CENTRO NAZIONALE SANGUE

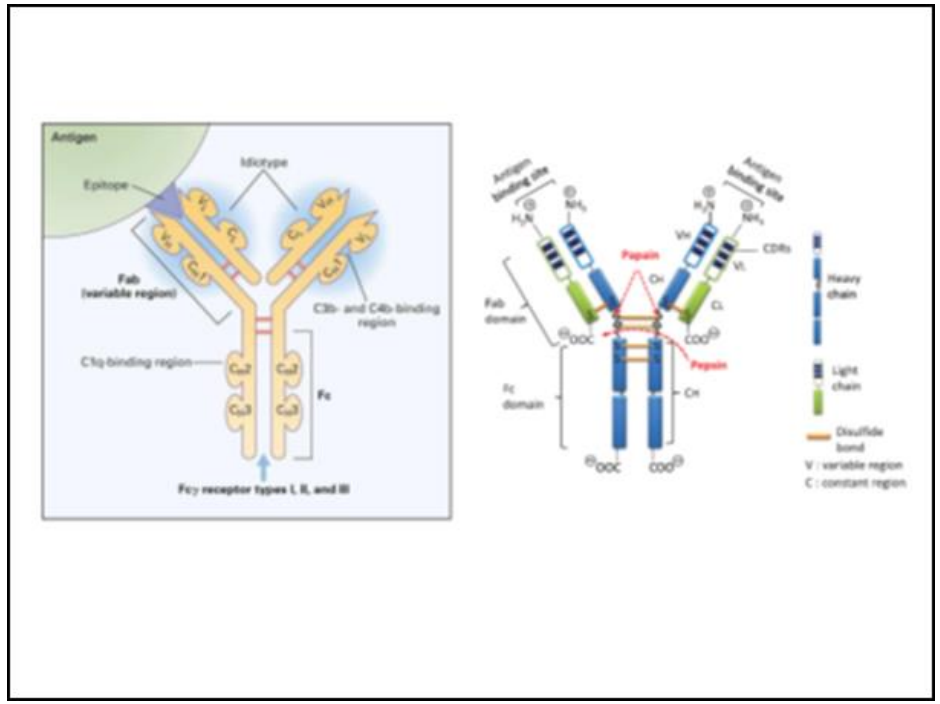
ISTITUTO SUPERIORE DI SANITÀ

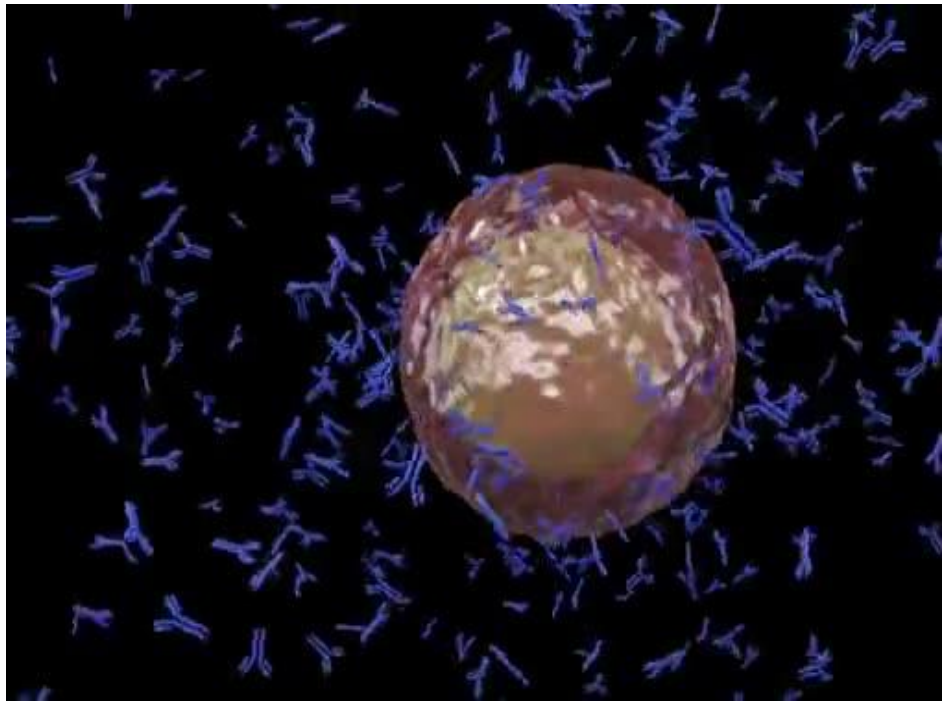
The supply of plasma-derived medicinal products in the future of Europe
Rome, April 28 and 29, 2022

