ITALIAN PRIMARY IMMUNODEFICIENCIES STRATEGIC SCIENTIFIC COMMITTEE

COMMON VARIABLE IMMUNODEFICIENCY

Recommendations for Diagnosis and Treatment

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Cohordinator Primary Immunodeficiencies Network:	Prof. Alberto G. Ugazio Ospedale Bambin Gesù Roma
Scientific Committee:	Prof. C. Agostini (PD) Prof. L. Armenio (BA) Prof. Cao (CA) Dott. E. Castagnola (GE) Dott. G. Cazzola (VR) Prof. Dammacco (BA) Prof. S. Del Giacco (CA) Prof. D. De Mattia (BA) Prof. M. Duse (BS) Dott. M. Gattorno (GE) Prof. GL. Marseglia (PV) Prof. M. Masi (BO) Prof. G. Marone (NA) Prof. L.D. Notarangelo (BS) Prof. G. Paolucci (BO) Prof. A. Pession (BO) Prof. M. Pietrogrande (MI) Prof. MC. Pietrogrande (MI) Prof. C. Pignata (NA) Prof. A. Plebani (BS) Prof. P. Rossi (Roma) Prof. A. Stabile (Roma) Prof. P.A. Tovo (TO) Prof. A. Vierucci (FI)
Responsible:	Prof. Isabella Quinti Dipart. Medicina Clinica Università “La Sapienza” Roma
Data Review Committee:	Prof. ssa Isabella Quinti (Roma) Prof. Alessandro Plebani (BS) Dott.ssa Annarosa Soresina (BS) Dott. Roberto Rondelli (BO)
Data management and analysis:	Centro Operativo AIEOP Pad. 23 c/o Centro Interdipartimentale di Ricerche sul Cancro “G. Prodi” Via Massarenti, 9 40138 Bologna

CENTRES

CODE AIEOP	INSTITUTION	RAPRESENTATIVE
0901	ANCONA Clinica Pediatrica Ospedale Salesi ANCONA Tel.071/36363 Fax 071/36281	Prof. Coppa Prof. P.Pierani
0311	ASOLA(MN) Divisione di Pediatria Ospedale di Asola Tel. 0376/721309 Fax 0376/720189	Dott.G.Gambaretto
1301	BARI Dipart. Biomed.dell'Età Evolutiva Clinica Pediatrica I P.zza G. Cesare 11 70124 BARI Tel. 080/5542295 Fax 080/5542290 e-mail: demattia@bioetaev.uniba.it baldo.martire@bioetaev.uniba.it	Prof. D. De Mattia Dott.B.Martire
1307	BARI Clinica Pediatrica III Università di Bari P.zza Giulio Cesare 11 70124 BARI Tel. 080/5592844 Fax 080/5478911 e-mail:fabiocardinale@libero.it	Prof. L. Armenio Dott. F. Cardinale
1306	BARI Dip.di Scienze Biomediche e Oncologia umana Sez. Medicina Interna Policlinico P.zza G. Cesare 11 70125 BARI Tel. 080/5478822-860 Fax 080/5478820	Prof. F. Dammacco Dott.ssa M. Prete
0603	BOLOGNA Clinica Pediatrica Via Massarenti 11 40138 BOLOGNA Tel. 051/6363649 Fax 051/6364679 e-mail: paolucci@almadns.unibo.it masi@med.unibo.it	Prof. G.Paolucci Prof. M. Masi Dott.ssa A. Miniaci
0605	BOLOGNA Div. Pediatria Ospedale "Maggiore" Largo Nigrisoli, 2 40133 BOLOGNA	Prof. G. Ambrosioni Dott.ssa P.Alvisi

