İmmunoglobulin Kullanımı

Dr. Emre Çeçen

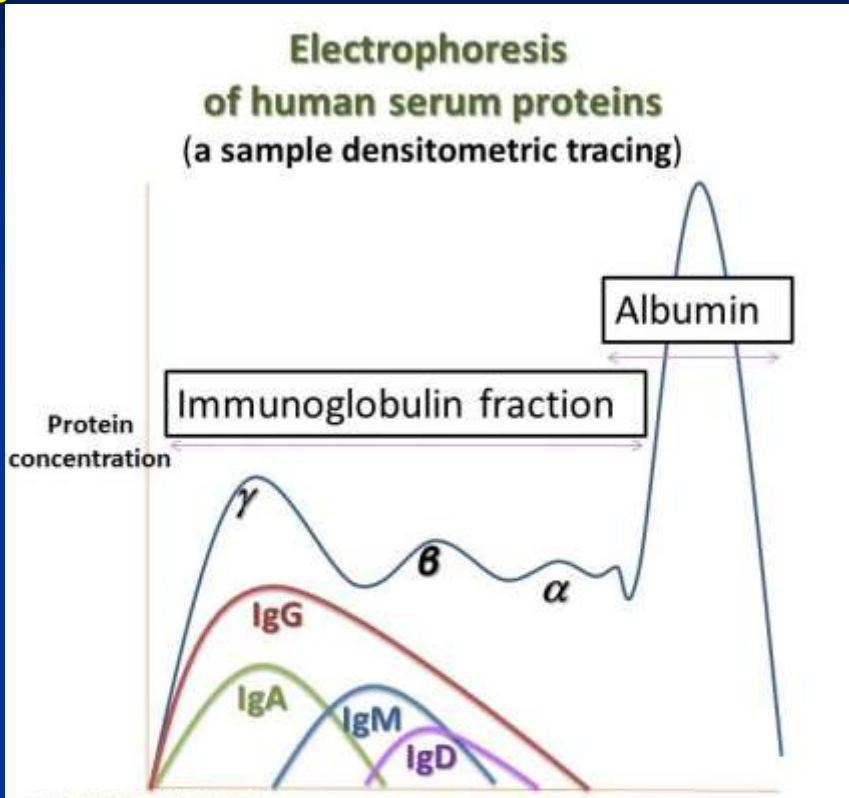
İmmünoglobulinler

- **Antikor aktivitesi** gösteren ve kendilerinin oluşmasına neden olan **antijenlerle özgül olarak birleşebilme** özelliğinde olan glikoprotein yapısında moleküller
- Plazma proteinlerinin % 20'sini oluştururlar

İmmünoglobulinler

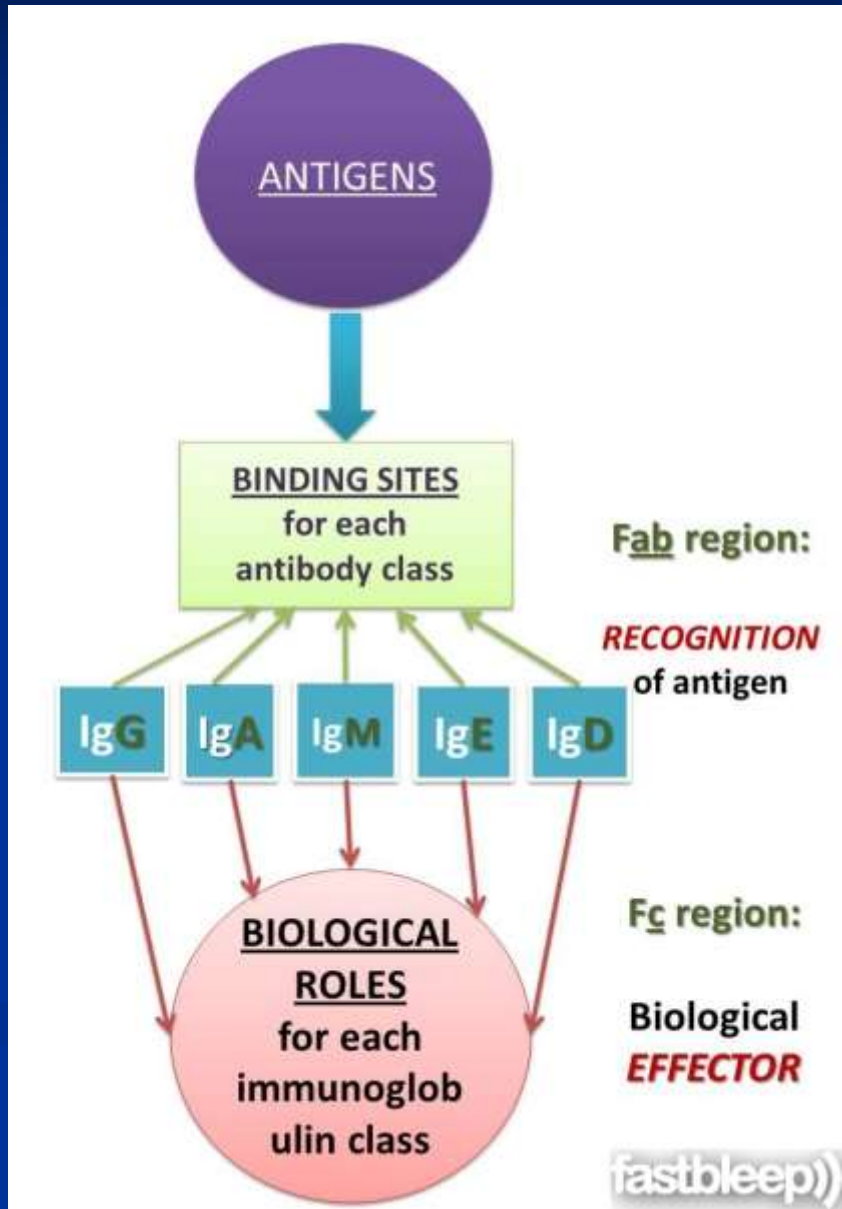
- Serum proteinlerinin elektroforezinde, başlıca gamma globulin kısmında yer alırlar

- Bu nedenle immünglobulin adı verilir ve Ig şeklinde gösterilirler



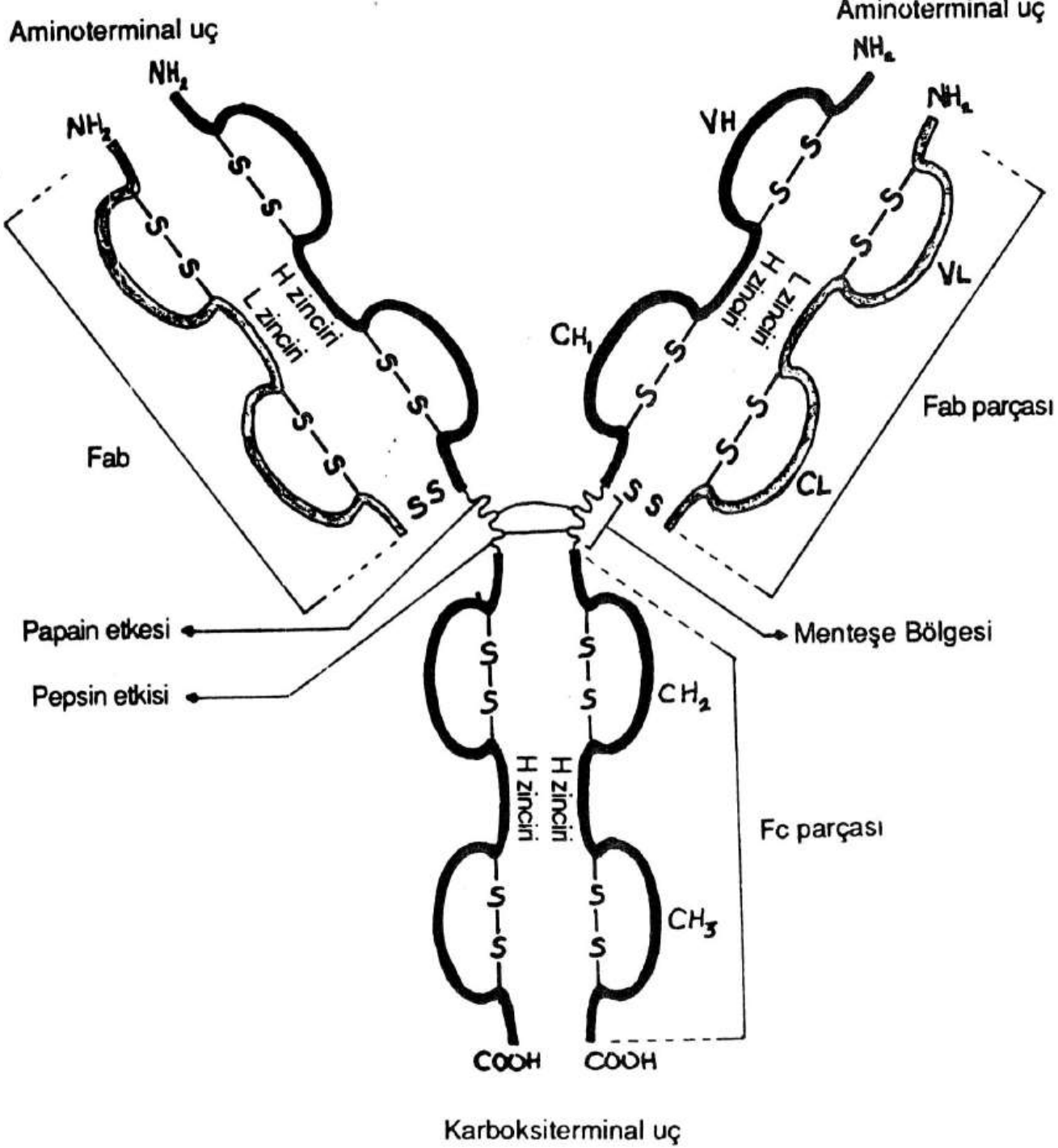
İmmünoglobulinler

- Antijenik uyarım sonucu B-lenfositlerin değişimi ile oluşan plazma hücreleri tarafından sentezlenirler
- Antijen spesifik
- Salgılanabilir veya membrana bağlı
- Kan, doku ve lenf içinde bulunur



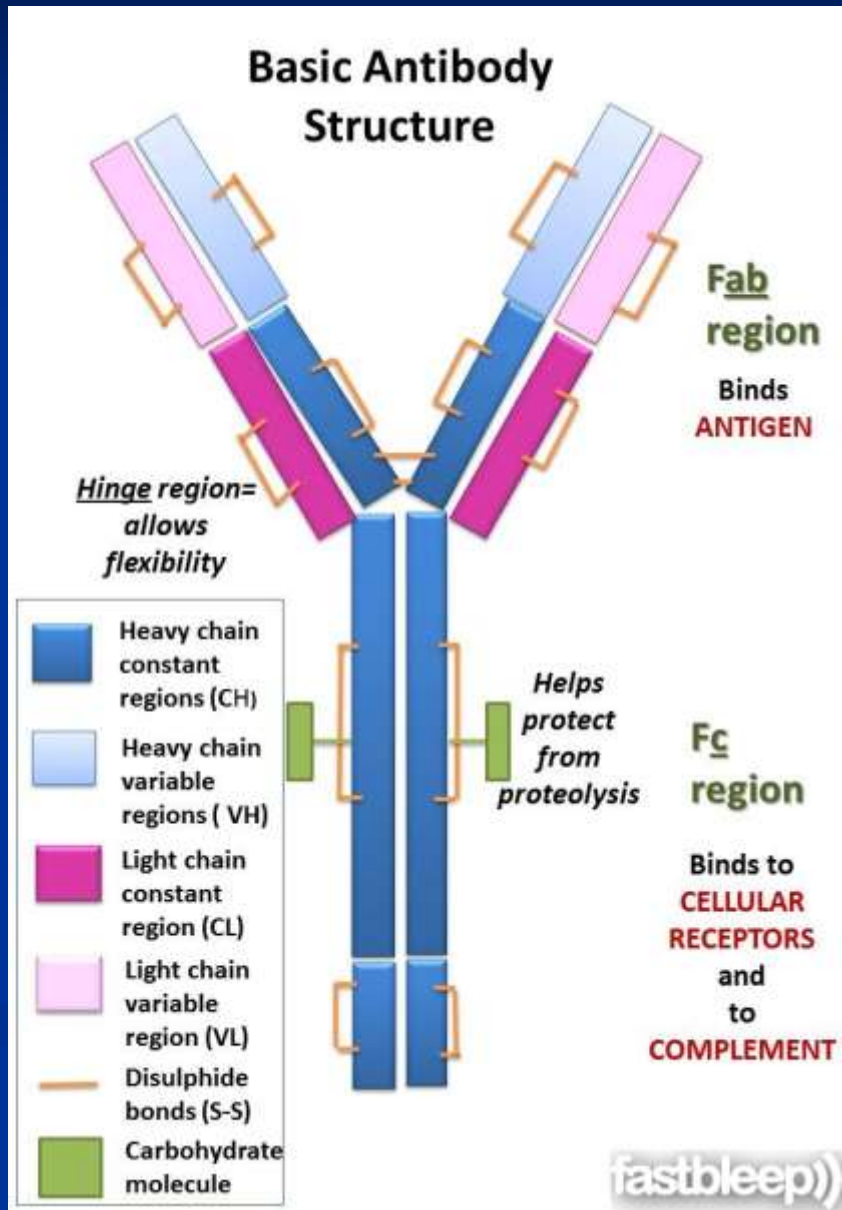
İmmünoglobulinler

- Antikor moleküllerinin farklılıkları,
  - karbonhidrat miktarları
  - elektroforez hızları
  - molekül ağırlıkları
  - aminoasit yapıları
  - taşıdıkları H (=ağır) polipeptid zinciri tipi gibi özelliklere dayanmaktadır
- **Bir Ig molekülünün sınıfını onun ağır zincirin sabiti belirler**


Aminoterminal uç
Aminoterminal uç
NH2
NH2
NH2
NH2
S—S
H zinciri
L zinciri
VH
VL
CH1
CL
Fab
Fab parçası
Papain etkesi
Pepsin etkisi
Menteşe Bölgesi
CH2
CH3
Fc parçası
COOH
COOH
Karboksiterminal uç

İmmünoglobulinler

- Hafif zincir = L zinciri (Light)
  - K (kappa)
  - λ (lambda)



İmmünoglobulinler

- Ağır zincir = H zinciri (Heavy)
  - IgG γ (gamma) H zinciri
  - IgM μ (mü) H zinciri
  - IgA α (alfa) H zinciri
  - IgD δ (delta) H zinciri
  - IgE ε (epsilon) H zinciri