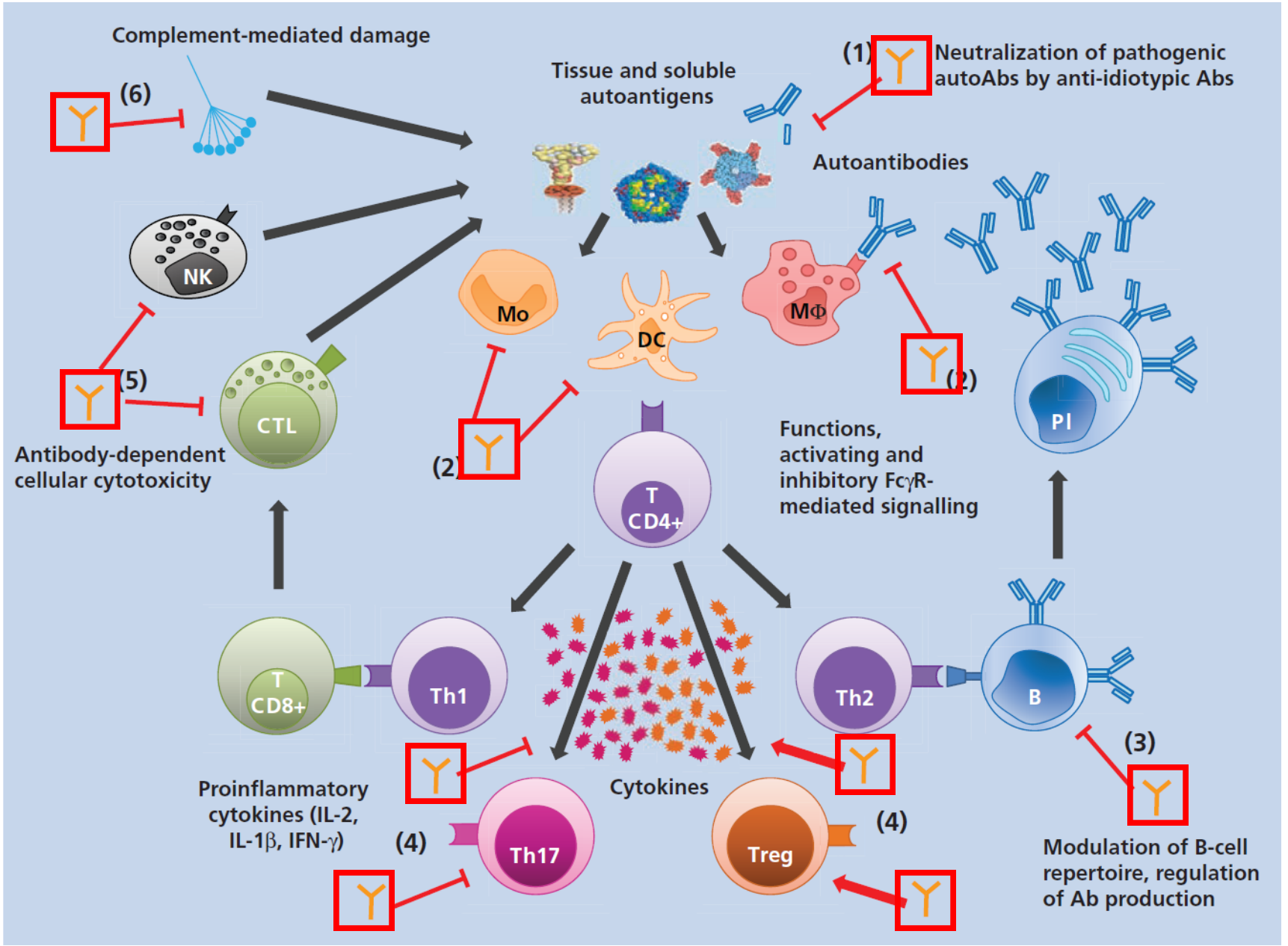
Clinical use and future trends

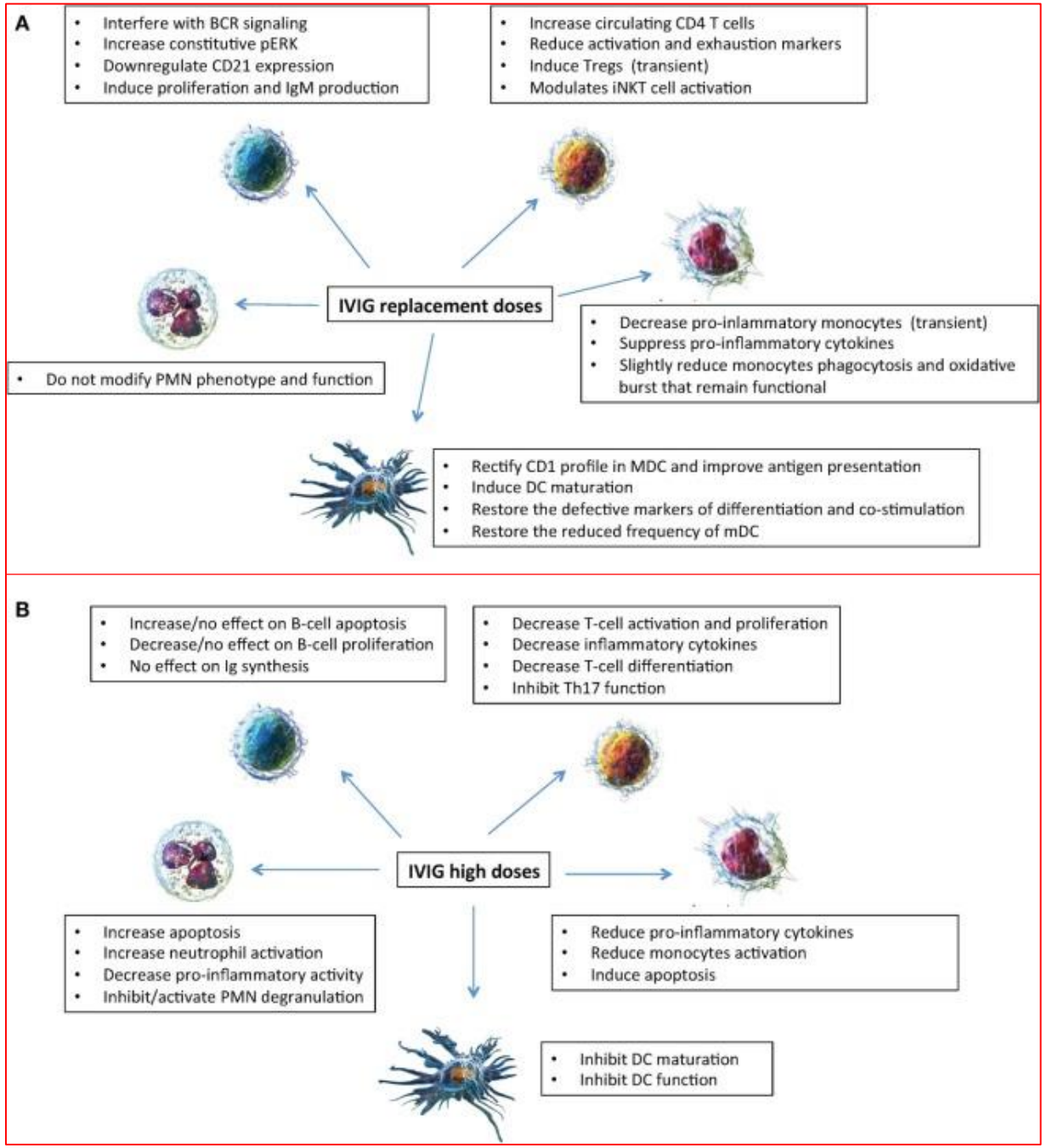
Polyvalent immunoglobulins

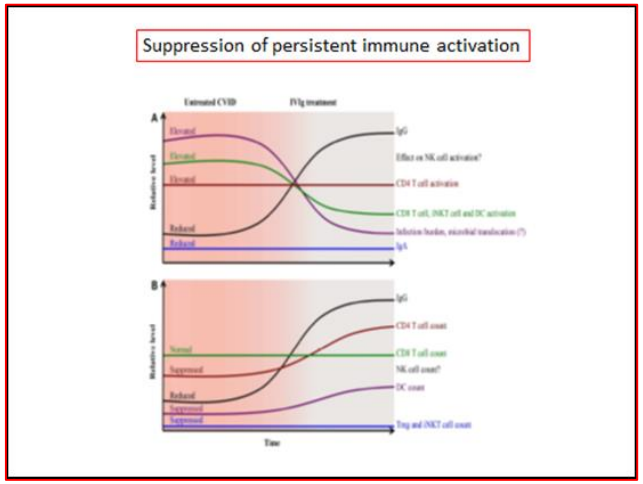
Isabella Quinti, MD, PhD
Professor of Internal Medicine
Sapienza University of Rome


Antigen
Epitope
Idiotype
Fab
(variable region)
C3b- and C4b-binding
region
C1q-binding region
Fc
FcγR receptor types I, II, and III
Antigen
binding site
Papain
Fab
domain
Fc
domain
CDRs
Heavy
chain
Light
chain
Disulfide
bond
V : variable region
C : constant region