	Tel. 051/6478564 Fax 051/6478949	
0305	BRESCIA Clinica Pediatrica Spedali Civili P.le Spedali Civili, 1 25123 BRESCIA Tel. 030/3995887- 700 Fax 030/3388099 e-mail: plebani@med.unibs.it soresina@master.cci.unibs.it duse@master.cci.unibs.it notarang@med.unibs.it	Prof. L.D. Notarangelo Prof. A. Plebani Prof. M. Duse Dott.ssa A. Soresina
1602	CAGLIARI Centro TMO Ospedale Microcitemico Clinica Pediatrica Univ. Cagliari Via Jenner 09121 CAGLIARI Tel. 070/6095512 Fax 070/6095694 e-mail: fcossu@mcweb.unica.it	Prof. Cao Dott. F. Cossu
1603	CAGLIARI Allergologia e Immunol. Clinica Policlinico Universitario Via S.Giorgio 12 09124 CAGLIARI Tel.070/60286240 Fax 070/60286212 e-mail: manconip@pacs.unica.it	Prof. S. Del Giacco Prof. P. Manconi
1901	CAMPOBASSO Div. Pediatrica Ospedale Cardarelli ASL3 Centromolise Campobasso Località Tappino 86100 Campobasso Tel. 0874/4092272 Fax 0874/4092273	Dott. I. Evangelista
1401	CATANZARO Div. Ematologia Ospedale Civile “A. Pugliese” Viale Pio X 88100 CATANZARO Tel. 0961/883069/883205 Fax 0961/883250 e-mail saveriomagro@libero.it	Dott. S. Magro Dott. S. Morgione
1404	CATANZARO U.O. di Pediatria Univ. degli Studi di Catanzaro Ospedale Pugliese Viale Pio X 88100 CATANZARO Tel. 0961/ 883007 Fax 0961/883489/727305 e-mail pstrisciuglio@unicz.it	Prof. P. Strisciuglio Dott.ssa E.Anastasio

	elisa.anastasio@tin.it	
1502	CATANIA Div. Ematologia-Oncologia Ped. Clin. Pediatrica Università Catania Via A. Doria, 6 95123 CATANIA Tel. 095/256497 Fax 095/330636/222532 e-mail: antoscio@hotmail.com	Prof. G. Schillirò Dott. ssa A. Sciotto
0312	COMO Divisione Pediatria Azienda Osped. "Sant'Anna" Via Napoleone 60 22100 COMO Tel. 031/5855353 Fax 031/5855948 e-mail: pediatria@hsacomo.org	Dott. Maurizio. Sticca
403	COSENZA U.O. Pediatria Ospedale "Annunziata" Via Migliori 1 87100 Cosenza tel.0984/681343 Fax 0984/681315 luicarp@libero.it	Dott.ssa M. Candusso Dott. L. Carpino
0701	FIRENZE Dipart. di Pediatria Ospedale "A. Meyer" Via L. Giordano, 13 50132 FIRENZE Tel. 055/5662542 Fax 055/570380 e-mail: azzaric@unifi.it c.azzari@meyer.it	Prof. G. Bernini Dott.ssa C. Azzari
0202	GENOVA Seconda Divis. Pediatria Istituto G. Gaslini P.zza G. Gaslini 5 16147 GENOVA Tel. 010/5636428 FAX 010/3776590 e-mail: eliocastagnola@ospedale-gaslini.ge.it marcogattorno@ospedale-gaslini.ge.it	Dott. E. Castagnola Dott. M.Gattorno
0315	MANTOVA Pediatria Ospedale Poma Via Albertoni 1 46100 MANTOVA Tel. 0376/201454 Fax 0376/201772	Dott. G. Pastorelli Dott.ssa S. Fasoli Dr. Gambaretto
1504	MESSINA Genetica e Immunologia Pediatrica Az. "G.Martino" Via Consolare Valeria Gazzi 98100 MESSINA	Prof. C. Salpietro

