and continuous antibiotic prophylaxis with a cephalosporin or co-trimoxazole instituted at half/third of the dosage taken in a single evening dose.

A specific form (**Form 23.03**) is available for patients presenting anaphylactic reactions and should be sent to the AIEOP Operation Office: the data collected will constitute a database to devise specific laboratory tests, nationwide surveillance of adverse reactions to intravenous immunoglobulin administration and to plan safe and adequate intervention strategies.

**3.1.3.3 Intravenous transmission of infectious agents.** Current legislation on the control of blood products ensures that to our current knowledge IVIG can be considered safe for all known viruses. However, hepatitis C virus (HCV) has been transmitted in the past to CVID patients undergoing replacement therapy. For this reason a search for the viral genome (HCV RNA) should have been undertaken regularly in all patients already receiving IVIG. According to the FDA no case of HCV transmission by IgG infusion has been reported since viral inactivation procedures were introduced. In any case it is extremely important to update the surveillance of viral diseases transmitted by IgG infusion.

### **What to do**

Yearly aliquots of serum from each patient enrolled should be stored at  $-80^{\circ}\text{C}$ . In addition, the search for HCV RNA should be done at least once a year.

## 4. RECOMMENDATIONS ON THE MANAGEMENT OF ASSOCIATED ILLNESS

### 4.1 Treatment of infectious episodes

#### 4.1.1 Upper airway infections

Purulent rhinitis, otitis, sinusitis: should be treated promptly with antibiotics until symptoms have resolved completely. The choice of antibiotic is based on epidemiological findings showing that *H. influenzae*, *St. pneumoniae* and *M. catharralis* are the most common pathogens responsible for infection (table)

| Antibiotic                      | Adult dose (mg/die) | Child dose (mg/kg/die) | N.º doses | Route |
|---------------------------------|---------------------|------------------------|-----------|-------|
| Amoxicillin                     | 500-1000            | 40                     | 3         | os    |
| Amoxicillin/<br>Clavulanic acid | 1000                | 50                     | 2         | os    |
| TMP/SMX                         | 800/160             | 7/35                   | 2         | os    |
| Cefixime                        | 400                 | 8                      | 1         | os    |
| Cefaclor                        | 250                 | 40                     | 3         | os    |
| Ceftriaxone                     | 1000                | 40-80                  | 1         | im    |
| Clarithromycin                  | 250                 | 15                     | 2         | os    |
| Azithromycin                    | 500                 | 10                     | 1         | os    |

Treatment for otitis should last ten days, whereas treatment for sinusitis should be prolonged for three weeks. Intravenous antibiotics are recommended to treat complications like mastoiditis and cellulitis.

Chronic sinusitis and nasal polyposis. Seek an otolaryngologists's advice for possible rhinofibrosomy with a view to surgery.

#### 4.1.2 Lower airway infection

Pneumonia. The expectorate should be cultured to identify the pathogen responsible and empirical antibiotic treatment promptly adjusted on the basis of the antibiogram. If pneumonia caused by *Pneumocystis carinii* is clinically suspected diagnostic confirmation with BAL is required. Treatment entails a combination of Dapsone +TMP or TMP/SMZ.

All CVID patients must follow a respiratory physiotherapy programme devised by a physiatrist.

Following recent evidence of permanent pulmonary sequelae (bronchiectasias) even in asymptomatic patients, a high resolution lung CT scan is recommended when clinically indicated every five years from the age of ten years.

### 4.1.3 Bowel infections

Diagnosis should be established by repeat culture notifying the analysis laboratory to search for specific pathogens (*Giardia lamblia*, *Campylobacter*, *Shigella*, *Salmonella*, *E.coli enteropathogens*, *Cryptosporidium*) and if necessary (negative stool culture and persistent symptoms) bioptic examination of the jejunal mucosa during OGDS. Treatment is summarised in the table.

