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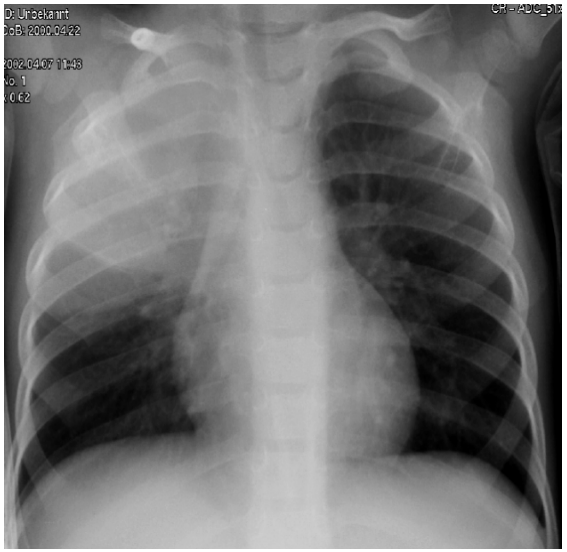
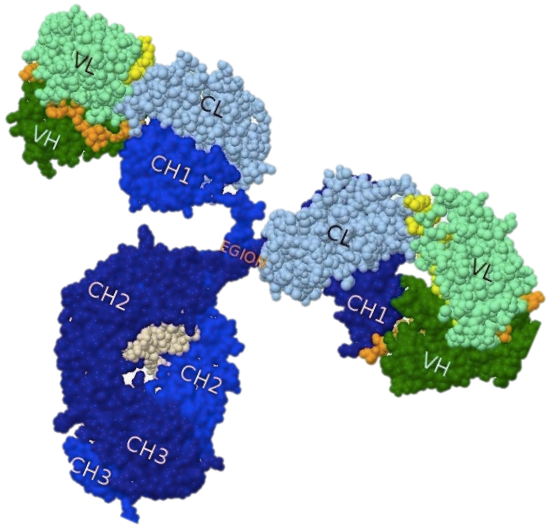




An overview of latest IG therapy advances

What‘s new about the good old therapy?

Klaus Warnatz

Centrum für Chronische Immundefizienz

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

Disclosures

I have received honoraria as a speaker from Baxalta/Shire, Biotest, CSL Behring, Octapharma, Pfizer.

I have participated as a consultant on advisory boards of CSL Behring, Grifols, LFB.

I have received a scientific grant from Baxalta, BMS, CSL Behring.