	Tel. 090/2213114 e-mail: carmelo.salpietro@unime.it	
0314	MILANO Clinica Pediatrica II Università di Milano Via Commenda 9 20122 MILANO Tel. 02/57992496 Fax 02/50320210 e-mail: mariacristina.pietrogrande@unimi.it	Prof.ssa MC. Pietrogrande Dott.ssa F. Rusconi Dott.ssa RM. DellePiane Dott.ssa Panisi
0316	MILANO Ist. Clinici Perfezionamento Div. Medicina Generale P.zza San Barnaba 8 20123 MILANO Tel. 02/57992672 FAX 02/57992659	Dott. G. Cambiaghi
0317	MILANO Dip. Medicina e Chirurgia Università di Milano Pol San Marco Corso Europa 7 24040 ZINGONIA-OSIO SOTTO Tel. 035/886308 FAX 035/886308 e-mail: maurizio.pietrogrande@unimi.it	Prof. M. Pietrogrande
0318	MILANO Un.di ricerca Clin Pediatrica HSR TIGET Istituto Scientifcico HS Raffaele Via Olgettina 58 MILANO Tel. 02/26434668 Fax 02/26434671 e-mail: m.roncarolo@hsr.it a.aiuti@hsr.it	Prof.ssa MG. Roncarolo Dott. A. Aiuti
0302	MONZA Clinica Pediatrica Ospedale “S. Gerardo” Via Donizetti 106 20052 MONZA Tel. 039/2333513 Fax 039/2301646 e-mail: masera@xquasar.it	Prof. G. Masera Prof. A. Biondi Dott.ssa A. Sala
1207	NAPOLI Unità Specialistica di Immunologia Dipart. di Pediatria Univ. Studi di Napoli “Federico II” Via Pansini 5 80131 NAPOLI Tel. 081/664632 Fax 081/5451278 e-mail: pignata@unina.it	Prof. C. Pignata
1203	NAPOLI Divisione di Pediatria-Ematologia	Prof. V. Poggi Dott. G. Menna

	Ospedale "Pausilipon" Via Posillipo 226 80123 NAPOLI Tel. 081/2205410 Fax 081/2205418	
1208	NAPOLI I Div. Med. Pediatrica Ospedale Santobono Via M. Fiore 6 80100 NAPOLI Tel. 081/2205636 Fax 081/2205608	Dott. R. Di Nardo
1209	NAPOLI Pediatria Ospedale S. Leonardo ASL NA5 Via Castellammare di Stabia 80054 GRAGNANO (NA) Tel. 081/8711782 Fax 081/8729341 e-mail: adapuzzo@libero.it	Dott. A. D'Apuzzo
1210	NAPOLI I Div. Pediatria Osp. SS. Annunziata Via Egiziaca A Forcella 80139 NAPOLI Tel. 081/2542504– 2600 Fax 081/2542635 antpelliccia@tiscali.it	Dott. A. Pelliccia
1204	NAPOLI II Pediatria Ospedale Annunziata ASLNA1 Tel. 081/2542544-634 Fax 081/2542635	Dott. A. Correra
1211	NAPOLI Centroperladiagnosi e cura ID prim. Immunologia e Allergologia Clinica Univ. Studi di Napoli "Federico II" Via Pansini 5 80131 NAPOLI Tel. 081/7462261, FAX 081/2203998 e-mail: spadaro@unina.it	Prof. G. Marone Dott. G. Spadaro
0401	PADOVA Clinica Oncoematol. Pediatrica Università di Padova Via Giustiniani 3 35128 PADOVA Tel. 049/8218003 FAX 049/8213510 e-mail: luigi.zanesco@unipd.it giuseppe.basso@unipd.it mariacaterina.putti@unipd.it	Prof. L. Zanesco Prof. G. Basso Dott. MC. Putti
0410	PADOVA Dip. Medicina Clinica e Sperim.	Prof. G. Semenzato Prof. C. Agostini