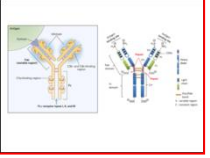

Complement-mediated damage
(6)
Tissue and soluble autoantigens
(1)
Neutralization of pathogenic autoAbs by anti-idiotypic Abs
Autoantibodies
NK
Mo
DC
MΦ
(5)
CTL
Antibody-dependent cellular cytotoxicity
(2)
(2)
PI
Functions, activating and inhibitory FcγR-mediated signalling
T CD4+
T CD8+
Th1
Th2
B
Proinflammatory cytokines (IL-2, IL-1β, IFN-γ)
Cytokines
(3)
(4)
Th17
Treg
(4)
Modulation of B-cell repertoire, regulation of Ab production





Front Immunol. 2017; 8: 697

Modulatory Effects of Antibody Replacement Therapy to Innate and Adaptive Immune Cells



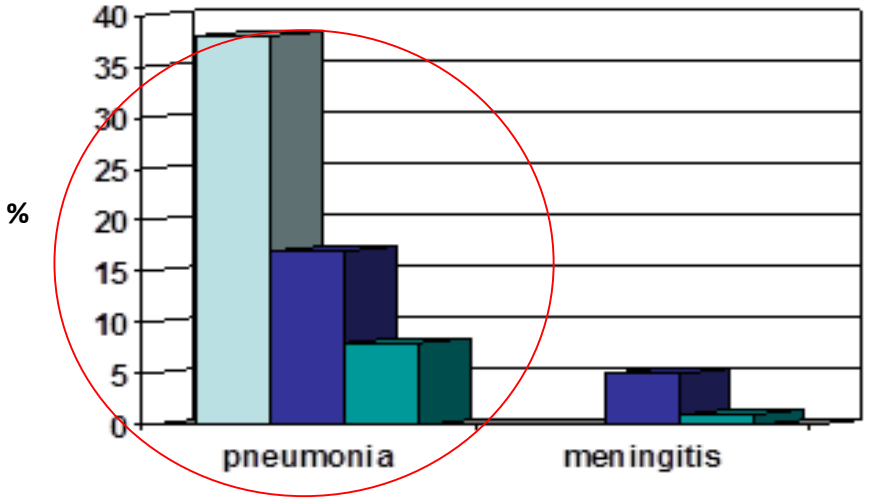
It is universally accepted that immunoglobulin therapy is a life-saving treatment in patients with humoral PID

In primary antibody deficiencies, immunoglobulin treatment is obviously replacing a missing feature

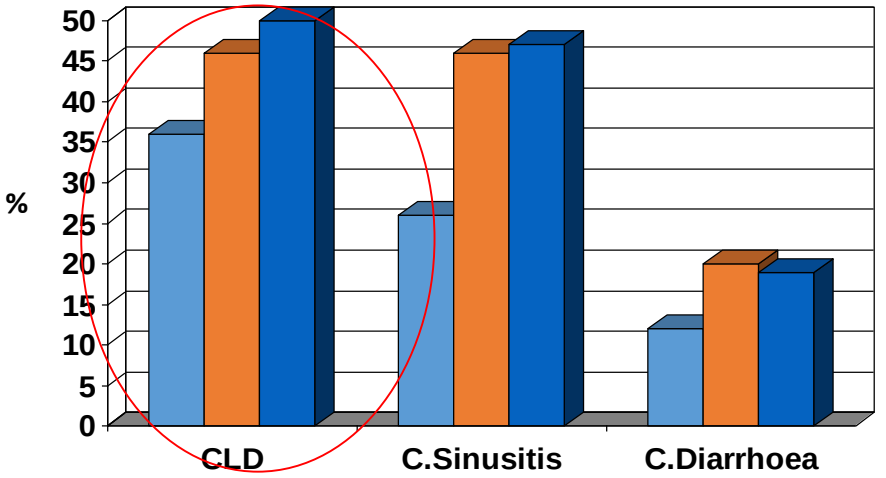
Journal of Clinical Immunology, Vol. 27, No. 3, May 2007 (© 2007)
DOI: 10.1007/s10875-007-9075-1

Long-Term Follow-Up and Outcome of a Large Cohort of Patients with Common Variable Immunodeficiency

ISABELLA QUINTI,[1,10] ANNAROSA SORESINA,[2] GIUSEPPE SPADARO,[3] SILVANA MARTINO,[4] SIMONA DONNANNO,[1] CARLO AGOSTINI,[5] PIGNATA CLAUDIO,[6] DAMMACCO FRANCO,[7] ANNA MARIA PESCE,[1] FEDERICA BORGHESE,[1] ANDREA GUERRA,[1] ROBERTO RONDELLI,[8] ALESSANDRO PLEBANI,[2] and WITHIN THE IPINET (Italian Primary Immunodeficiency Network)[9]