Immunoglobulin replacement therapy

Historical overview on the first targeted therapy

1901 Nobel prize discovery of Ig

PIONEERS

1952
First use of SCIG in a patient

1980
SCIG Slow regiment (not feasable)

1991
SCIG 20ml/h Scandi-navia

2009
SCIG rapid push USA

ESTABLISHED

1953
IMIG (painful, subtherapeutic dosage)

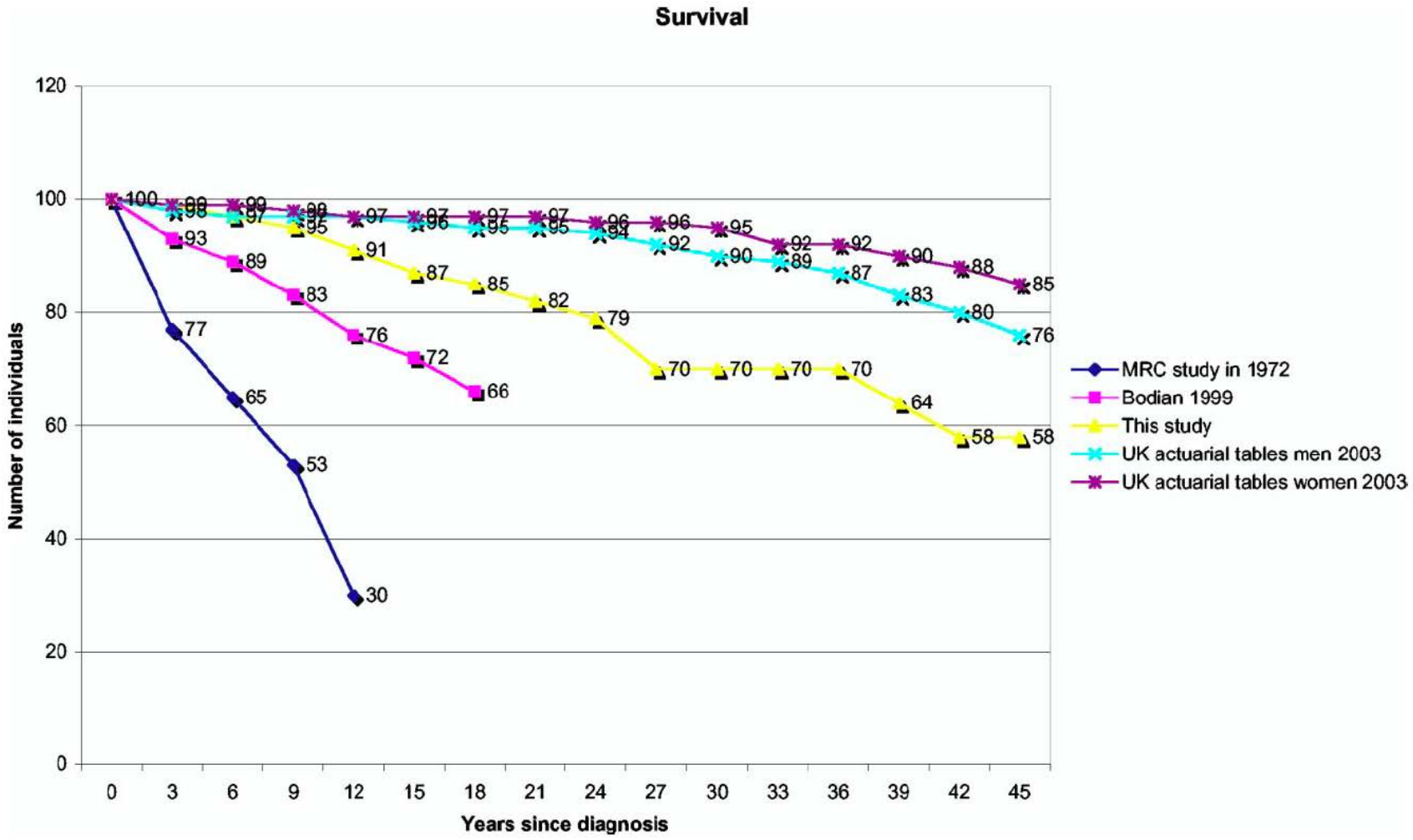
1978
IVIG

2003
SCIG

2013
HySCIG

History of immunoglobulin replacement

Improving life of our patients



Chapel et al Blood 2008

Immunoglobulin replacement therapy

Current challenges of the therapy

Highest possible and affordable access for the whole world

Highest possible safety

Highest comfort during the different life situations and needs

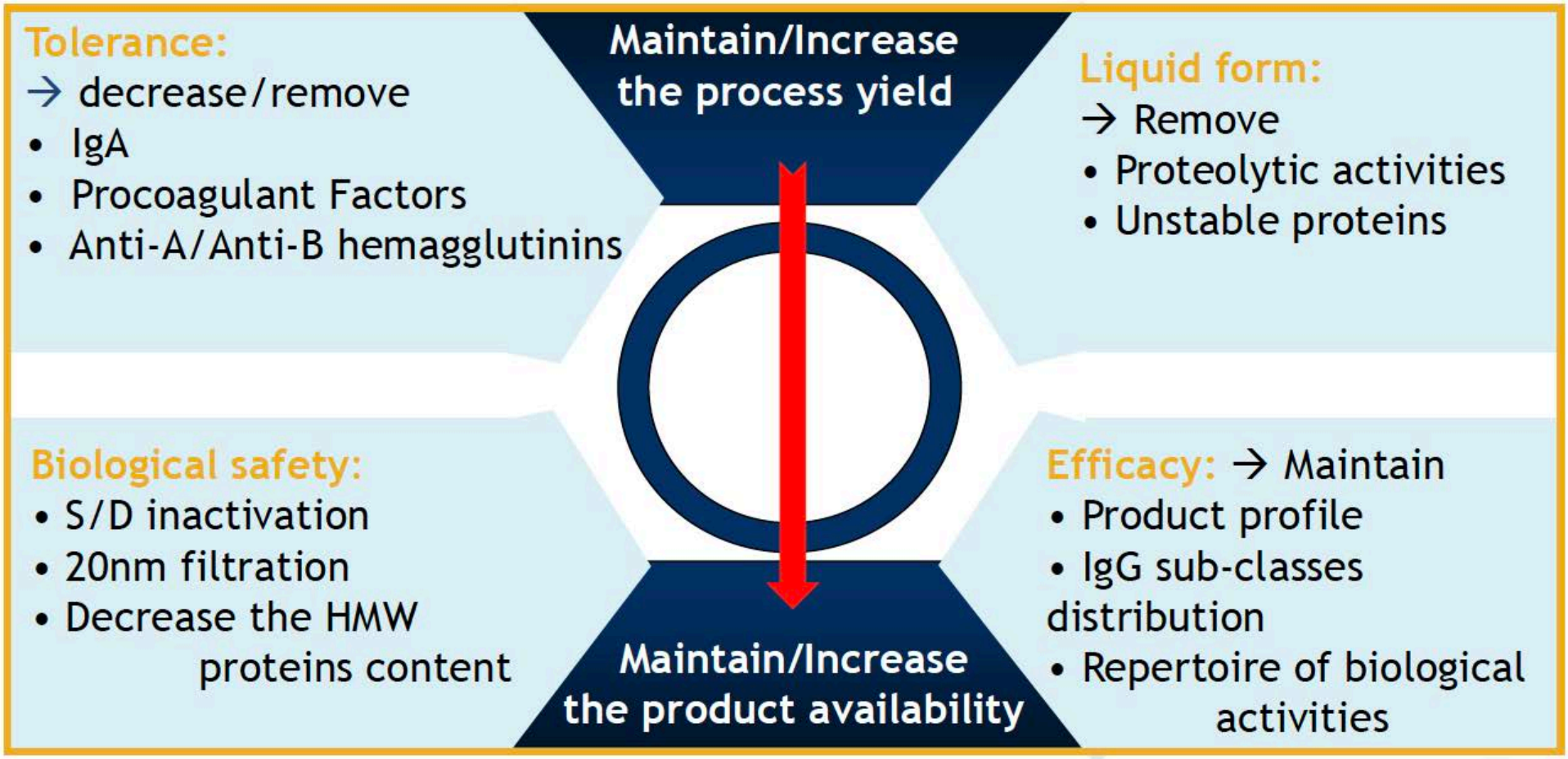
- Recognition of the individual needs
- sc vs iv
- Lowest possible frequency of application (number of needles to treat)

