Supplement:

Supplemental table S1: Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Level	Evidence
1	Systematic review of randomized trials
2	Randomized trial or observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study
4	Case-series, case-control studies, or historically controlled studies
5	Mechanism-based reasoning

Supplemental table S2: Grading of recommendation levels

A	Strong recommendation
B	Recommendation
0	Insufficient evidence for recommendation

Supplemental table S3: Classification of consensus

>95% of participants approved	Strong consensus
>75-95% of participants approved	Consensus
50-75% of participants approved	Approved by majority
<50% of participants approved	No consensus

Supplemental table S4: ESID Registry – Working definitions for clinical diagnosis of PID (see *https://esid.org/Working-Parties/Registry/Diagnosis-criteria*)

Common variable immunodeficiency disorder (CVID)	**At least one of the following:** • increased susceptibility to infection • autoimmune manifestations • granulomatous disease • unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency **AND** marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age); **AND** at least one of the following: • poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination where defined • low switched memory B cells (<70% of age-related normal value) **AND** secondary causes of hypogammaglobulinaemia have been excluded **AND** diagnosis is established after the 4th year of life (but symptoms may be present before) **AND** no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life): • CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200 • % naive CD4: 2-6y <25%, 6-16y <20%, >16y <10% • T cell proliferation absent

Supplemental table S5: ESID Registry – Working definitions for clinical diagnosis of PID: unclassified antibody deficiency

Unclassified antibody deficiency	**At least 1 of the following 4:** • Recurrent or severe bacterial infections • Autoimmune phenomena (especially cytopenias) • Polyclonal lymphoproliferation • Affected family member **AND at least one of the following**: • marked decrease of at least one of total IgG, IgG1, IgG2, IgG3, IgA or IgM levels • failure of IgG antibody response(s) to vaccines **AND** secondary causes of hypogammaglobulinaemia have been excluded (infection, protein loss, medication, malignancy) **AND** no clinical signs of T-cell related disease **AND** does not fit **any** of the other working definitions (**ex**cluding 'unclassified immunodeficiencies')

Table S6: Summary on treatment of GLILD in CVID patients

Intervention	**n**	**Type of pulmonary lesion**	**Outcome**	**Reference**
Monotherapies:				
Steroids	17	GLILD (14)* COP (1) LIP (2)	CR: 4 (29%)/PR: 4 (29%)/NR: 6 (42%) CR: 100% CR: 1 (50%)/PR: 1 (50%) OR: 65%	(119) (143) * steroids followed by MMF maintenance (144) (145) (146)
Infliximab	4	GLILD	PR: 3 (75%)/NR: 1 (25%)	(147) (119)
MMF	3	GLILD	PR: 2 (66%)/NR: 1 (33%)	(148)
RTX	2	GLILD	CR: 1 (50%)/PR: 1 (50%)	(119)
Cyclophosphamide	2	GLILD	NR: 100%	(119)
CsA	2	LIP (1) GLILD (1)	CR: 1 NR: 1 OR: 50%	(149) (119)
Hydroxychloroquine	1	GLILD	NR: 100%	(119)
Rapamycin	1	GLILD	PR: 100%	(119)
IVIg	2	GLILD	CR: 100%	(150) (151)
Combination therapies:				
RTX & Aza	9	GLILD	CR: 1 (11%)/PR: 7 (77%)/NR: 1 (11%)	(115-117)
RTX & MMF	1	GLILD	CR: 100%	(118)

Aza: Azathioprine; CsA: Cyclosporine A; IVIg: intravenous immunglobulines; MMF: Mycophenolat Mofetil; MTX: Methotrexate; RTX: Rituximab. CR: complete remission; PR: partial remission; OR: overall response rate; NR: no response

Table S7: Summary on treatment of extra-pulmonary granulomatous lesions in CVID patients

Intervention	n	Localisation	Outcome	Reference
		cutaneous		
IVIg	2	cutaneous	CR: 1 (50%)/PR: 1 (50%)	(152, 153)
Infliximab	4	cutaneous	CR: 100%	(147, 154) (155) (147)
Eternacept	2	cutaneous	CR: 1 (50%)/PR: 1 (50%)	(156) (157)
Steroids	2	cutaneous	CR: 1 (50%)/PR:1 (50%)	(119)
Steroids and Aza	1	cutaneous	PR:100%	(158)
		visceral		
Steroids	54	Liver Kidney (2) Liver (17) Lung (13) Spleen/lymph nodes (12) GI-Tract (4) Bone marrow (2) CNS (3) *31 pat. with 51 x granulomatous organ lesions	PR:1 (100%) PR: 2 (100%) CR: 2 (12%)/PR:6 (35%)/NR: 9 (53%) CR: 3 (23%)/PR: 4 (31%)/NR: 6 (46%) CR: 5 (42%)/PR: 5 (42%)/NR: 2 (16%) PR:0/NR :4 (100%) PR:1 (50%)/NR: 1 (50%) CR: 3 (100%) **OR: 32/54 (59%)**	(159) (160) (161) (119)
Cyclophosphamide	6	Lung (2) Liver (5) other (3) *6 pat. with 10 x granulomatous organ lesions	CR: 4 (40%)/PR: 3 (30%)/ NR: 3 (30%)	(119)
Infliximab	6	Liver and lung	CR: 1 (17%) PR: 4 (66%) NR: 1 (17%) OR: 83%	(147) (162)
Hydroxychloroquine	4	Lung(1) Liver (2) other (4) *4 pat. with 7 x granulomatous organ lesions	CR: 1 (14%)/ PR: 1 (14%)/ NR: 5 (71%)	(119)
RTX	3	Lung (2) Liver (2) other (2) *3 pat. with 6 x granulomatous organ lesions	CR: 3 (50%)/ PR 3(50%)/NR: 0	(119)
MTX	2	Liver (1) other (2) *2 pat. with 3 x granulomatous organ lesions	CR: 1 (33%)/PR: 1 (33%)/ NR: 1 (33%)	(119)
Azathioprine	2	Liver (1) other (1)	NR: 100%	(119)
MMF	1	Lung (1)	NR: 100%	(119)
CyA	1	Lung (1)	NR: 100%	(119)
Rapamycin	1	Lung (1)	PR: 100%	(119)
Steroids and Aza	1	LIver and bone marrow	NR:1	(158)