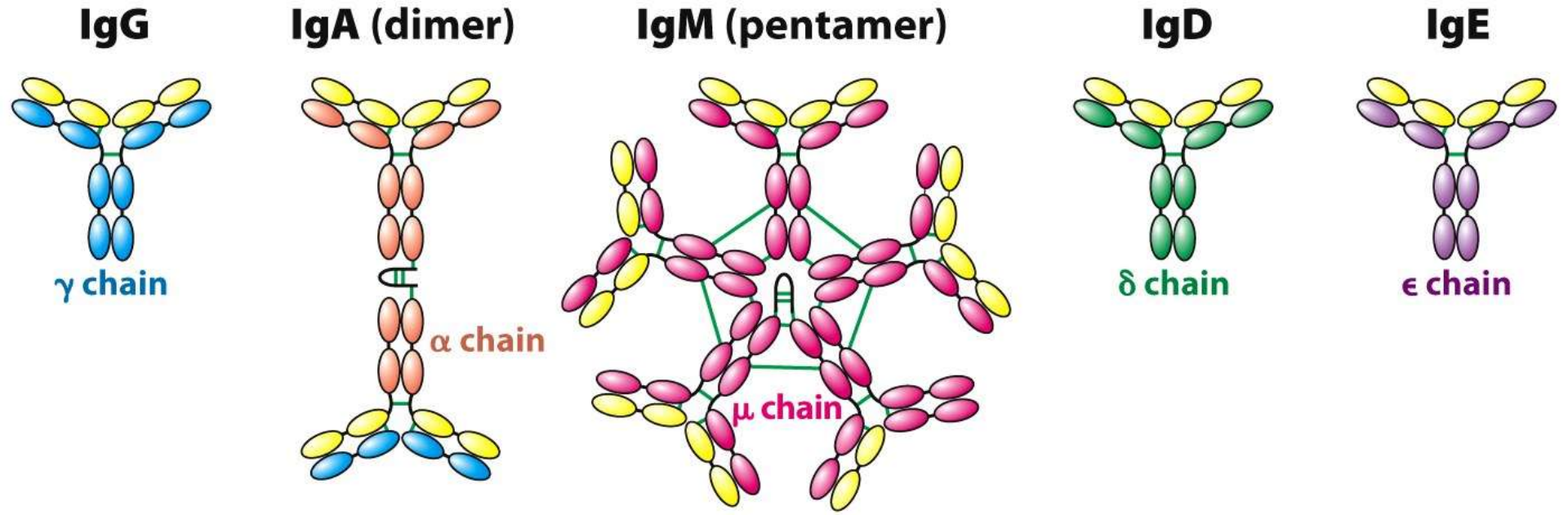


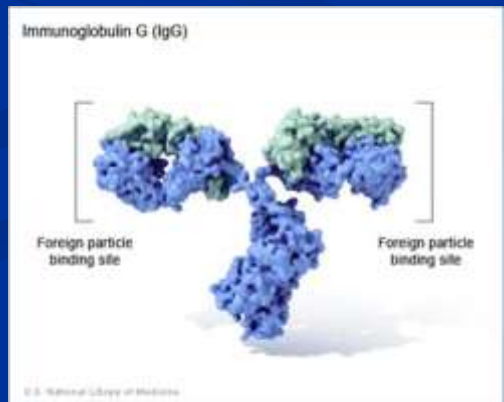
Figure 34.8
Biochemistry, Seventh Edition

IgG

- IgG moleküllerinde antijenik ve menteşe gölgesinde iki ağır zincir arasındaki disülfid bağının sayısı açısından farklılık gösteren dört alt grup saptanmıştır.

- IgG'lerin
  - %65 IgG1
  - %23 IgG2

  (kapsüllü bakterilerin polisakkarit antijenlerine karşı yanıttan sorumlu)
  - %8 IgG3
  - %4 IgG4



IgG

- Klasik yoldan komplemanı aktive eden iki Ig'den biridir (diğeri IgM)
- Yarı ömrü 21 gün
- Birçok hücrede (özellikle fagositik hücrelerde) IgG'yi Fc kısmından bağlayan yüzey reseptör bulunur ve IgG opsonizasyonla fagositozu güçlendirirler

IgM

- Serumdaki immünglobulünlerin %10'unu oluşturur
- En büyük Ig'dir ve **makroglobulin** de denir
- IgM moleküllerinin büyük bir kısmı (%80'i) dolaşan kandadır. Dokulardaki yoğunluğu daha azdır.
- Plasentadan geçemezler

IgM

- İlk ve en erken sentezlenen Ig
- Yarı ömrü kısa, 7 gün
- Kompleman bağlama gücü de en yüksek Ig
- Fagositozu kolaylaştırır.
- İnsanda, serumdaki kan gruplarına ait izoantikorlar (anti-A ve anti-B) IgM sınıfı antikorlardır.
- Ayrıca B lenfosit yüzeyindeki Ig reseptörler de monomer IgM yapısındadır.

IgA

- Yapısı IgG'ye benzer.
- IgA molekülleri hem IgG gibi monomer halde (bir temel birim), hem de iki veya daha fazla monomerin J bağlayıcı polipeptid zinciri ile bağlanması sonucu dimer (iki temel birimli) veya trimer (üç temel birimli) halde bulunabilmektedir

IgA

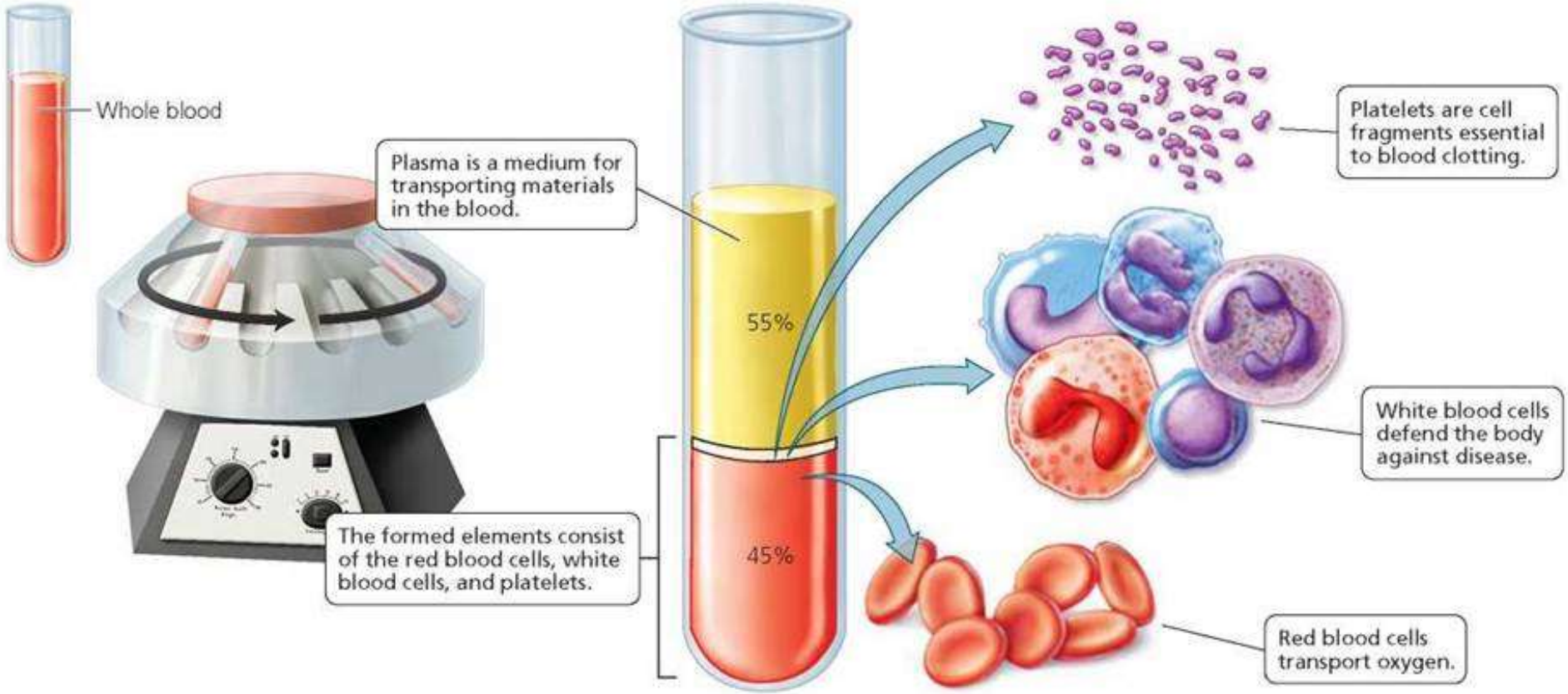
- İnsan serumundaki Ig'lerin %15'ini oluşturur.
- Serumdaki IgA'ların %80'i monomer yapıdadır
- Salgısal IgA molekülleri sIgA şeklinde gösterilirler. Salgısal IgA, serum
- IgA'sından farklılık gösterir. sIgA'da ek olarak salgısal parça (= Transport parça) bulunur

IgD

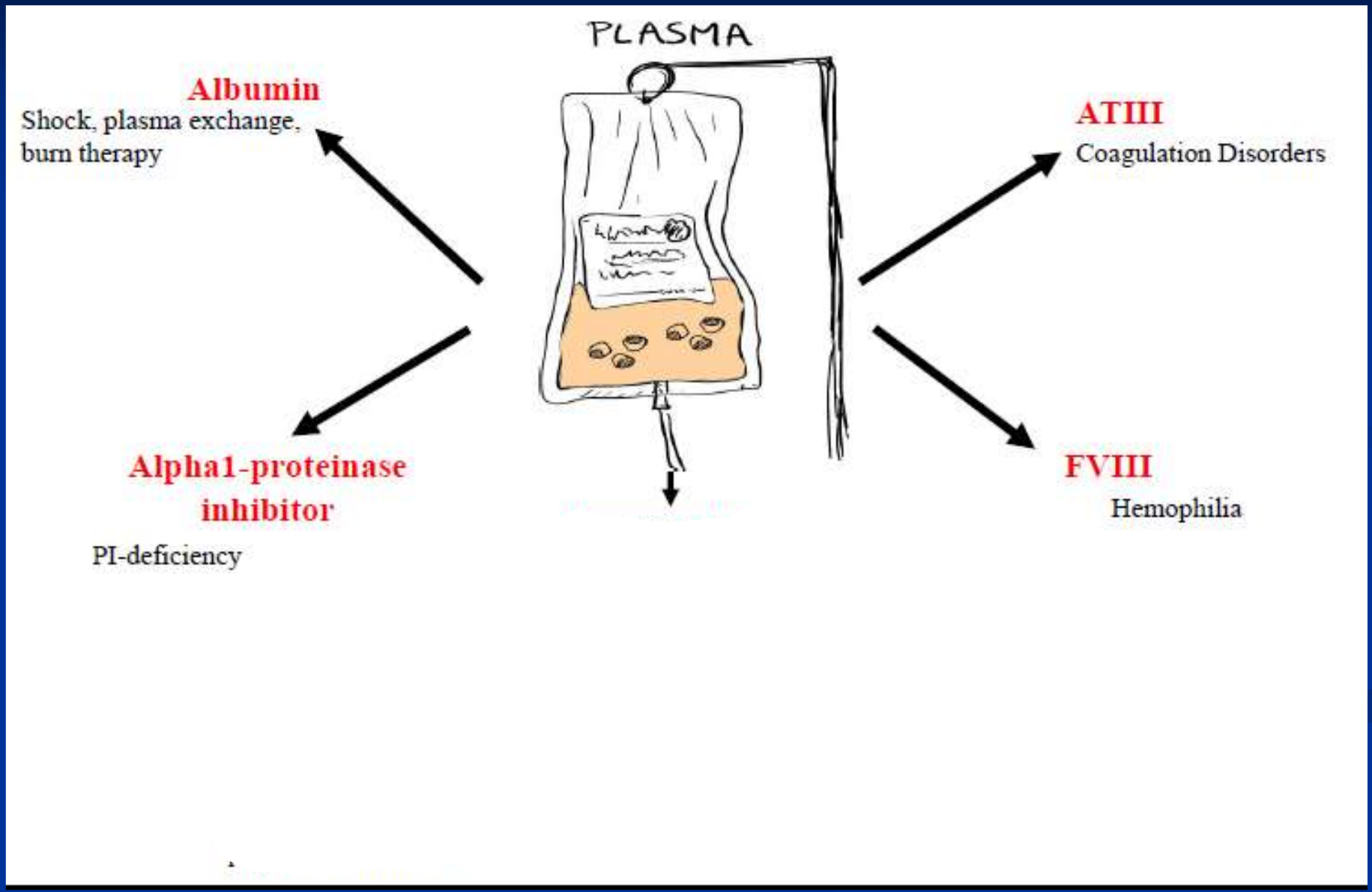
- Serumdaki immünglobulinlerin %0.2 kadarını oluşturur
- Antikor aktivitesi olduğu kanıtlanamamıştır ve asıl işlevinin belli değil.
- IgM ile birlikte, B lenfositlerin yüzeylerinde bulunur.
- B-lenfositlerin farklılaşmasında rol oynar (hücre aktivasyonunda reseptör)
- Yarı ömrü 2 gün

IgE

- Ig'lerin %0.004'ünü oluşturur
- Fc parçası ile **mast hücresi ve bazofil lökositlere bağlanabilme özelliğindedir** ve bağlandığı zaman bu hücreleri duyarlı hale getirirler
- **Komplemanı aktive etmez**
- Yarı ömrü 2 gün


Whole blood
Plasma is a medium for transporting materials in the blood.
55%
45%
The formed elements consist of the red blood cells, white blood cells, and platelets.
Platelets are cell fragments essential to blood clotting.
White blood cells defend the body against disease.
Red blood cells transport oxygen.