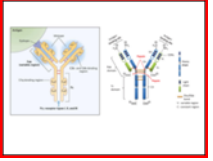


Acute infections

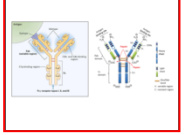


Chronic infections

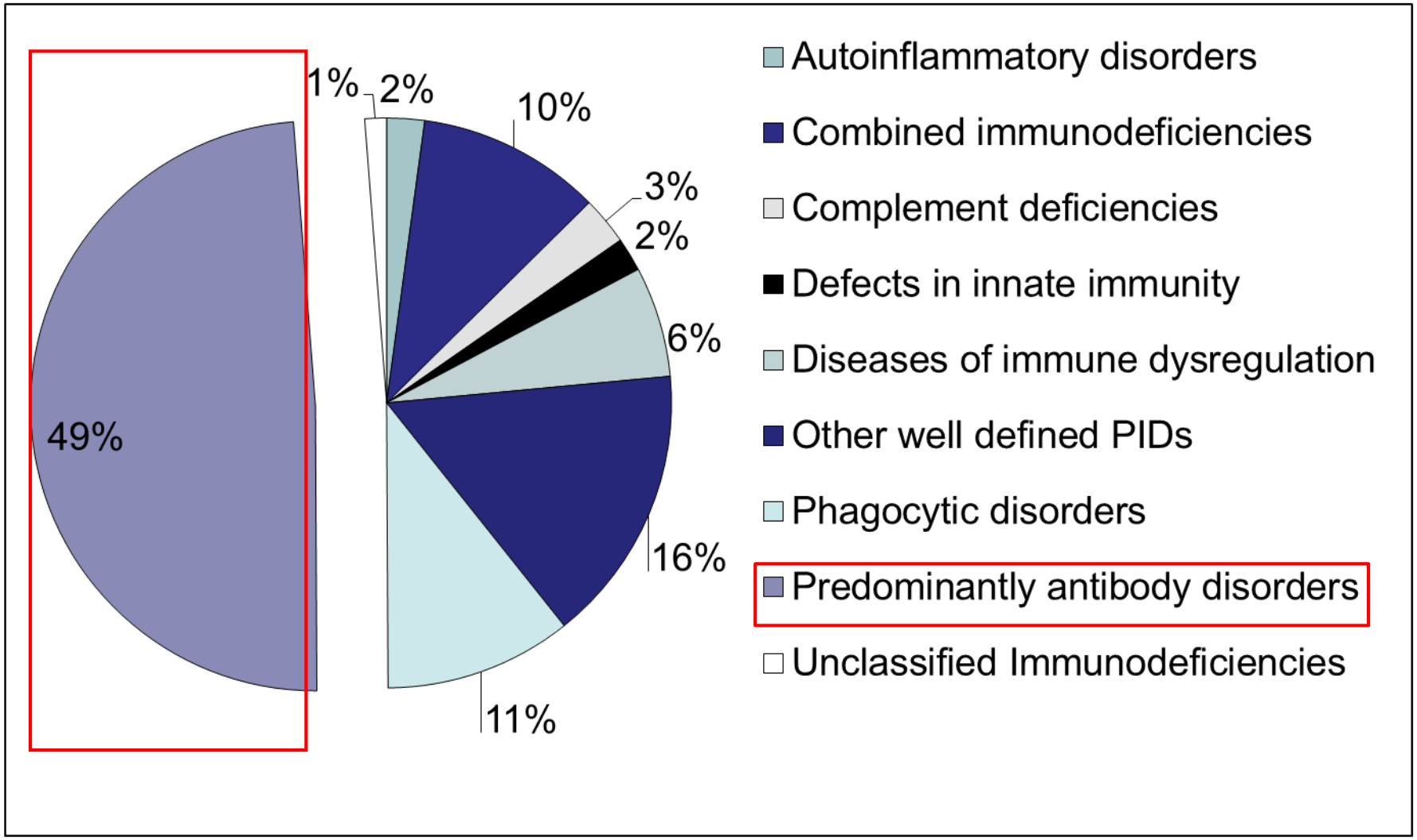
CLD: Chronic Lung Disease



Efficacy: lesson from registries



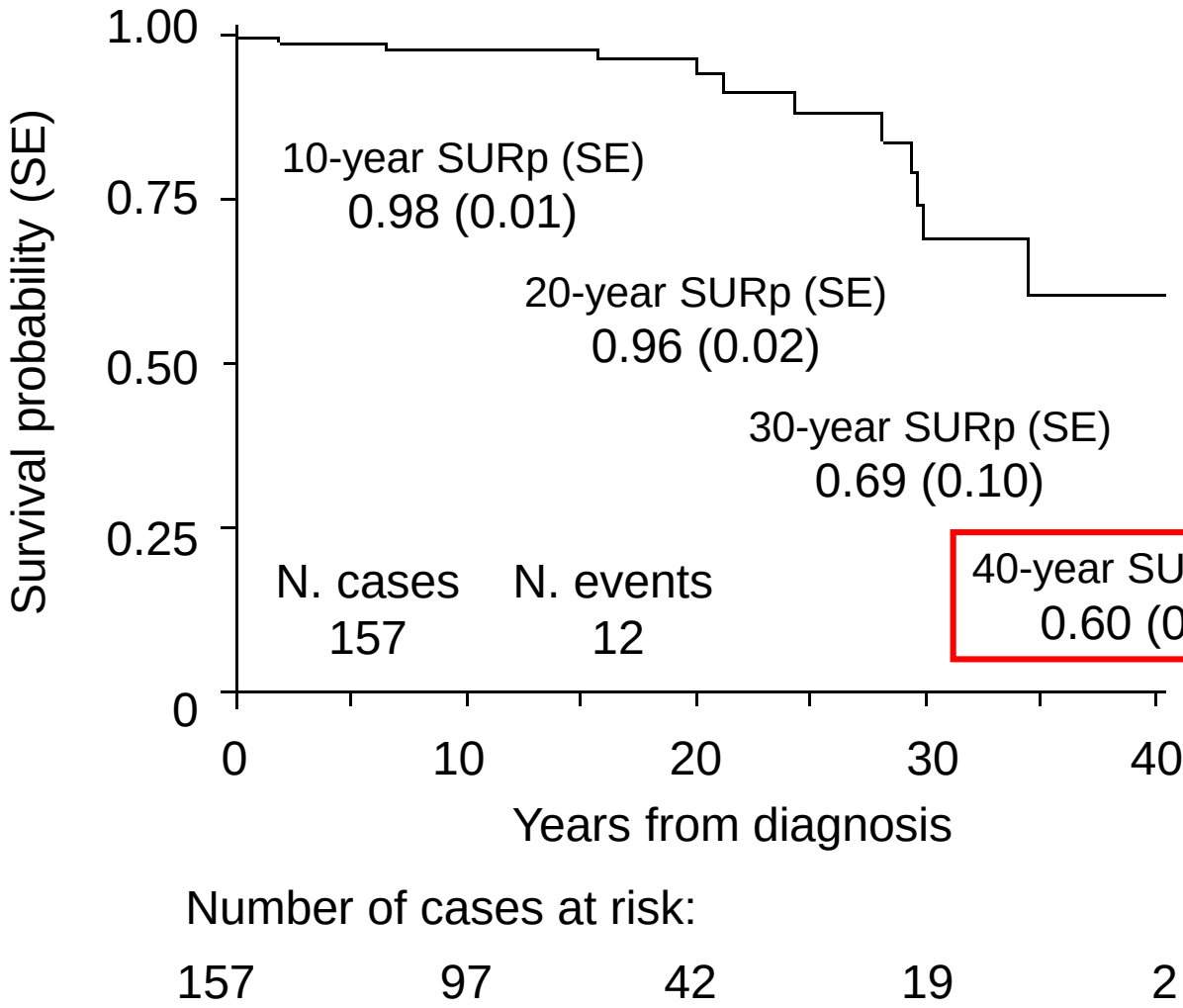
ESID registry, 2019



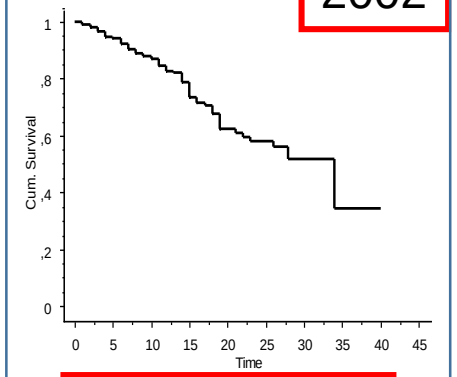
N=28.000

Probability of survival in XLA patients over four decades

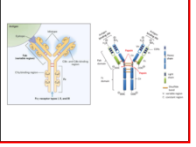
2018



2002



40-year SURp (SE)
0.35 (0.21)



Clinical phenotypes of primary antibody deficiencies are quite variable also within the same disease