| Pathogen               | Drug   | Dose (child)                            | Dose (adult)                     |
|------------------------|--|---|----------------------------------|
| <i>Giardia lamblia</i> | Metronidazole*                               | 15 mg/kg/die 3 times daily for 5 days   | 250 mg 3 times daily for 5 days  |
|                        | Tinidazole*                                  | 50 mg/kg single dose (max 2 days)       | 2 g single dose                  |
|                        | Furazolidone                                 | 6 mg/kg/die 4 times daily for 7-10 days | 100mg 4 times daily for 10 days  |
|                        | Albendazole                                  | 400 mg/die single dose for 5 days       | 400mg single dose for 5 days     |
|                        | Paromomycin                                  |   | 10mg/kg 3 times daily for 7 days |
| <i>Campylobacter</i>   | Erythromycin                                 | 50 mg/kg/die 4 times daily for 5-7 days | 500mg 4 times daily for 7 days   |
|                        | Ciprofloxacin                                |   | 500mg twice daily for 5 days     |
|                        | Azithromycin                                 |   | 500 mg single dose for 3 days    |
| <i>Yersinia</i>        | Cefotaxime                                   |   |                                  |
|                        | Tetracycline                                 |   |                                  |
|                        | Aminoglycosides                              |   |                                  |
|                        | Co-trimoxazole                               |   |                                  |
| <i>Salmonella</i>      | Ampicillin                                   |   |                                  |
|                        | Ciprofloxacin                                |   |                                  |
| <i>Shigella</i>        | TMP/SMX                                      |   |                                  |
| <i>Cryptospridium</i>  | Paromomycin+ azithromycin                    |   |                                  |
| <i>H.pylori</i>        | Clarithromycin+ metronidazole or amoxicillin |   |                                  |

\*Metronidazole: first choice

\*Tinidazole: first choice

### 4.1.4 Hepatitis

CVID patients' susceptibility to hepatotropic viruses is linked to the greater risk of exposure to blood products (transfusions, plasma, immunoglobulins) rather than the underlying disease. As hepatitis C virus (HCV) has been transmitted in the past to CVID patients undergoing replacement therapy a search for the viral genome (HCV RNA) should already have been undertaken regularly in all patients already receiving IVIG. No new cases have been reported to date but patients on IVIG should still undergo a search for HCV RNA once a year or whenever they present unexplained raised transaminase levels.

The diagnosis of chronic liver disease should be established non invasively by liver and spleen ultrasound to be done in all patients on diagnosis of CVID and yearly thereafter. Ultrasound investigation will determine any liver enlargement, the echogenicity of the hepatic parenchyma,

splenomegaly (present in more than 50% of CVID patients) and the echogenicity of the splenic parenchyma, any accessory spleens (common) and enlarged or abnormal abdominal lymph nodes.

#### **4.2 Assessment of nutritional status and treatments**

As already outlined under clinical symptoms, roughly half of all CVID patients have chronic diarrhoea which may evolve into moderate malabsorption. For this reason the following anthropometric and biochemical parameters should be monitored periodically to assess nutritional status:

- Weight
- Height
- Body mass index (BMI)
- Albuminaemia
- Serum cholinesterase

In addition to specific treatment of the underlying cause (management of *Giardia lamblia* disease, infections or chronic inflammatory bowel disease), patients with impaired nutritional status must follow a nutrition schedule based on a correct diet and intravenous food supplements according to a tailor-made intervention devised in agreement with the hospital nutritionist.

#### **4.3 Diagnosis and treatment of autoimmune complications**

Diagnosis of autoimmune diseases in CVID patients must be established according to specific criteria for each illness. Plainly, the antibody deficiency hampers the interpretation of tests based on the presence of antibodies which may be negative (but not always). Diagnosis is therefore based on clinical criteria together with invasive and non invasive tests for organ-specific disease. Once diagnosis has been established patients must be given specific treatments for each illness (immunosuppressant therapy, steroids, etc.) at the commonly used doses and therapeutic protocols. Immunodeficiency is not a contraindication to treatment which should only be reduced or suspended during acute infection. Special attention must be paid to monitoring chronic infections (sinusitis, otitis, chronic bronchopneumopathy with bronchiectasias, intestinal giardiasis) and treatment should aim at sterilizing the infectious foci. As the efficacy of IVIG is well-established in some autoimmune diseases (autoimmune thrombocytopenic purpura and other autoimmune cytopenias, chronic inflammatory polyneuropathy, dermatomyositis) and suggested as a possible treatment for others (SLE, RA, systemic sclerosis, Sjögren's syndrome, systemic vasculitis) this therapy should always be entertained for CVID patients with autoimmune illness. The dose fixed in the IVIG treatment protocol must be increased up to the doses deemed therapeutic in these illnesses (2g/kg body weight, divided into a variable number of doses for 1-5 consecutive days/month depending on the disease).

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