- Dünyada en sık kullanılan plazma ürünü



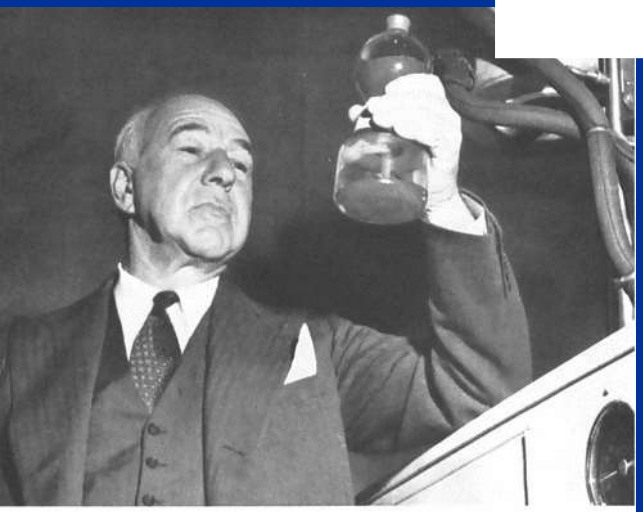
Temel endüstriyel üretim metodu 1939'da Edwin Cohn tarafından tanımlanan
Günümüzde fazlasıyla modifiye edilmiş "**alkol çöktürme yöntemi**"

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

OCTOBER 1939

PROTEINS AS CHEMICAL SUBSTANCES
AND AS BIOLOGICAL COMPONENTS

EDWIN J. COHN



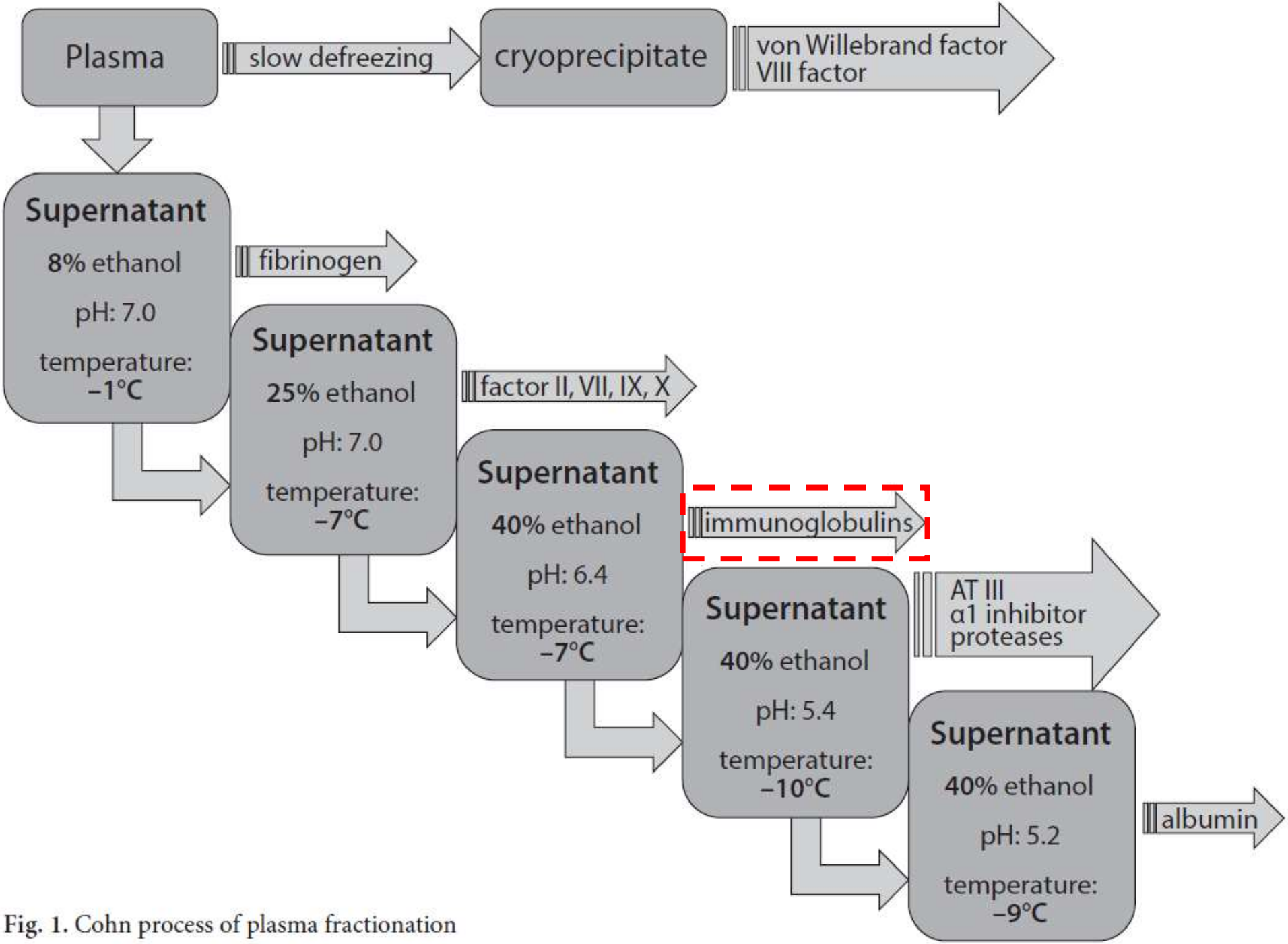


Fig. 1. Cohn process of plasma fractionation

Plazma

- Fraksiyonasyon
- Pürifikasyon
- Stabilizasyon
- Patojenlerin ayrılması ve inaktivasyon
- Formülasyon ve kompozisyon

IVIG

- Soğuk alkol ile damıtma
- Arıtma
- Çöktürme
- Düşük pH
- Yağ asidi/alkol
- Çözücü/deterjan
- Pastörizasyon
- Nanofiltrasyon

- Soğuk alkol ile damıtma
- Arıtma
- Çöktürme
- Düşük pH
- Yağ asidi/alkol
- Çözücü/deterjan
- Pastörizasyon
- Nanofiltrasyon

Son ürün:
IgG,IgA, IgM,
IgG F(ab)2 parçaları,
solübl CD4, CD8,
TGFβ

IVIG preparatları

- WHO standartları
  - En az 1000 verici havuzundan elde edilmeli
  - Mümkün olan en az miktarda IgA içermeli
  - *In vivo* birikim yapabilecek, koruyucu stabilleştirici içermemeli
  - IgG molekülleri mümkün olduğunca modifiye olmamalı

IVIG preparatları

- Preparatlar %90 üzerinde pürifiye polivalan IgG içerir
  - Üretimlerinde küçük farklılıklar
    - Prosedür
    - Stabilleştiriciler
      - Sükroz, glukoz, maltoz
      - Agregasyon önleyicileri
        - Glisin, prolin
    - Na içeriği
    - Saklama koşulları
    - Raf ömrü

IVIG preparatları arasındaki farklılıklar

- Formülasyon (sıvı, liyofilize)
- Volüm yükü / konsantrasyon
- Osmolarite
- Sodyum içeriği
- Şeker içeriği
- pH
- IgA içeriği

Formülasyon (sıvı, liyofilize)

- Ürünler sıvı veya liyofilize (dondurarak kurutulmuş)
- Liyofilize ürünlerin derişimi %3-%12
- Kullanıma hazır sıvı ürünlerin derişimi %5 ve %10
- Liyofilize ürünlerde yan etkiler daha fazla
  - Bu durum seyrelticinin tipine (SF, D5W, distile su)
  - Hazırlanma biçimine
  - Yüksek osmolariteye
  - Sallama sırasında protein denatürasyonuna bağlı olabilir

Hacim yükü

- Toplam sıvı miktarı özellikle küçük bebeklerde, yaşlılarda, kalp ve böbrek hastalarında önemlidir
- Bu durumda yüksek derişimli, daha az sıvı miktarı içeren ürün kullanılmalıdır.
  - Vücut ağırlığı 70 kg olan bir hasta 2 gr/kg dozunda %5'lik 100 ml olan solüsyondan toplam 2800 ml alacaktır, eğer %10'luk derişime sahip solüsyon kullanılırsa toplam sıvı miktarı 1400 ml olacaktır

Sodyum içeriği

- Sodyum içeriği genellikle eser ile %0.9 arasındadır
- Bazı liyofilize ürünlerin hazırlanmasında %2'lik SF kullanılır ve ürünün tuz miktarını artar
  - Tromboembolik olayların görülmesini arttırır

Şeker içeriği

- Şeker (sorbitol, glukoz, sukroz) bazı ürünlerde çökelti oluşumunu azaltmak için kullanılır
- Bazı ürünlerde şeker yoktur
- Renal yan etkiler %90 sukroz içeren ürünlerde görülür (osmotik nefrozis?)
- Diyabetli hastalarda dikkate alınmalıdır

Osmolarite

- Ürünün şeker ve tuz içeriği osmolariteyi belirler
- Hiperosmolarite tromboembolik olaylara yol açabilir
- Liyofilize ürünler hiperosmolar duruma neden olur

pH

- Çökelti oluşmasını önleyecek optimum pH 4.0-4.5'dur
- Bu pH'da dengeleyici olarak şekere gerek yoktur
- Düşük pH ile flebit ilişkisi ?

IgA içeriği

- Preparatlar bir miktar IgA içerir
- IgA düzeyi selektif olarak düşük olan hastalarda anti-IgA antikorlar üretilebilir
- IgA'ya karşı reaksiyon oldukça nadirdir
- Anti-IgA antikor taraması önerilmez

	İVİG risk faktörleri					
Hasta risk faktörleri	Volüm yükü	Şeker	Na^+	Osmol	pH	IgA
Kardiyak hastalık	+		+	+		
Renal hastalık	+	+	+	+		
Tromboz riski	+		+	+		
Anti IgA ab						+
Diyabetik hasta		+				
Yaşlı hasta	+	+	+	+		
Çocuk	+		+	+	+	

IVIG ürünleri	Özellikler						
	pH	Ozmolalite (mOsm/kg)	Sodyum	Stabili-zatör	Ürün formu	Konsan-trasyon	IgA (mg/ml)
Kiovig	4.6-5.1	240-300	yok	glisin	sıvı	%10	≤0,14
Octagam	5.1-6.0	280-300	≤ 30 mEq/L	maltoz	sıvı	%5	≤0,2
Flebogamma	5.0-6.0	342-350	<3.2 mEq/L	sorbitol	sıvı	%5	<0,05
Tegeline	6.6	belirtil-memiş	2 mg/ml	sükroz	liyofilize	%5	<800
Vigam	4.8-5.1	240	3.2 mmol/g immünglobulin	sükroz	sıvı	%5	<0,014
Ig Vena	4.0	belirtil-memiş	yok	maltoz	sıvı	%5	<0,25
GenIVIG	4	belirtil-memiş	belirtil-memiş	maltoz	sıvı	%5	belirtil-memiş
Ronsenglob	belirtil-memiş	belirtil-memiş	belirtil-memiş	maltoz	sıvı	%5	belirtil-memiş

İlaç Seçimi

Etki mekanizması

- Enfeksiyonlara karşı koruma
  - Hipogamaglobulinemi, antikor eksikliği sendromları veya immün yetmezliklerde yeterli antikor konsantrasyonu sağlar
- Alloimmünizasyon
  - Rh uygunsuzluğu
    - Anti D kaplanmış eritrositlerin makrofaj aracılıklı temizlenmesi
    - İmmün yanıt oluşmadan antijen spesifik B hücrelerinin down regülasyonu

Etki mekanizması

- İnflamatuar/otoimmün işlemlerin baskılanması
- Dalak ve karaciğerdeki fagositik hücrelerdeki Fc resptörleri ile etkileşim/blok
- Dentritik hücre (DH) farklılaşma/olgunlaşma inhibisyonu
  - Yüksek tedavi edici dozlarda sistemik lupus eritematosus (SLE) hastalarında DH gelişimini engelleyerek HLA ve CD80/CD86 ekspresyonunu engeller.
  - Tam tersi düşük dozlarda ise DH diferansiyasyonunda etkindir. Yaygın değişken immün yetmezlik durumunda bozuk olan DH gelişimi IVIG ile düzelmektedir

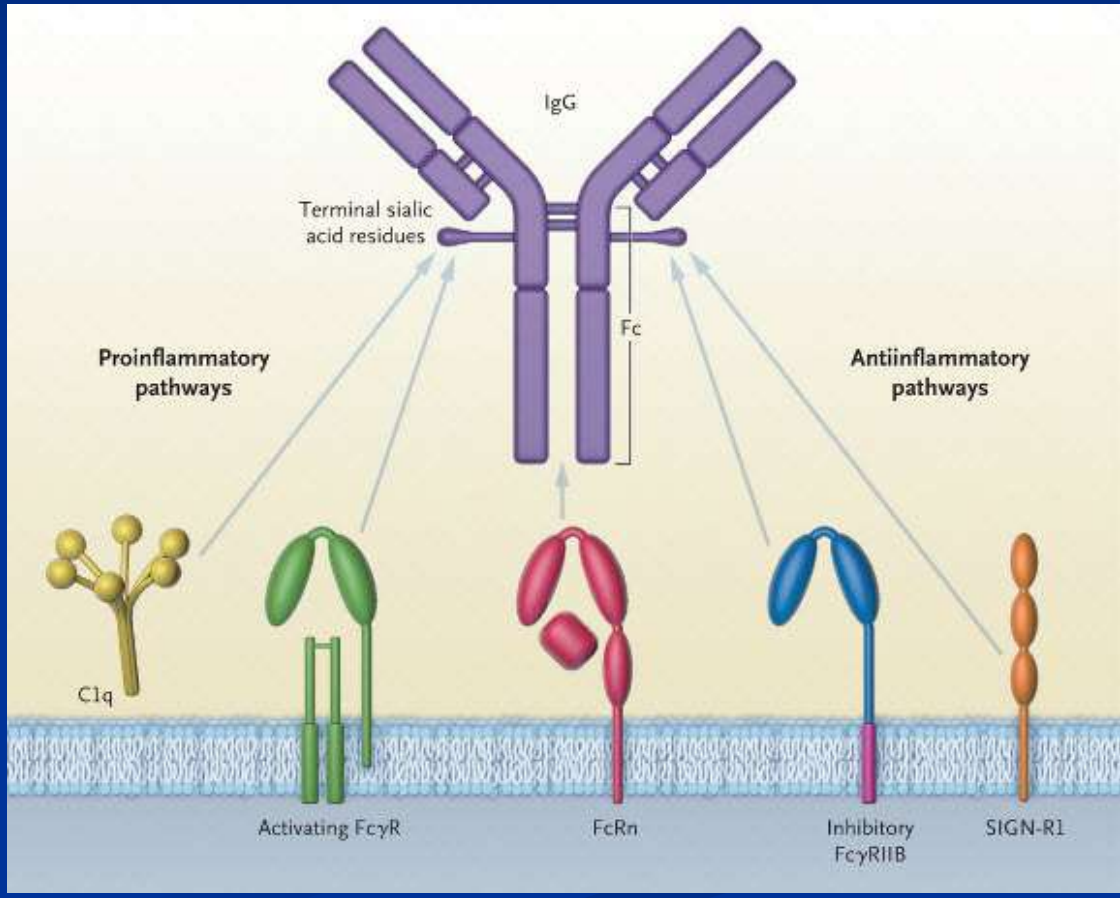
Etki mekanizması

- Periferik kan monositlerinin (CD14,CD16), proinflamatuar altgruplarının redüksüyonu ve bu hücrelerin sitokin üretiminin baskılanması

- Lökosit adhezyon molekülünün vaskuler endoteline bağlanmasının blokajı
  - Farelerde orak hücre krizinde bu şekilde fayda sağladığı gösterilmiş
  - Kawasaki hastalığında benzer etki olabilir

Etki mekanizması

- IVIG içindeki anti-fas ligant antikorları ile fas-ligant aracılıklı apoptozisin blokajı
  - Keratinosit ölümü ile karakterize TEN sendromunda* hastalık progresyonunu önlediği gösterilmiş
- Effektör makrojajlarda inhibitör Fc gamma RIIB reseptörlerinin indüksiyonu