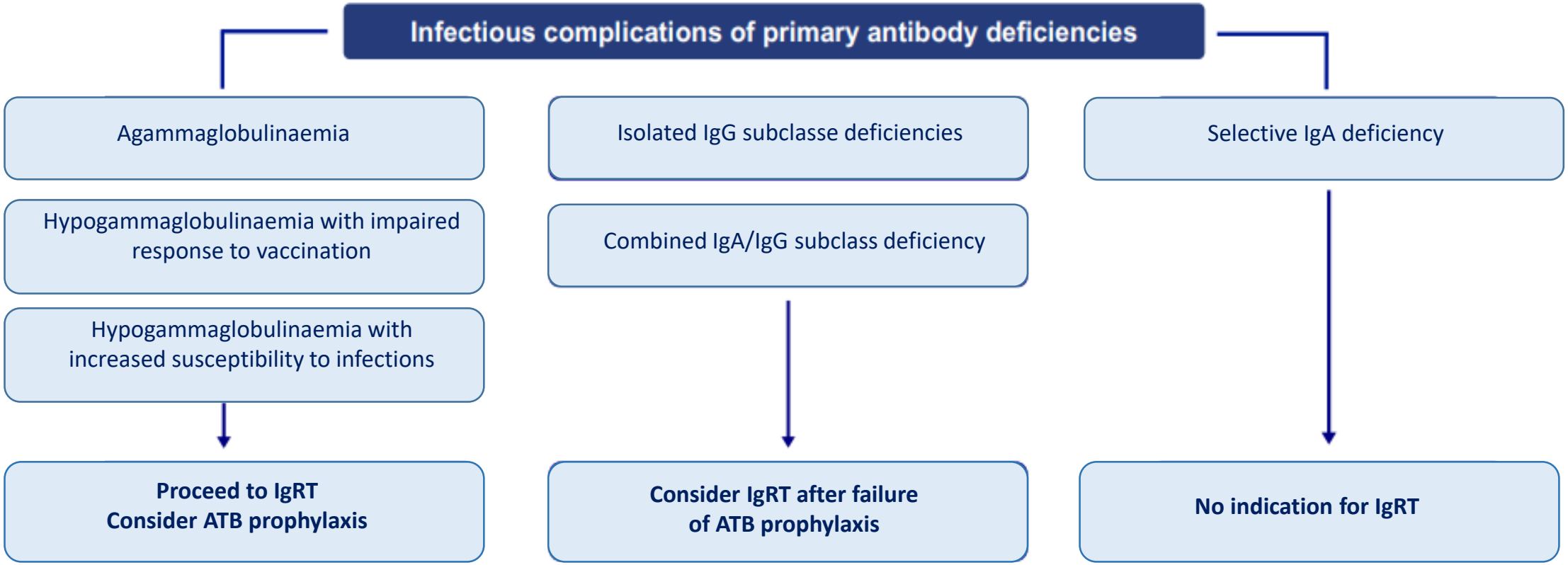
Risk factors for recurrent pneumonias:

- **serum IgG <400 mg/dl**
- **low frequency of memory B cells and of IgM memory B cells**
- **very low IgA serum level (<7 mg/dl)**
- **presence of bronchiectasis**
- **absence of response to vaccination**

Treatment choice

- Clinical judgment
- Individual tolerability
- Personal preference
- Compliance
- Periodical re-assessment after the firsts administrations (and training)

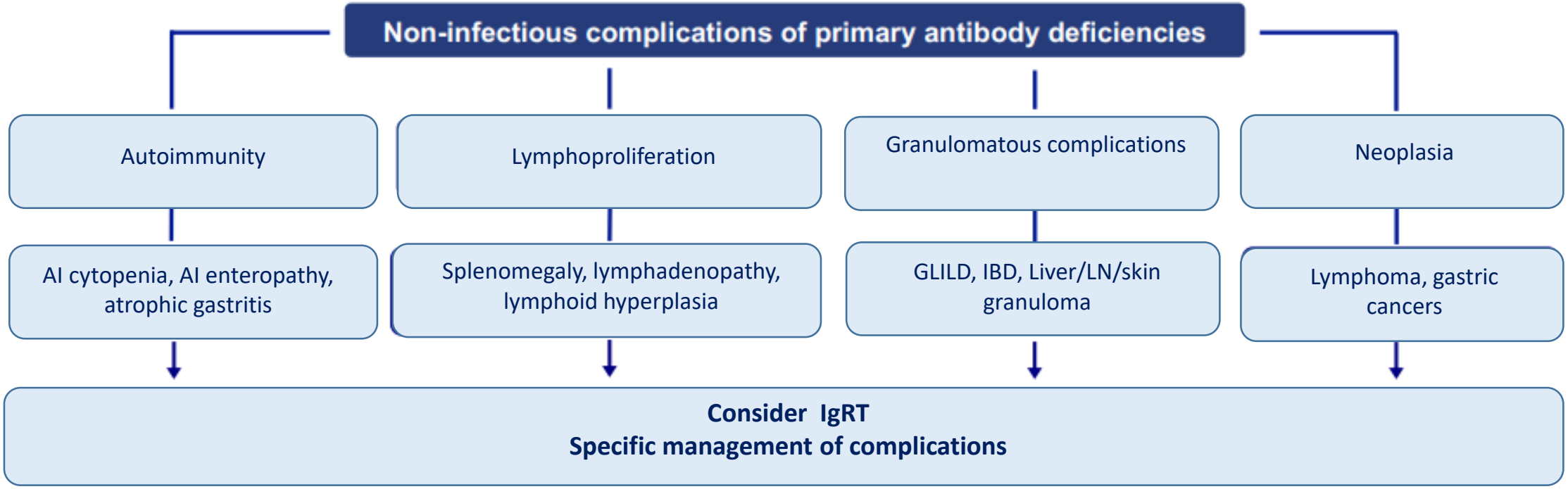
Algorithm for management of infectious complications



ATB- antibiotics; IgRT- immunoglobulin replacementy therapy;

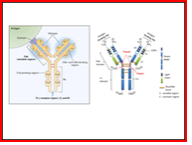
Adapted from Sediva, A., et al. (2021). "Medical Algorithm: Diagnosis and Management of Antibody Immunodeficiencies." *Allergy*.

Algorithm for management of non-infectious complications



ATB- antibiotics; IgRT- immunoglobulin replacementy therapy; AI- autoimmne; GLILD- granulomatous lymphocytic interstitial lung disease; IBD- inflammatory bowel disease; LN- lymph node

Adapted from Sediva, A., et al. (2021). "Medical Algorithm: Diagnosis and Management of Antibody Immunodeficiencies." *Allergy*.



Health-Related Quality of Life

Health care delivery systems are quickly changing in response to economic pressures and concerns about quality of care.

The system of care is itself an important determinant of patient outcomes.