	Immunologia Clinica Via Giustiniani 2 35128 PADOVA Tel. 049/8212299 FAX 049/8754179 e-mail: carlo.agostini@unipd.it	
1505	PALERMO U.O. Clinica Pediatrica Via Benedettini 1 90100 PALERMO Tel. 091/6666038 - 6249 Fax 091/421630 e-mail: istped@mbox.unipa.it	Prof. GM. Amato
1501	PALERMO Oncoematologia Pediatrica Via Benedettini 1 90100 PALERMO Tel. 091/6666130-015 Fax 091/421630 e-mail:arico@ospedalecivicopa.org	Dott.M.Aricò Dott.A.Trizzino
0601	PARMA Oncoematologia Pediatrica Dip. di Pediatria Az. Ospedaliera di Parma Via A. Gramsci 14 43100 PARMA Tel. 0521/702222/702210 Fax 0521/702360 e-mail: gcizzi@ao.pr.it pbertolini@ao.pr.it	Dott. G. Izzi Dott.ssa P. Bertolini
0319	PAVIA Clinica Pediatrica Policlinico “S.Matteo” P.le Golgi 2 27100 PAVIA Tel. 0382/502770-557-629 Fax 0382/527976 e-mail: gl.marseglia@smatteo.pv.it r.maccario@smatteo.pv.it	Prof. G. Rondini Prof.GL. Marseglia Prof.ssa R.Maccario Dott.ssa G. Bossi
0303	PAVIA Oncoematologia Pediatrica IRCCS, Policlinico San Matteo P.le Golgi 2 27100 PAVIA Tel.0382/502607 Fax 0382/501251 e-mail: f.locatelli@smatteo.pv.it	Dott. F. Locatelli Dott. M. Zecca
0903	PESARO U.O. Pediatria Neonatologia Az. Ospedaliera San Salvatore P.le Cinelli 4 61100 PESARO Tel. 0721/362310 Fax 0721/362311 e-mail: pediatria.ps@abanet.it	Dott. L. Felici

0703	PISA Clinica Pediatrica III Via Roma 66 56100 PISA Tel. 050/992840-2222 Fax 050/888622 e-mail: p.macchia@clp.med.unipi.it rita.consolini@clp.med.unipi.it	Prof. P. Macchia Dott.ssa R. Consolini Dott. C. Favre
0607	RIMINI Divisione Pediatria Ospedale "Infermi" Via Settembrini 11 47900 RIMINI Tel. 0541/705210 Fax 0541/705360	Prof. V. Vecchi Dott.ssa P. Sacchini Dott.ssa G. Rinaldi
1110	ROMA Div.ne di Immunoinfettivologia Ospedale Bambino Gesù P.zza S. Onofrio 4 00165 ROMA Tel. 06/68592508 Fax 06/68592508 e-mail: ugazio@opbg.net rossi@opbg.net livadiotti@opbg.net	Prof. A.G. Ugazio Prof. P. Rossi Dr.ssa Livadiotti
1107	ROMA Clinica Pediatrica Università Cattolica Sacro Cuore Largo Gemelli 8 00135 ROMA Tel. 06/30514348-4290 Fax 06/3051343 e-mail: iclpe@RM.unicatt.it	Prof. A. Stabile
1108	ROMA Ist. Clinica Pediatrica Università "La Sapienza" Viale Regina Elena 325 00163 ROMA Tel. 06/4404994 e-mail: margherita.bonamico@uniroma1.it giovanni.nigro@uniroma1.it	Dott. G.Nigro Prof.M.Bonamico
1109	ROMA Dipart. Medicina Clinica Università "La Sapienza" Viale dell'Università 37 00186 ROMA Tel. 06/49972036 Fax 06/49972037 e-mail: quinti@uniroma1.it	Prof.ssa I. Quinti Dr.ssa V. Guazzi
1111	ROMA Centro Interdisciplinare Pediatria Policlinico Tor Vergata Univ. Tor Vergata Viale Oxford 81 00133 ROMA tel.06/20900529	Prof. P.Rossi Prof. V.Moschese