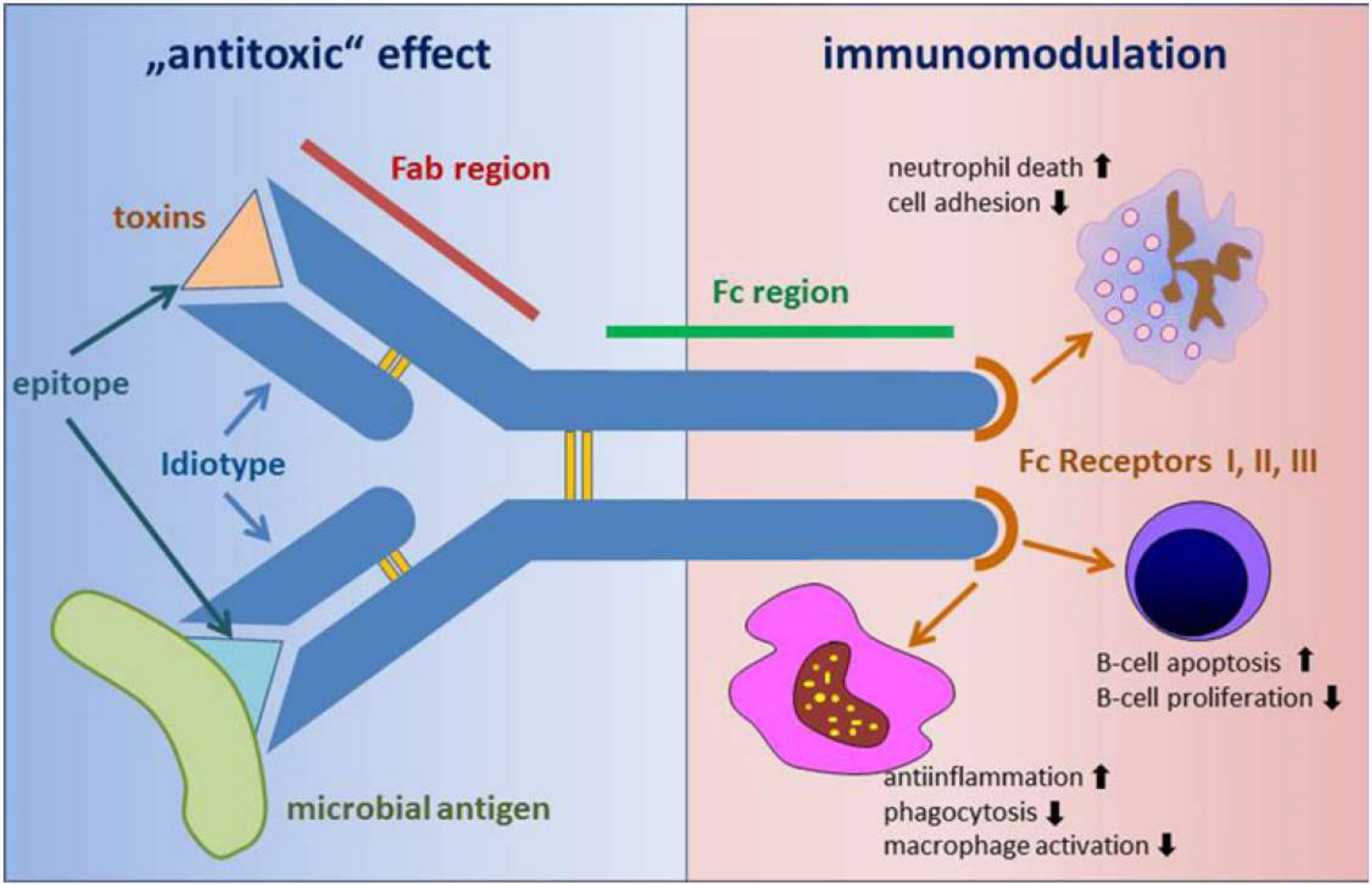
* Toksik Epidermal Nekrolizis

Etki mekanizması

- Anti-idiyotipik antikorların eklenmesi, klirensi arttırmayla sonuçlanan dolaşan otoantikorlara veya antikor üretiminde down regülasyonla sonuçlanan B hücre reseptörlerine bağlanabilir
  - Hemofili, faktör VIII inhibitöre karşı IVIG

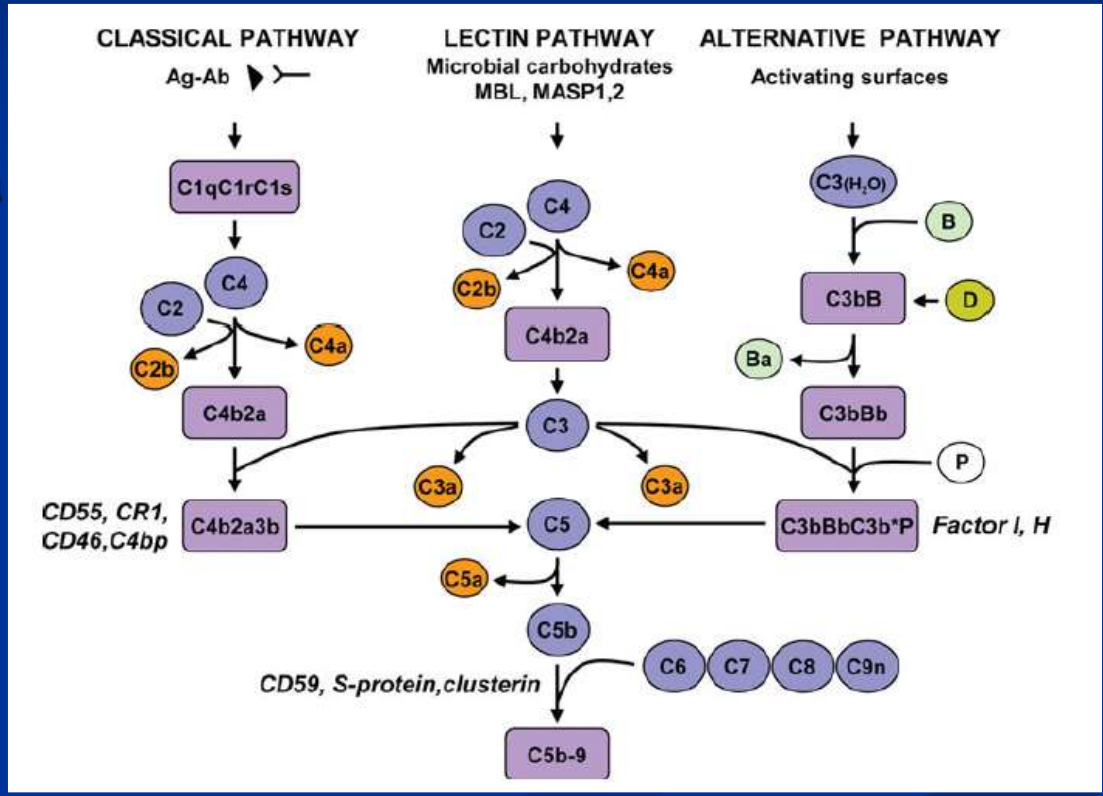
Etki mekanizması

- Mikrobiyal toksinlere karşı nötrolizan antikorların yanıtı
  - Stafilokoksik toksik şok sendromu, ciddi grup A strep. enfeksiyonları ve Kawasaki sendromunda nötrolizan antikorlar, stafilokoksik toksinlere ve streptokok süperantijenlerine yönelir ve sitokin üretimini azaltır
  - Shiga toksin aracılıklı HUS

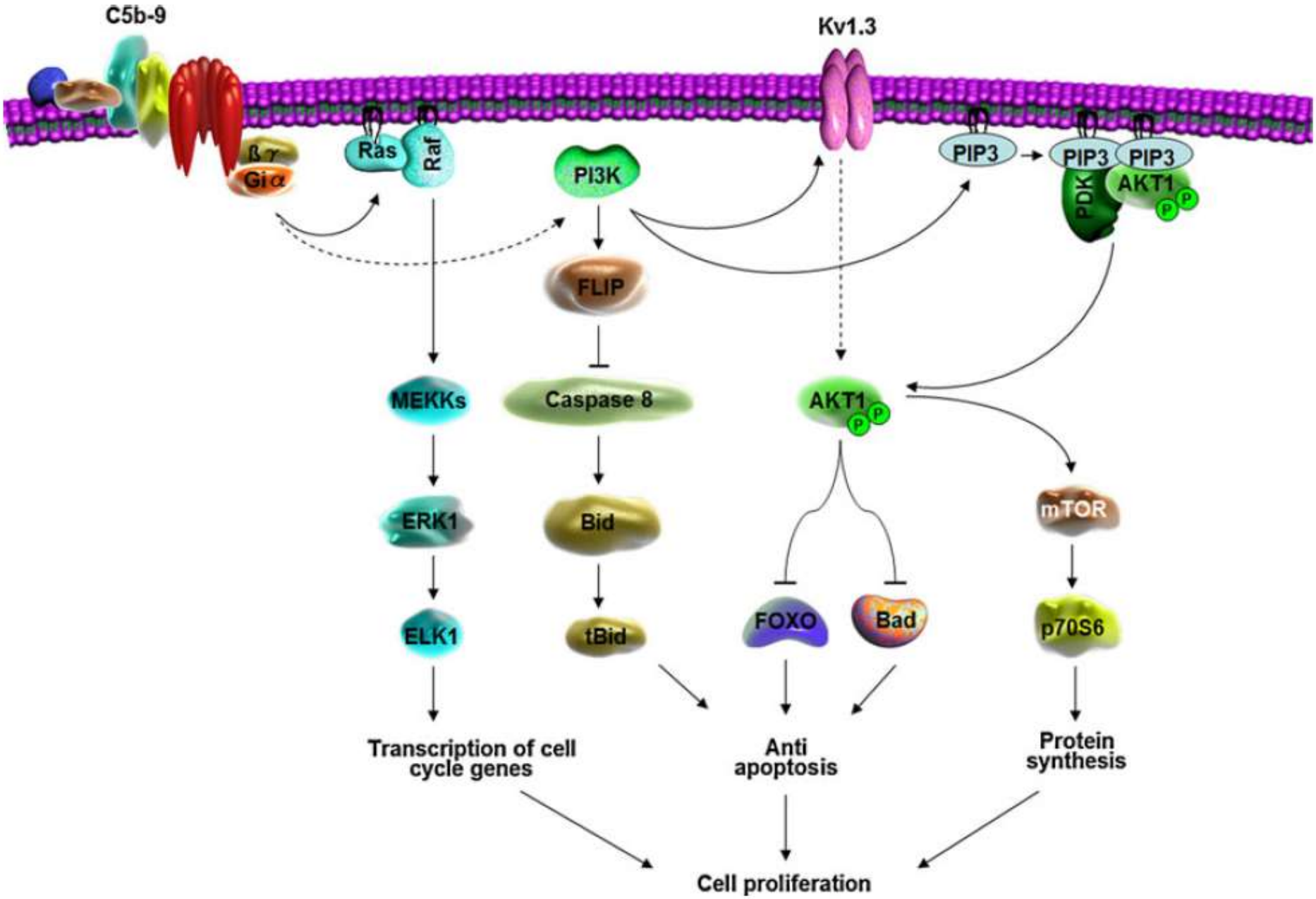

„antitoxic“ effect
immunomodulation
Fab region
toxins
Fc region
neutrophil death ⬆
cell adhesion ⬇
epitope
Idiotype
Fc Receptors I, II, III
B-cell apoptosis ⬆
B-cell proliferation ⬇
antiinflammation ⬆
phagocytosis ⬇
macrophage activation ⬇
microbial antigen

Etki mekanizması

- Kompleman sistem üzerine etkiler
- İmmün kompleks depozitlerin çözünürlüğü ve klerensi ve/veya C4b ve MAK* (C5b-9) gibi aktive kompleman komponenetlerinin hedef dokulara bağlanmasının inhibisyonu
- Ciddi dermatomyozit, GB†, MG# ve Kawasaki hastalığında bu etki.
- C3b, C5a ve C5a üzerine etkiler



*MAK; Membran Atak Kompleks
†GBS; Guillain Barre sendromu
#MG; Miyasteni Gravis

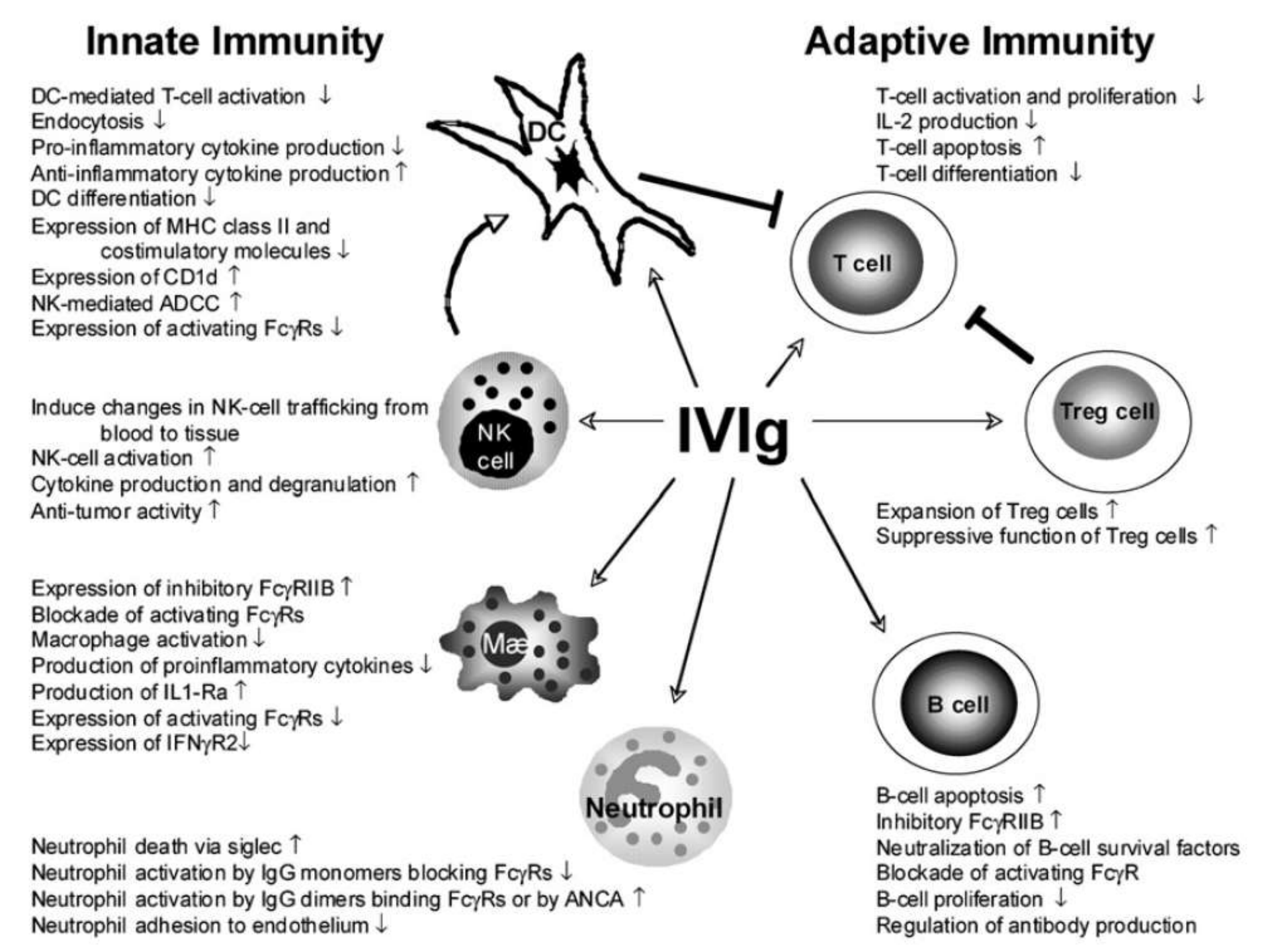

C5b-9
Kv1.3
ß γ
Giα
Ras
Raf
PI3K
PIP3
PIP3
PIP3
PDK
AKT1
P
P
FLIP
MEKKs
Caspase 8
AKT1
P
P
ERK1
Bid
mTOR
ELK1
tBid
FOXO
Bad
p70S6
Transcription of cell cycle genes
Anti apoptosis
Protein synthesis
Cell proliferation