Protective coverage of all relevant pathogens

Immunoglobulin replacement therapy

Factors to consider during production

Provided by LFB Biomedicaments



Forms of immunoglobulin replacement

Improving life of our patients

IV

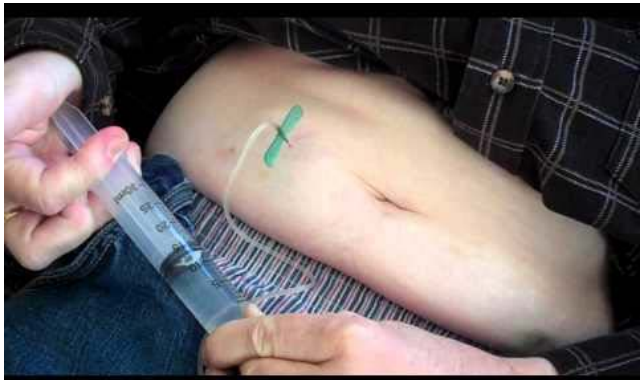
5/10% IgG: 0,4g/kgBW/3-4wk

SC

10%IgG 0,4g/kgBW/3-4wk
+ recombinant human Hylaronidase:

16%/16,5%/20% IgG:
0,1g/kgBW/wk

Push

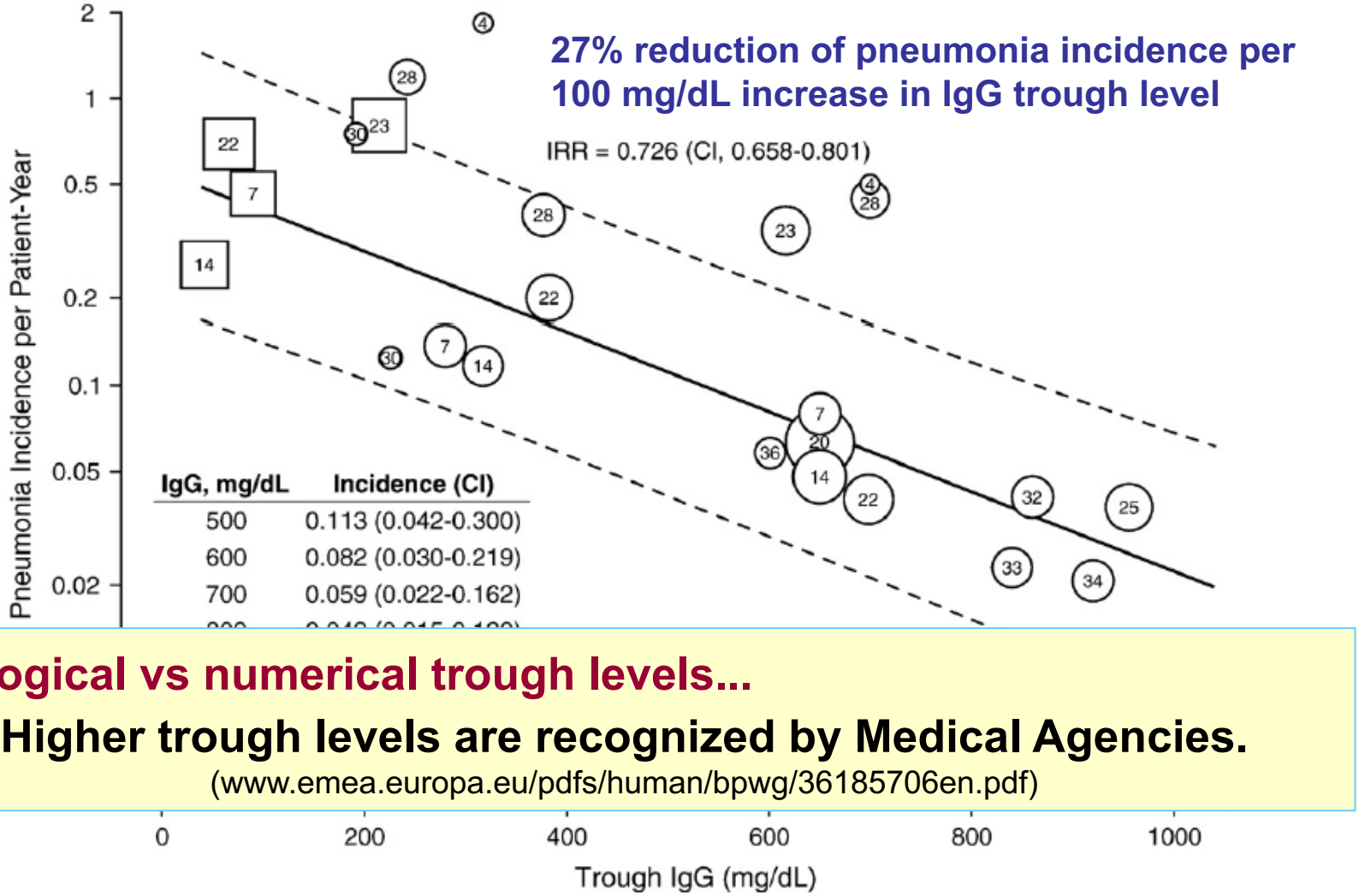


Pump

http://article.wn.com/view/2012/08/22/

Dose of IgG replacement

Individualized therapy



Biological vs numerical trough levels...