	fax 06/20900530 e-mail:moschese@med.uniroma2.it	
0702	SIENA Dipart. Di Pediatria Univ. di Siena V.le Bracci 16 53100 SIENA tel. 0577/263415 fax 0577/263415 e-mail:pediatria@unisi.it	Prof. G. Morgese Dott. Acquaviva
0313	TREVIGLIO(BG) Div. di Pediatria Ospedale di Treviglio P.zza Ospedale 1 24047 TREVIGLIO (BG) Tel. 0363/424273 Fax 0363/424400	Dott. L. Re Dott. R. Cogliati
0408	TREVISO Div. Pediatrica Osped. Regionale Treviso Via Ospedale 7 31100 TREVISO Tel. 0422/322266 Fax 0422/322232 e-mail: gdezan@ulss.tv.it	Dott. G. De Zan Dott.ssa S.Strafella
0501	TRIESTE Clinica Pediatrica Ospedale Infantile “Burlo Garofolo” Via dell’Istria 65/I 34137 TRIESTE Tel. 040/3785342 Fax 040/3785494 e-mail: tamaro@burlo.trieste.it rabusin@burlo.trieste.it	Prof. P. Tamaro Dott. M. Rabusin
0105	TORINO Dip. Scienze Ped. e dell’Adolescenza Osp. Infantile Regina Margherita P.zza Polonia 94 10126 TORINO Tel. 011/3135798 Fax 011/ 3135517 e-mail: tovo@pediatria.unito.it silvana.martino@unito.it	Prof. PA. Tovo Dott.ssa S. Martino
0309	VARESE Clinica Pediatrica Università di Pavia Ospedale “F. Del Ponte” P.zza Biroldi 1 21100 VARESE Tel. 0332/285300- 299231-299390 Fax 0332/235904	Prof. L. Nespoli Dott.ssa M. Marinoni
0405	VENEZIA Dipart. Oncologia ed Ematologia Oncologica Ospedale P.F. Calvi	Prof. A. Porcellini

	Largo S. Giorgio 2 NOALE (VE) Tel. 041/5896221 Fax 041/5896259 e-mail: emanoale@tin.it	
0409	VERONA Centro Fibrosi Cistica Ospedale Civile di Verona P.le Stefani 1 37126 VERONA Tel. 045/8072294 FAX 045/8072042 e-mail: giantonio.cazzola@mail.azosp.vr.it	Dott. GA. Cazzola

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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 splemomegaly, 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

Infectious complictions	**%**
Recurrent bronchitis, sinusitis, otitis	98
Pneumonia	76.6
Viral hepatitis	6.5
Herpes zoster	3.6
Enteritis due to *Giardia lamblia*	3.2
Infection due to *Pneumocystis carinii*	2.8
Pneumonia due to mycoplasma	2.4
Chronic mucocutaneous candidiasis	1.2
Enteritis due to *Salmonella*	1.2
Sepsis	1.2
Enteritis due to *Campylobacter*	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)

Differential diagnosis of hypogammaglobulinaemias
Drug-induced: - antimalarials - captopril - carbamazepine - glucocorticoids - fenclofenac - gold salts - penicillamine - phenytoin - sulfasalazine
Genetic disorders: - hyper-IgM syndrome - transcobalamin II deficiency and hypogammaglobulinaemia - X-linked agammaglobulinaemia - X-linked (EBV-associated) lymphoproliferative syndrome
Chromosome abnormalities: - chromosome 18q syndrome - monosomy 22 - trisomy 8 - trisomy 21
Infectious diseases: - HIV - congenital rubella - congenital CMV infection - congenital Toxoplasma infection - mononucleosis
Tumours: - chronic lymphoid leukaemia - hypogammaglobulinaemia with thymoma (Good's syndrome) - non Hodgkin's lymphoma - B-cell tumours
Systemic diseases: - immunoglobulin hypercatabolism immunodeficiency - immunodeficiency due to excessive immunoglobulin loss (nephrosis, severe burns, lymphangectasia, severe diarrhoea) - cryoglobulinaemia

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 (SIIIC 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 (**From 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°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.° doses**	**Route**
Amoxicillin	500-1000	40	3	os
Amoxicillin/ 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 sinusititis 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 rhinofibroscopy 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 physiokinesitherapy 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)
Giardia lamblia	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
Campylobacter	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
Yersinia	Cefotaxime		
	Tetracycline		
	Aminoglycosides		
	Co-trimoxazole		
Salmonella	Ampicillin		
	Ciprofloxacine		
Shigella	TMP/SMX		
Cryptospridium	Paromomycin+ azithromycin		
H.pylori	Clarithromycin+ metroinidazole 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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