Etki mekanizması

- "Düzenleyici T hücreleri"nde (Tregs) değişiklikler
- MS fare modelinde IVIG, CD4+CD25+FoxP3+Tregs genişlemesi ve pro-inflamatuar Th17 yolağının inhibisyonu ile hastalık progresyonunu önlediği gösterilmiş
- IVIG ile tedavi edilen Kawasaki hastalarında Tregs artışı,
- Yüksek doz IVIG alan otoimmün hastalıklı kişilerde dolaşan Tregs aktivasyonun arttığı gösterilmiş

Etki mekanizması

- Patolojik IgG'nin hızlandırılmış klirensi
- IgG transport sisteminin vaskuler endoteliyal hücrelerindeki FcRn reseptörlerini satüre eden, total plasma IgG konsantrasyonunun artışı sırasında görülebilir.
- Reseptör satüre olduğunda, IgG serum seviyesine bağlı olarak degrede olur
- FcRn reseptörü IgG'nin uzun yarı ömründen sorumlu
  - Fare çalışmaları, ITP'de IVIG uzun etkisi kısmen bu mekanizma ile açıklanabilir


Innate Immunity
Adaptive Immunity
DC-mediated T-cell activation ↓
Endocytosis ↓
Pro-inflammatory cytokine production ↓
Anti-inflammatory cytokine production ↑
DC differentiation ↓
Expression of MHC class II and costimulatory molecules ↓
Expression of CD1d ↑
NK-mediated ADCC ↑
Expression of activating FcγRs ↓
DC
T-cell activation and proliferation ↓
IL-2 production ↓
T-cell apoptosis ↑
T-cell differentiation ↓
T cell
Induce changes in NK-cell trafficking from blood to tissue
NK-cell activation ↑
Cytokine production and degranulation ↑
Anti-tumor activity ↑
NK cell
IVIg
Treg cell
Expansion of Treg cells ↑
Suppressive function of Treg cells ↑
Expression of inhibitory FcγRIIB ↑
Blockade of activating FcγRs
Macrophage activation ↓
Production of proinflammatory cytokines ↓
Production of IL1-Ra ↑
Expression of activating FcγRs ↓
Expression of IFNγR2↓
Mæ
B cell
Neutrophil
B-cell apoptosis ↑
Inhibitory FcγRIIB ↑
Neutralization of B-cell survival factors
Blockade of activating FcγR
B-cell proliferation ↓
Regulation of antibody production
Neutrophil death via siglec ↑
Neutrophil activation by IgG monomers blocking FcγRs ↓
Neutrophil activation by IgG dimers binding FcγRs or by ANCA ↑
Neutrophil adhesion to endothelium ↓

Endikasyonlar (FDA)

- Birincil immün yetmezlikler
- KLL ilişkili hipogamaglobulinemi
- Pediatrik HIV enfeksiyonu
- ITP
- Kawasaki sendromu
- GVHH önlenmesi ve transplant ilişkili enfeksiyonlar
- Kronik inflamatuar demyelinizan nöropati

Endikasyonlar

- İmmün yetmezlik durumları
  - Primer immün yetmezlik
  - Ciddi protein kaybı
  - Hematopoetik hücre nakli sonrası
  - Kronik lenfositik lösemi
  - Multipl myeloma
  - İmmünoglobulin üretimini baskılayan tedaviler

Endikasyonlar

- Enfeksiyonlar
  - KLL (IV antibiyotik veya hospitalizasyon gerektiren tekrarlayan enfeksiyonlarla birlikte)
  - Kronik parvo virus enfeksiyonu (anemi ile birlikte)
  - Tekrarlayan veya şiddetli *Clostridium Difficile* enfeksiyonu
  - Kızamık maruziyeti sonrası profilaksi (kişi immün yetmezlikli veya non-immün ise)
  - Bazı enterovirüs enfeksiyonları

Endikasyonlar

- Otoimmün/inflamatuar durumlar
  - Neonatal alloimmün trombositopeni
  - Otoimmün hemolitik anemi
  - Kazanılmış Faktör VIII inhibör
  - Guillain-Barre sendromu
  - Kawasaki hastalığı
  - Kronik inflamatuar demiyelinizan polinöropati
  - Multifokal motor nöropatiler
  - Bazı HIV ilişkili nöropatiler

Endikasyonlar

- Alloimmün durumlar
  - Post transfüzyon purpura
  - Kanamalı platalet alloimmünizasyonu
  - Antikor aracılı organ nakil reddi
  - Hiperhemolitik kriz

Kullanıldığı Diğer (Faydalı-Tartışmalı) durumlar

- Nörolojik Hastalıklar
  - Diyabetik proksimal nöropati
  - Yüksek doz steroidin etkisiz olduğu kazanılmış yaygın ensefalomyelit
  - Otoimmün ansefalit
  - Kompleks rejiyonal ağrı sendromu
  - Nöromiyotoni
  - Dirençli çocukluk çağı epilepsisi
  - Opsoklonus, miyoklonus
  - Akut idiyopatik disotonomi
  - Kronik fasyal ağrı

Kullanıldığı Diğer (Faydalı-Tartışmalı) durumlar

- Tekrarlayan gebelik kaybı
- Başarısız tüp bebek uygulamaları
- Transplantasyon
- PANDAS
  (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
- Yenidoğan sepsisi
- Graves oftalmopatisi
- Adrenolökodistrofi
- Alzheimer hastalığı
- Amliyotropik lateral skleroz
- TEN
- Steven-Johnson sendromu
- Atopik dermatit
- Astım
- Kistik fibrozis
- Otizm
- SLE
- Sistemik juvenil idiyopatik artrit
- Sistemik vaskülit ve ANCA (+) hastalıklar
- Ağır antifosfolipit sendromu

GVHH önlenmesi ve transplant ilişkili enfeksiyonlar

Hematopoetik hücre nakli sonrası

Abstract Send to:

Ann Intern Med. 2003 Jul 1;139(1):8-18.

Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial.

Cordonnier C[1], Chevret S, Legrand M, Rafi H, Dhédin N, Lehmann B, Bassompierre F, Gluckman E; GREFIG Study Group.

Author information

Abstract

BACKGROUND: The universal use of prophylactic immunoglobulin in stem-cell transplantation has not been supported by strong evidence of benefit. Results of most trials were reported before effective drugs for cytomegalovirus infection and disease were available, and no trial was placebo controlled.

OBJECTIVE: To assess the role and the dose-effect relationship of immunoglobulin in the prophylaxis of complications after allogeneic stem-cell transplantation.

DESIGN: Multicenter randomized, double-blind, dose effect placebo-controlled study.

SETTING: 19 stem-cell transplantation centers in France.

PATIENTS: 200 patients who had allogeneic stem-cell transplantation from HLA-identical sibling donors between 1998 and 2000.

INTERVENTION: Immunoglobulin at doses of 50 mg/kg of body weight, 250 mg/kg, or 500 mg/kg weekly from day -7 to day 100 after transplantation or placebo.

MEASUREMENTS: Cumulative incidence of infection, graft-versus-host disease, veno-occlusive disease, interstitial pneumonia, and transplantation-related mortality at 6 months; overall survival at 2 years after transplantation.

RESULTS: Immunoglobulin had no benefit over placebo; 92% of patients in the pooled immunoglobulin group and 90% of patients in the placebo group had one or more infections (difference, 2 percentage points [95% CI, -8 to 12 percentage points]). Cumulative incidences of interstitial pneumonia, graft-versus-host disease, transplantation-related mortality, and overall survival were similar in patients receiving placebo and those receiving immunoglobulin; no dose-effect relationships were evident. Grade 3 (severe) veno-occlusive disease occurred more frequently as the immunoglobulin dose increased (P = 0.01).

CONCLUSIONS: Use of prophylactic immunoglobulin in allogeneic recipients of stem-cell transplant from HLA-identical sibling donors is not recommended.

Comment in

Summaries for patients. Immunoglobulin in patients with stem-cell transplants. [Ann Intern Med. 2003]

ORIGINAL ARTICLE

Allogeneic stem cell transplantation: low immunoglobulin levels associated with decreased survival

A-C Norlin[1], D Sairafi[1,2], J Mattsson[1,2], P Ljungman[3], O Ringdén[1,2] and M Remberger[1,2]

[1]*Department of Clinical Immunology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden;* [2]*Center for Allogeneic Stem Cell Transplantation, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden and* [3]*Department of Hematology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*

Persistan düşük IgG düzeyleri SCT sonrası ölüm için risk faktörü

The aim of this study was to evaluate the effects and kinetics of IgG levels after allogeneic stem cell transplantation (SCT). This study retrospectively examines 179 consecutive patients undergoing SCT between 1995 and 2002. Diagnoses included acute and chronic leukemia ($n=136$), solid tumors ($n=11$), other malignancies ($n=16$) and non-malignant diseases ($n=16$). Standard myeloablative conditioning was given to 146 patients, and 33 patients received reduced intensity conditioning. Serum samples for measurement of IgG levels were collected 3, 6 and 12 months after SCT, and then yearly. IgG levels increased after SCT throughout the study period. Factors that were associated with low IgG levels after SCT were acute graft-versus-host disease (GVHD), patient age $\leqslant 30$ years, female donor-to-male recipient, not receiving anti-thymocyte globulin and type of GVHD prophylaxis. Compared to patients with moderately low or normal levels as measured twice during the first year after transplantation, patients with low IgG levels (<4 g/l) showed a decreased survival rate (54 vs 71%, $P=0.04$) and an increased incidence of transplant-related mortality (27 vs 9%, $P<0.01$). IgG levels generally increase after SCT. Persistent low levels of IgG are a risk factor for death after SCT.

Bone Marrow Transplantation (2008) **41**, 267–273; doi:10.1038/sj.bmt.1705892; published online 12 November 2007

Keywords: SCT; IgG; infections; TRM

Immunoglobulin Prophylaxis in Hematopoietic Stem Cell Transplantation: Systematic Review and Meta-Analysis

Pia Raanani, Anat Gafter-Gvili, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, and Ofer Shpilberg

ABSTRACT

Purpose
Because the role of immunoglobulins (IVIG) prophylaxis in patients undergoing hematopoietic stem-cell transplantation (HSCT) has not been established in terms of survival and infection prevention, we conducted a meta-analysis evaluating these issues.

Methods
Systematic review and meta-analysis of randomized-controlled trials comparing prophylaxis with polyvalent IVIG or cytomegalovirus (CMV)-IVIG and control or another preparation or dose. PUBMED, Cochrane Library, LILACS, and conference proceedings were searched. Two reviewers appraised the quality of trials and extracted data. Relative risks (RRs) with 95% CIs were estimated and pooled.

Results
Thirty trials including 4,223 patients undergoing bone marrow transplantation (BMT) were included. There was no difference in all-cause mortality when polyvalent IVIG or CMV-IVIG was compared to control (RR, 0.99; 95% CI, 0.88 to 1.12; and RR, 0.86; 95% CI, 0.63 to 1.16, respectively). There was no difference in clinically documented infections when polyvalent IVIG was compared with control (RR, 1.00; 95% CI, 0.90 to 1.10; five trials). CMV infections were not significantly reduced with either polyvalent IVIG or CMV-IVIG. Interstitial pneumonitis was reduced with polyvalent IVIG in older studies but not in the more recent ones, nor in studies assessing CMV-IVIG. Polyvalent IVIG increased the risk for veno-occlusive disease (RR, 2.73; (95% CI, 1.11 to 6.71). Graft-versus-host disease was not affected.

Conclusion
Because there is no advantage in terms of survival or infection prevention, IVIG does not have a role in HSCT.

J Clin Oncol 27:770-781. © 2008 by American Society of Clinical Oncology

Retrospective analysis of weekly intravenous immunoglobulin prophylaxis versus intravenous immunoglobulin by IgG level monitoring in hematopoietic stem cell transplant recipients

Joshua E. Howell, Alison M. Gulbis, Richard E. Champlin and Muzaffar H. Qazilbash

Patients undergoing allogeneic hematopoietic stem cell transplant (allo HCT) have a higher incidence of infections partly due to secondary hypogammaglobulinemia. We evaluated the role of IVIG in allo HCT patients who received prophylactic IVIG 200 mg/kg once weekly regardless of IgG level (Group 1, *n* = 115) compared with patients who received IVIG based on IgG level <400 mg/dL (Group 2, *n* = 114). Primary endpoints were the utilization of IVIG, incidence of veno-occlusive disease (VOD), graft-versus-host disease (GVHD), and documented infections within the first 100 days after allo HCT. Patients in both groups were similar except for a higher number of matched unrelated donor (MUD) transplants in Group 2 (62 vs. 41, *P* = 0.01). There were no significant differences in the incidence all grades of GVHD (55 vs. 50), VOD (2 vs. 0) or infections in the two groups except for a higher incidence of para-influenza infections in group 1 (9 vs. 0, *P* = 0.003) coinciding with the flu season. We recommend monthly monitoring of IgG level and replacement only if IgG level is <400 mg/dL. Am. J. Hematol. 87:172–174, 2012.

- **Profilaktik** IVIG 200 mg/kg/hafta (Grup 1, n = 115)
- **IgG düzeyi <400 mg/dL** ise IVIG (Grup 2, n = 114).
- IVIG kullanımı, VOD, GVHD, ve kanıtlanmış enfeksiyon <100 gün
- **Fark yok**
  - GVHD (55 vs. 50),
  - VOD (2 vs. 0)
  - Enfeksiyon (para-influenza >grup 1 (9 vs. 0, P = 0.003).