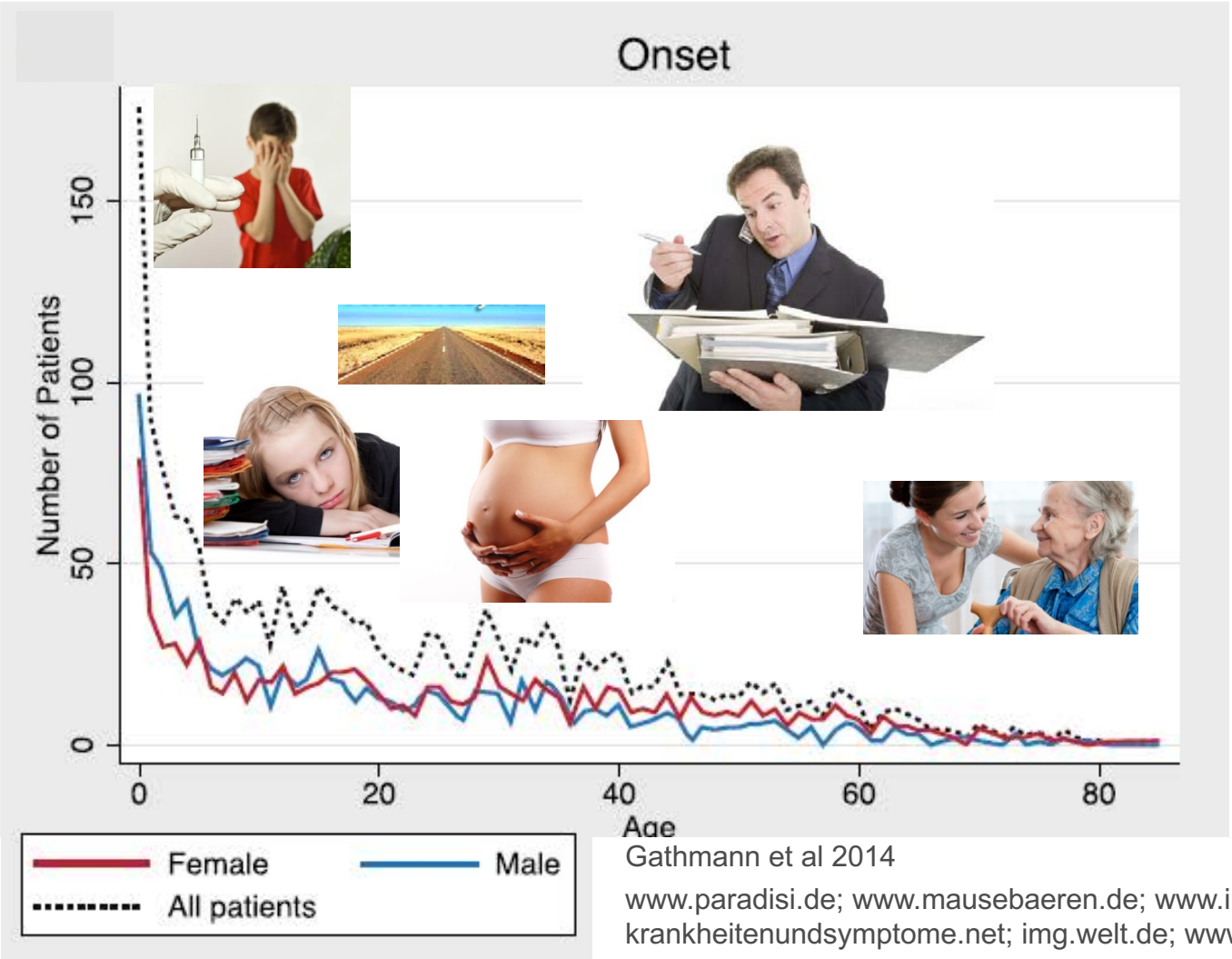
Higher trough levels are recognized by Medical Agencies.

(www.emea.europa.eu/pdfs/human/bpwg/36185706en.pdf)

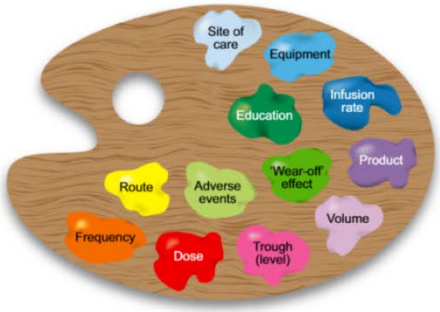
Orange al JACI 2006 Bonagura et al JACI 2008
Quinti et al JoCI 2011 Lucas et al JACI 2011
Orange et al Clin Immunol 2010

Immunoglobulin replacement therapy

Lifelong requirement – individualized therapy



Gathmann et al 2014



Jolles et al 2014

www.paradisi.de; www.mausebaeren.de; www.in-australien.com; krankheitenundsymptome.net; img.welt.de; www.pflege-in-hessen.de

Courtesy S.Goldacker

Selection criteria of route for Ig replacement

Factors influencing iv vs sc replacement therapy

Patient/Parent choice

Living conditions (hygiene, climate, etc)

Previous infusion reaction

Compliance

Access to physician

Comorbidities

Immunoglobulin replacement therapy

Lifelong requirement – individualized therapy – How to choose?

12 Simple questions to help you and your doctor choose your best treatment option

Immunoglobulin replacement treatment is a life-long therapy and it is important for your doctor to know more about the patients' lifestyle and preferences.

Patients survey to identify factors important in route of administration decision making

Immunoglobulin therapy experience
Immunoglobulin therapy preferences
Personal preferences and lifestyle
Soft/ emotional questions

GRIFOLS

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Immunoglobulin replacement therapy

Factors in iv application

Which iv immunoglobulin?