Elucidating the effects of the system of care on **patient outcomes** requires new methodologic approaches in order to identify **what works in which setting and under what conditions.**

Original Article

Development and Initial Validation of a Questionnaire to Measure Health-Related Quality of Life of Adults with Common Variable Immune Deficiency: The CVID_QoL Questionnaire

Original Article

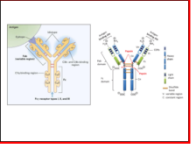
Health-Related Quality of Life in Common Variable Immunodeficiency Italian Patients Switched to Remote Assistance During the COVID-19 Pandemic

Federica Pulvirenti, MD, PhD[a], Francesco Cinetto, MD, PhD[b,*], Cinzia Milito, MD, PhD[c,*], Livia Bonanni, MD[a], Anna Maria Pesce, MD[a], Giorgia Leodori, MD[a], Giulia Garzi, MD[a], Marzia Miglionico, MD[c], Stefano Tabolli, MD[c], and Isabella Quinti, MD, PhD[c] *Rome and Padova, Italy*

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-019-0592-5

ORIGINAL ARTICLE

Health-Related Quality of Life in Patients with CVID Under Different Schedules of Immunoglobulin Administration: Prospective Multicenter Study



Immunoglobulin treatments

In the recent past we have been observing:

- An increase in the demand for plasma and in the consequent need to increase the number of donors
- Changes in methods to improve IgG recovery and to increase productivity as a response to growing clinical demand
- Introduction of immunoglobulin treatments with higher concentration and different ways of administration
- Changes in the timing of administration with an increase in the rate of infusion

Le principali indicazioni autorizzate:

- Sindromi da immunodeficienza primaria con alterata produzione di anticorpi

- Immunodeficienze secondarie (SID) in pazienti con infezioni gravi o ricorrenti, trattamento antimicrobico inefficace e che presentano dimostrata incapacità di produrre anticorpi specifici (PSAF)* o livelli sierici di IgG < 4 g/l.
  - *PSAF = incapacità di produrre un aumento di almeno 2 volte del titolo di anticorpi IgG ai vaccini pneumococcico polisaccaridico e contenenti l'antigene polipeptidico

- Trombocitopenia Immune Primaria (ITP), in pazienti ad alto rischio di emorragia o prima di interventi chirurgici, per il ripristino della conta piastrinica

- Sindrome di Guillain-Barré (GBS)

- Malattia di Kawasaki (in concomitanza con acido acetilsalicilico)

- Polineuropatia demielinizzante infiammatoria cronica (CIDP)

- Neuropatia motoria multifocale (MMN)

Primary immune deficiencies (IDs)

- They represent the only absolute indication being the Ig life-saving drug for these diseases.

- Already a shortage of the s.c. product is being observed, which is widely used in patients with primitive IDs: in the face of this, it would be sufficient to block off-label use to guarantee patients with primitive IDs

- There are 5,000 patients with primary immune deficiencies in Italy, who require a total of 2000 Kg of Ig (total Italian consumption 2020: 7000 Kg)

- 1300 Kg are of Ig sc (the total Italian consumption in 2020 was 1700 Kg) and 700 kg of Ig ev (total Italian consumption 2020: 5200 kg).

Secondary immune deficiencies and haematological diseases

- In secondary IDs, not all patients need Ig therapy: before resorting to supplementary therapy, in compliance with the European legislation also implemented by AIFA, the functional defect of Ig must be documented with antigenic stimulation test with pneumococcal Ag

- It is not known whether, and possibly to what extent, a functional test is used in the hematology wards before accessing supplementary therapy

- It is necessary to work on the rationalization of resources, and for this purpose to collect data on the use of the product at national level

- Today, Ig is attributed an absolute efficacy and little is considered the presence of possible adverse events, so it is necessary to insist on training.

Utilization of intravenous or subcutaneous immunoglobulins in secondary immune deficiency (ULTIMATE): A retrospective multicenter study

Clin Immunol. 2020 Jun;215:108419. doi: 10.1016/j.clim.2020.108419

- Indications for IgRT
  - non-Hodgkin lymphoma (22.3%)
  - multiple myeloma (20.7%)
  - chronic lymphocytic leukemia (17.4%)
  - other (21.5%).

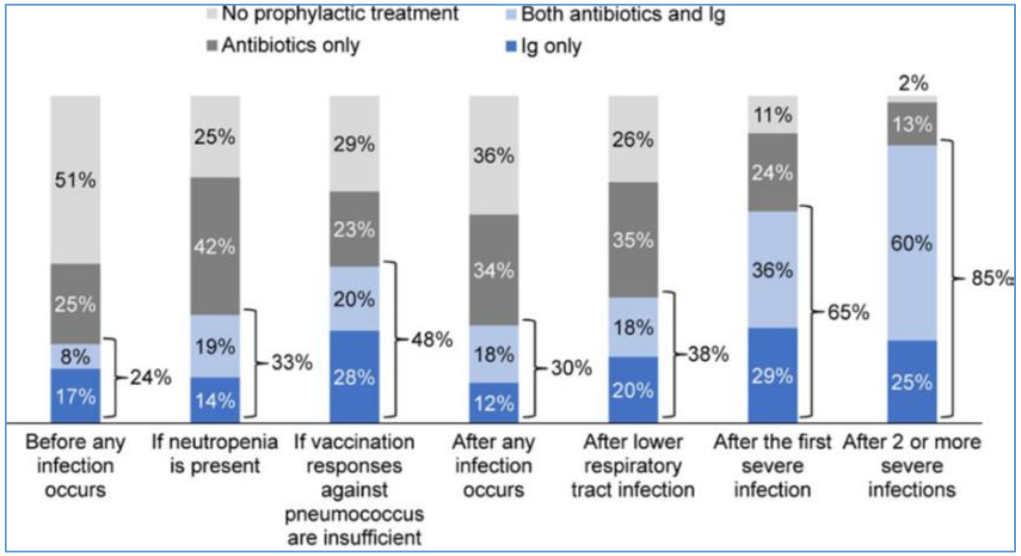
  - 196 (53.3%) received prophylactic antibiotics and 262 (76.2%) had an IgG level < 4 g/L before IgRT initiation.

- Only 24.2% of patients with SID who received IgRT met EMA recommendations, which suggests a misuse of IgRT in SID.