ORIGINAL ARTICLE

Incidence and risk factors for hypogammaglobulinemia in pediatric patients following allo-SCT

H Frangoul[1], E Min[2], W Wang[3], R Chandrasekhar[3], C Calder[1], M Evans[1], B Manes[1], K Bruce[4], V Brown[1], R Ho[1] and J Domm[1]

We evaluated the incidence and risk factors for hypogammaglobulinemia after allogeneic hematopoietic SCT (HSCT) in pediatric patients. Ig levels were measured pre-transplant, every 2 weeks until day 100 and then monthly post SCT in 185 patients undergoing myeloablative HSCT. Median age was 9 years; 142 (77%) had malignant disease and 114 (62%) received stem cells from an unrelated source. Hypogammaglobulinemia (IgG <500 mg/dL) developed in 143 (77%) of the patients at a median of 56 days (range 15–339) post SCT. The cumulative incidence of hypogammaglobulinemia at 1 year was higher among patients who developed acute GVHD (97% vs 54%, $P<0.001$), and for those receiving stem cells from an unrelated source (94% vs 51%, $P<0.001$). The cumulative incidence of TRM was significantly higher for patients with hypogammaglobulinemia ($P=0.026$). In multivariable analysis, lower pre-transplant IgG level ($P<0.001$), younger age ($P=0.012$), diagnosis of malignant disease ($P<0.001$), receiving unrelated SCT ($P<0.001$) and development of acute GVHD ($P<0.001$) were all significantly associated with higher risk of hypogammaglobulinemia post HSCT. We conclude that hypogammaglobulinemia is common, following allogeneic HSCT in pediatric patients, especially in those with malignant diseases, those who receive an unrelated transplant or patients who develop GVHD.

Bone Marrow Transplantation (2013) **48,** 1456–1459; doi:10.1038/bmt.2013.76; published online 27 May 2013

Keywords: hypogammaglobulinemia; allo-SCT; children; IVIG; IgG; GVHD

- %77 oranında hipogamaglobulinemi, ortanca 56 gün
- Hipogamaglobulinemi, GVHH gelişenlerde ve akraba dışı vericilerde sık
- Kümülatif TRM insidansı, hipogamaglobulinemili hastalarda yüksek

Çok değişkenli analizde,

- Düşük pre-transplant IgG düzeyi, küçük yaş, altta yatan malign hastalık, akraba dışı verici, GVHH gelişimi hipogamaglobulinemi için risk faktörleri

Pediatr Blood Cancer 2015;62:890–896

Hypogammaglobulinemia in Children after Allogeneic Hematopoietic Stem Cell Transplantation: A Cytokine Mediated Immunoglobulin Isotype Class Switch Arrest?

Mikael Sundin, MD, PhD,[1,2]* Mats Remberger, PhD,[3,4] Henric Lindqvist, MD,[1] Brigitta Omazic, MD, PhD,[3,5] Berit Sundberg,[3] Mehmet Uzunel, PhD,[3] and Jacek Winiarski, MD, PhD[1,2]

Background. Hypogammaglobulinemia (hypo-IgG) is common early post-HSCT in children, occasionally necessitating long-term immunoglobulin (Ig) G replacement therapy. IgG replacement may not reduce mortality, although infectious complications are decreased ***Procedure.*** Clinical data and samples from 86 children were analyzed retrospectively with the aim to identify risk factors for developing long-term hypo-IgG (i.e., requiring ≥3 months IgG replacement) post-HSCT and studying the underlying biology. Laboratory studies covered serum cytokines, *IGHG2* genotyping and routine laboratory investigations. Results were analyzed statistically. ***Results.*** Forty-eight percent of the children developed long-term hypo-IgG. These children were younger (<5 years) and had higher acute GvHD incidence, but had better overall survival (88% vs. 69%, $P = 0.036$). Significantly lower Ig levels post-HSCT but equal immune cell recovery were seen in patients with long-term hypo-IgG compared with those of transient or no hypo-IgG. Pre-HSCT IL-6 and -7 and post-HSCT BAFF and APRIL levels were significantly higher in the long-term hypo-IgG group. ***Conclusions.*** Findings suggests an unfavorable cytokine milieu for graft-derived immune recovery, possibly inducing Ig isotype class switch arrest. Younger age, acute GvHD, and higher pre-HSCT IL-6 levels were identified as significant risk factors for long-term hypo-IgG. Long-term hypo-IgG post-HSCT does not need to be unfavorable and could be an effect of deteriorated cytokine signaling. Pediatr Blood Cancer 2015;62:890–896.

Key words: IgG; immunoglobulin; pediatric; subcutaneous; substitution

Uzun dönem (≥3 ay) hipogamaglobulinemi incelenmiş
%48 oranında saptanmış
Bu hastalar, <5 yaş ve GVHH insidansı yüksek çocuklar
(bunlarda OS yüksek !!)

Comparison of prophylactic use of intravenous immunoglobulin versus Pentaglobin® in pediatric patients after hematopoietic stem cell transplantation

Azık F, Bayram C, Erkoçoğlu M, Tezer H, Yazal Erdem A, Işık P, Avcı Z, Özbek N, Tavil B, Tunc B. (2016) Comparison of prophylactic use of intravenous Ig versus Pentaglobin® in pediatric patients after hematopoietic stem cell transplantation. *Pediatr Transplant*, 20: 276–283. DOI: 10.1111/petr.12636.

Abstract: There are few studies evaluating the use of IgM-enriched IVIG (Pentaglobin®) in HSCT recipients. This study aimed to compare the efficacy of prophylactic use of IVIG versus prophylactic use of Pentaglobin® within the first 100 days after allogeneic HSCT. We performed a prospective, randomized study of the use of prophylactic IVIG versus prophylactic use of Pentaglobin® in patients after allogeneic HSCT. The first dose of IVIG or Pentaglobin® was given before conditioning regimen and after transplant was given on day +1, +8, +15, and +22. And then, it was given if IgG level was below 400 mg/dL. Twenty-seven patients in IVIG group and 32 patients in Pentaglobin® group were included in the study. There were no significant differences in the duration of neutropenia, hospitalization, fever, and in the number of pyrexial episode, septicemia, bacteremia, local infection, CMV infection, acute GVHD, VOD, and adverse events between the IVIG group and Pentaglobin® group. Randomized placebo-controlled trials are needed to conclude that utilization of IVIG or Pentaglobin® has no beneficial effect in HSCT.

Fatih Azık[1], Cengiz Bayram[1], Mustafa Erkoçoğlu[2], Hasan Tezer[3], Arzu Yazal Erdem[1], Pamir Işık[1], Zekai Avcı[1], Namık Özbek[1], Betül Tavil[1] and Bahattin Tunc[1]

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Key words: intravenous immunoglobulin – Pentaglobin® – hematopoietic stem cell transplantation – children – infections

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Accepted for publication 13 October 2015

İmmünoglobulin üretimini baskılayan tedaviler

Incidence of Hypogammaglobulinemia in Patients Receiving Rituximab and the Use of Intravenous Immunoglobulin for Recurrent Infections

Carla Casulo, Jocelyn Maragulia, Andrew D. Zelenetz

211, rituximab alan
B hücreli lenfoma hastası
179 (%85) hasta ilaç öncesi normal IgG
Tedavi sonrası bunların %38.5'inde hipogam
İdame alanlarda risk belirgin.

Abstract

Rituximab targets normal B cells and tumor B cells. We used a unique data-mining tool to identify patients with lymphoma who were treated with rituximab and who had serial pre and post rituximab immunoglobulin concentrations evaluated. After treatment, 39% (69/179) of patients had low levels of immunoglobulin G. Recurrent sinopulmonary infections were seen in 6.6% (14/211). Intravenous immune globulin appeared to reduce the frequency of infection.

Background: Rituximab has altered the treatment approach to B-cell malignancies and other diseases. Reports consider that rituximab had limited impact on serum immunoglobulins. However, anecdotes suggest that rituximab can cause symptomatic hypogammaglobulinemia. This retrospective study examined the relationship among rituximab, hypogammaglobulinemia, and treatment of symptomatic hypogammaglobulinemia with intravenous immune globulin (IVIG). **Methods:** Patients with serial quantitative serum immunoglobulin (SIgG) concentrations before and subsequent to rituximab administration at Memorial Sloan-Kettering Cancer Center were identified. Information regarding rituximab administration, SIgG concentrations, frequency of infection, and administration of IVIG were recorded. **Results:** Between December 1998 and April 2009, 211 patients with B-cell lymphoma treated with rituximab and with serial SIgG concentrations were identified. One hundred seventy-nine (85%) patients had normal SIgG before rituximab, 32 (15%) had low SIgG. After rituximab use, hypogammaglobulinemia was identified in 38.54% of patients with initially normal SIgG. The risk was greater in patients who received maintenance rituximab. Symptomatic hypogammaglobulinemia that prompted IVIG administration developed in 6.6% of patients. **Conclusions:** In this data set, rituximab administration was associated with a high frequency of hypogammaglobulinemia, particularly symptomatic hypogammaglobulinemia, among patients who received multiple courses of rituximab. Baseline and periodic monitoring of SIgGs is appropriate in patients who receive rituximab.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 2, 106-11
Keywords: Gamma globulin, Hypogammaglobulinemia, Infections, Lymphoma, Rituximab

8.4 Prevention and treatment of infections

This protocol is very intensive and meticulous attention and measures to prevent and treat infection are essential. Blood should be taken at diagnosis to determine the antibody status to common viruses and to act as a baseline in the event of subsequent infections. Cultures may be taken at the start of intensification blocks and during treatment according to local protocols.

Preventive measures

- Mouth and skin care should be provided, especially in the diaper region.
- Because of the high risk of Pneumocystis Carinii Pneumonitis (PCP), it is mandatory to start PCP prophylaxis not later than at day 28 of the induction therapy. The prophylaxis should be interrupted in the HD-MTX courses as indicated in section 4.2 and 4.4.
- Preventive measures against bacterial infections should be taken according to the local policy of each centre.
- During neutropenia after HD-ARA-C, infections with particularly the gram positive Streptococcus viridans can occur, complicated by ARDS. (Centres may wish to consider prophylaxis during the neutropenic phase after HD-AraC with oral penicillin).
- Prevention of fungal infection may be achieved using an oral anti-fungal drug, e.g. oral Amphotericin or nystatin suspension. When oral prophylaxis with antifungal suspensions is not possible or there is manifest thrush, alternatively Fluconazole 6 mg/kg/day orally twice a day may be given.
- Mouth care is important in the prevention of infection.
- Because of their young age and the intensive chemotherapy regimen, most of the children develop severe hypogammaglobulinemia that often lasts until the end of maintenance. It is recommended to monitor serum IgG levels monthly and to give replacement therapy (IVIg) to maintain IgG level above 5 g/L.
- A potential large number of infants will not have been infected previously with the Varicella-Zoster Virus (Herpesvirus Varicellae). If there has been an exposure of the patient with an individual with varicella, Varicalla Zoster Immunoglobulin (VZIG) needs to be administered within 72 hours of exposure. The administration of VZIG to a patient extends the incubation period to 18-21 days. Nevertheless specific VZIG is not available in many countries. In that case, chemoprophylaxis with acyclovir 40-80 mg/kg/day PO in 4 divided doses starting 7-9 days after exposure (second viremic phase) is recommended. In case of manifest varicella infection, complications with pneumonia or encephalitis can be avoided by prompt treatment with intravenous acyclovir (500 mg/m^2 q 8 hr IV). In case of active disease the chemotherapy

INTERFANT-06

INTERNATIONAL COLLABORATIVE TREATMENT PROTOCOL FOR INFANTS UNDER ONE YEAR WITH ACUTE LYMPHOBLASTIC OR BIPHENOTYPIC LEUKEMIA

Because of their young age and the intensive chemotherapy regimen, most of the children develop severe hypogammaglobulinemia that often lasts until the end of maintenance. It is recommended to monitor serum IgG levels monthly and to give replacement therapy (IVIg) to maintain IgG level above 5 g/L.

- AML-BFM 2013 protokolünde çocuk ve adolesanlarda İVİG'in rutin profilaktik kullanımı önerilmiyor
- Kök hücre nakli sonrası ve IgG serum düzeyi <200mg/dL olan olgularda kullanımının yararını gösteren bazı çalışmalar var

Spesifik İmmunglobulinler

- Varicella-Zoster Ig
- Hepatit B Ig
- Palivizumab (persistan RSV enfeksiyonu)

Pediatrik Onkolojide Nadir IVIG Uygulamaları

TÜRK PEDİATRİK ONKOLOJİ GRUBU (TPOG)

NÖROBLASTOM –2009 TEDAVİ PROTOKOLÜ

"TPOG - NB – 2009"

Opsomyoklonus varlığında

Birinci basamak tedavi

1.hafta tedavisi: Deksametazon 20 mg/m^2/doz/gün, 1 saatlik IV infüzyon, 3 gün verilecek. (Beraberinde omeprazol)

2.hafta tedavisi: Deksametazon 20 mg/m^2/doz/gün, 1 saatlik IV infüzyon, 3 gün verilecek. (Beraberinde omeprazol)

(klinik bulgular çok şiddetliyse 1 gr/kg/doz/gün, 1 defa, intravenöz immünglobulin tedaviye eklenebilir)

CureSearch
Children's Oncology Group

ANBL00P3

Activated: March 15, 2004
Closed:
Co-Disciplines: None

Version Date: 09/06/11
Amendment: #6

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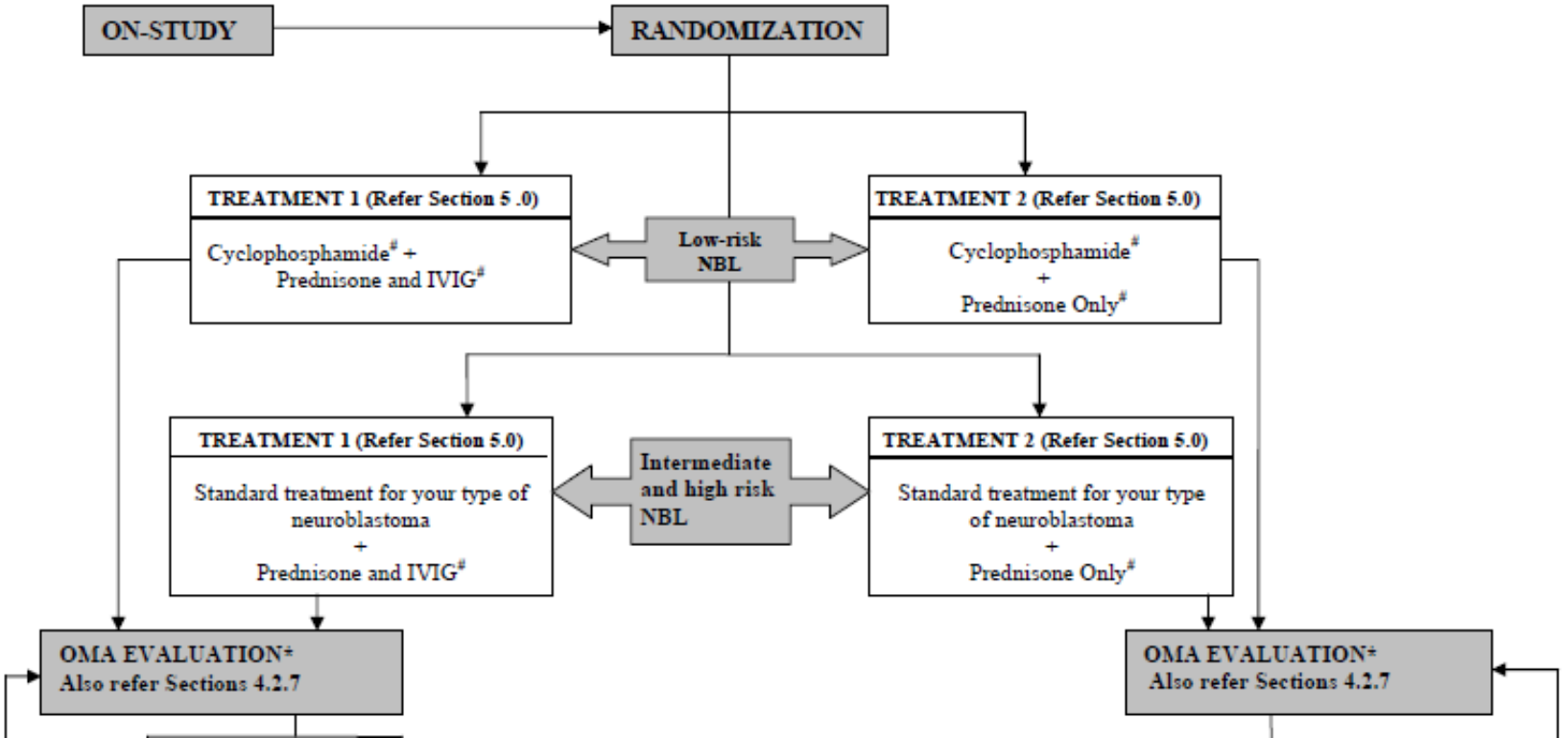
CHILDREN'S ONCOLOGY GROUP

ANBL00P3

A PHASE III RANDOMIZED TRIAL OF INTRAVENOUS GAMMAGLOBULIN THERAPY FOR PATIENTS WITH NEUROBLASTOMA ASSOCIATED OPSOCLONUS-MYOCLONUS-ATAXIA SYNDROME TREATED WITH CHEMOTHERAPY AND PREDNISONE

DESIGN SCHEMA:



PL011

A Randomized Clinical Trial of Cyclophosphamide and Prednisone with or without Intravenous Immunoglobulin (IVIG) for the Treatment of Neuroblastoma Associated Opsoclonus Myoclonus Ataxia Syndrome (OMA): A Children's Oncology Group Trial

Pedro de Alarcon, University of Illinois College of Medicine at Peoria, Pediatrics, Peoria, IL, United States; Wendy B. London, Boston Children's Hospital, Oncology, Boston, MA, United States; Arlene Naranjo, University of Florida Children's Oncology Group, Biotatistics, FL, United States; Mark Gorman, Boston Children's Hospital, Neurology, Boston, MA, United States; Jessica A Panzer, Children's Hospital of Philadelphia, Neurology, Philadelphia, PA, United States; Susan Cohn, University of Chicago, Pediatrics, Chicago, IL, United States; John Maris, Children's Hospital of Philadelphia, Oncology, Philadelphia, PA, United States; Katherine K Matthay, University of California San Francisco, Pediatrics, San Francisco, CA, United States

Background: To determine if cyclophosphamide and prednisone (CP) is an effective treatment of OMA and if the addition of IVIG improves the response to cyclophosphamide and prednisone. , Background: OMA, an immunologically mediated paraneoplastic syndrome, affects 2-3% of children with neuroblastoma. Most children have low-stage neuroblastoma and survive their tumor but are handicapped by neurological sequelae. Steroid immunosuppression has been the established treatment for this disorder with other immunosuppressants reported as effective in case reports or case series. We report here preliminary data on the only randomized clinical trial for this disorder.

Methods: Children age ≤8 years, newly diagnosed with neuroblastoma associated OMA, were randomized to receive six monthly treatments of IVIG (1 gm/kg) with CP (Rx1) or six monthly treatments of CP alone (Rx2). Children with intermediate or high risk neuroblastoma that required chemotherapy for their tumor received stage-specific chemotherapy instead of cyclophosphamide. The best overall OMA response was selected from evaluations at 2 months, six months and one year using a standardized OMA response scale evaluating stance, gate, arm and leg function, opsoclonus, and mood/behavior. Patients who crossed over from Rx2 to Rx1 were considered OMA non-responders.

Results: 53 eligible subjects were enrolled, 26 on Rx1 and 27 on Rx2. Thirty-three of 52 evaluable patients responded to therapy, 21 on Rx1 (81%) and 12 on Rx2 (46%)(p=0.0096). Eleven patients in Rx2 crossed over to Rx1 and were automatically considered non-responders. Eighteen subjects had an OMA relapse requiring further treatment. One subject died of infection after high-dose chemotherapy and autologous stem cell recue for high risk neuroblastoma. The 3-year disease (OMA) free survival is 60.9±7.9%.

Conclusion: The addition of IVIG to CP significantly improved the short-term response over CP alone Follow up is ongoing to determine the long-term disease (OMA) free survival rate and the long-term neurological outcome of OMA.

Pediatr Blood Cancer 2008;50:308–311

Treatment of Neurodegenerative CNS Disease in Langerhans Cell Histiocytosis With a Combination of Intravenous Immunoglobulin and Chemotherapy

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Background. In rare cases, patients with Langerhans cell histiocytosis (LCH) develop neurodegenerative CNS disease (ND-CNS-LCH). Management of ND-CNS-LCH has not been established. ***Methods.*** We treated five pediatric patients with a combination of intravenous immunoglobulin (IVIG) and chemotherapy (steroid ± vinblastine ± 6-mercaptopurine ± methotrexate). Prior to the therapy, three of the five patients had cerebellar ataxia while the remaining two had abnormal MRI findings without apparent neurological deficits. IVIG was given monthly or twice monthly at the dosage of 250–400 mg/kg/dose. ***Results.*** The four patients administered more than 23 doses of IVIG and chemotherapy remained in a stable condition and did not show significant progression signs in neurological deficits or brain MRI findings during the 30-month follow-up period (median; range: 19+ to 38+) following the initiation of therapy for ND-CNS-LCH. ***Conclusion.*** The IVIG-containing treatment may be promising for ND-CNS-LCH; however, its effectiveness remains to be further tested in more patients as well as in a randomized trial. Pediatr Blood Cancer 2008;50:308–311.

Key words: high dose intravenous immunoglobulin (IVIG); Langerhans cell histiocytosis; neurodegenerative CNS disease

Pediatr Blood Cancer 2010;54:416–423

Neurodegenerative Central Nervous System Langerhans Cell Histiocytosis and Coincident Hydrocephalus Treated With Vincristine/Cytosine Arabinoside

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Background. Central nervous system (CNS) complications of Langerhans cell histiocytosis (LCH) include mass lesions and a neurodegenerative (ND) syndrome with ataxia, dysarthria, dysmetria, learning and behavior difficulties and/or characteristic changes on brain MRIs. Hydrocephalus has rarely been reported in LCH. LCH lesions of the orbit, mastoid and temporal bones (''CNS-Risk'' lesions) and diabetes insipidus predispose patients to ND-CNS-LCH. Treatment options have been limited and only a case series using trans-retinoic acid (ATRA) and intravenous immunoglobulin (IVIG) have been published. ***Methods.*** We have used cytosine arabinoside (ARA-C) with or without vincristine to treat eight patients with ND-CNS LCH. Patients: Seven male children and one young adult male with clinical and radiologic ND-CNS-LCH were treated with a regimen of vincristine 1.5 mg/m^2 on day 1 and ARA-C 100 mg/m^2 daily for 5 days or ARA-C alone monthly for 4–19 months. Seven patients were evaluated with an ataxia rating scale (ARS) and all with serial MRIs of the brain. ***Results.*** Five of seven patients had decreases in their ARS scores and/or decreased T2 hyperintense lesions on MRI images. Grade 2 neutropenia was the most frequent adverse event. Vincristine-associated neuropathy occurred in two patients. Hydrocephalus caused symptoms and signs that confounded the diagnosis and management of ND-CNS-LCH in all four patients affected with both. ***Conclusions.*** Subtle changes in neurologic function may be complicated by hydrocephalus. Vcr/ARA-C or ARA-C were an effective therapies for some ND-CNS LCH patients. A clinical trial using this and possibly other modalities such as IVIG or ATRA should be done. Pediatr Blood Cancer 2010;54:416–423.

Key words: ataxia; hydrocephalus; CNS-Langerhans' cell histiocytosis; cytosine arabinoside; neurodegenerative disease; treatment; vincristine

DOI 10.1007/s12185-014-1717-5

ORIGINAL ARTICLE

Follow-up of pediatric patients treated by IVIG for Langerhans cell histiocytosis (LCH)-related neurodegenerative CNS disease

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Clofarabine associated capillary leak syndrome in a child with lymphoma successfully treated with intravenous immunoglobulin

ABSTRACT

Clofarabine is an effective drug in relapsed leukemia and lymphoma that has some adverse effects which can be fatal like capillary leak syndrome (CLS). Identification and management of CLS is important that may result in mortality. Although prophylactic treatment with steroids may prevent CLS and improve survival, intravenous immunoglobulins are used in the treatment with great success in steroid resistant cases. However, the knowledge about the effects and the dose of intravenous immunoglobulins (IVIG) in pediatric patients is limited. Herein, we reported a patient with relapsed lymphoma who developed CLS successfully and was treated with IVIG.

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Intravenous Immunoglobulin in the Treatment of Severe Methotrexate-induced Acral Erythema

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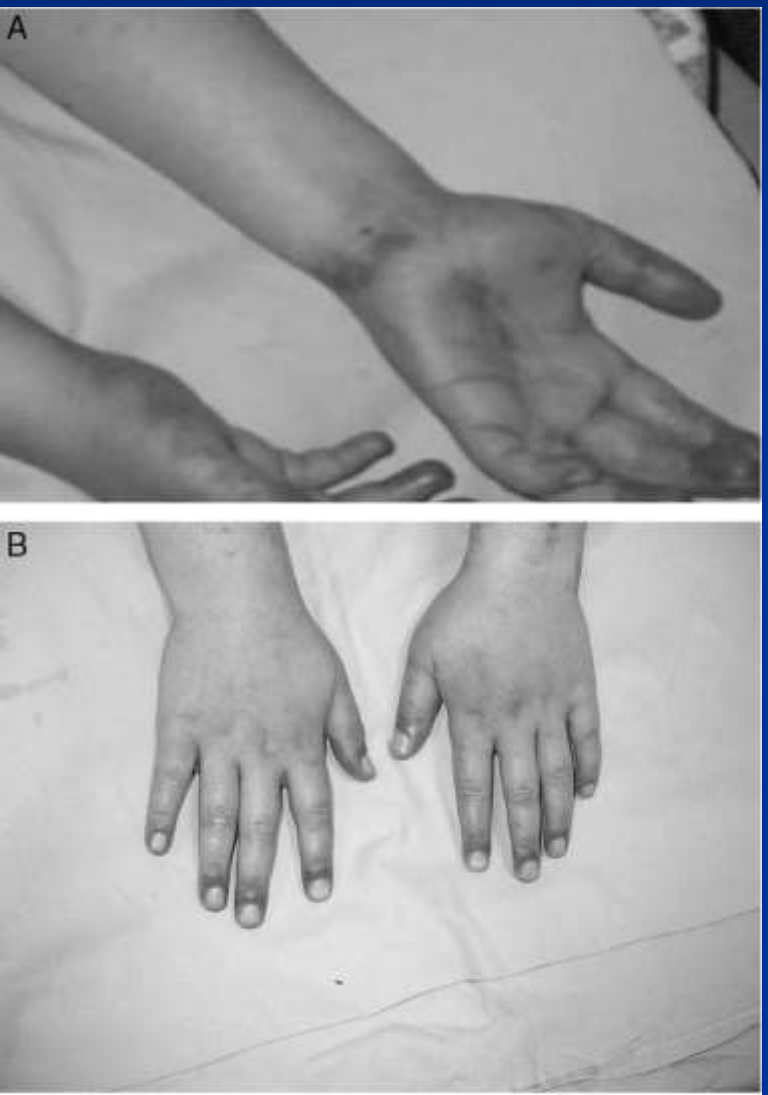
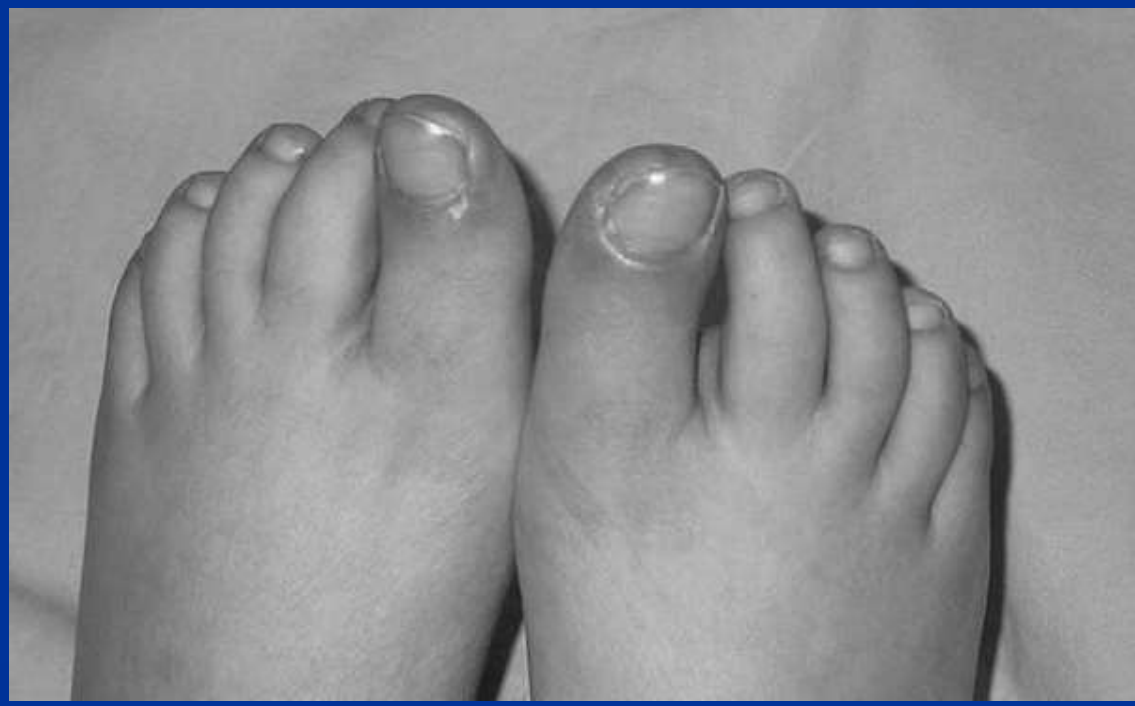


(*J Pediatr Hematol Oncol* 2008;30:391–393)



Uygulama şekli

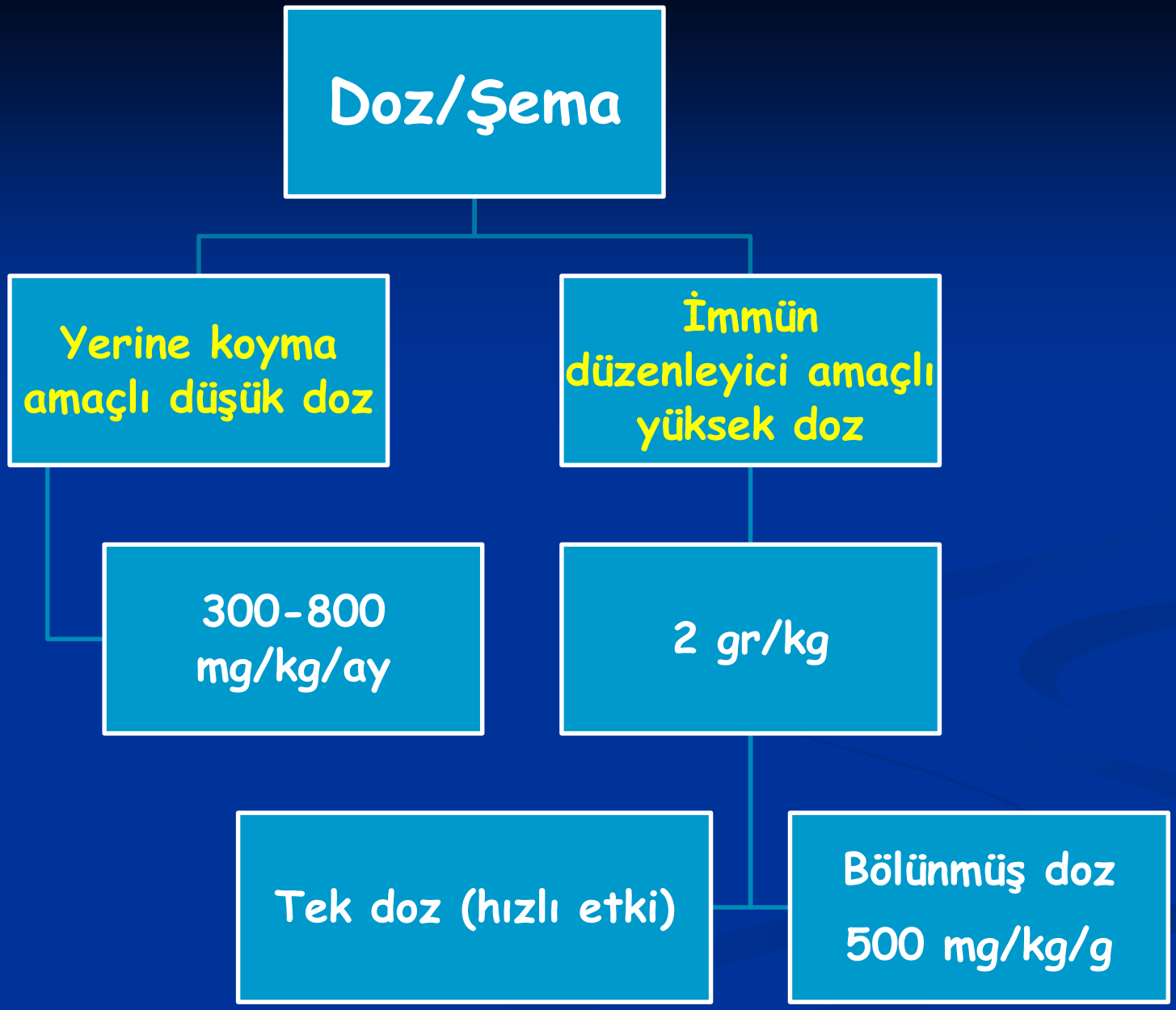
- İntravenöz Ig (IVIG)
- Subkutan Ig (SCIG)
- IGIM

Uygulama ve Hazırlık (IVIG için)

- Hastane
- Onam
- HIV, HBV, HCV, TKS, KCFT, BFT
- Ürün ısıtılmamalı (Oda ısısı)
- Bulanıklık, partikül içermemeli.
- Son kullanma tarihi kontrol edilmeli
- İnfüzyon öncesi hastanın vital bulguları kontrol edilmeli
- Adrenalin, difenhidramin, İV sıvılar, anaflaksi kiti ve diğer acil girişim malzemeleri hazır bulundurulmalıdır

Uygulama ve Hazırlık

- Daha önceki infüzyonlarda yan etki oluşmuşsa antihistaminik, asetaminofen veya kosteroitle premedikasyon
- İnfüzyon sırasında, her hız değişimde ve saat başı vital bulgular denetlenmelidir
- İnfüzyondan sonrada ortaya çıkabilecek yan etkiler yönünden hastalar bilgilendirilmelidir (72 saate kadar akut yan etkiler çıkabilir)
- Hastanın hekiminin onayı alınmadan ürün değişikliği yapılmamalıdır


Doz/Şema
Yerine koyma amaçlı düşük doz
İmmün düzenleyici amaçlı yüksek doz
300-800 mg/kg/ay
2 gr/kg
Tek doz (hızlı etki)
Bölünmüş doz 500 mg/kg/g

Yerine koyma tedavisinin hedefi

- Preinfüzyon IgG düzeyini > 500 mg/dl tutmak (ideal düzey 650-1,000 mg/dl)
- Asıl hedef enfeksiyonların azalması /olmaması
- Çok ağır hipogamaglobulinemi (IgG<100 mg/dl)
  - İlk doz toplam 800 mg/kg, 2 günde bölünmüş dozda
- Kronik, tedaviye dirençli sinüs enfeksiyonu veya ilerleyici akciğer hasarı (bronşiektazi) olan seçilmiş hastalarda 800 mg/kg/3-4 hafta

Yerine koyma tedavisi

- IgG metabolizması kişisel farklılıklar gösterir
- Aktif enfeksiyon, endokrin ve otoimmün hastalıklar IgG katabolizmasını arttırır
- Serum IgG düzeyi, kararlı duruma gelinceye kadar infüzyon öncesinde her 2 ayda bir ölçülür
- IgG düzeyi daha sonra 6 ayda bir denetlenir

IVIG infüzyon hızı

Başlangıç
- 0.01-0.03 ml/kg/dk
- 0.5 mg/kg/dk %5'lik solüsyon

Artış
- 15-30 dk arayla hızı 2 katına çık

Maksimum
- 0.08-1.0 ml/kg/dk
- 4 mg/kg/dk %5'lik solüsyon

İzlem

Yan etkilerin önlenmesi

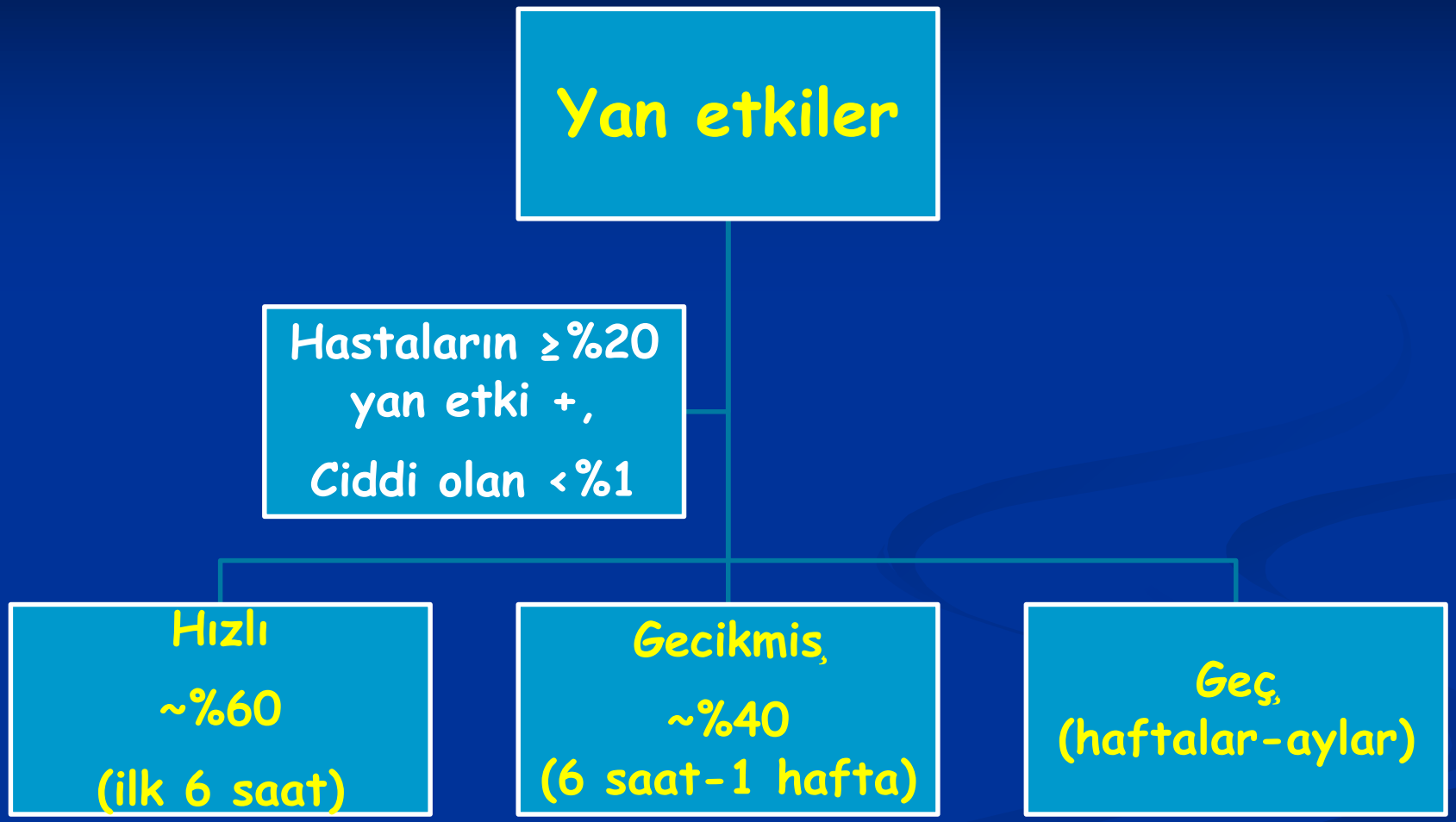
- İnfüzyon hızını yavaşlatmak veya 15-30 dk ara vermek birçok reaksiyonu düzeltir
- Hafif yan etkilerde antihistaminik ve NSAİİ, daha ağır yan etkilerde hidrokortizon
- Ürün değişikliği
- Daha önce yan etki görülen hastalarda infüzyon öncesi premidekasyon (antihistaminik, nonsteroit antiinlamatuvar, hidrokortizon) uygulanır

Yan etkilerin önlenmesi

- Aktif enfeksiyonu olan hastalarda
  - Hızlı kompleman aktivasyonuna ikincil olarak ciddi yan etkiler görülebileceğinden, antimikrobiyal tedavi sonrası IVIG başlanmalıdır
  - Bu durum IVIG tedavisini de geciktirmemelidir
  - En düşük dozlarda (0.01 ml/kg/dk) IVIG başlanmalı ve doz aşamalı olarak arttırılmalıdır
- Aseptik menenjit gibi nörolojik yan etkiler yüksek doz IVIG uygulanan hastalarda gelişebilir
  - IVIG infüzyonu ile birlikte 3 gün süresince 2 mg/kg/gün dozunda prednison verilebilir

Obez hastalarda doz

- Kesin tanımlanmış standart bir yaklaşım yok
- Obez/morbid obez hastalar için yetersiz kanıtlar var
- IBW (İdeal vücut ağırlığı)
- ABW (adjusted body weight=Dosing weight)
- Klinik yanıta göre doz modifikasyonu


Yan etkiler
Hastaların ≥%20
yan etki +,
Ciddi olan <%1
Hızlı
~%60
(ilk 6 saat)
Gecikmiş
~%40
(6 saat-1 hafta)
Geç
(haftalar-aylar)

Hızlı yan etkiler

- Uygulama alanında ağrı, şişlik, kızarıklık
- Ateş, titreme, yüzde kızarıklık
- Baş ağrısı, bulantı, kusma
- Anksiyete, yorgunluk
- Kas-eklem ağrıları
- Hipo/hipertansiyon
- Anaflaktik/anaflaktoik reaksiyon
  - IgA eksikliği olan hastalarda anaflaksi
- Transfüzyon ilişkili akut akciğer hasarı
- Transfüzyon ilişkili volüm yüklenmesi

Gecikmiş yan etkiler

Tromboembolik komplikasyonlar:

- Trombofilisi olan hastalarda
- Yüksek doz ve hızlı infüzyon sonrası
- Arteryel veya venöz tromboz daha sık

- **Sıklık, %0.5-15**
- Sekonder hipogamaglobulinemili hastalarda IVIG tedavisini izleyen 0-1 günde Mİ veya iskemik strok riski 3 kat fazla
- **1 yıl IVIG tedavisi almış kişilerde ciddi tromboembolik olay riski ~%1**
- Nedenleri
  - Kan viskozitesini arttırır
  - Eritrosit agregasyonunu destekleyebilir
  - Ekzojen IgG, trombosit platalet aktivasyonunu uyarabilir, vazospazm yapabilir
  - Faktör XIa IgG ile ko-pürifiye olabilir veya tam olarak çıkarılamamış olabilir

Gecikmiş yan etkiler

- Nörolojik yan etkiler:
  - Migren benzeri baş ağrısı
  - Aseptik menenjit (yüksek dozda)
- Nefrolojik yan etkiler:
  - Akut böbrek yetersizliği (yüksek dozda) (%1)
    - Genellikle 4-10 gün içinde kendiliğinden iyileşme
  - Hiponatremi ve psödohiponatremi
    - sükroz, proteinler ve lipitler ile ilişkili

Gecikmiş yan etkiler

- Hematolojik yan etkiler:
  - Coomb's testi pozitifliği
  - Hemolitik anemi
    - Ürün içerisindeki eritrosit alloantikorlarına (anti-Rh(D) anti-A, anti-B) bağlı
  - Geçici nötropeni
    - İmmünoglobulin veya kompleman aracılı nötrofil aktivasyonuna ve artmış adezyon molekülleri aracılığı ile gelişen noötrofil agregasyonuna bağlı olabileceği düşünülmektedir.
    - Anti-nötrofil antikor veya siyalik asit bağlayan immünglobulin benzeri lektinlerin de rolü olduğu düşünülmektedir

- Dikkatiniz için teşekkürler