No relevant differences between different products in regard to:

Age, Exspiration time (24-36months), size of package,

storage at room temperature (2-25°, some products restricted to 6-9months)

IgG Subclass distribution

Differences in regard to

IgA content: lowest in Gammagard, Privigen, IqYmune

Stabilizers: Maltose in Octagam, Ig Vena, D-Sorbitol in Flebogamma

AA in: Privigen, Gamunex, Kiovig, Intratect, IqYmune

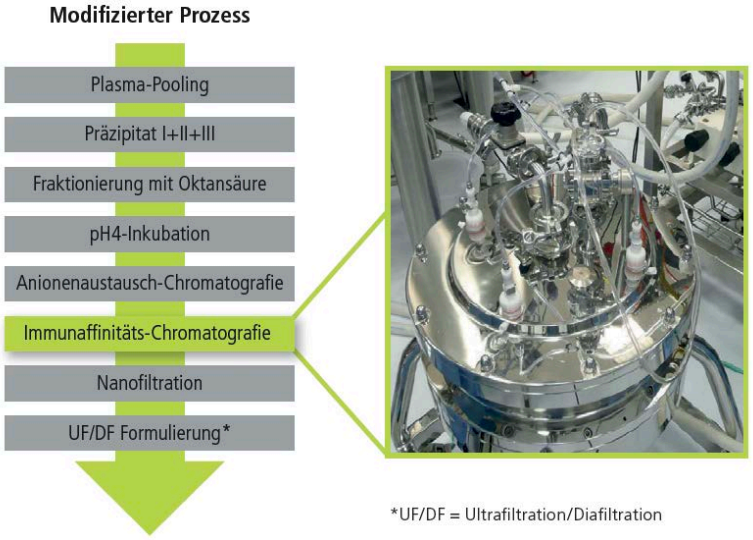
Isoagglutinin reduction: reported for Privigen, IqYmune

Immunoglobulin replacement therapy

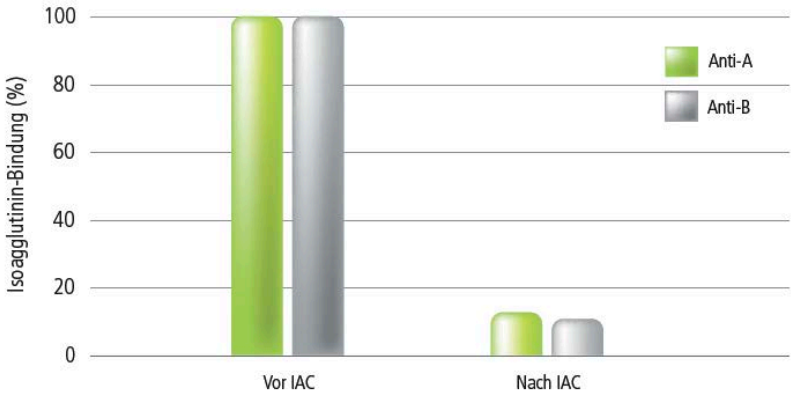
Isoagglutinin removal

Provided by CSL Behring

Immune affinity Chromatography (IAC)