Current clinical practice and challenges in the management of secondary immunodeficiency in hematological malignancies

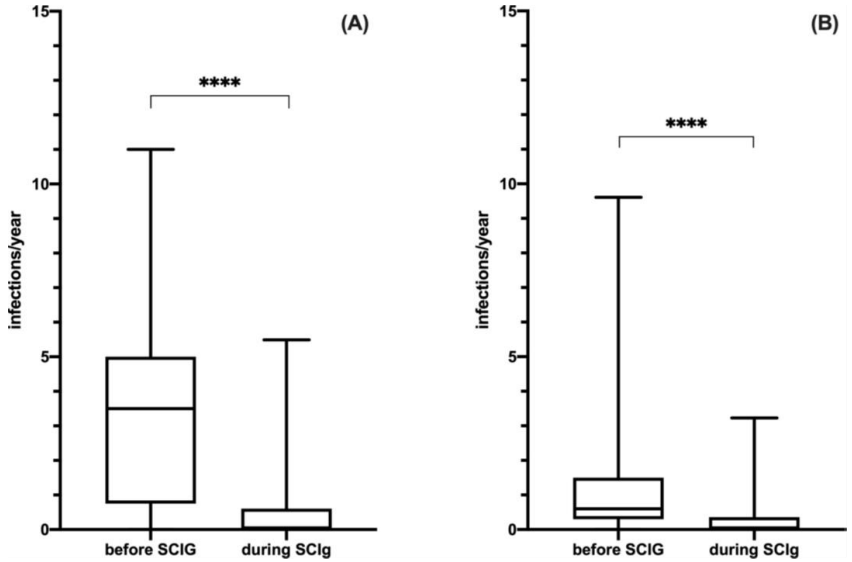
Eur J Haematol. 2019;102:447–456

- Serum immunoglobulin was measured in 83% of patients with multiple myeloma, 76% with chronic lymphocytic leukemia, and 69% with non-Hodgkin lymphoma.
- Most physicians (85%) prescribed IgRT after ≥2 severe infections.
- In Italy, Germany, Spain, and the United States, immunoglobulin use was above average, while in the UK considerably fewer patients received IgRT.
- The use of subcutaneous immunoglobulin was highest in France (34%) and lowest in Spain (19%).
- Immunologists measured specific antibody responses, performed test immunization, implemented IgRT, and used subcutaneous immunoglobulin more frequently than physicians overall.
- Clinical practice did not reflect treatment guidelines, highlighting the need for robust clinical studies on IgRT in this population and harmonization between countries and disciplines.



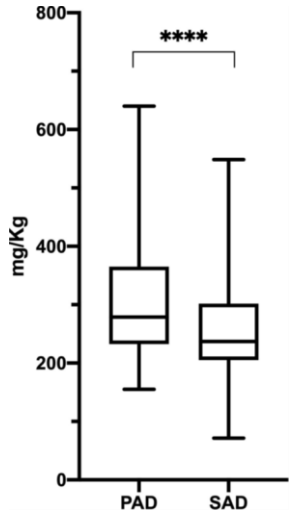
Subcutaneous immunoglobulins replacement therapy in secondary antibody deficiencies: Real life evidence

Cinetto F, et al. (2021) PLoS ONE 16(3): e0247717.

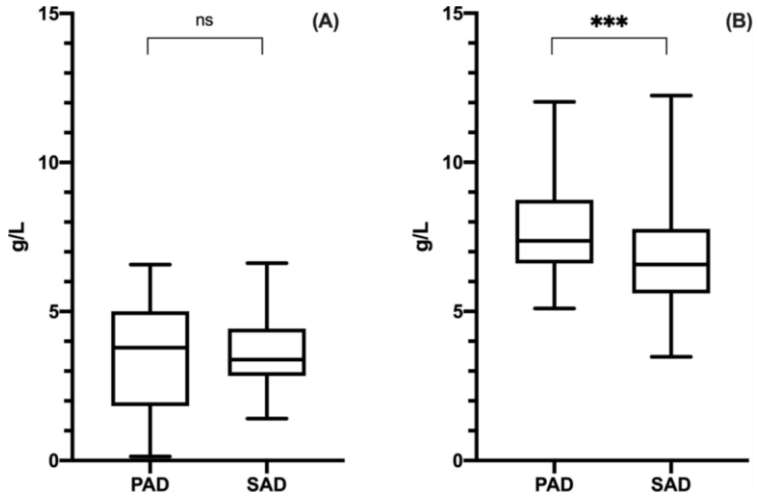


SCIG are equally effective in reducing annual infectious rate both in SAD and PAD patients.

SAD patients required lower SCIG dosage and lower IgG through level



Steady state SCIG dosage in PAD and SAD patients



IgG at baseline and trough levels in PAD and SAD patients

Ig in the transplantation of hematopoietic precursors

- The use in allogeneic transplantation is based on mostly American clinical studies and is associated with the FDA registration for the protective effect against infections.

- It will be useful to understand at a national level what is the use of Ig in this area and its impact on national needs

- It is therefore proposed to detect national consumption by area of use and in the specific area of transplantation and to define priorities according to the availability of the product

Neurological diseases

- Neuropathies have certainly contributed to shifting consumption towards Ig s.c.
- This is what happened for the Multifocal CIPD, in which the use of s.c. Ig could be replaced by Ig IV in consideration of the best clinical result in terms of relapses at 6 months.
- Therapeutic apheresis can be an alternative to Ig
- Some neurological pathologies respond to Ig therapy, without knowing the mechanism of action and clinical response: knowledge about it should be deepened, and therapy protocols in other areas could also be reviewed
- Many neurological diseases are treated with Ig requested off label, but it is not considered possible to prohibit its use.
- Unfortunately, there is a lack of control tools for verifying how appropriate the therapy is, both for the recognized indications and for the off label.

European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision

Eur J Neurol. 2021;28:3556–3583

- Both IVIg and oral or IV corticosteroids are first-line treatments for CIDP.
- TF did not recommend an overall preference for either treatment modality and weakly recommended either IVIg or corticosteroid treatment
- There is little or no difference in short-term improvement of disability with IVIg in comparison with oral prednisolone or long-term improvement after IV methylprednisolone.
- Clinical improvement after IVIg, however, may be faster and the adherence seems to be better after IVIg than after IV methylprednisolone
- Efficacy of SCIg, compared with placebo, has been demonstrated. There is insufficient evidence that a higher dose (0.4 g/kg weekly) is superior to a lower dose (0.2 g/kg weekly) for maintenance treatment

Changing trends in IVIG use in pediatric patients: A retrospective review of practices in a network of major USA pediatric hospitals

Balch A, et. al, . Int Immunopharmacol. 2019 Nov;76:105868. doi: 10.1016/j.intimp.2019.105868.

- Most of IVIG prescriptions were off-label.
- Kawasaki disease, ITP, GBS, and treatment of patients undergoing antineoplastic chemotherapy were top IVIG conditions.
- The most significant increase was observed in the IVIG usage for the treatment of unspecified neutropenia and septicemia.

Intravenous immune globulin and thromboembolic adverse events in patients with hematologic malignancy

Ammann EM, et al. *Blood*. 2016;127(2):200-207. doi:10.1182/blood-2015-05-647552

- TEEs reported in 0.5% to 15% of patients treated with IVIg
- Acute myocardial infarction and ischemic stroke risk was 3 times higher during days 0 to 1 following IVIg treatment in patients with secondary hypogammaglobulinemia (2724 new users of IVIg)
  - chronic lymphocytic leukemia (CLL)
  - multiple myeloma (MM)
- In patients treated with IVIg for 1 year, the estimated increase in the absolute risk of a severe thromboembolic event was ∼1%

COVID-19 in PID patients

The **paucity of clinical symptoms** observed in patients with primary defects of antibody immunity can be explained by an absence of inflammatory response of innate immunity due to regular administration of human polyvalent immunoglobulins and by a weak response of adaptive immunity, a picture similar to that described in immunocompetent individuals with asymptomatic SARS-CoV-2 infection

Conclusions

- It is necessary to proceed with a national, **immediate Alert for hospitals and clinicians,** in order to communicate the Ig deficiency: the information must start from AIFA / Ministry, upon proposal of the CNS , shared with the scientific societies.