Aza: Azathioprine; CsA: Cyclosporine A; IVIg: intravenous immunglobulines; MMF: Mycophenolat Mofetil; MTX: Methotrexate; RTX: Rituximab. CR: complete remission; PR: partial remission; OR: overall response rate; NR: no response

Supplement M1: Search strategy in PUBMED (http://www.ncbi.nlm.nih.gov/pubmed/) using the following MeSH terms and keywords.

Search strategy (a) use of immunoglobulin replacement therapy in primary antibody deficiency:

> (cvid OR common variable immunodeficiency OR primary antibody deficiency OR hypogamma-globulinemia OR hypogammaglobulinemia OR x-linked agammaglobulinemia OR XLA OR agammaglobulinemia OR hyper IgE OR HIES OR HIGM OR hyper IgM OR selective antibody deficiency OR specific antibody deficiency OR IgG-subclass deficiency OR subclass-deficiency OR subclass deficiency OR PID OR primary immunodeficiency OR primary immunodeficiency disorder OR primary immunodeficiency disease OR primary humoral immunodeficiency OR antibody immunodeficiency OR selective IgM deficiency OR selective IgM-deficiency OR selective IgA-deficiency OR selective IgA deficiency OR transient hypogammaglobulinemia OR transient hypogammaglobulinemia of infancy) AND (SCIG OR subcutaneous immunoglobulin OR IVIG OR intravenous immunoglobulin OR immunoglobulin replacement OR gamma-globulin OR gammaglobulin OR IGIV OR immunoglobulin prophylaxis OR management OR immunoglobulin therapy OR intravenous IgG preparation OR prophylactic therapy OR immunoglobulin G replacement OR intravenous immunoglobulin therapy OR immunoglobulin substitution) NOT (HIV OR AIDS OR secondary OR cancer OR kawasaki OR lymphoma)

Search strategy (b) immune cytopenia:

> (cvid OR common variable immunodeficiency OR primary antibody deficiency OR primary immunodeficiency OR higm OR hyper igm syndrome OR XLA OR agammaglobulinemia) AND (immune thrombopenic purpura OR autoimmune thrombopenia OR autoimmune thrombocytopenia OR thrombocytopenia OR immune cytopenia OR autoimmune cytopenia OR aiha OR AHA OR autoimmune hemolytic anemia)

Search strategy (c) granulomatous disease including interstitial lung disease:

> (cvid OR common variable immunodeficiency OR primary antibody deficiency OR higm OR hyper igm syndrome OR XLA OR agammaglobulinemia) AND (interstitial lung disease OR GLILD OR GL-ILD OR granulomatous lymphocytic interstital lung disease OR LIP OR lung fibrosis OR granuloma OR granulomatous disease OR pulmonary manifestation OR pulmonary fibrosis) AND treatment NOT (polyangiitis OR CGD)

Search strategy (d) APDS I / II, CTLA4 deficiency, LRBA deficiency:

> (APDS OR PASLI OR activated phosphoinositide 3-kinase delta syndrome OR PI3KCD OR PI3(K) OR PI3KR1 OR PIK3R1 OR PIK3CD OR p110delta OR LRBA OR LPS responsive beige like anchor protein OR CTLA4 OR cytotoxic t cell ligand 4) AND (immunodeficiency OR immunodeficiencies OR PID)

Search strategy (e) bronchiectasis:

> (cvid OR common variable immunodeficiency OR primary antibody deficiency OR hypogamma-globulinemia OR hypogammaglobulinemia OR x-linked agammaglobulinemia OR XLA OR agammaglobulinemia OR agammaglobulinaemia hyper IgE OR HIES OR HIGM OR hyper IgM OR selective antibody deficiency OR specific antibody deficiency OR IgG-subclass deficiency OR subclass-deficiency OR subclass deficiency OR PID OR primary immunodeficiency OR primary immunodeficiency disorder OR primary immunodeficiency disease OR primary humoral immunodeficiency OR antibody immunodeficiency OR selective IgM deficiency OR selective IgM-deficiency OR selective IgA-deficiency OR selective IgA deficiency OR transient hypogammaglobulinemia OR transient hypogammaglobulinemia of infancy) AND (bronchiectasis OR non-CF bronchiectasis) NOT (secondary OR leukemia OR lymphoma OR HIV OR AIDS OR malignancy OR cancer)

1 Supplement M2: records of search strategy

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Term	Retrieved records (after filtering for "Human" and "English")	Included records	Exclusion criteria
(a)	7165 (4685)	147	Records related to diagnostics or secondary antibody deficiency
(b)	726	23	Records related to diagnostics, secondary causes, autoimmune lymphoproliferative syndrome (ALPS)
(c)	300	26	Records related to diagnostics, non-PID-related granulomatous disease (e.g. sarcoidosis)
(d)	302 (282)	19	Diagnostics, case reports
(e)	374	5	Diagnostics, cystic fibrosis (CF)-related bronchiectasis, secondary causes of bronchiectasis

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