Isoagglutinins before and after IAC



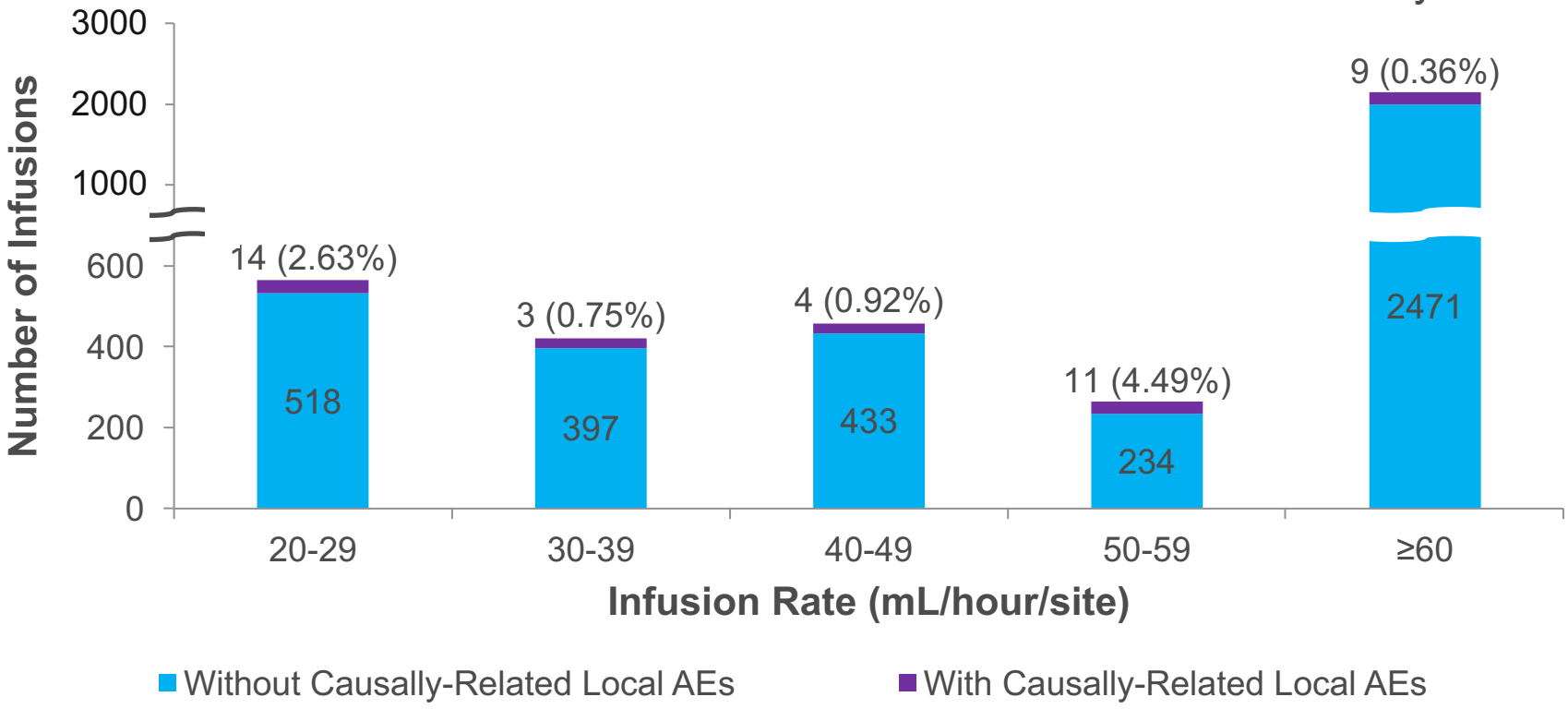
Specific antibody titers

Spezifische Antikörper	Mittlere Antikörper-Konzentration (IU/mg) vor IAC (n=10)*	nach IAC (n=10)*
Anti-Parvovirus B19	3,6 ± 0,6	3,4 ± 0,6
Anti-Hepatitis-B-Virus Oberflächen-Antigen	0,07 ± 0,02	0,07 ± 0,02
Anti-Streptolysin	16,2 ± 2,3	16,3 ± 2,0
Anti-Tetanustoxin	0,41 ± 0,05	0,38 ± 0,03
Anti-Poliomyelitis-Virus	0,31 ± 0,14	0,30 ± 0,15
Anti-Varizellen-Virus	0,19 ± 0,01	0,19 ± 0,01
Anti-Masern-Virus	0,23 ± 0,07	0,29 ± 0,06
Anti-Cytomegalie-Virus	0,56 ± 0,06	0,51 ± 0,04
Anti-Diphterietoxin	0,07 ± 0,003	0,07 ± 0,01

Immunoglobulin replacement therapy

Factors in sc application: Infusion Rate

20% sc preparation
Provided by Shire



- No Association Between Infusion Rate per Site and Causally-Related Local AEs

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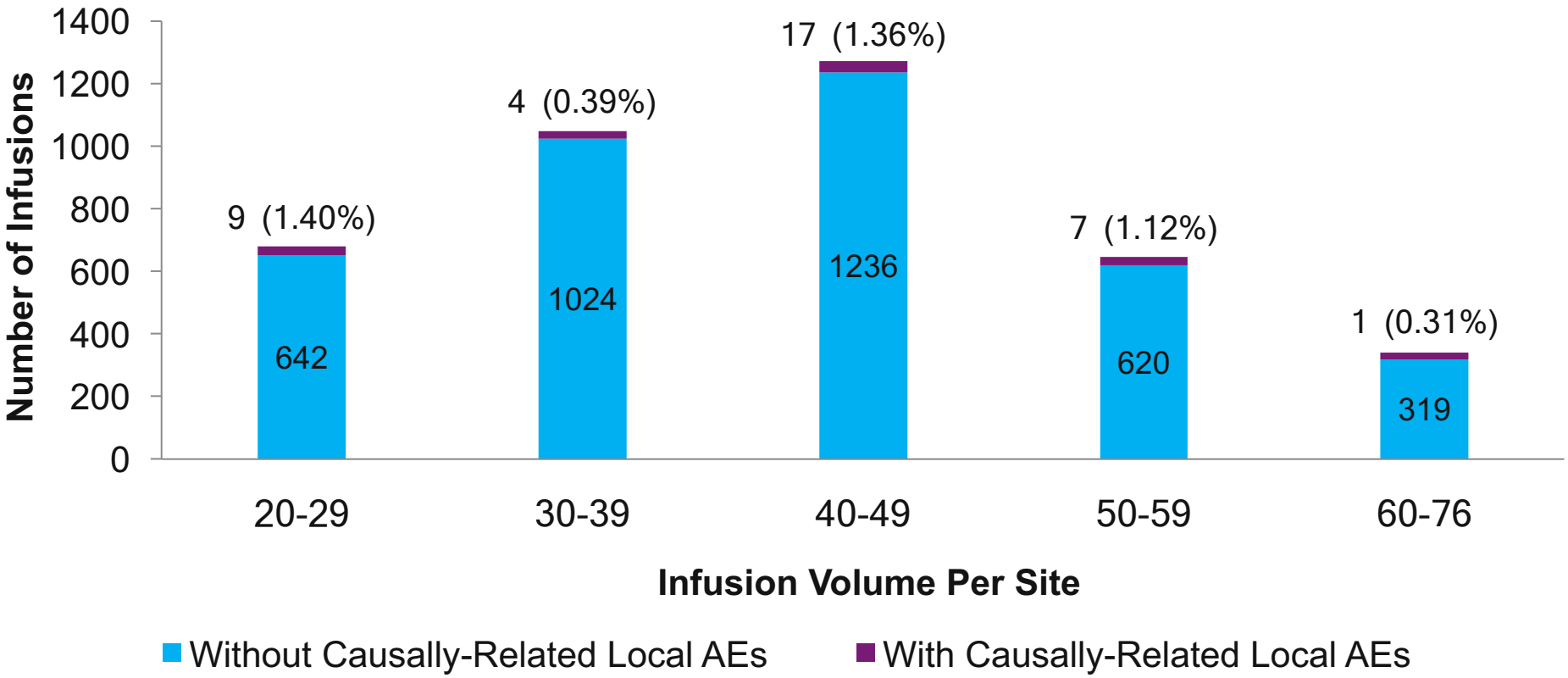
Suez et al. J Clin Immunol 2016;36(7):700–712.