- The Alert will have to recall the need for the appropriateness of use, but also the protection of patients for whom the Ig are lifesaving.

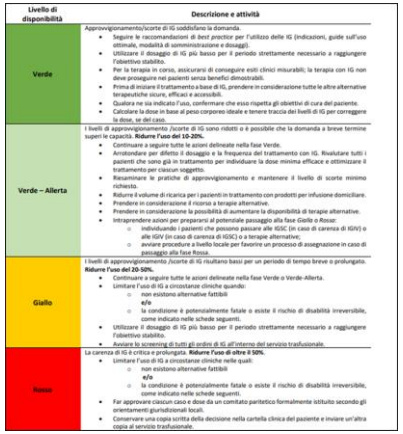
- The scientific societies, will share the content of the informative text in their respective Boards of Directors before it is sent.

- These first actions must be concluded as quickly as possible, given the urgency imposed by the situation.

- Based on what will emerge, it will be possible to proceed to prepare the Recommendations for the correct use of Ig by providing three possible scenarios: absolute deficiency, relative deficiency, availability of the drug. For each of these situations, priority indications will be provided based on the degree of scientific evidence.

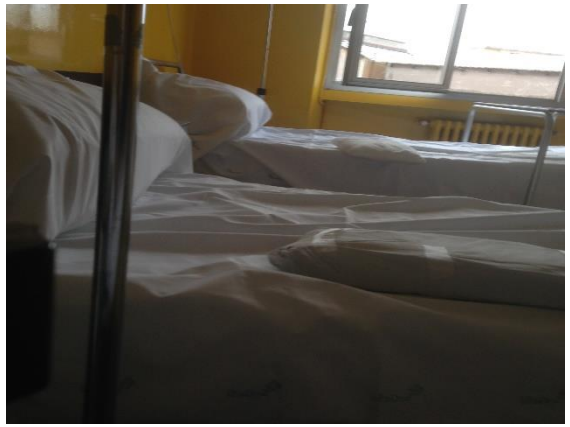
"DOCUMENTO DI INDIRIZZO SULL'USO DELLE IMMUNOGLOBULINE UMANE IN CONDIZIONI DI CARENZA" pubblicato da AIFA il 23/02/22 sul proprio sito e disponibile al seguente link: https://www.aifa.gov.it/-/documento-indirizzo-aifa-cns-uso-immunoglobuline-umane-condizioni-carenza

Il "Documento di indirizzo sull'uso delle immunoglobuline umane in condizioni di carenza" è frutto di un lavoro multidisciplinare condotto con il contributo di Società Italiana di Emaferesi e Manipolazione Cellulare (SidEM), Società Italiana di Medicina Trasfusionale e Immunoematologia (SIMTI), Società Italiana di Ematologia (SIE), Società Italiana di Neurologia (SIN), Società Italiana di Farmacia Ospedaliera e dei Servizi Farmaceutici delle Aziende Sanitarie (SIFO) e Gruppo Italiano trapianto di midollo osseo e di cellule staminali emopoietiche (GITMO).



Livello di disponibilità	Descrizione e attività
Verde	Approvvigionamento/scorte di IG soddisfano la domanda. • Seguire le raccomandazioni di best practice per l'utilizzo delle IG (indicazioni, guide sull'uso ottimale, modalità di somministrazione e dosaggi). • Utilizzare il dosaggio di IG più basso per il periodo strettamente necessario a raggiungere l'obiettivo stabilito. • Per la terapia in corso, assicurarsi di conseguire esiti clinici misurabili; la terapia con IG non deve proseguire nei pazienti senza benefici dimostrabili. • Prima di iniziare il trattamento a base di IG, prendere in considerazione tutte le altre alternative terapeutiche sicure, efficaci e accessibili. • Qualora ne sia indicato l'uso, confermare che esso rispetta gli obiettivi di cura del paziente. • Calcolare la dose in base al peso corporeo ideale e tenere traccia dei livelli di IG per correggere la dose, se del caso.
Verde – Allerta	I livelli di approvvigionamento /scorte di IG sono ridotti o è possibile che la domanda a breve termine superi le capacità. **Ridurre l'uso del 10-20%.** • Continuare a seguire tutte le azioni delineate nella fase Verde. • Arrotondare per difetto il dosaggio e la frequenza del trattamento con IG. Rivalutare tutti i pazienti che sono già in trattamento per individuare la dose minima efficace e ottimizzare il trattamento per ciascun soggetto. • Riesaminare le pratiche di approvvigionamento e mantenere il livello di scorte minimo richiesto. • Ridurre il volume di ricarica per i pazienti in trattamento con prodotti per infusione domiciliare. • Prendere in considerazione il ricorso a terapie alternative. • Prendere in considerazione la possibilità di aumentare la disponibilità di terapie alternative. • Intraprendere azioni per prepararsi al potenziale passaggio alla fase Giallo o Rosso: o Individuando i pazienti che possono passare alle IGSC (in caso di carenza di IGIV) o alle IGIV (in caso di carenza di IGSC) o a terapie alternative; o avviare procedure a livello locale per favorire un processo di assegnazione in caso di passaggio alla fase Rossa.
Giallo	I livelli di approvvigionamento /scorte di IG risultano bassi per un periodo di tempo breve o prolungato. **Ridurre l'uso del 20-50%.** • Continuare a seguire tutte le azioni delineate nella fase Verde o Verde-Allerta. • Limitare l'uso di IG a circostanze cliniche quando: o non esistono alternative fattibili **e/o** o la condizione è potenzialmente fatale o esiste il rischio di disabilità irreversibile, come indicato nelle schede seguenti. • Utilizzare il dosaggio di IG più basso per il periodo strettamente necessario a raggiungere l'obiettivo stabilito. • Avviare lo screening di tutti gli ordini di IG all'interno del servizio trasfusionale.
Rosso	La carenza di IG è critica e prolungata. **Ridurre l'uso di oltre il 50%.** • Limitare l'uso di IG a circostanze cliniche nelle quali: o non esistono alternative fattibili **e/o** o la condizione è potenzialmente fatale o esiste il rischio di disabilità irreversibile, come indicato nelle schede seguenti. • Far approvare ciascun caso e dose da un comitato paritetico formalmente istituito secondo gli orientamenti giurisdizionali locali. • Conservare una copia scritta della decisione nella cartella clinica del paziente e inviare un'altra copia al servizio trasfusionale.

Grazie!



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