Immunoglobulin replacement therapy

Factors in sc application: Infusion volume/site

20% sc preparation
Provided by Shire



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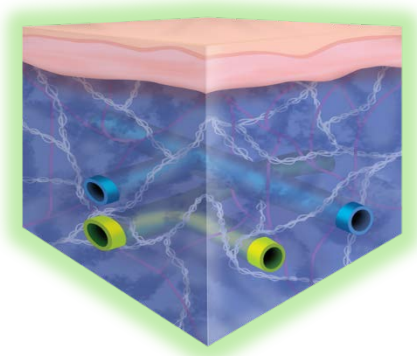
Immunoglobulin replacement therapy

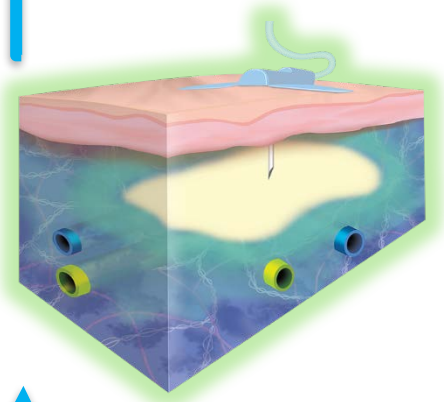
Facilitated sc application: Mode of action

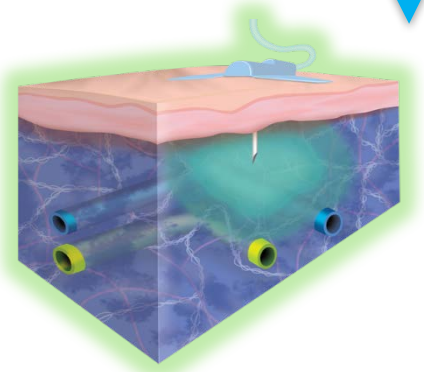
Provided by Shire

Hyaluronan is rapidly resynthesized. Normal tissue permeability is fully restored within 24 to 48 hours[1]

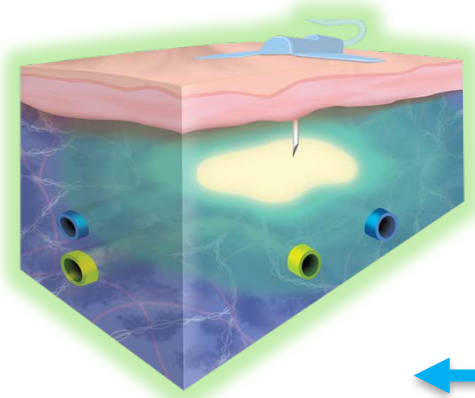


Hyaluronan:
- Confines conventional SCIG infusions to a limited area
- Restricts absorption of Ig into the lymphatics
- Reduces bioavailability[1]





rHuPH20 decreases infusion restrictions caused by hyaluronan permitting[1,2]
- Up to 20-fold larger volumes
- Up to 10-fold faster infusions



rHuPH20 rapidly, reversibly and temporarily depolymerizing Hyaluronan[1-3]
- Increases the SC tissue permeability
- Enhancing fluid flow

Illustrations adapted from Frost 2007.

rHuPH20=Recombinant Human Hyaluronidase; Ig=immunoglobulin; SCIG=subcutaneously administered immunoglobulin.

1. Wasserman RL, et al. *J Allergy Clin Immunol.* 2012;130(4):951-957. **2.** Bookbinder LH, et al. *J Control Release.* 2006;114:230-241.
3. HYLENEX recombinant (hyaluronidase human injection) Prescribing Information. Halozyme Therapeutics, Inc; 2012.

Immunoglobulin replacement therapy

Facilitated sc application: Data of the Phase III trial

Provided by Shire

A Phase III and extension study of fSCIG showed that it **allows administration of up to 600 mL SCIG in patients >40kg every 3-4 weeks in a single infusion site in the course of ~2 hours.**[1]

3.5 years of combined trial data demonstrated:

- Low infection rates similar to SCIG and IVIG[1]
    - 0.025 VASBI/patient year (upper 99% CI limit: 0.046) and 2.97 all infections/patient year (95% CI 2.51-3.47)[1]
- Safety profile
    - No drug-related serious AE in the phase 3 study[1]
    - Lower rate of systemic ARs relative to IVIG[2] but higher than regular SCIG
    - 98.7% (231/234) of local ARs were mild or moderate
- Protective serum IgG trough levels: 10.7 g/L (median with 3 week intervals)[1]

SCIG, subcutaneous immunoglobulin; fSCIG, facilitated subcutaneous immunoglobulin; IVIG intravenous immunoglobulin; VASBI, validated acute serious bacterial infection; AE, adverse event; AR, adverse reaction

1. Wasserman, RL. *Immunotherapy* 2017; Epub ahead of print
2. Wasserman, RL *et al. J Allergy Clin Immunol* 2012;130:951-7

Individualised immunoglobulin therapy

Some parameters for decision of route

Medical aspects

SAE to IVIG

Anti IgA Ab / Absent IgA+ B cells

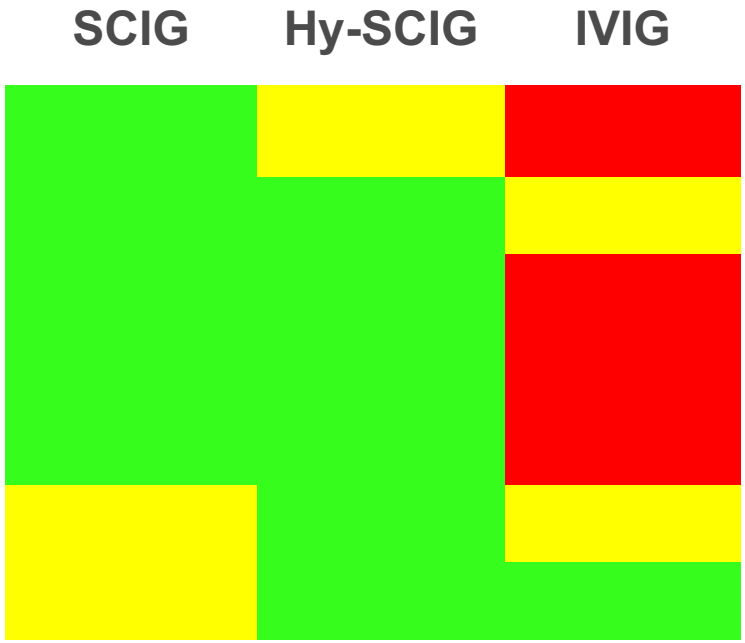
Renal insuff.

Cardiac insuff.

Thrombo-embolic risk

Patients with high catabolism/loss

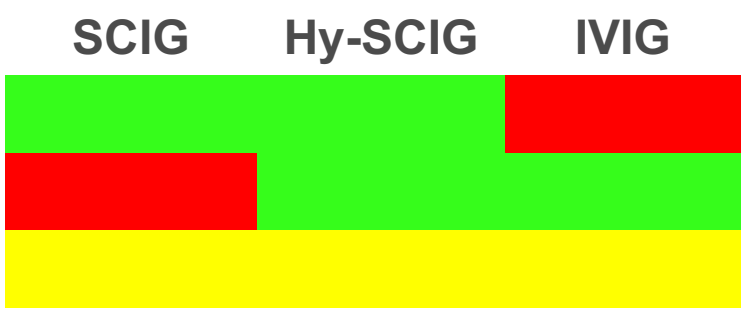
High dosage



Home therapy / self administered

doctors office / foreign administered

Needle phobia



Other aspects

Immunoglobulin replacement therapy

Future

Electronic documentation and surveillance of treatment through apps

Broader accessibility for all products

Broader indication in SID

Additional routes of application: Nasal ? Gastrointestinal ?

IgG preparations enriched for specific antibodies

Synthetic IgG preparation with high specificity against most common pathogens ?

Reset of the humoral immune system in some patients?

Summary

Better diagnosis, better treatment, better life

Immunoglobulin replacement is the baseline therapy for patients with relevant hypogammaglobulinemia!

IgG treatment is the best targeted therapy for infection only patients.

Individual trough levels need to keep the patient infection free.

A broad repertoire of treatment options allows for optimized individual therapies. All available products are suitable with some differences in regard to IgA content, stabilizer and reduction of isoagglutinins. There are insufficient comparative data between the different products available.

There is still a broad range of side effects (usually grade I-II) which seek for optimization of therapy.

Immune dysregulation is not sufficiently controlled by IgG and requires additional therapy.

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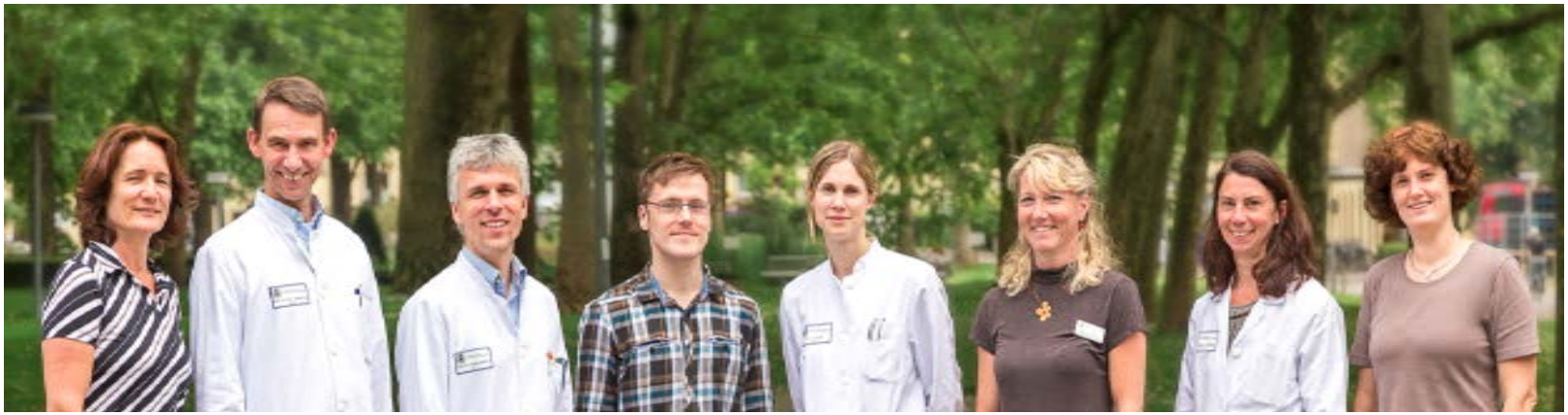

Thank you for your attention

Thank you to the patients and their families

Klaus.warnatz@uniklinik-freiburg.de

jmcn Jeffrey Modell Centers Network

CCI Centrum für Chronische Immundefizienz

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung