ROL DE LA PLASMAFÉRESIS EN LAS GLOMERULOPATÍAS

ECULIZUMAB

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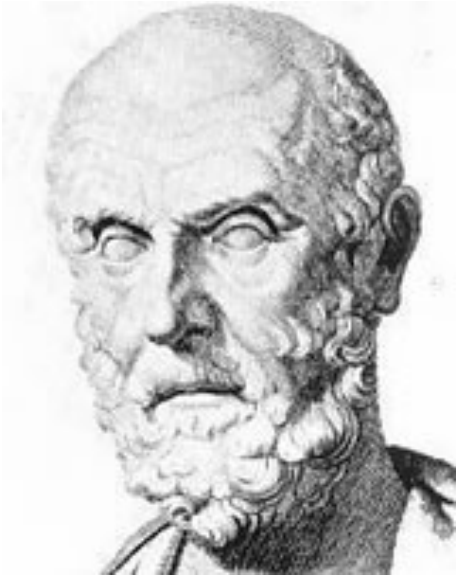
Aphaireín
αφαρειν

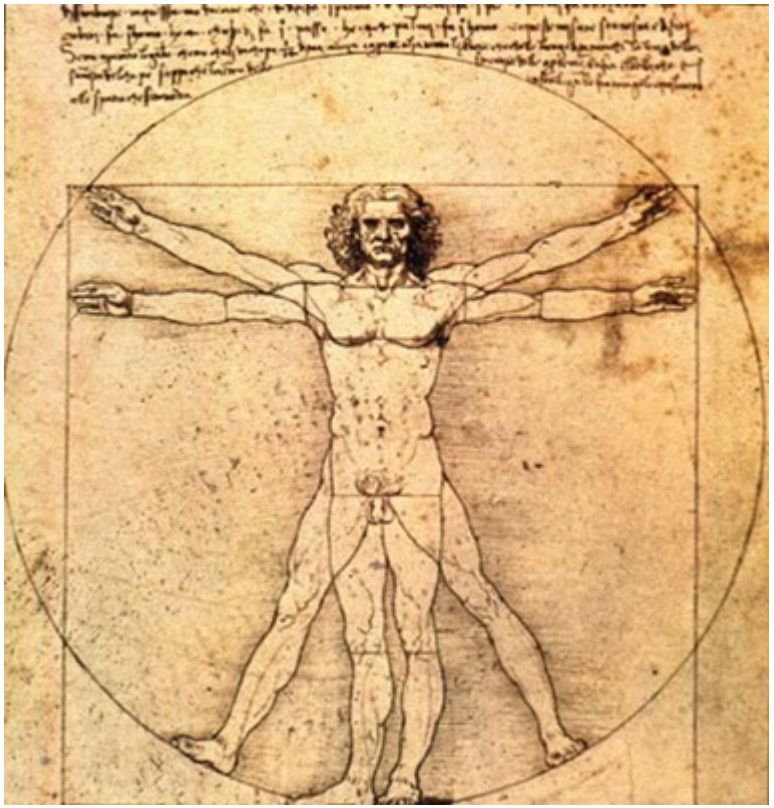
FÉRESIS: LLEVARSE, QUITAR O REMOVER UNA PARTE DEL TODO

EL HOMBRE, A LO LARGO DE LA HISTORIA, SIEMPRE HA INTENTADO ELIMINAR DEL TORRENTE CIRCULATORIO AQUELLOS MALOS HUMORES O TOXINAS

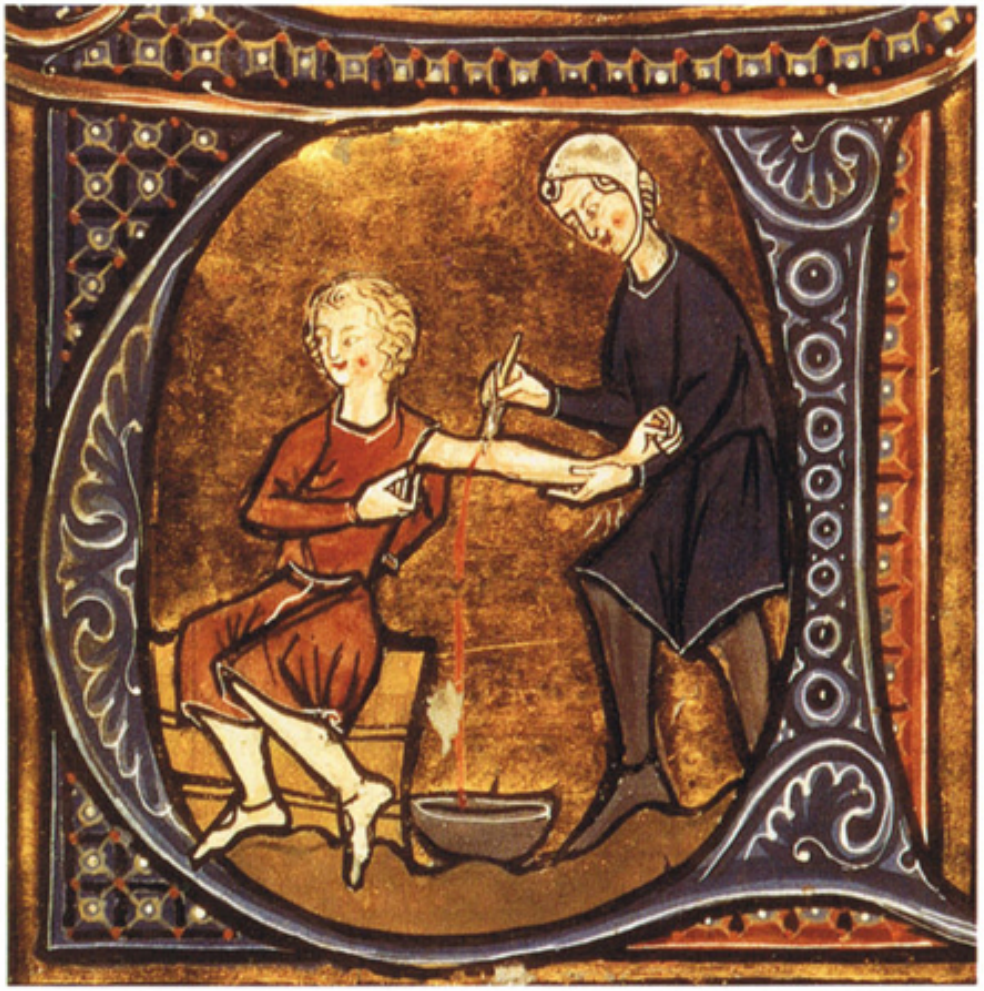
LA SANGRÍA TUVO SU ORIGEN EN LAS ANTIGUAS CIVILIZACIONES DE EGIPTO Y GRECIA Y SE UTILIZÓ CON FIDELIDAD Y ENTUSIASMO DURANTE MÁS DE 2500 AÑOS



"SANGRA EN LA AFECCIONES AGUDAS, SI LA ENFERMEDAD PARECE FUERTE Y CUANDO LOS PACIENTES SE ENCUENTRAN EN EL VIGOR DE LA VIDA"



EN EL RENACIMIENTO LA SANGRÍA
ERA MUY POPULAR



EL SEGUNDO TEXTO MÉDICO EDITADO EN LA IMPRENTA DE GÜTENBERG EN 1462 FUE ***EL CALENDARIO DE SANGRÍAS***

LA AFÉRESIS TERAPÉUTICA TIENE COMO FINALIDAD PRINCIPAL LA EXTRACCIÓN Y ELIMINACIÓN DEL PLASMA DE AQUELLOS COMPONENTES CONSIDERADOS PATOGÉNICOS
DE UNA ENFERMEDAD

1. LA SUSTANCIA A REMOVER DEBE SER SUFICIENTEMENTE GRANDE (>5000 Da) PARA LA CUAL OTRAS TÉCNICAS DEPURADORAS SEAN INEFICACES (HD,HF, HDF)

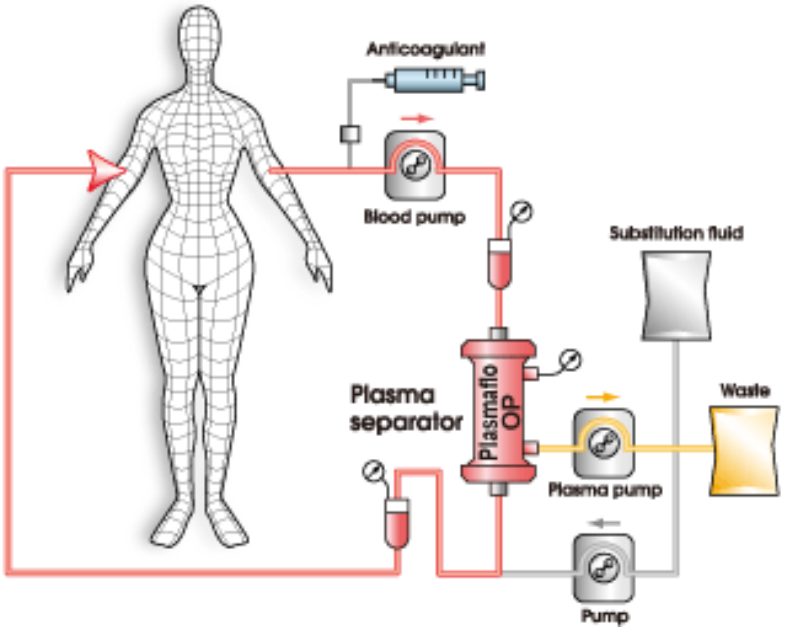
2. LA SUSTANCIA A REMOVER DEBE TENER UNA VIDA MEDIA PROLONGADA PARA QUE DESPUÉS DE SU EXTRACCIÓN TARDE TIEMPO EN REGENERARSE

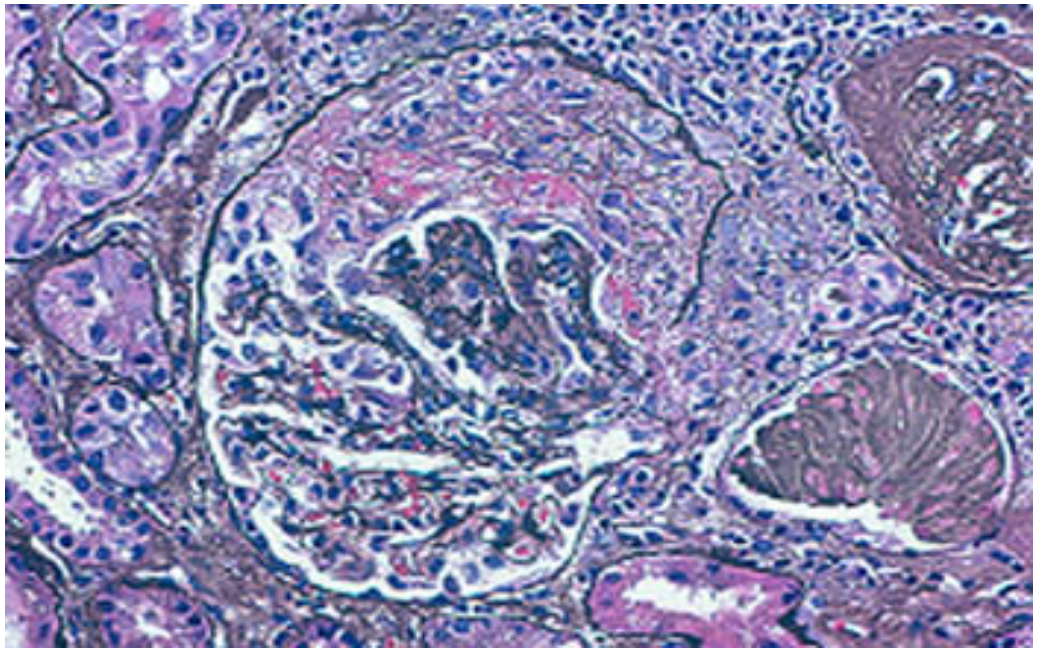
3. LA SUSTANCIA A REMOVER SEA TÓXICA, Y PARCIAL O TOTALMENTE RESISTENTE AL TRATAMIENTO CLÍNICO CONVENCIONAL

4. LA ENFERMEDAD CURSA UN PATRÓN RÁPIDAMENTE PROGRESIVO O SUBAGUDO

5. ES UN APOYO A UN TRATAMIENTO MÉDICO

Plasma Exchange (PE) treatment diagram





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REVIEW

Benefits and limitations of plasmapheresis in renal diseases: an evidence-based approach

Sanjeev Baweja · Kate Wiggins · Darren Lee · Susan Blair · Margaret Fraenkel · Lawrence P. McMahon

Received: 21 September 2010 / Accepted: 8 November 2010 / Published online: 10 December 2010

Abstract In use for over 50 years, the rationale for plasmapheresis remains based largely on case series and retrospective studies. Recently, results from several randomized controlled trials, meta-analyses, and prospective studies have shown plasmapheresis may be of benefit in various renal diseases, and have provided insights into more rational use of this therapy. A multicenter trial by the European Vasculitis Study Group has shown it is the preferred additional form of therapy for patients with anti-neutrophil cytoplasmic antibody-associated glomerulonephritis and severe renal failure. A recent study conducted at Mayo Clinic also found it effective at reversing renal failure from myeloma-related cast nephropathy if serum free light chain levels were reduced by at least 50%. In addition, a Cochrane review has analyzed the available evidence for its use in thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. The objective of this article is to review recent and past evidence and, thereby, the current indications for treatment in renal disease.

Keywords Plasmapheresis · Renal failure · Renal transplantation · Renal diseases

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Introduction

Plasmapheresis, or plasma exchange, is an extracorporeal blood-purification process whereby plasma is removed from the patient and artificially replaced. Abel [1] first described the process in the dog in 1914 but the first therapeutic plasmapheresis was performed by Schwab and Fehay [2] in two patients with macroglobulinemia in 1960. Since then, it has been widely used to remove either proven or presumed large-molecular-weight pathogens from the circulation. These include antibodies, immune complexes, monoclonal proteins, endotoxins, drugs, and cholesterol-containing lipoproteins [3]. It is essentially symptomatic therapy, removing or replacing a product rather than addressing any underlying pathology, although some theoretical immune-modulatory effects of plasmapheresis have also been proposed [4–7].

Several plasmapheresis techniques are currently available. Centrifugation-based plasma separators are most widely used, because the required blood flow can easily be achieved by cannulating a large peripheral vein, thus avoiding the need to access central veins. Other conventional forms of plasmapheresis include membrane plasma separation, cryofiltration apheresis, immunoadsorption, and chemical affinity column apheresis [8]. Compared with centrifugal devices, membrane filtration has the advantages of less platelet loss, less hemolysis, and minimum equipment requirements. Membrane filtration can be performed by using standard hemodialysis equipment, and patients with kidney injury who require both hemodialysis and plasmapheresis can receive each sequentially. However, although faster and more efficient, there seems little or no clinical advantage compared with centrifugal devices [9–11].

The amount of plasma to be replaced during plasmapheresis must be determined in relation to the patient's

estimated plasma volume (EPV), which can be calculate by use of the formula [12]:

$$EPV = [0.065 \times \text{weight (kg)}] \times (1 - \text{hematocrit}).$$

The decline in immunoglobulin levels after a single plasmapheresis is misleading, because extravascular immunoglobulins enter the vascular space at the rate of 1–3% per hour, yielding a post-treatment increase which begins to plateau after 24 h, at which time there will be a further opportunity for immunoglobulin removal. Usually, if production rates are modest, at least daily exchanges for 3 days will be required to remove 70% of the patient's initial burden, and 5 separate treatments during a 7 to 10-day period will remove 90% of the patient's initial total body burden. If production rates are high, additional treatments may be required [12–14].

The overall complication rate during plasmapheresis is approximately 10% (reports vary from 1.4 to 20%) and mostly occurs in patients receiving fresh frozen plasma (FFP) as replacement fluid. The most frequent complications are symptoms of hypocalcemia, hypovolemia, and anaphylactoid reactions [15] Serious adverse events occur in <3% of patients and the procedure-related mortality rate is very low (0.0–0.05%) [16, 17]. In particular, the infection rate does not seem to be higher in immunocompromized patients [18]. Some patients taking ACE inhibitors may experience atypical symptoms such as flushing, hypotension, bradycardia, dyspnea, and abdominal cramping [19].

The latest guidelines for use of plasmapheresis were published by the American Society for Apheresis in June 2007 [20–23]. Current indications for renal diseases are displayed in Table 1. Recently, results from several randomized controlled trials (RCTs), meta-analyses, and prospective studies have shown plasmapheresis may be of benefit in various renal diseases, and have provided some insight into more rational use of this therapy, although many of the guidelines are still not based on results from RCTs.

Anti-glomerular basement membrane (Anti-GBM) disease

Anti-glomerular basement membrane disease, when accompanied by pulmonary hemorrhage, is known as Goodpasture's disease [24]. It is caused by circulating antibodies directed against the non-collagenous domain of the α-3 chain of type IV collagen [25]. In 1975, before the introduction of plasmapheresis [26], mortality was 86–96% either from pulmonary hemorrhage or renal failure [27–29]. Since then, many uncontrolled trials or case reports have demonstrated the clinical benefits of plasmapheresis [30–36].

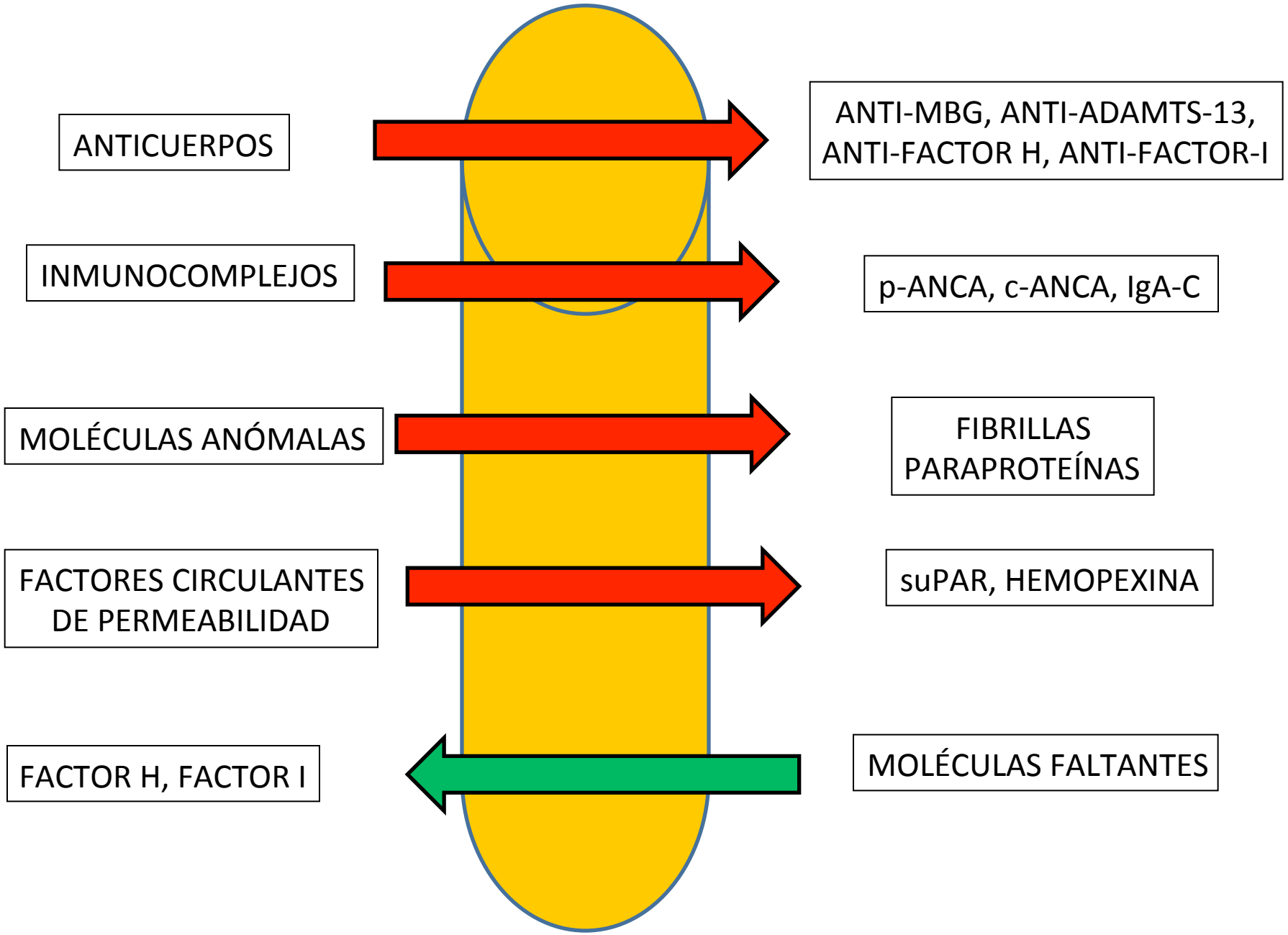
Table 1 Indications for plasmapheresis in renal diseases (modified from Ref. [20])

Disease	Rating
Anti-GBM disease	1
Rapidly progressive glomerulonephritis	2
Thrombotic thrombocytopenic purpura	1
Hemolytic uremic syndrome	3–4
Cryoglobulinemia	1
Multiple myeloma cast nephropathy	3
Hyperviscosity syndrome (Waldenström's macroglobulinemia)	1
Removal of cytotoxic antibodies in transplant candidate	2
Renal allograft rejection	2
Focal segmental glomerulosclerosis (recurrence after transplantation)	2
Rheumatoid arthritis/rheumatoid vasculitis	2
Antiphospholipid antibody syndrome	2
Systemic lupus erythematosis	4
Scleroderma	4

Rating: 1, standard therapy, but not mandatory; 2, available evidence tends to suggest efficacy, conventional therapy usually tried first; 3, inadequately tested at this time; 4, no demonstrated value in controlled trials

[illegible]ne randomized study has compared the immunosuppressive therapy alone (prednisone and cyclophosphamide) with immunosuppression and plasmapheresis [37]. Seventeen patients with anti-GBM disease were studied. Only 2 of 8 patients who received plasmapheresis became dialysis-dependent, in comparison with 6 of 9 in the immunosuppression alone group. Patients treated with plasmapheresis had a more rapid disappearance of anti-GBM antibodies, with mean serum creatinine value half that of the control group. Patients with <30% crescents and well preserved renal functions did well with either treatment, whereas patients with severe crescentic involvement and impaired glomerular filtration rate uniformly did poorly.

The largest published series of long-term outcomes of anti-GBM disease is from the Hammersmith Hospital, London [38]. All 71 patients received a standard regimen of plasmapheresis, oral prednisolone, and oral cyclophosphamide. Plasmapheresis (50 mL/kg to a maximum of 4 L) was performed daily for at least 14 days or until anti-GBM titers were undetectable. One-year patient and renal survival were 100 and 95%, respectively, when creatinine was <500 μmol/L (5.7 mg/dL), 83 and 82% when creatinine was ≥500 μmol/L but not dialysis-dependent, and 65 and 8% when patients were dialysis-dependent at onset. Five-year patient and renal survival were 94 and 94%, 80 and 50%, and 44 and 13%, respectively. All patients who required immediate dialysis and had 100% crescents on


ANTICUERPOS
ANTI-MBG, ANTI-ADAMTS-13, ANTI-FACTOR H, ANTI-FACTOR-I
INMUNOCOMPLEJOS
p-ANCA, c-ANCA, IgA-C
MOLÉCULAS ANÓMALAS
FIBRILLAS PARAPROTEÍNAS
FACTORES CIRCULANTES DE PERMEABILIDAD
suPAR, HEMOPEXINA
FACTOR H, FACTOR I
MOLÉCULAS FALTANTES

ANTI-MBG,
ANTI-ADAMTS-13,
ANTI-FACTOR H,
ANTI-FACTOR-I

ENFERMEDAD DE GOODPASTURE

PTT

SUHa

p-ANCA, c-ANCA, IgA-C

VASCULITIS

FIBRILLAS
PARAPROTEÍNAS

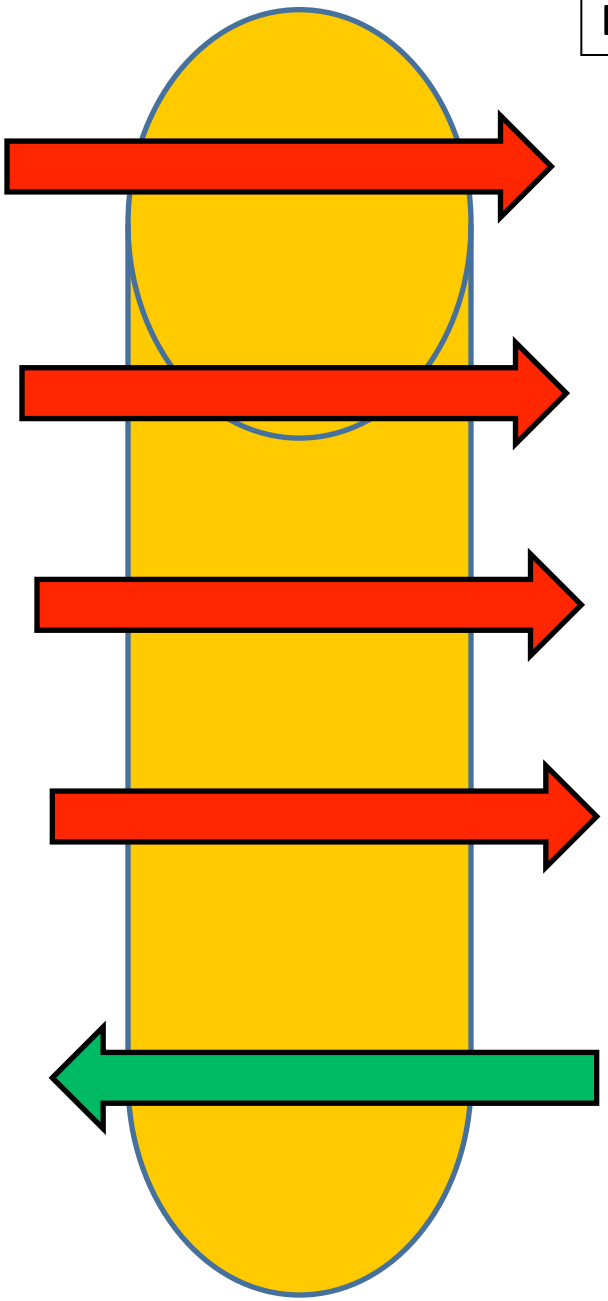
CRIOGLOBULINAS
MIELOMA MÚLTIPLE

suPAR, HEMOPEXINA

FSGS

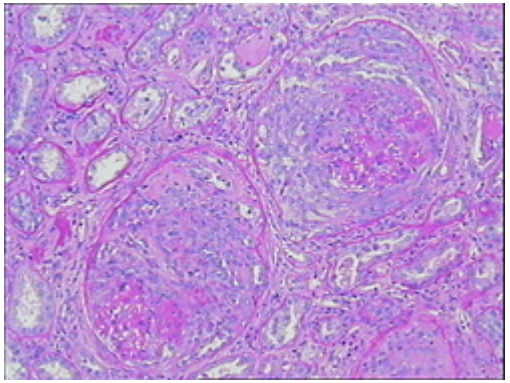
SUHa

MOLÉCULAS FALTANTES



ENFERMEDAD DE GOODPASTURE

ANTI-MBG



VASCULITIS

p-ANCA, c-ANCA, IgA-C

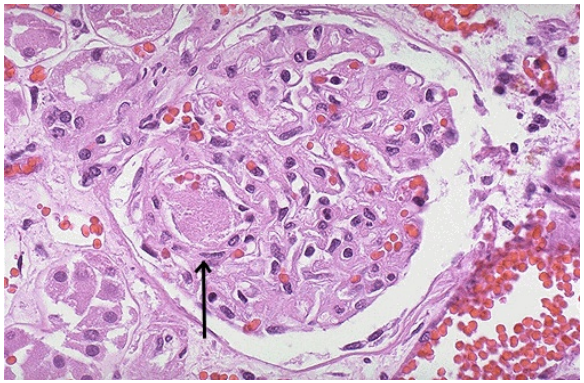
PTT

ANTI-ADAMTS-13

ADAMTS-13

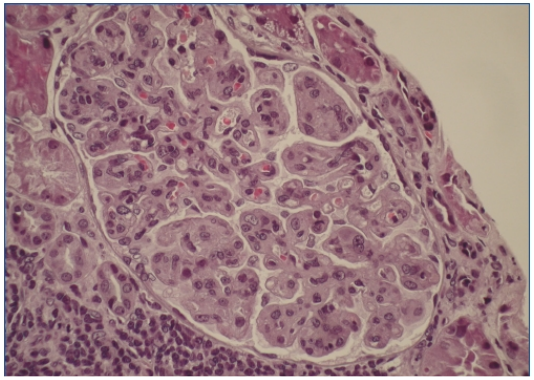
SUHa

ANTI-FACTOR H, ANTI-FACTOR-I

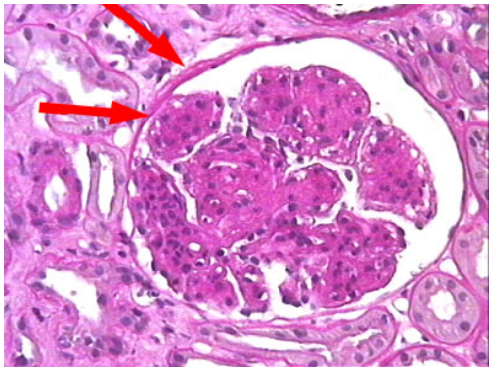


FACTOR H, FACTOR-I, MCP, TMD

CRIOGLOBULINAS
PARAPROTEÍNAS



FIBRILLAS
CADENAS LIVIANAS



FSGS

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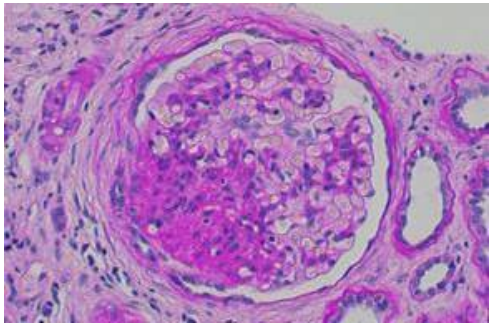

ENFERMEDAD DE GOODPASTURE | **ANTI-MBG**

1. LA SUSTANCIA A REMOVER DEBE SER SUFICIENTEMENTE GRANDE (>5000 Da) PARA QUE OTRAS TÉCNICAS DEPURADORAS SEAN INEFICACES (HD,HF, HDF)

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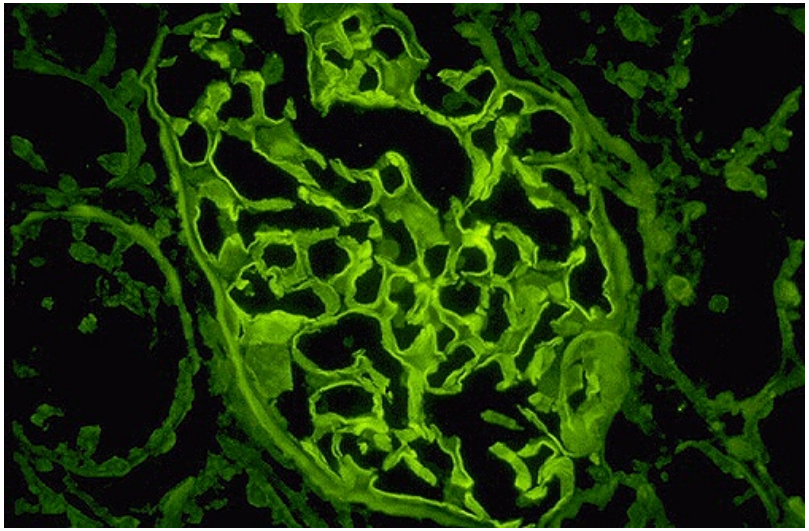
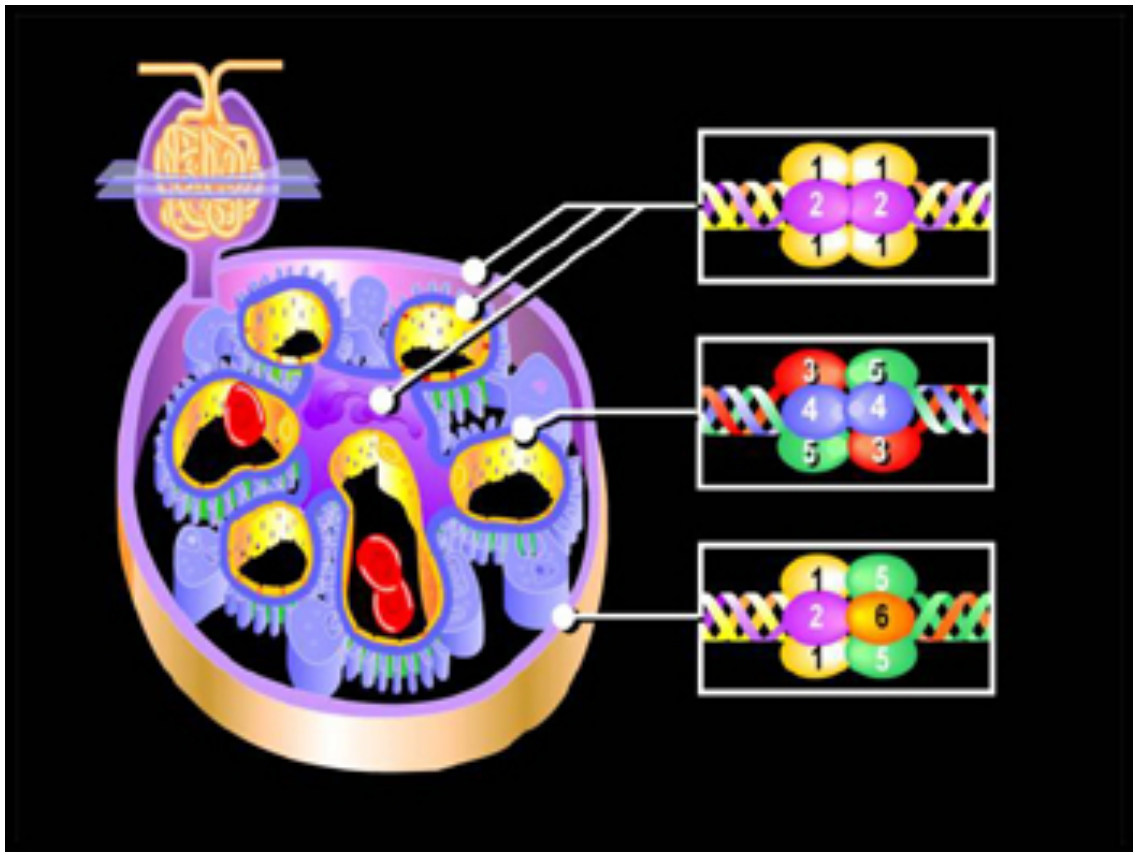


ENFERMEDAD DE GOODPASTURE | **ANTI-MBG**

1. LA SUSTANCIA A REMOVER DEBE SER SUFICIENTEMENTE GRANDE (>5000 Da) PARA QUE OTRAS TÉCNICAS DEPURADORAS SEAN INEFICACES (HD,HF, HDF)

IgG =150,000 Da



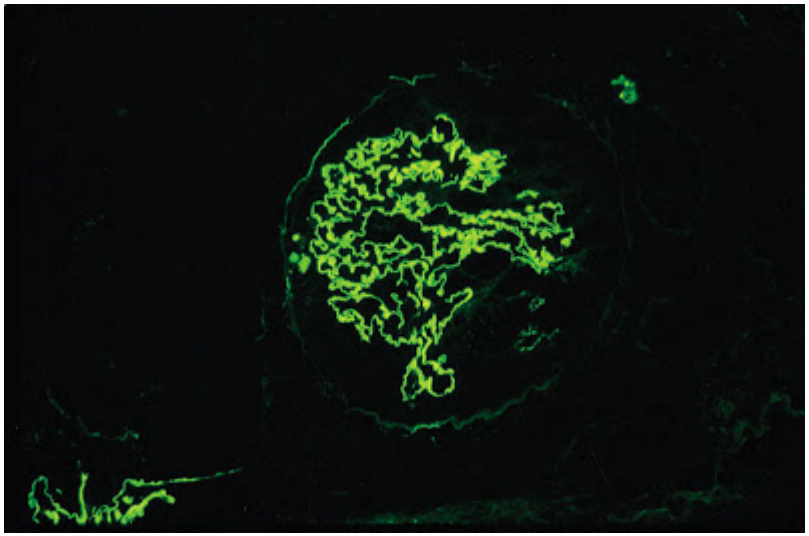
ENFERMEDAD DE GOODPASTURE | **ANTI-MBG**

2. LA SUSTANCIA A REMOVER DEBE TENER UNA VIDA MEDIA PROLONGADA PARA QUE DESPUÉS DE SU EXTRACCIÓN TARDE TIEMPO EN REGENERARSE

The Participation of Macrophages, Glomerular Procoagulant Activity, and Factor VIII in Glomerular Fibrin Deposition

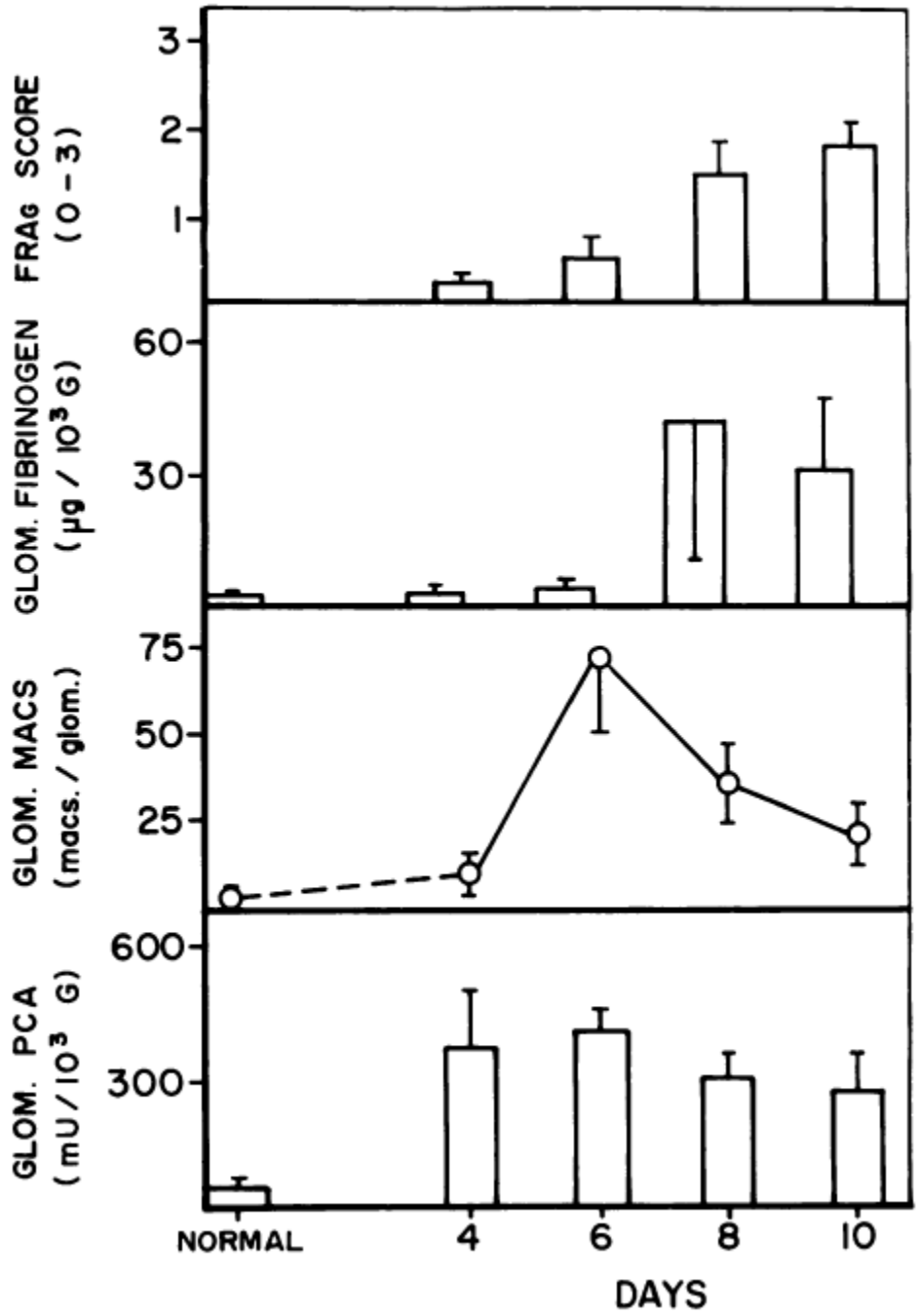
Studies on Anti-GBM Antibody-Induced Glomerulonephritis in Rabbits

PETER G. TIPPING, MB BS, B Med Sci, PhD, and
STEPHEN R. HOLDSWORTH, FRACP PhD



21 días

Am J Pathol 1986; 124: 10-17



Am J Pathol 1986; 124: 10-17

ENFERMEDAD DE GOODPASTURE **ANTI-MBG**

3. LA SUSTANCIA A REMOVER DEBE SER TÓXICA, Y PARCIAL O TOTALMENTE RESISTENTE AL TRATAMIENTO CLÍNICO CONVENCIONAL

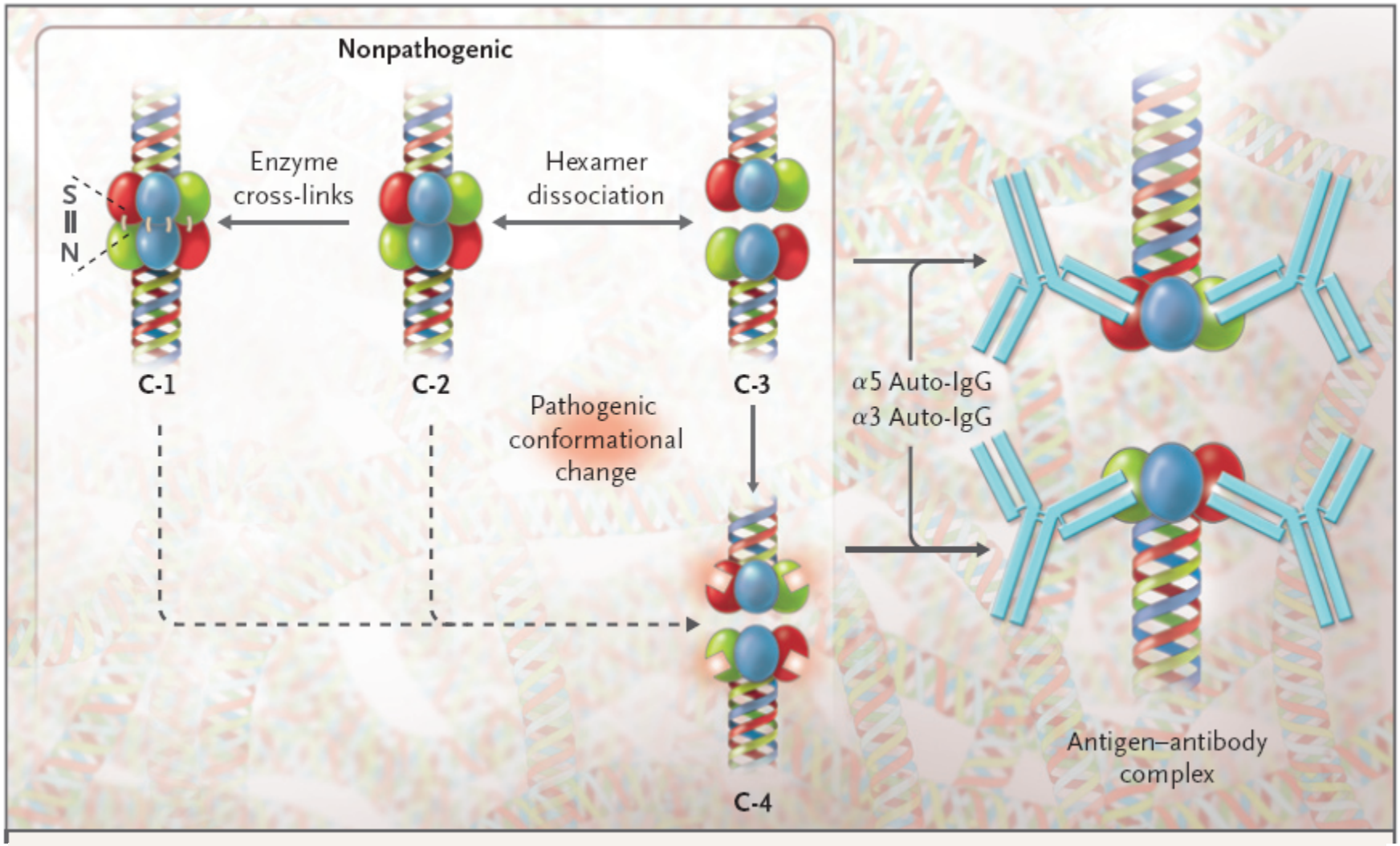
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Molecular Architecture of the Goodpasture Autoantigen in Anti-GBM Nephritis

Vadim Pedchenko, Ph.D., Olga Bondar, Ph.D., Agnes B. Fogo, M.D., Roberto Vanacore, Ph.D., Paul Voziyan, Ph.D., A. Richard Kitching, M.D., Ph.D., Jörgen Wieslander, M.D., Ph.D., Clifford Kashtan, M.D., Dorin-Bogdan Borza, Ph.D., Eric G. Neilson, M.D., Curtis B. Wilson, M.D., and Billy G. Hudson, Ph.D.

N ENGL J MED 363;4 NEJM.ORG JULY 22, 2010



The diagram shows a portion of the collagen IV network with the α345 noncollagenous-1 (NC1) hexamer tethered to the triple-helical domain. The different possible NC1 conformers shown are the cross-linked form stabilized by sulfilimine bonds (conformer 1 [C-1]), the non–cross-linked form (C-2), and the form in which the NC1 hexamers are dissociated into trimers (C-3). In Goodpasture's disease the latter may undergo a conformational change resulting in the formation of neoepitopes shown as white squares on the α3NC1 (red) and α5NC1 (green) subunits of C-4, eliciting antibody formation and subsequent binding to conformers C-3 and C-4. Conformers C-1 and C-2 have the potential to be transformed into the pathogenic conformer C-4.

ENFERMEDAD DE GOODPASTURE **ANTI-MBG**

4. LA ENFERMEDAD CURSA UN PATRÓN RÁPIDAMENTE PROGRESIVO O SUBAGUDO

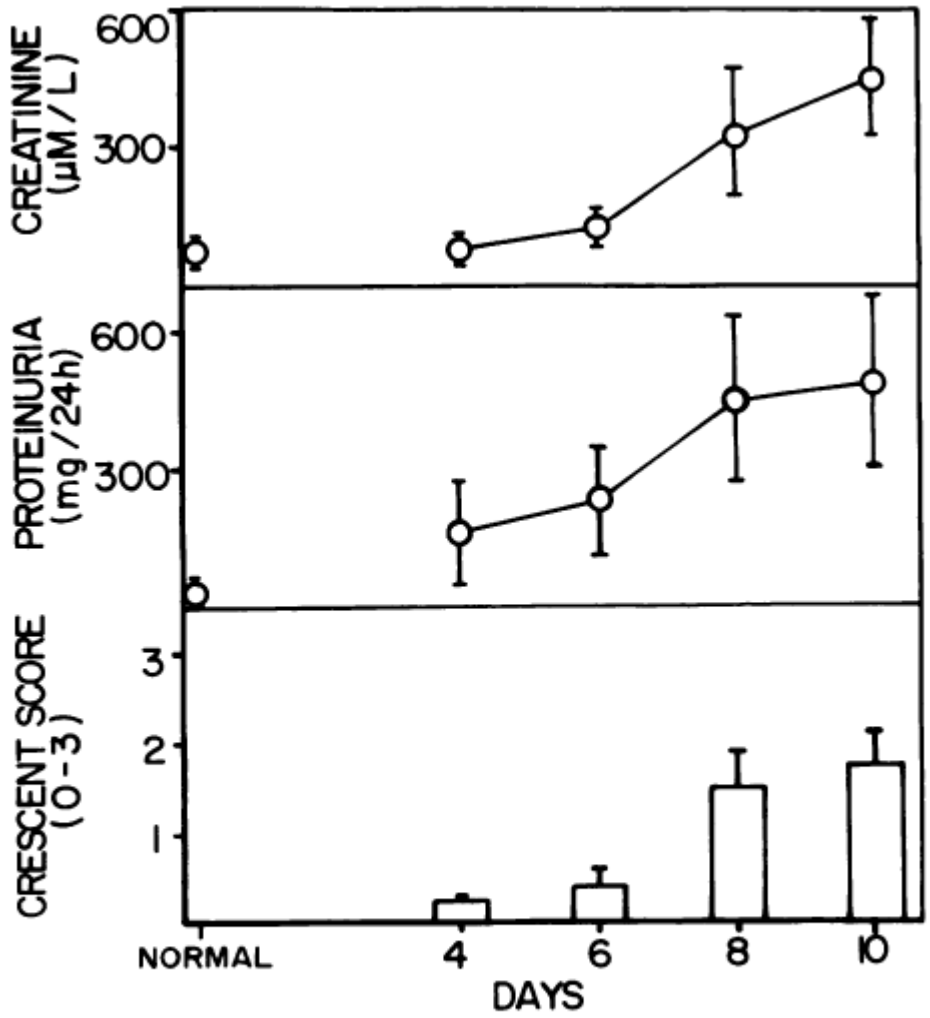
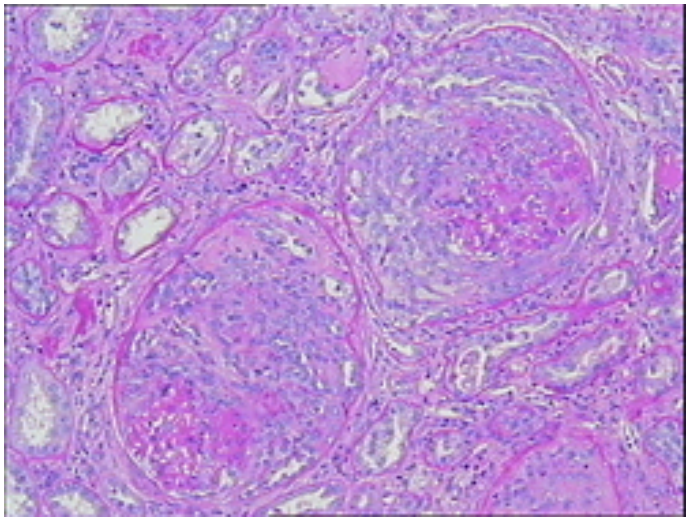


Figure 3—The serum creatinine concentrations, 24-hour urinary protein excretions, and glomerular crescent scores on Days 4, 6, 8, and 10 after initiation of anti-GBM GN in rabbits. The values for normal rabbits are also shown.



Am J Pathol 1986; 124: 10-17

ENFERMEDAD DE GOODPASTURE | **ANTI-MBG**

5. ES UN APOYO A UN TRATAMIENTO MÉDICO

Evaluar creatinina al diagnóstico: Cr 4?-5?-7? mg/dL

METILPREDNISOLONA 500-1000 mg/día por 3 días
MEPREDNISONA 1mg/kg/día (≤ 60 mg/día) x 2 semanas;
luego tapering en 6-9 meses

CICLOFOSFAMIDA 15 mg/kg/cada 3 semanas por 3-6 ciclos;
Se puede pasar a vía oral 2 mg/kg/día por 1 año

PLASMAFÉRESIS: recambio 50 mL/kg (≤ 4 litros) por sesión/día por 14 días
y evaluar evolución clínica y tasa de síntesis de los anticuerpos anti-MBG (titulación).
Si se continúa, se puede proseguir en días alternos.
Se repone con solución fisiológica más albúmina humana al 5%.
Agregar 150-300 mL de plasma congelado al final de cada sesión.

VASCULITIS

p-ANCA, c-ANCA, IgA-C

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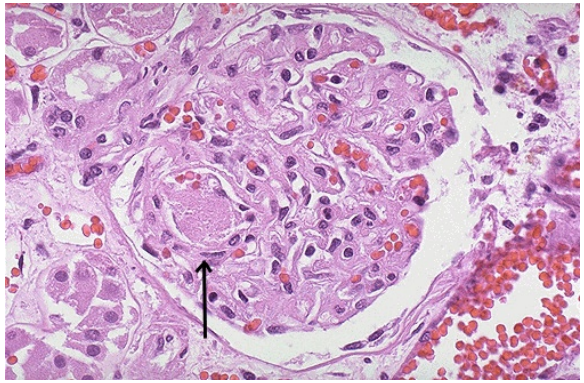


Mammals
5,600 species estimated
5,501 (**98**%) species discovered

Birds
10,500
10,064 (**96**%)

Reptiles
12,000
9,547 (**80**%)

Amphibians
15,000
6,771 (**45**%)

Fish
45,000
32,400 (**72**%)

Crustaceans
150,000
47,000 (**31**%)

Mollusks
200,000
85,000 (**43**%)

Arachnids
600,000
102,248 (**17**%)

Insects
5,000,000
1,000,000 (**20**%)

SERVICIO DE NEFROLOGÍA

Pertea and Salzberg *Genome Biology* 2010, 11:206
http://genomebiology.com/2010/11/5/206

Genome Biology

REVIEW

Between a chicken and a grape: estimating the number of human genes

Mihaela Pertea and Steven L Salzberg*

Abstract

Many people expected the question 'How many genes in the human genome?' to be resolved with the publication of the genome sequence in 2001, but estimates continue to fluctuate.

Ever since the discovery of the genetic code, scientists have been trying to catalog all the genes in the human genome. Over the years, the best estimate of the number of human genes has grown steadily smaller, but we still do not have an accurate count. Here we review the history of efforts to establish the human gene count and present the current best estimates.

The first attempt to estimate the number of genes in the human genome appeared more than 45 years ago, while the genetic code was still being deciphered. Friedrich Vogel published his 'preliminary estimate' in 1964 [1], based on the number of amino acids in the alpha- and beta-chains of hemoglobin (141 and 146, respectively). Knowing that three nucleotides corresponded to each amino acid, he extrapolated to compute the molecular weight of the DNA comprising these genes. He then made several assumptions in order to produce his estimate: that these proteins were typical in size (they are actually smaller than average); that nucleotide sequences were uninterrupted on the chromosomes (introns were discovered more than 10 years later [2,3]); and that the entire genome was protein coding. All these assumptions were reasonable at the time, but later discoveries would reveal that none of them was correct. Vogel then used the molecular weight of the human haploid chromosomes to correctly calculate the genome size as 3×10^9 nucleotides, and dividing that by the size of a 'typical' gene, came up with an estimate of 6.7 million genes.

*Correspondence: salzberg@umd.edu
Center for Bioinformatics and Computational Biology, University of Maryland, College Park, MD 20742, USA

Even at the time, Vogel found this number 'disturbingly high,' but no one suspected in 1964 that most human genes were interrupted by multiple introns, nor did anyone know that vast regions of the human genome would turn out to contain seemingly meaningless repetitive sequences. Since Vogel's initial attempt, many scientists have tried to estimate the number of genes in the human genome, using increasingly sophisticated molecular tools. Over the years, the number has gradually come down, in a process that has been humbling at times, as we realized that many other species - even plants - are predicted to have more genes than we do (Figure 1). An estimate of 100,000 genes appeared in the 1990 joint National Institutes of Health (NIH)/Department of Energy (DOE) report on the Human Genome Project [4]; this was apparently based on a very rough (and incorrect) calculation that typical human genes are 30,000 bases long, and that genes cover the entire 3-gigabase genome.

Many people, including many geneticists, expected that we would have a definitive gene count when the human genome was finally completed, and indeed one of the main surprises upon the initial publication of the human genome in February 2001 [5,6] was that the number had again dropped, quite precipitously. However, as we shall see, the publication of the human genome did not come anywhere close to producing a precise gene list or even a gene count, and in the years since the number has continued to fluctuate. As a result, even today's best estimates still have a large amount of uncertainty associated with them.

In order to count genes, we need to define what we mean by a 'gene', a term whose meaning has changed dramatically over the past century. For our discussion, we will restrict the definition of gene to a region of the genome that is transcribed into messenger RNA and translated into one or more proteins. When multiple proteins are translated from the same region due to alternative mRNA splicing, we will consider this collection of alternative isoforms to be a single gene. In this respect, our definition of a gene is equivalent to what may also be called a chromosomal locus. We will exclude non-protein-coding RNA genes (such as microRNAs (miRNAs) and small nuclear RNAs (snRNAs)), in part

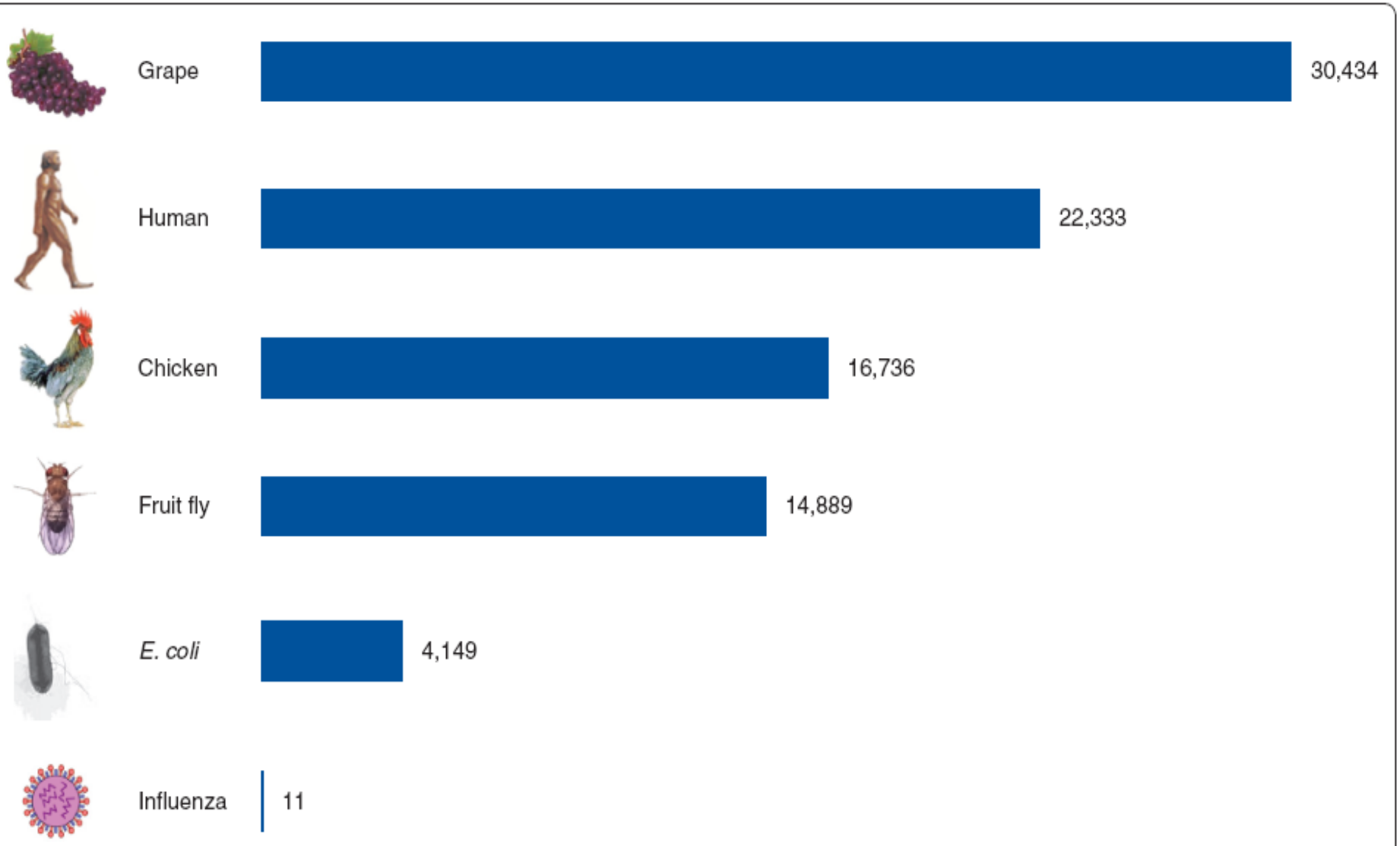
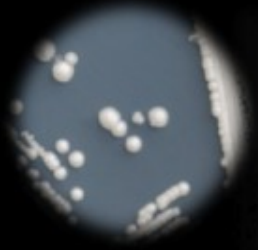


Figure 1. Gene counts in a variety of species. Viruses, the simplest living entities, have only a handful of genes but are exquisitely well adapted to their environments. Bacteria such as *Escherichia coli* have a few thousand genes, and multicellular plants and animals have two to ten times more. Beyond these simple divisions, the number of genes in a species bears little relation to its size or to intuitive measures of complexity. The chicken and grape gene counts shown here are based on draft genomes [50,51] and may be revised substantially in the future.

Fruit Fly
44%

Mouse
92%

Yeast
26%



Chimp
98%

Plant
18%

85%

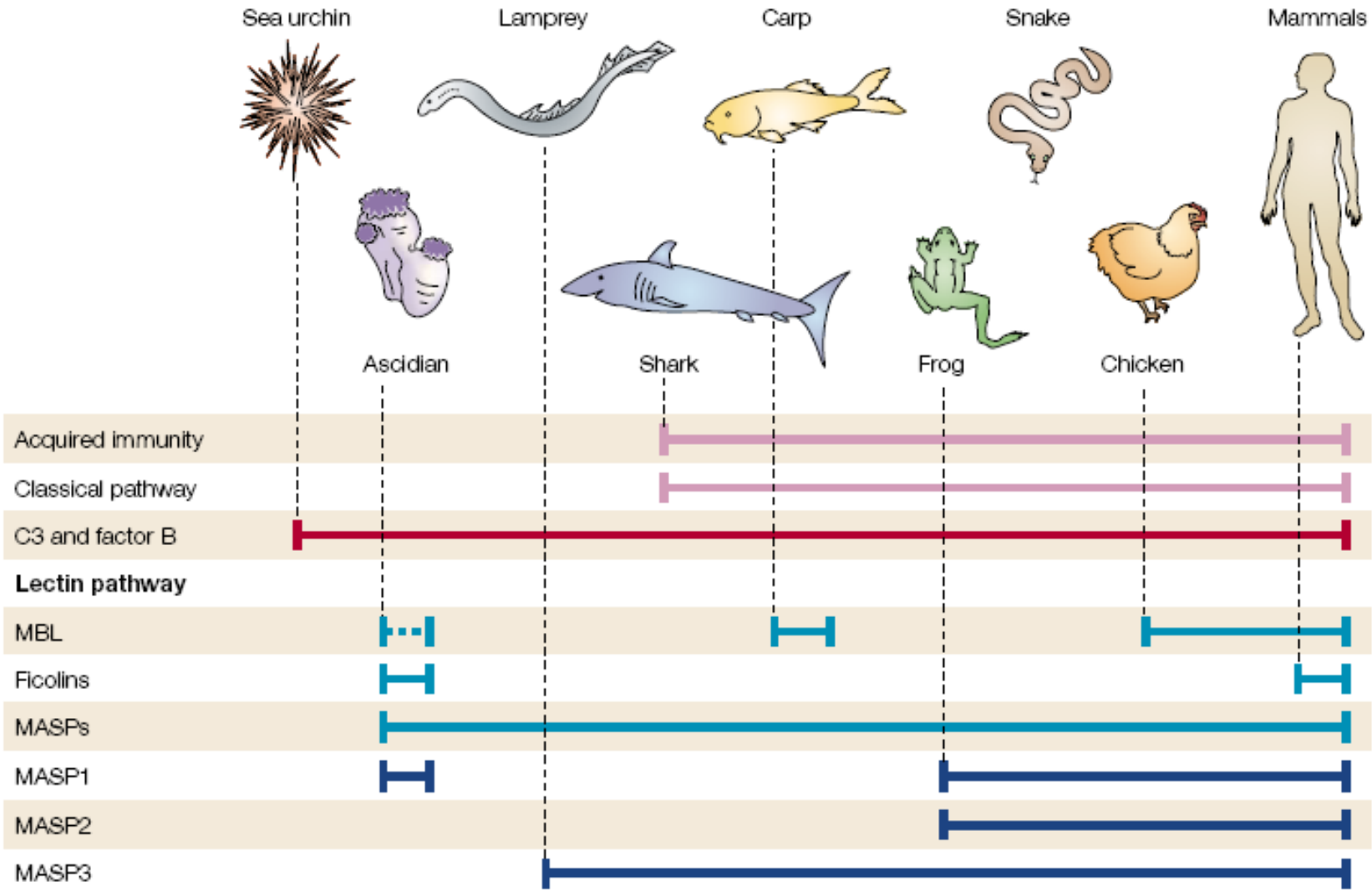
24%

47%

wiseGEEK

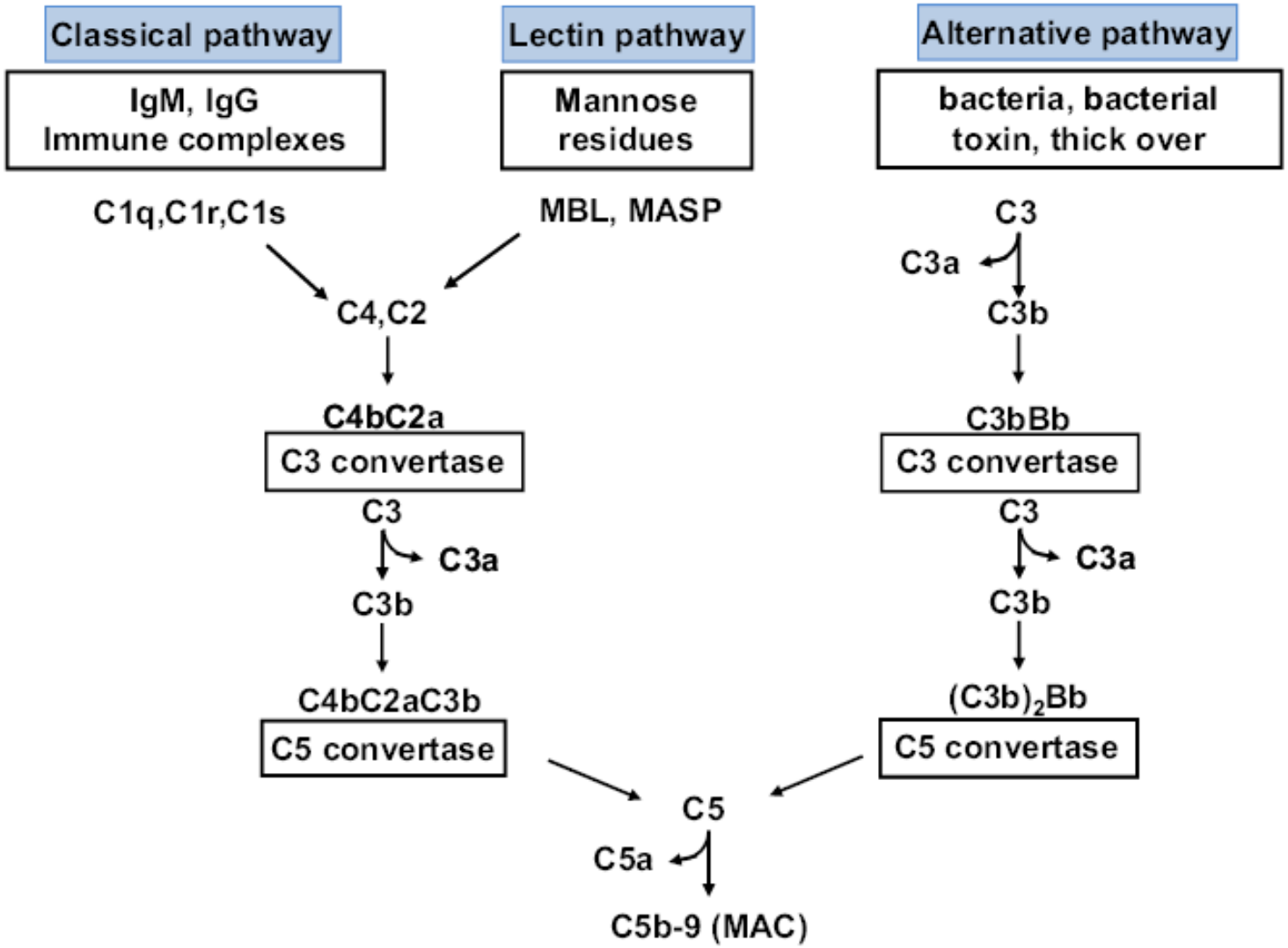
What percent of your genes do you share?

www.23andme.com



HOSPITAL BRITANICO
DE BUENOS AIRES

SERVICIO DE NEFROLOGÍA

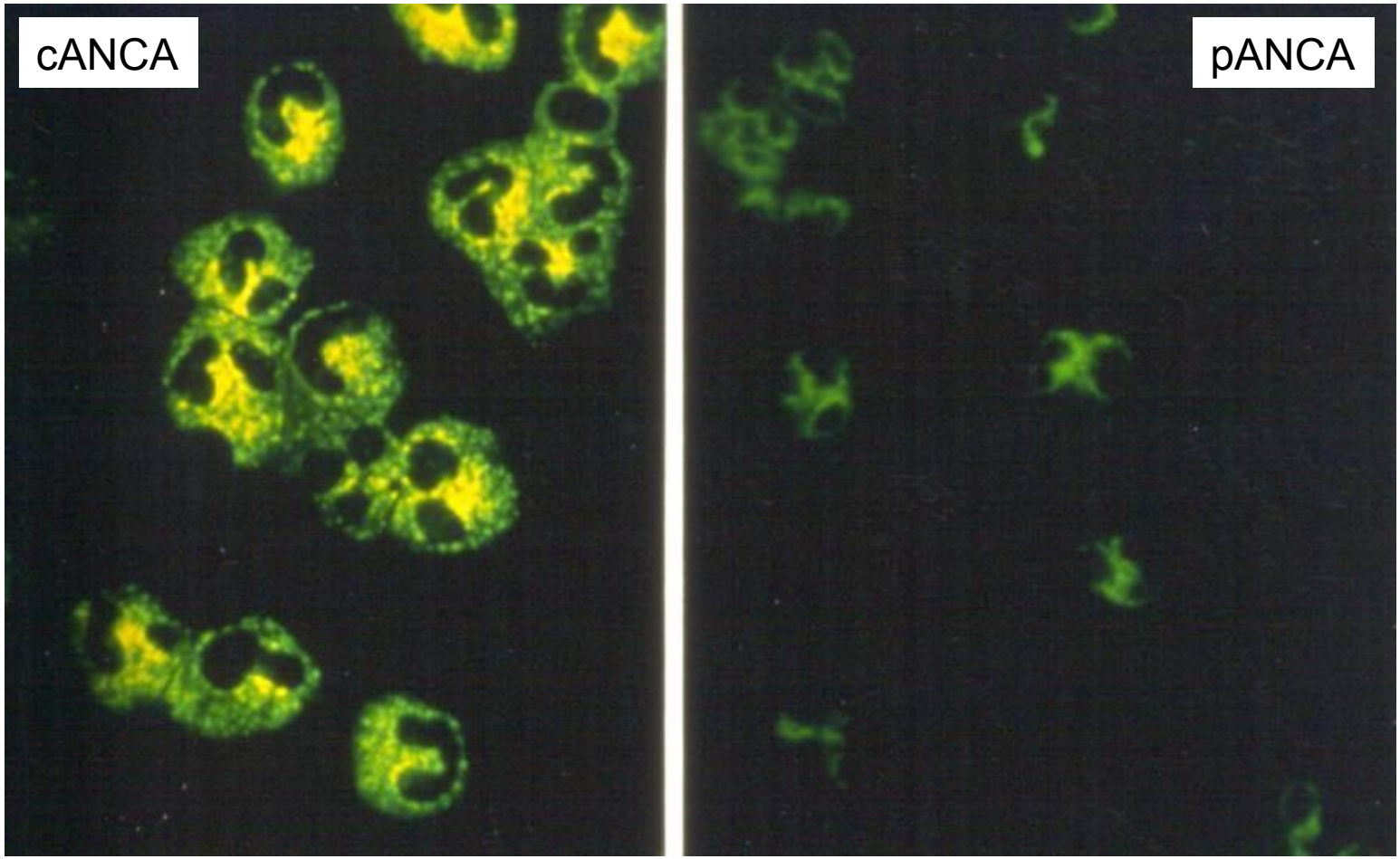

Classical pathway
IgM, IgG
Immune complexes
C1q,C1r,C1s
Lectin pathway
Mannose
residues
MBL, MASP
Alternative pathway
bacteria, bacterial
toxin, thick over
C3
C3a
C3b
C4,C2
C4bC2a
C3 convertase
C3
C3a
C3b
C4bC2aC3b
C5 convertase
C3bBb
C3 convertase
C3
C3a
C3b
(C3b)2Bb
C5 convertase
C5
C5a
C5b-9 (MAC)

VASCULITIS

p-ANCA, c-ANCA, IgA-C

1. LA SUSTANCIA A REMOVER DEBE SER SUFICIENTEMENTE GRANDE (>5000 Da) PARA QUE OTRAS TÉCNICAS DEPURADORAS SEAN INEFICACES (HD,HF, HDF)

IgG =150,000 Da



VASCULITIS

p-ANCA, c-ANCA, IgA-C

New pathophysiological insights and treatment of ANCA-associated vasculitis

Benjamin Wilde[1,2], Pieter van Paassen[1], Oliver Witzke[2] and Jan Willem Cohen Tervaert[1]

Kidney International (2011) **79,** 599–612

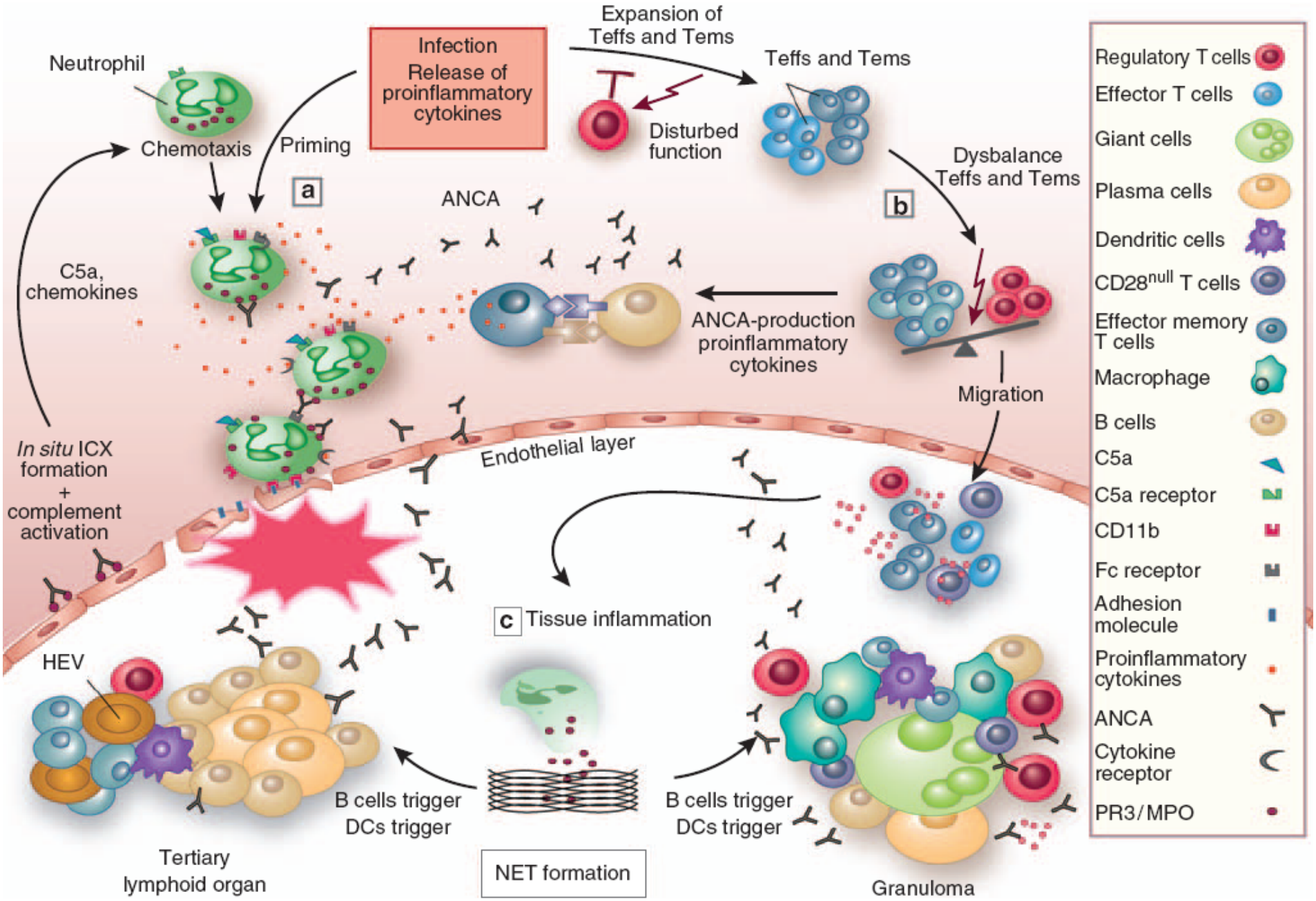
Complement in ANCA-Associated Vasculitis

J. Charles Jennette, MD, Hong Xiao, MD, and Peiqi Hu, MD

Seminars in Nephrology, Vol 33, No 6, November 2013, pp 557–564

VASCULITIS

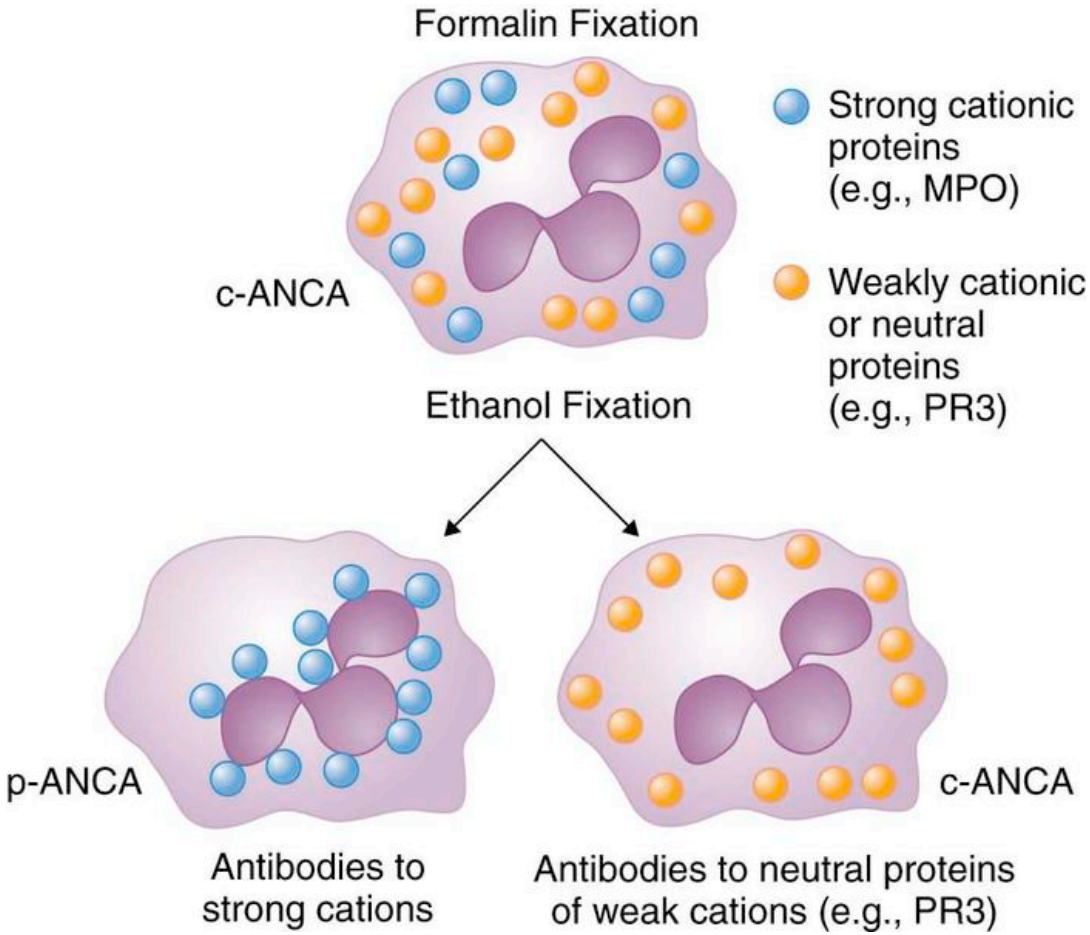
p-ANCA, c-ANCA, IgA-C



VASCULITIS **p-ANCA, c-ANCA, IgA-C**

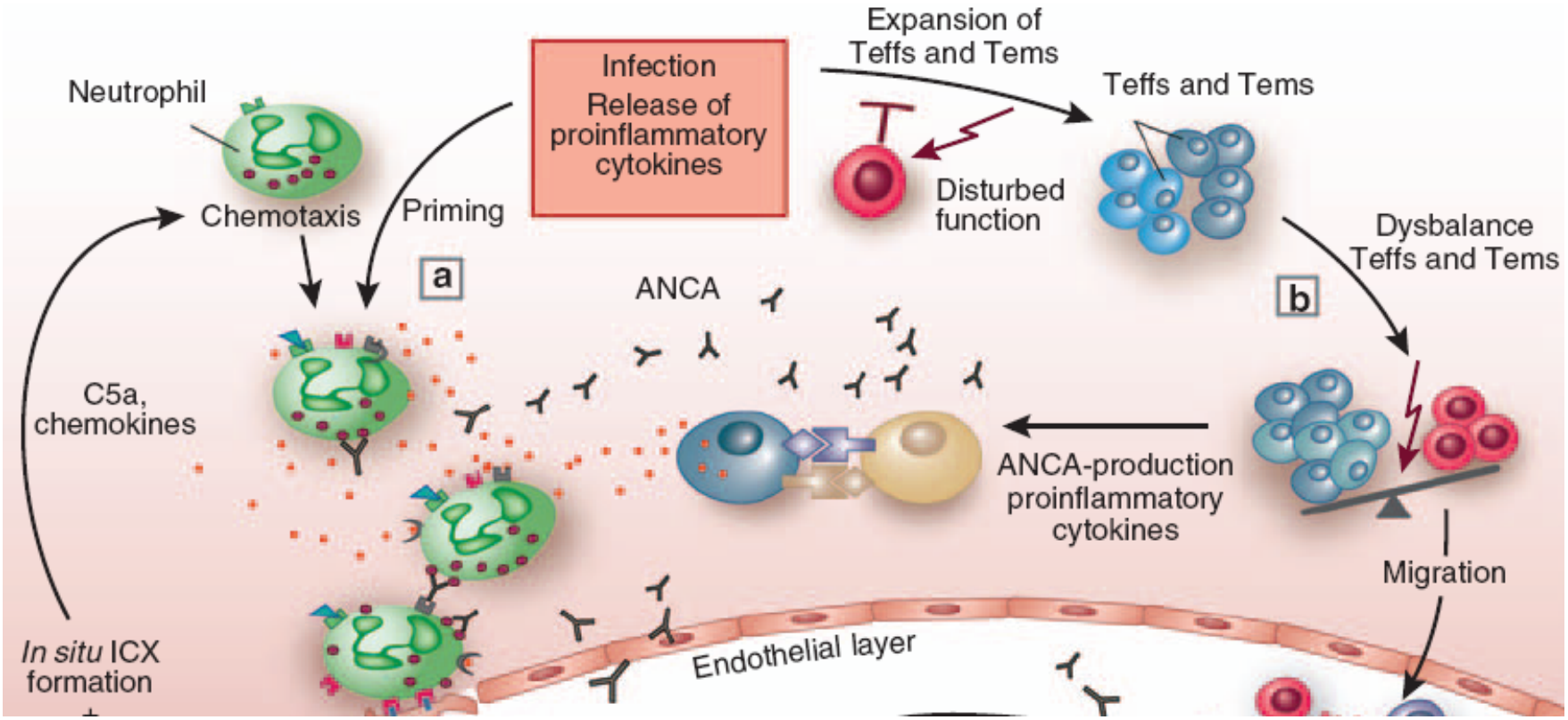
Hay 2 vías que contribuyen a los mecanismos involucrados en la vasculitis asociada a ANCA

1. La “vía clásica del neutrófilo’; esta vía causa vasculitis necrotizante.



VASCULITIS **p-ANCA, c-ANCA, IgA-C**

2. Hay una segunda vía llamada "vía de la célula T" que causa principalmente inflamación granulomatosa y promueve una vasculitis necrotizante.
Las infecciones suelen ser el punto de inicio de ambas vías.
Las infecciones gatillan el primado de neutrófilos, la upregulation de moléculas de adhesión sobre el endotelio, y la expansión de células efectoras (b)



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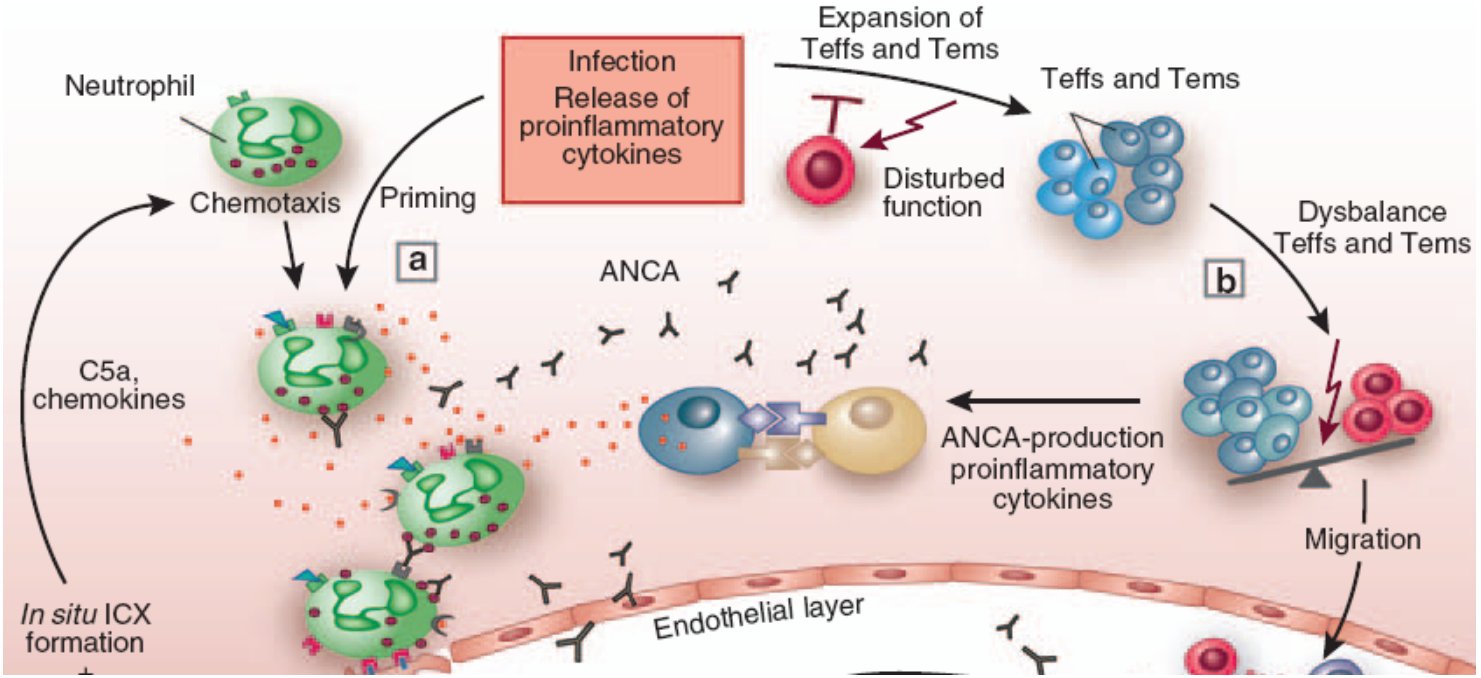
VASCULITIS **p-ANCA, c-ANCA, IgA-C**

Los neutrófilos aumentan la expresión en la superficie celular de los antígenos ANCA y de moléculas de adhesión.
El acople de la unión a los ANCA activa a los neutrófilos de varias formas:
(1) facilitando la adherencia al vaso y la capacidad de transmigración
(2) Produciendo y liberando radicales libres
(3) Degranulando y liberando enzimas incluyendo: mieloperoxidasa (MPO) y proteinasa-3 (PR3)



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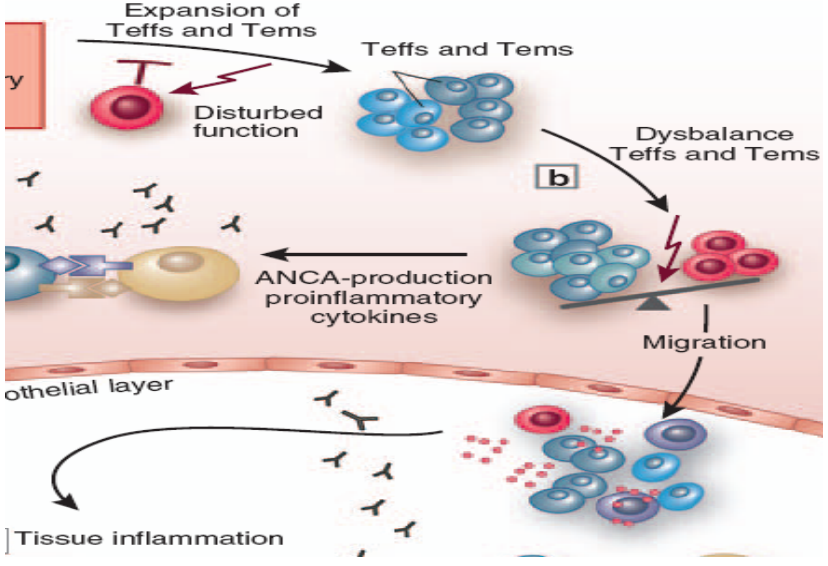
Se forman localmente complejos inmunes transitorios por unión de los ANCA a los PR3/ MPO pegándose a la célula endotelial.

Luego se activa el complemento, aumentando la degranulación de los neutrófilos.

Todo esto suma al desarrollo de vasculitis necrotizante.
Las células T efectoras de memoria (Tems) no son reguladas suficientemente por las T reguladoras (Tregs).

Esto lleva a un disbalance que resulta en una mayor liberación de citoquinas proinflamatoriaas promviendo mayor cebado de los neutrófilos.
La producción de los ANCA está facilitada por la interacción T-cell/B-cell

El pool expandido de Tems migran a otros órganos blanco como el riñón



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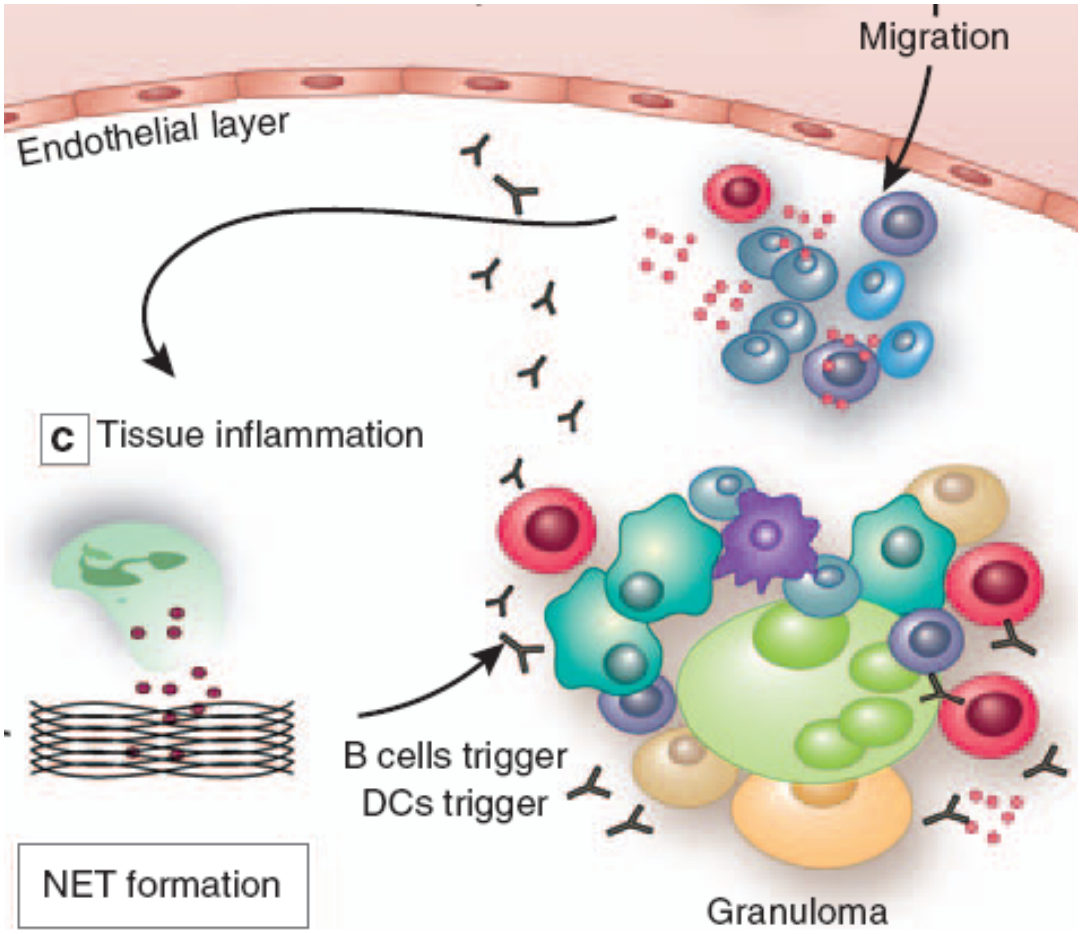
Dentro de los tejidos, las Tems llevan a la formación de granulomas, considerados ejecutantes de la destrucción tisular. Los granulomas están compuestos de células T, células B, células gigantes y células dendríticas.
Hay síntesis de ANCA en los granulomas



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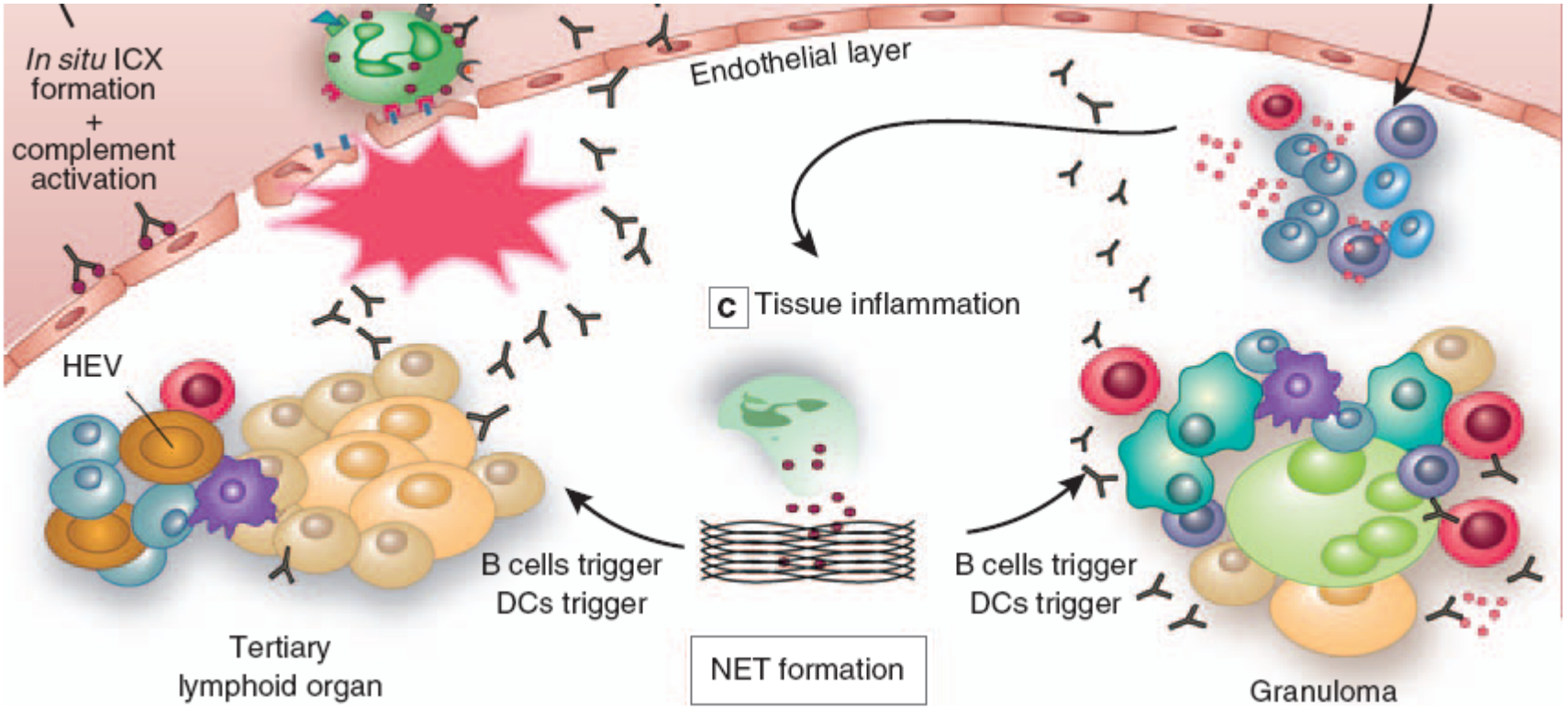
Los órganos linfoides terciarios son controladores locales de la inflamación tisular, como puede ser la inducción de Tregs.
El Neutrophil extracellular trap (NET) es una formación que ocurre en las lesiones como consecuencia de la apoptosis de los neutrófilos y de su degranulación.
Serina proteasas y de DNA abundan en estos NETs.
Los productos derivados de los NET activan a las células dendríticas y a las células B por medio de receptores tipo Toll. El Interferon alfa de las células dendríticas impacta en la regulación inmune local alterando la función de las células Tregs



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BUT

The origin of ANCA is unexplained so far

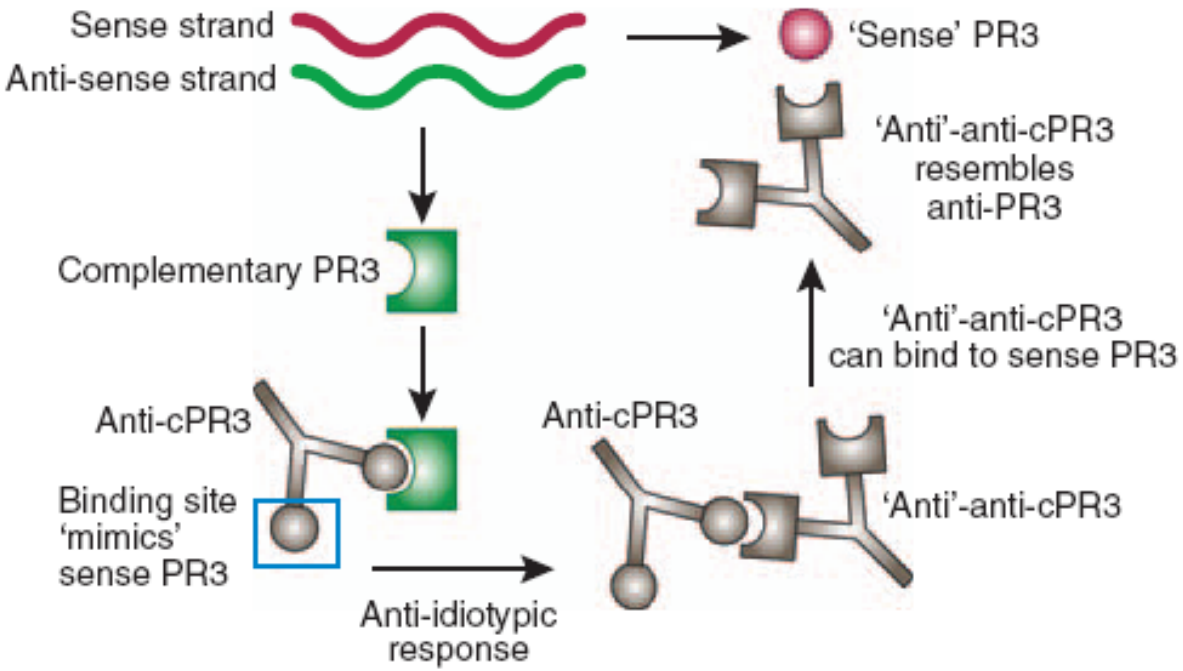


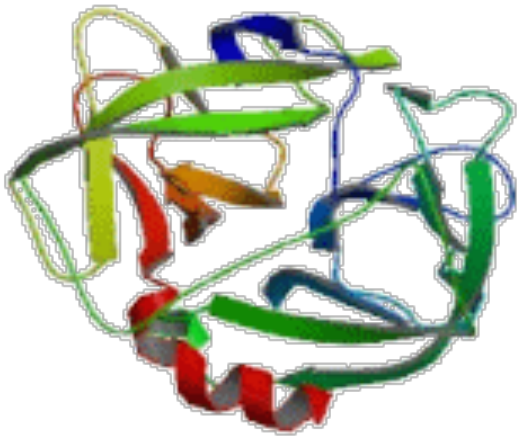
Figure 2 | The principle of the anti-idiotypic response in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

VASCULITIS

p-ANCA, c-ANCA, IgA-C

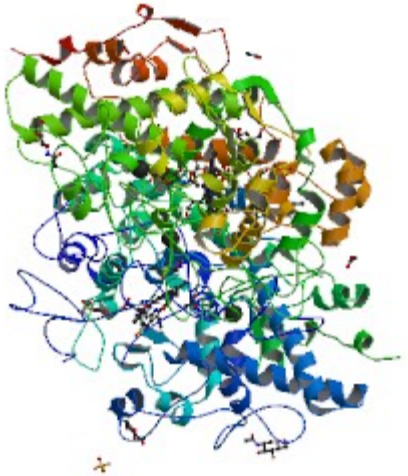
2. LA SUSTANCIA A REMOVER DEBE TENER UNA VIDA MEDIA PROLONGADA PARA QUE DESPUÉS DE SU EXTRACCIÓN TARDE TIEMPO EN REGENERARSE

IgG =150,000 Da



Proteinasa 3
PM = 32,000 Da

21 días

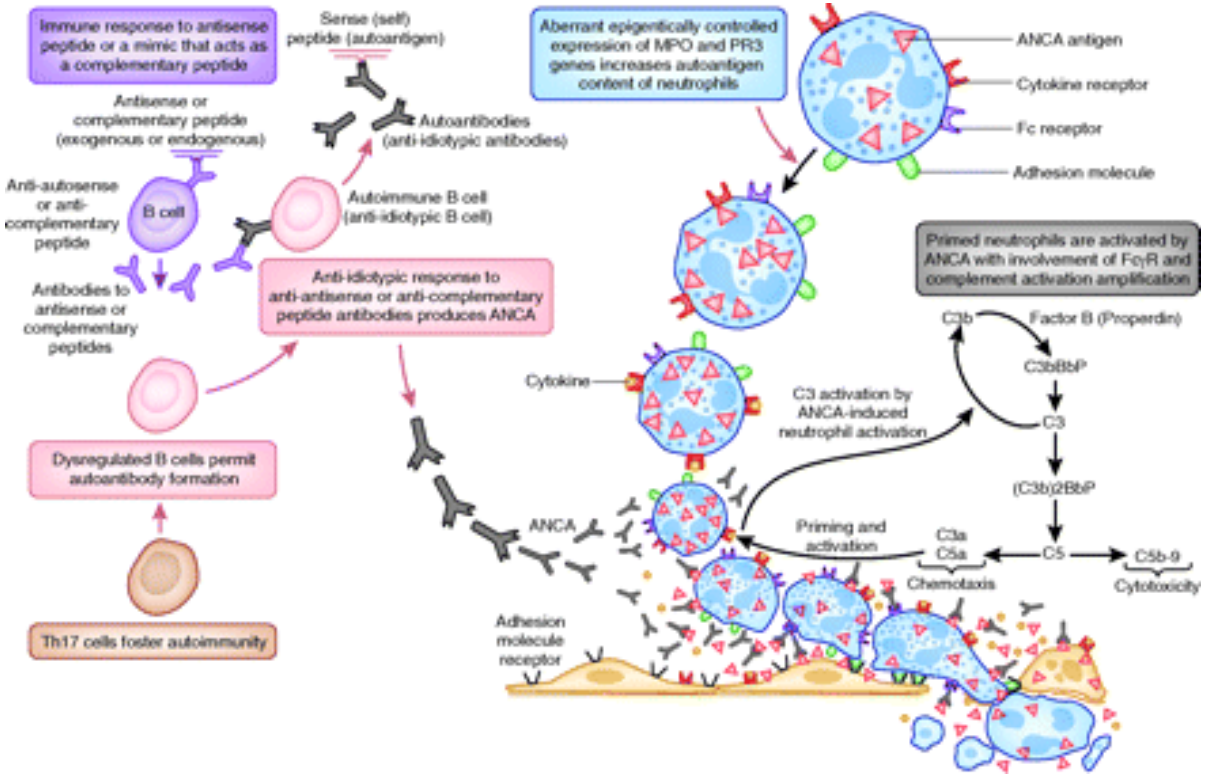


Mieloperoxidasa
PM= 149,000 Da

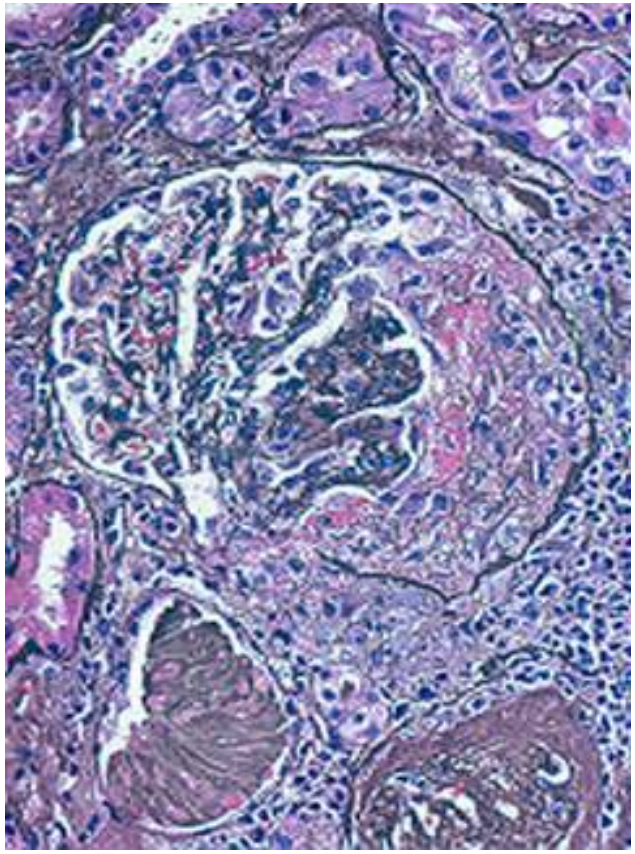
VASCULITIS

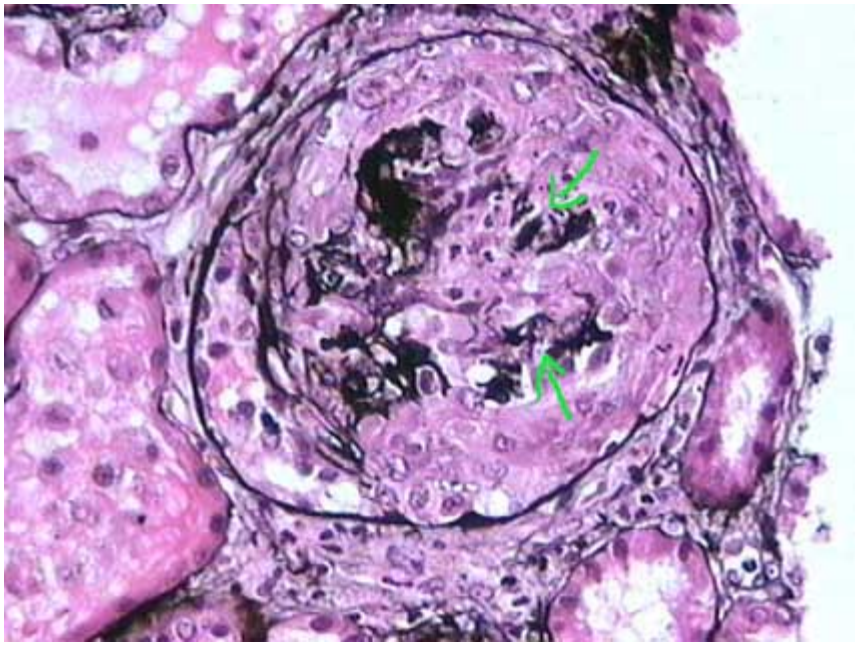
p-ANCA, c-ANCA, IgA-C

3. LA SUSTANCIA A REMOVER DEBE SER TÓXICA, Y PARCIAL O TOTALMENTE RESISTENTE AL TRATAMIENTO CLÍNICO CONVENCIONAL



4. LA ENFERMEDAD CURSA UN PATRÓN RÁPIDAMENTE PROGRESIVO O SUBAGUDO

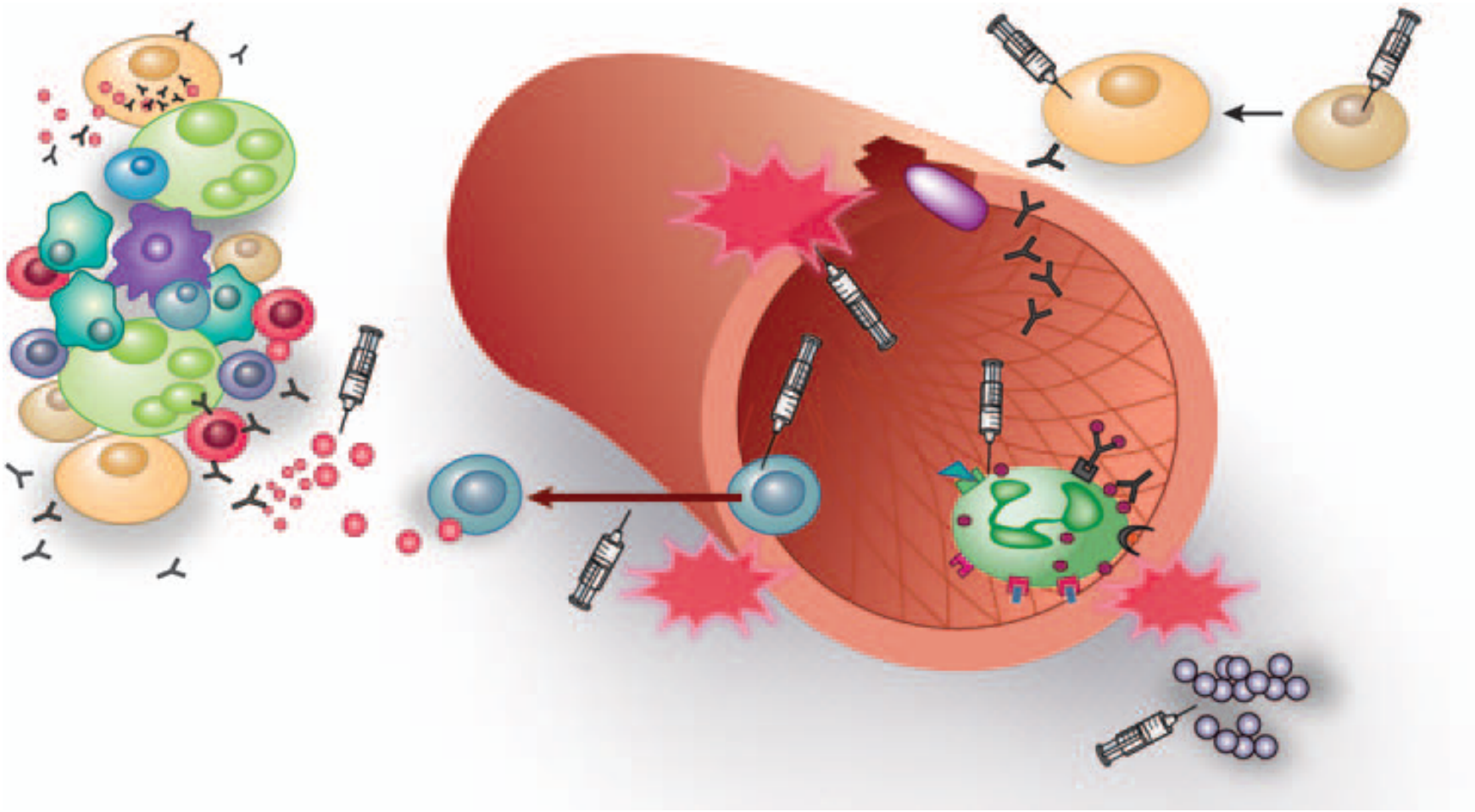




VASCULITIS

p-ANCA, c-ANCA, IgA-C

5. ES UN APOYO A UN TRATAMIENTO MÉDICO



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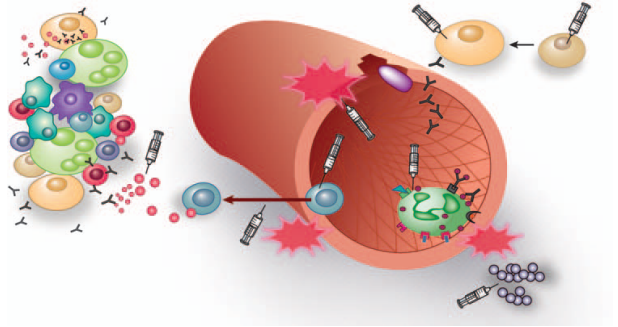
Kidney International (2011) 79, 599–612

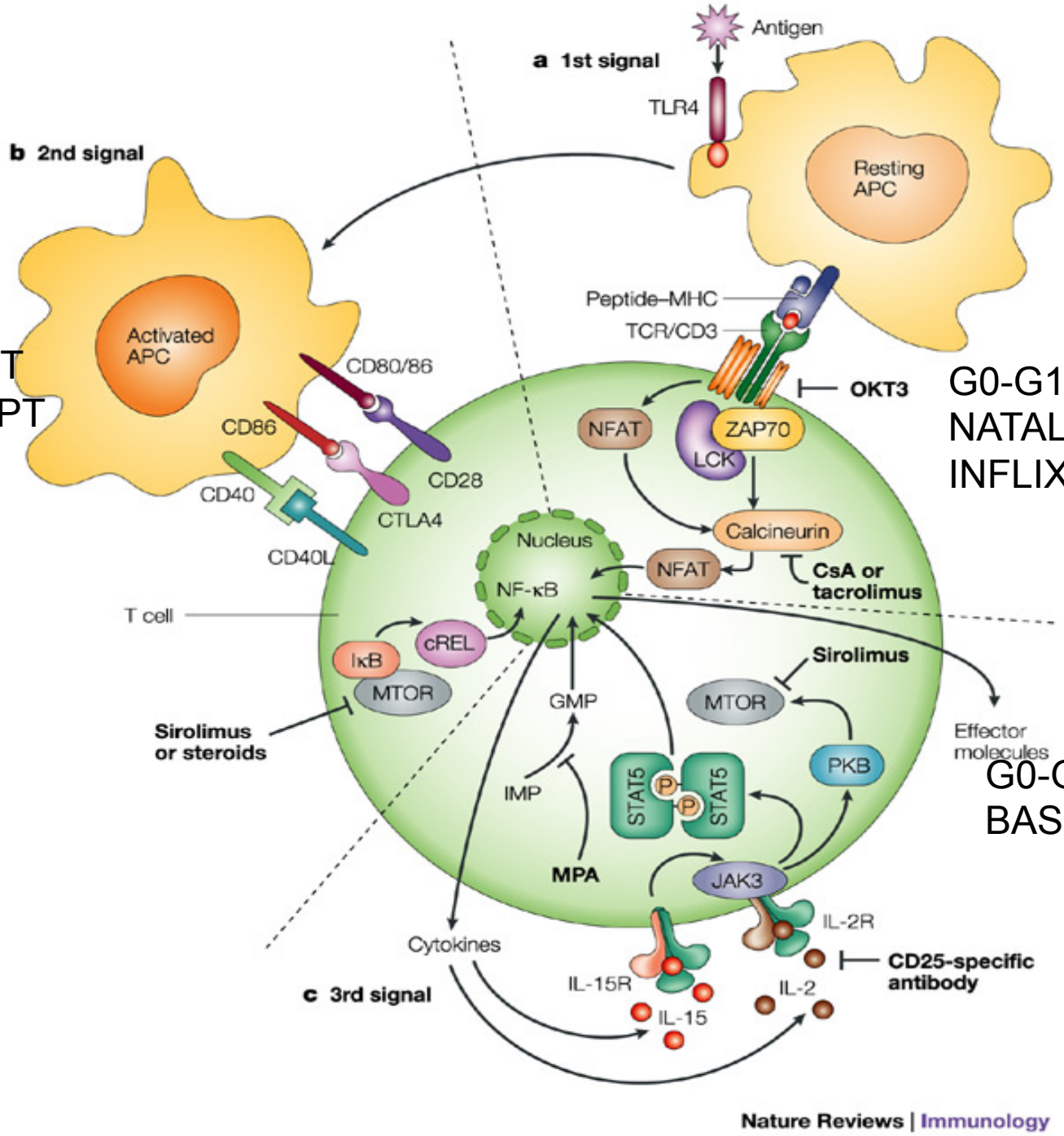


Metilpredinisolona 7 mg/kg/día x 3 días
Meprednisona 1 mg/kg día x 4 semanas y tapering
CY iv 0.5 g/m^2 x 6 meses o CY vo 2 mg/kg x 6-12 meses
Micofenolato por hasta 3 años

+ ?

Principle	Mechanism	Agent	Evidence	References
Depletion of effector T cells	Antibodies directed against CD25 deplete activated T cells	Basiliximab Daclizumab	Experimental + clinical evidence (RA+Tx) Ongoing RCT in AAV	179, 180 NCT0040248
Regulation of effector T cells	Blockade of CD28/CD80 dependent T cell activation	Abatacept, Belatacept (both CTLA-4 fusion proteins)	Experimental + clinical evidence (RA+Tx) Ongoing trial in AAV	172 NCT00468208
Block adhesion of neutrophils	Blockade of CD11b/ICAM-1 mediated adhesion to endothelium		Experimental evidence	18,178
Limit activation/ recruitment of neutrophils	Inhibition of C5 cleavage. Blockade of C5a receptor on neutrophils	Eculizumab, Pexelizumab (both anti-C5)	Experimental evidence	73, 74
Enhance vascular repair	Promote EPC mobilization and function	EPO Statins	Experimental + clinical evidence	173–176
Inhibition of migration	Blockade of a4-integrins on T cells	Natalizumab	Experimental + clinical evidence in MS	169, 170
Interfere with granuloma formation	Blockade of TNF-α	Infliximab Adalimumab	Experimental + clinical evidence in AAV	90, 134–136
Depletion of B cells	B-cell depletion by antibodies recognizing CD20/CD22	Rituximab, Epratuzumab (both anti-CD20)	Experimental + clinical evidence in AAV	118–122, 166, 177
Inhibition of B-cell maturation	Neutralization of BLys. Blockade of BLys-receptors on B cells	Belimumab (anti-BLys) Atacicept (anti-TACI)	Experimental evidence	118–122, 166, 177
Anti-microbial treatment	Reduction of microbial flora that might trigger disease flares	Cotrimoxazol	Experimental + clinical evidence in AAV	45, 48–51

G0-G1
ABATACEPT
BELATACEPT



G0-G1
NATALIZUMAB
INFLIXIMAB

G0-G1
BASILIXIMAB

S

Table 1 | Disease categories as defined by the European League Against Rheumatism[124]

Disease category	Definition
Localized	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ- or life-threatening disease
Generalized	Organ-threatening disease, if renal involvement: serum creatinine <5.6 mg/dl
Severe	Vital organ failure, if renal involvement: serum creatinine >5.6 mg/dl
Refractory	Disease progression despite therapy with cyclophosphamide and steroids

Table 2 | Recommendations for therapy of AAV by the European League Against Rheumatism[124]

Disease category	Recommended therapy	Grade of recommendation[a]	Level of evidence[b]
Remission induction			
Early systemic/localized disease	Methotrexate+steroids	B	1B
Generalized disease	Cyclophosphamide (i.v. or oral)+steroids	A	$1A^{WG/MPA}$ $1B^{CSS}$
Severe disease with renal failure	Adjunct: plasma exchange	A	1B
Maintenance therapy			
Low-dose steroids +	Azathioprine	A	1B
	Leflunomide	B	1B
	Methotrexate	B	2B

Abbreviations: ANCA-associated vasculitis; CSS, Churg–Strauss syndrome; i.v., intravenous; MPA, microscopic polyangiitis; RCT, randomized controlled trial; WG, Wegener's granulomatosis.

[a]Grade of recommendation: A, based on at least evidence level 1A/B; B, based on at least level 2 evidence or extrapolated recommendations from level 1 evidence.

[b]Levels of evidence: 1A, evidence from meta-analysis of RCT; 1B, from at least one RCT; 2B, from at least one type of quasi-experimental study.

VASCULITIS **p-ANCA, c-ANCA, IgA-C**

Plasmaféresis

Empleada en casos graves

De acuerdo a la fisiopatología, *considerar usarla en todos los casos con afección renal (RPGN, SM NEFRÍTICO, IRA, BIOPSIA CON DAÑO AGUDO SEVERO).*

Para remover anticuerpos

Alterar la función de los neutrófilos (inmunomodulación)

Prevenir la interacción leucocito-endotelio

Inhibir la vía alterna del complemento

Ajustar dosis y tratamiento a la respuesta del paciente

VASCULITIS

p-ANCA, c-ANCA, IgA-C

Chances of Renal Recovery for Dialysis-Dependent ANCA-Associated Glomerulonephritis

Robert A.F. de Lind van Wijngaarden,* Herbert A. Hauer,† Ron Wolterbeek,‡ David R.W. Jayne,§ Gill Gaskin,‖ Niels Rasmussen,¶ Laure-Hélène Noël,** Franco Ferrario,†† Rüdiger Waldherr,‡‡ Jan A. Bruijn,* Ingeborg M. Bajema,* and E. Christiaan Hagen;§§ for the European Vasculitis Study Group (EUVAS)

J Am Soc Nephrol 18: 2189–2197, 2007.

MEPEX RCT

PLASMAFÉRESIS VS METILPREDNISOLONA EN PULSOS

N = 151 PACIENTES-----se incluyeron 69 EN HEMODIÁLISIS

7 PLASMAFÉRESIS, 60 ml/kg cada sesión en 2 semanas

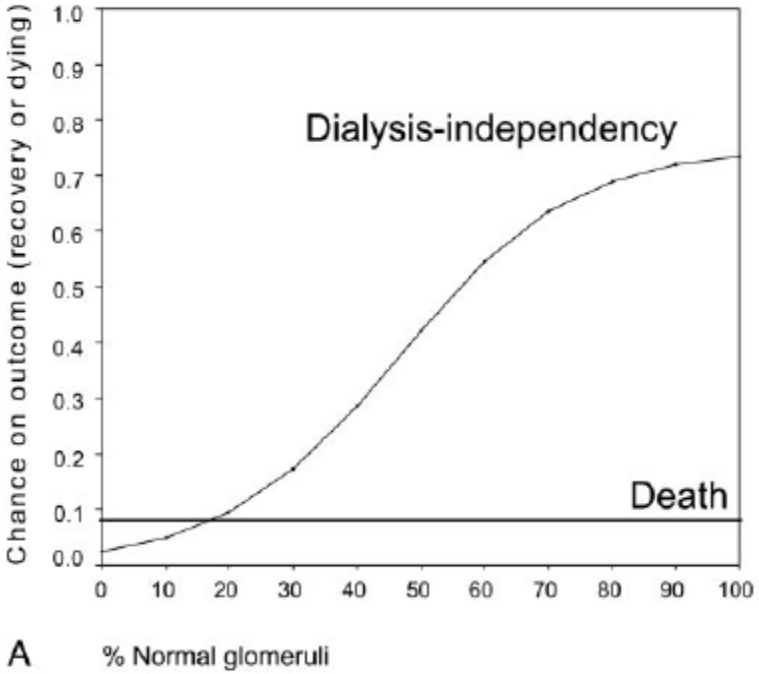
METILPREDNISOLONA iv en pulsos15 mg/kg x 3 días

TODOS CON CY vo

FUNCIÓN RENAL

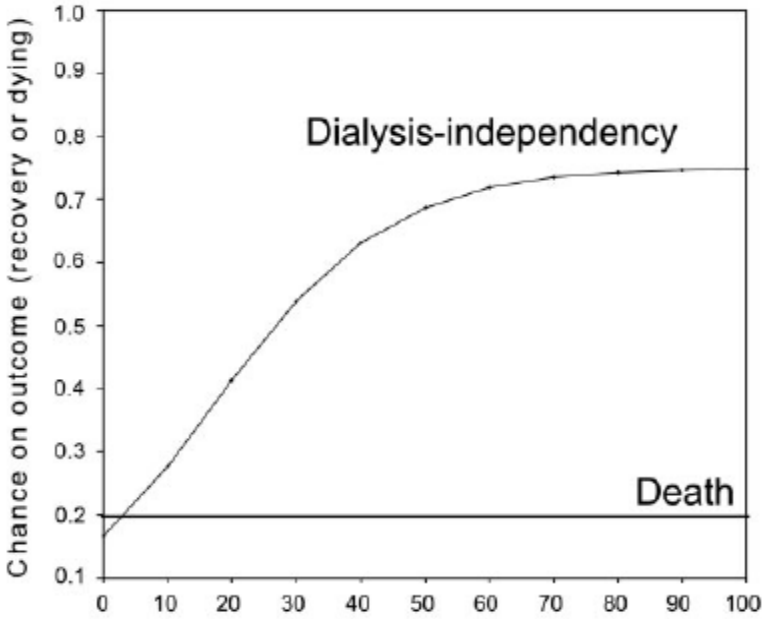
PLASMAFÉRESIS vs CORTICOIDES > a 3 MESES Y 5 AÑOS

CHANCES OF THERAPY-RELATED DEATH AND DIALYSIS INDEPENDENCE AFTER 1 YR RELATED TO THE PERCENTAGE OF NORMAL GLOMERULI IN A DIAGNOSTIC BIOPSY.



A

Patients who received IVMeP as adjunctive treatment and showed severe tubular atrophy in their biopsies (A)



B

Patients who received PE as adjunctive treatment and showed severe tubular atrophy in their biopsies (B).

Left of the point were the lines cross, the chance of dialysis independence drops below the chance of therapy-related death.

For the patients with IVMeP, this point is at 18% of normal glomeruli, whereas for the patients who were on PE, this point is at 2% of normal glomeruli.

J Am Soc Nephrol 18: 2189–2197, 2007.

CRIOGLOBULINAS
PARAPROTEÍNAS

FIBRILLAS
CADENAS LIVIANAS

1. LA SUSTANCIA A REMOVER DEBE SER SUFICIENTEMENTE GRANDE (>5000 Da) PARA QUE OTRAS TÉCNICAS DEPURADORAS SEAN INEFICACES (HD,HF, HDF)

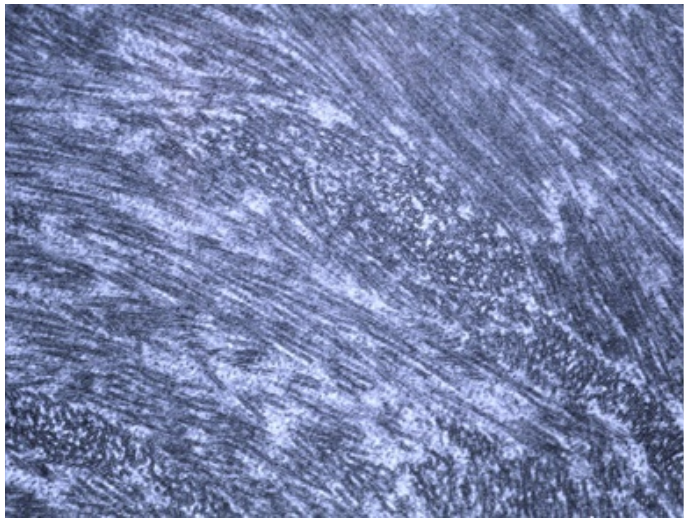


Table 1. Differences in gel filtration behavior between normal and cryoglobulin immunoglobulins and their fragments

Protein	Apparent molecular weight difference	
	Intact	Fab(μ or γ)
McE (IgM)	125,000	13,000*
Gre (IgM)	96,000	6,000*
Ger (IgG)	74,000	10,000†

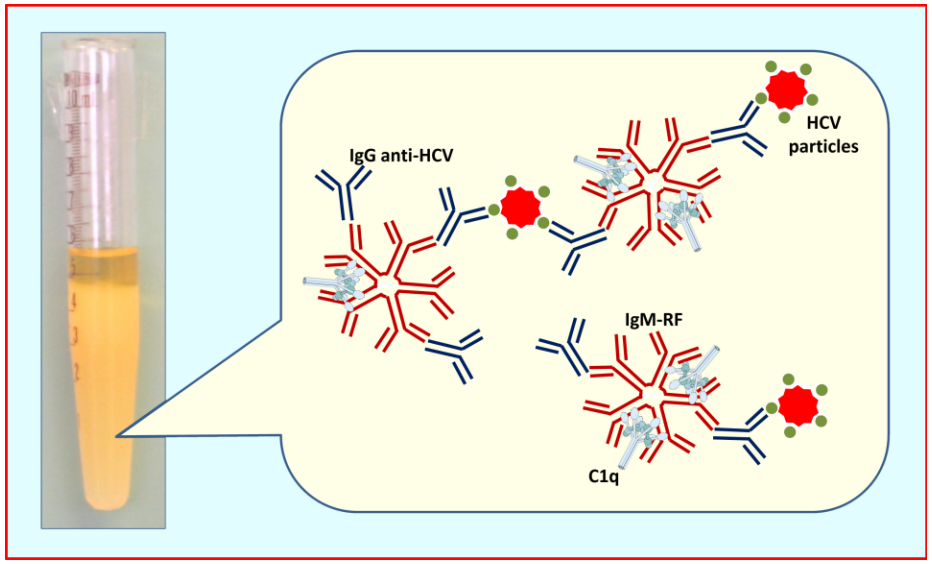
Proc. Natl. Acad. Sci. USA
Vol. 75, No. 7, pp. 3440—3444, July 1978
Medical Sciences

CRIOGLOBULINAS
PARAPROTEÍNAS

FIBRILLAS
CADENAS LIVIANAS

2. LA SUSTANCIA A REMOVER DEBE TENER UNA VIDA MEDIA PROLONGADA PARA QUE DESPUÉS DE SU EXTRACCIÓN TARDE TIEMPO EN REGENERARSE

El término crioglobulinemia (CG) se refiere a una condición patológica causada por la producción de inmunoglobulinas (Ig) circulantes que precipitan en el frío y se solubilizan reexpuestas al calor.



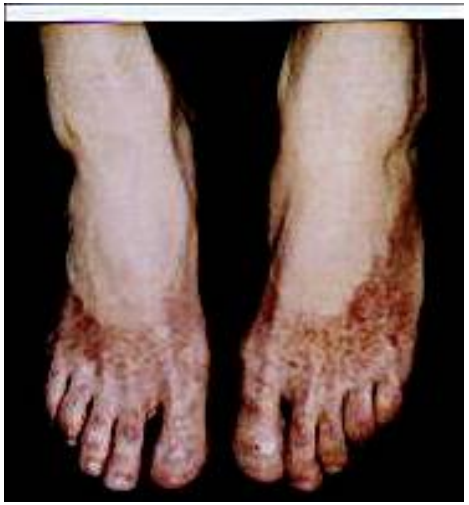
21 DÍAS

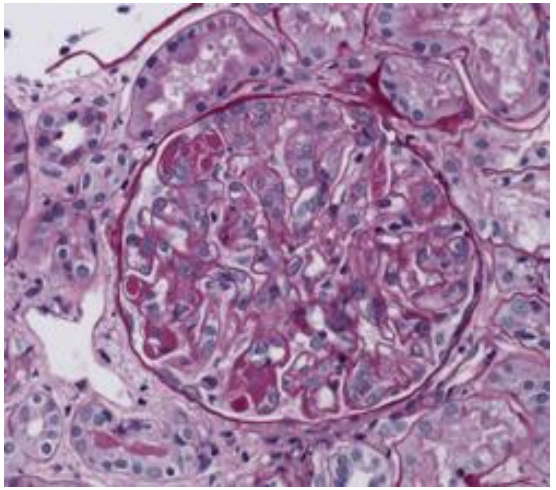
Las crioglobulinas se han dividido en 3 grupos basados en el tipo de Ig circulante.
Tipo 1: La crioglobulina es una Ig monoclonal generalmente asociada a MM o a enfermedad de Waldenstrom.
Tipo 2 y 3: se llaman CG mixtas, conteniendo al menos 2 tipos de Igs.

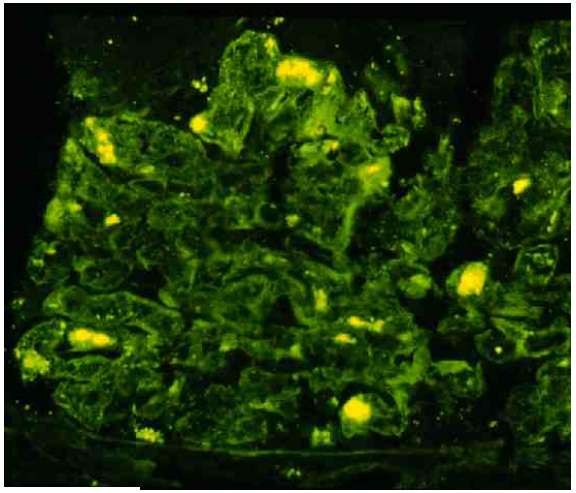
CRIOGLOBULINAS
PARAPROTEÍNAS

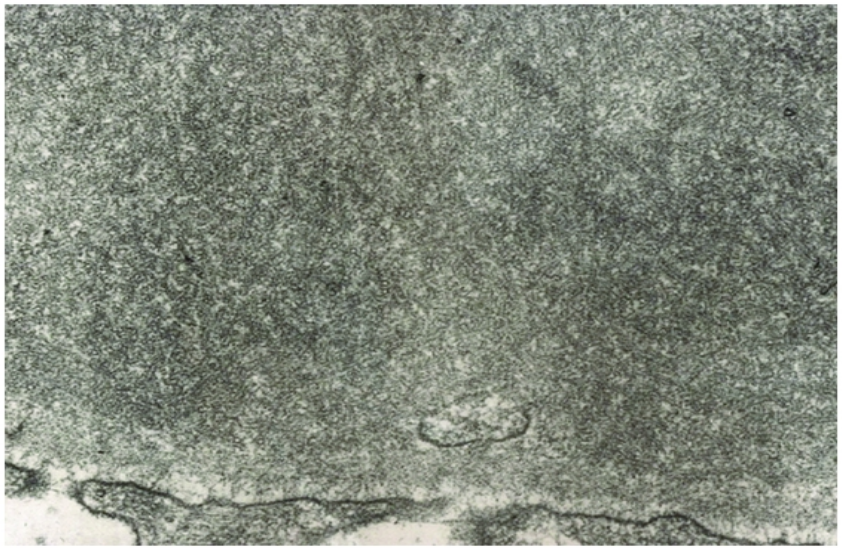
FIBRILLAS
CADENAS LIVIANAS

3. LA SUSTANCIA A REMOVER DEBE SER TÓXICA, Y PARCIAL O TOTALMENTE RESISTENTE AL TRATAMIENTO CLÍNICO CONVENCIONAL









CRIOGLOBULINAS
PARAPROTEÍNAS

FIBRILLAS
CADENAS LIVIANAS

4. LA ENFERMEDAD CURSA UN PATRÓN RÁPIDAMENTE PROGRESIVO O SUBAGUDO

- La enfermedad renal ocurre en menos del 25% de los pacientes al inicio del diagnóstico de CG, pero luego avanza hasta en un 50% de los casos.
- Un 25-30% se presentan con hematuria, proteinuria, hipertensión e injuria renal aguda.
- 20% presentan sindrome nefrótico.
- La glomerulonefritis rápidamente progresiva es rara
- 30% con vasculitis aguda con IRA

Las variantes histopatológicas son las de glomérulonefritis proliferativas con depósitos eosinófilos oclusivos en las luces capilares.

Un 10% se presenta como glomérulonefritis membranoproliferativas, y hasta un 30-50% pueden evolucionar a esta variante.

En estadíos avanzados se combinan con lesiones de esclerosis glomerular.

CRIOGLOBULINAS
PARAPROTEÍNAS

FIBRILLAS
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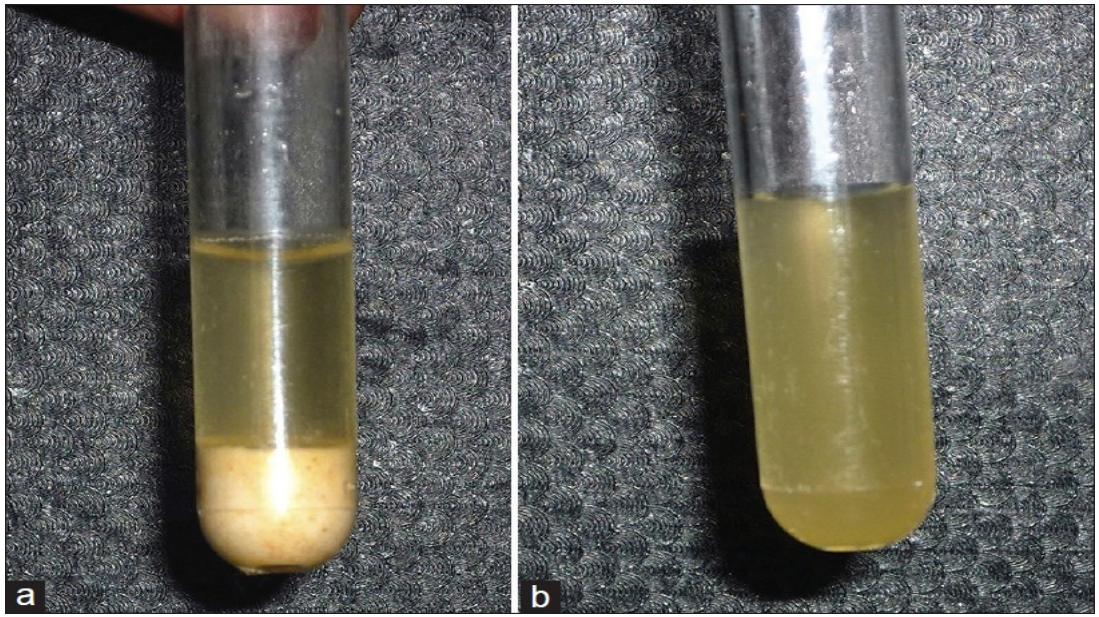
5. ES UN APOYO A UN TRATAMIENTO MÉDICO

INTERFERÓN PARA HCV, ESTEROIDES

PLASMAFÉRESIS con criocrito > 1%, hiperviscosidad, plts < 50,000 mm^3
petequias, clínica.

Volumen de recambio: 3 litros por sesión en días alternos por 5 sesiones
O hasta que el criocrito sea < 1% y la creatinina se normalice



PARAPROTEÍNAS

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El rol de la plasmaféresis está en discusión, si bien en casos de injuria renal aguda en la cual el componente M es elevado y hay un rol probado de las cadenas livianas en la fisiopatología de la disfunción renal, debería ser una herramienta útil de tratamiento, pero no lo es.

Talidomida- lenalinomida + Dx
Bortezomib iv o sc + CY/Melfalán + Dx
High cut-off hemodialysis (estudios MYRE, EuLite)
Gambro HCO 1100dialyzer. 1.1 m^2, coef 45 kD

SUHa

ANTI-FACTOR H, ANTI-FACTOR-I

Rol del Complemento en el SHUa

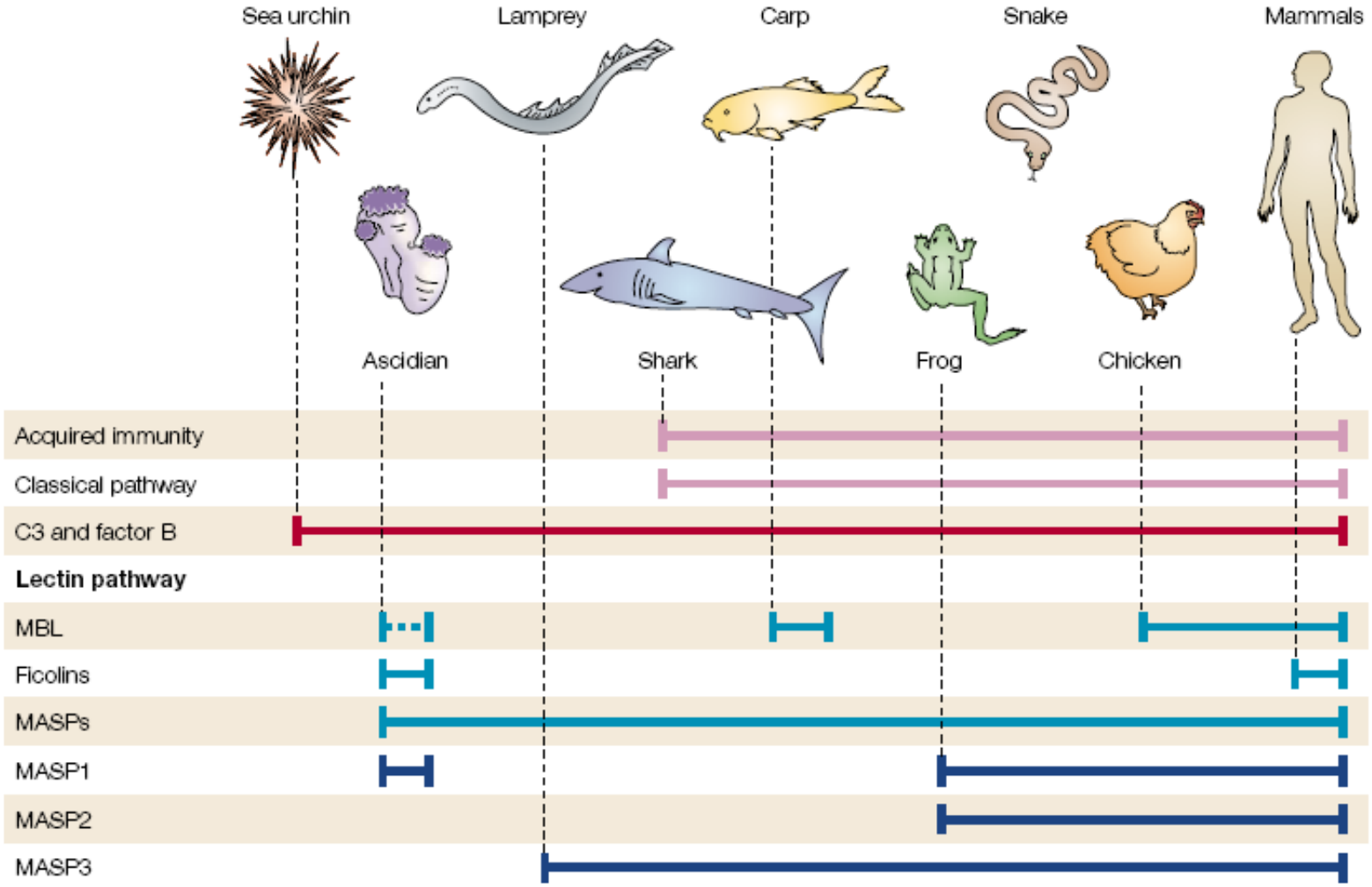
Los inhibidores naturales del complemento son necesarios para controlar el sistema del complemento

El sistema del complemento hace parte del sistema inmune de protección natural

La actividad se presenta de manera permanente mediante un proceso espontáneo llamado "tick-over" el cual permite la activación de una respuesta inmune en forma rápida

Los inhibidores naturales del complemento mantienen controlada la amplificación y previenen la actividad no controlada del complemento

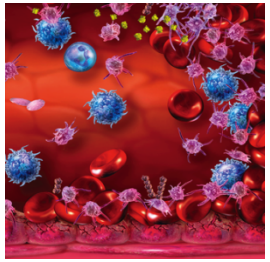
Cuando no está regulada, la actividad del complemento puede inducir MAT que puede conducir al daño orgánico progresivo


Sea urchin
Lamprey
Carp
Snake
Mammals
Ascidian
Shark
Frog
Chicken
Acquired immunity
Classical pathway
C3 and factor B
Lectin pathway
MBL
Ficolins
MASPs
MASP1
MASP2
MASP3

Diferentes causas diferencian el SHUa de la PTT

MAT mediada por el complemento (SHUa)

Causa subyacente:
Actividad crónica no controlada del complemento[1-5]

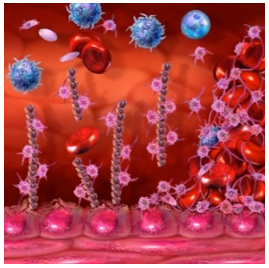


Los defectos genéticos en los activadores y/o inhibidores inducen la actividad crónica del sistema del complemento, causando daño celular endotelial y agregación plaquetaria continua[1-5]

Objetivo del tratamiento:
Regular la activación crónica y no controlada del complemento

MAT mediada por la deficiencia severa de ADAMTS13 (PTT)

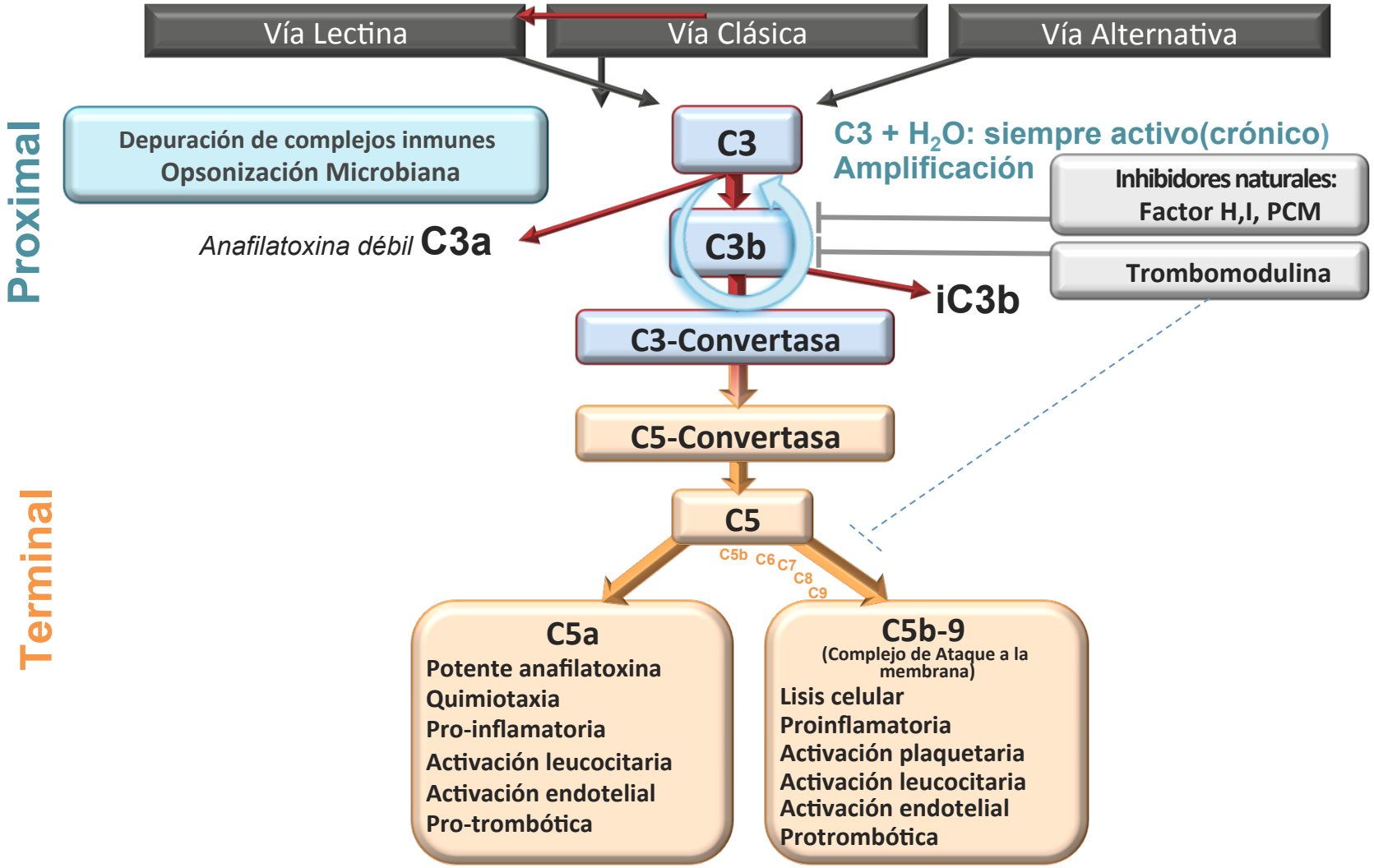
Causa subyacente:
Deficiencia severa de ADAMTS13 (≤5%)[6-10]



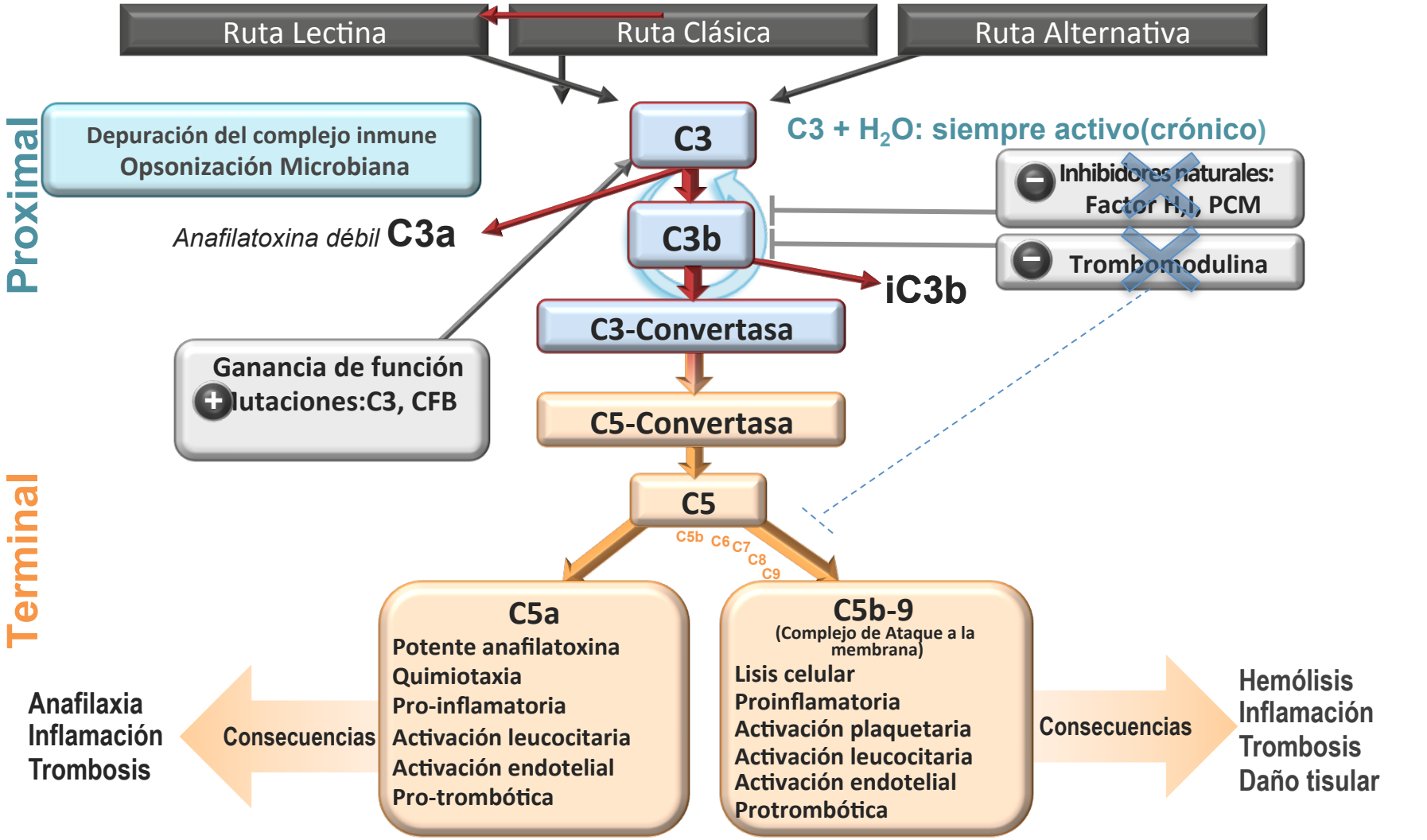
Una actividad insuficiente de ADAMTS13 (≤5%) deja el factor de von Willebrand sin escindir, lo que causa excesiva agregación plaquetaria[8,7,11,12]

Objetivo del tratamiento:
Eliminar los auto-anticuerpos contra ADAMTS13

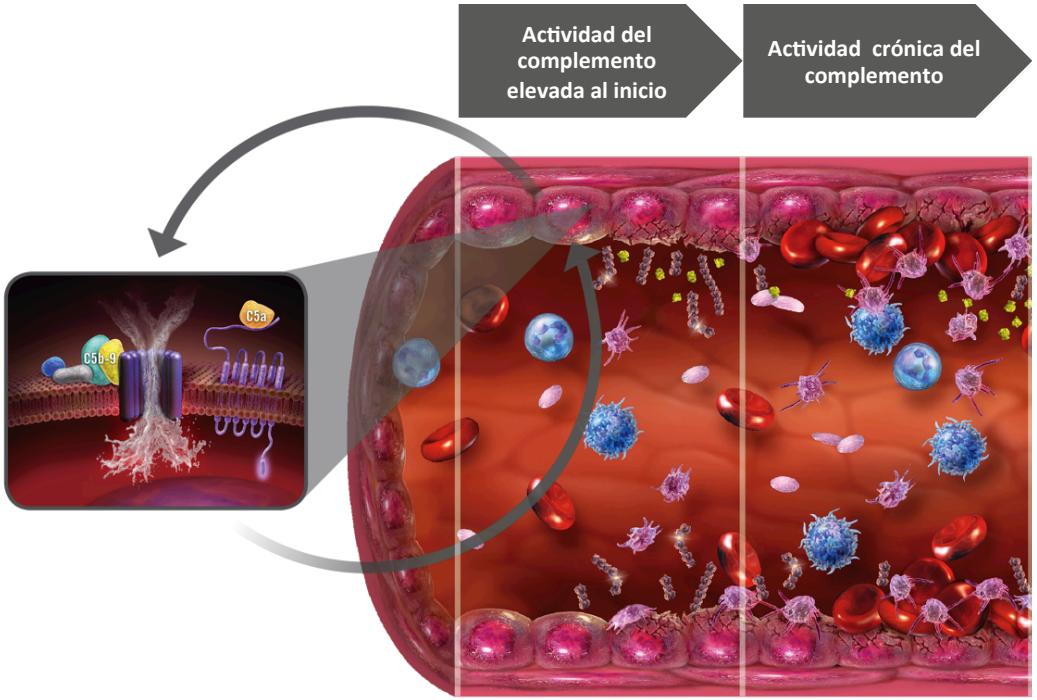
Los inhibidores naturales son necesarios para controlar el sistema del complemento



En el SHUa, la actividad crónica no controlada del complemento lleva daños severos



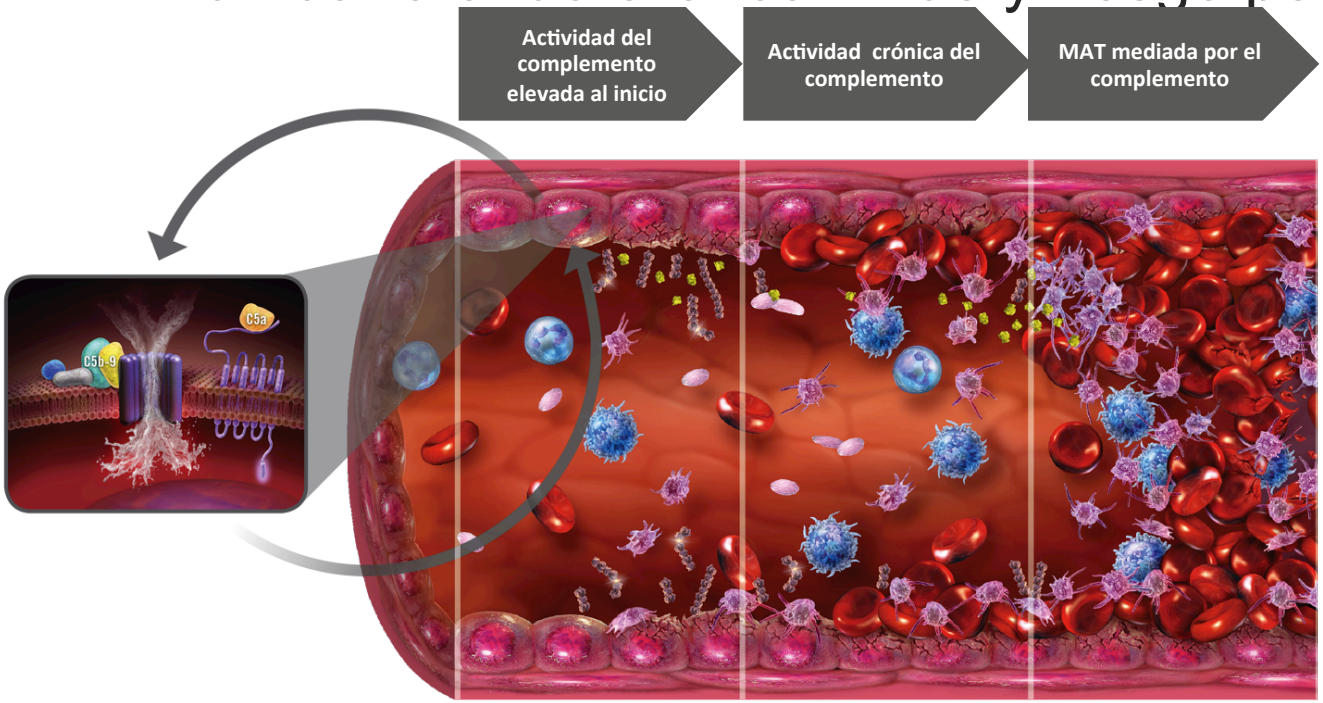
La actividad crónica no controlada del complemento resulta en un daño endotelial continuo y riesgo permanente de MAT



- El ensamblaje de múltiples complejos de C5b-9 en la superficie de las células endoteliales causa lesión endotelial y activación plauetaria[2-5]
- La unión de C5a al receptor de C5a resulta en una disminución de las propiedades anti-complemento y anti-trombóticas del endotelio[2,4,6,7]

glóbulo rojo | leucocito | plaqueta | leucocito activado | plaqueta activada | vWF | factores protrombóticos | esquistocito

La actividad crónica no controlada del complemento resulta en un daño endotelial continuo y riesgo permanente de MAT

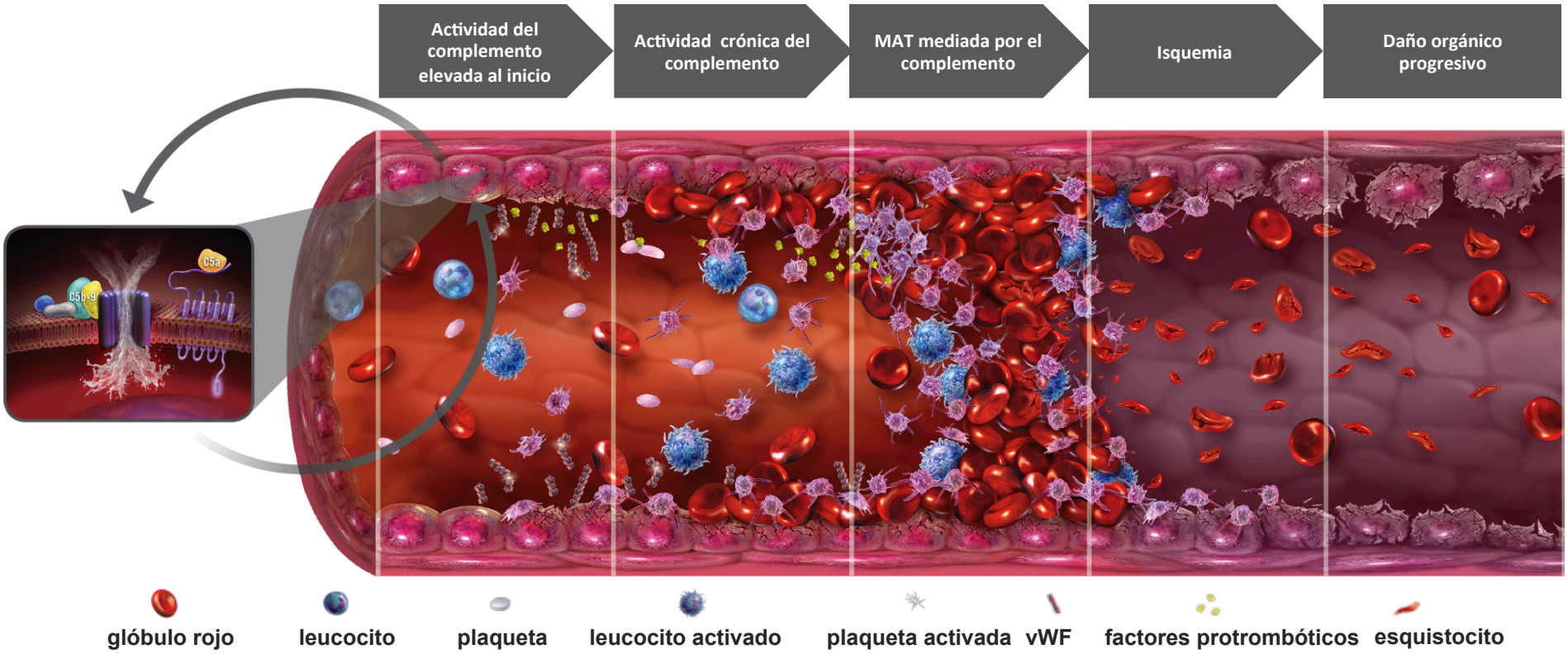


Células endoteliales interrumpidas:

- Liberan micropartículas activadoras del complemento, lo que resulta en un círculo vicioso de activación endotelial, amplificación del complemento y lesión endotelial permanente[2,3]
- Liberan proteínas de coagulación pro-trombóticas, activan las plaquetas y reclutan leucocitos, lo que resulta en la formación de trombos en los vasos sanguíneos pequeños en todo el cuerpo[2]

glóbulo rojo · leucocito · plaqueta · leucocito activado · plaqueta activada · vWF · factores protrombóticos · esquistocito

La actividad crónica no controlada del complemento resulta en un daño endotelial continuo y riesgo permanente de MAT



- La actividad no controlada del complemento causa lesión endotelial vascular permanente[2-5]
- Las lesiones resultantes de la MAT pueden progresar a daño multiorgánico irreversible[2-5]

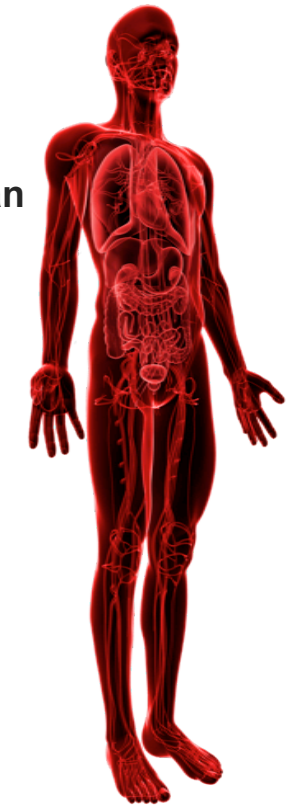
La MAT sistémica mediada por el complementio afecta en forma sistémica

Renal: Más del 50% de los pacientes progresan a ERET[1]
- Elevada creatinina[2,3]
- Proteinuria[4]
- Edema,[3] hipertensión maligna[5]
- Disminución en TFGe[6]

SNC: Hasta 48% de los pacientes presentan síntomas neurológicos[4]
- Desorientación[7]
- Apoplejía[7]
- Encefalopatía[5]
- Convulsión[4]

Blood:
- Trombocitopenia[1]
- Disminución en haptoglobina[1]
- Elevada LDH[1]
- Disminución en hemoglobina[1]
- Esquistocitos[1]

Visual:
- Oclusión ocular[8]



Cardiovascular: Hasta 43% de los pacientes experimentan síntomas cardiovasculares[4]
- Infarto del miocardio[9,16]
- Hipertensión[10]
- Vasculopatía difusa[6]
- Gangrena periférica[11,16]

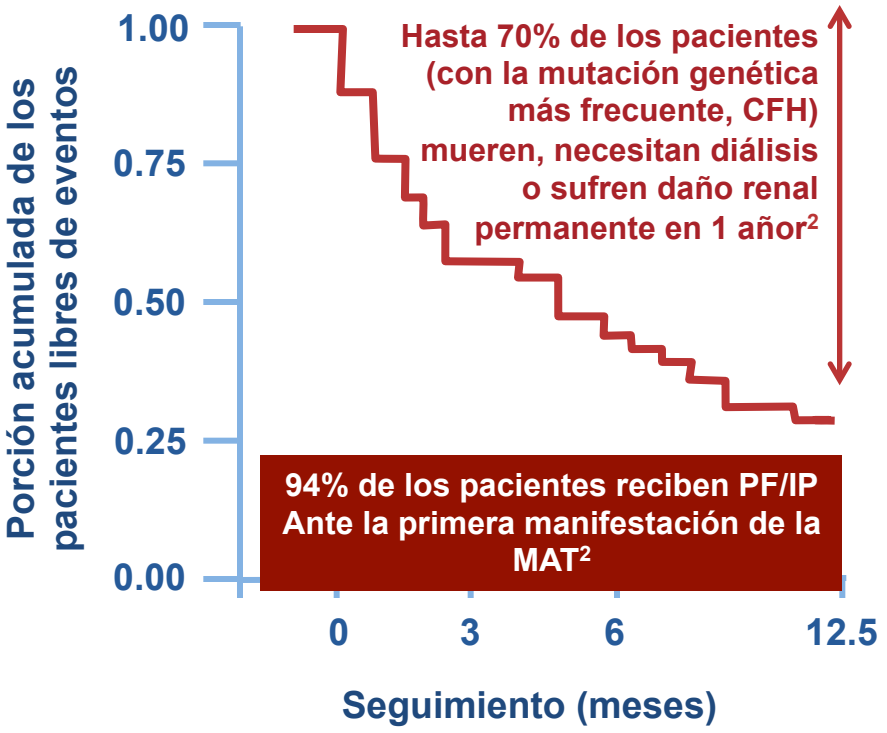
Gastrointestinal: 37% de los pacientes experimentan síntomas GI[12]
- Diarrea[13]
- Colitis[7]
- Náusea/Vómito[14]
- Pancreatitis[14]
- Dolor abdominal[7]
- Gastroenteritis[4]
- Necrosis hepática[4]

Pulmonar:
- Disnea[9]
- Hemorragia pulmonar[15]
- Edema pulmonar[9]

- Una evaluación clínica completa debe evaluar múltiples sistemas orgánicos

SHUa: Es una enfermedad crónica, cuya manifestación es la MAT mediada por el complemento y que puede tener consecuencias potencialmente fatales

- Los pacientes diagnosticados con SHUa están en riesgo inmediato y permanente de deterioro clínico progresivo a pesar del uso intensivo de plasmaféresis o infusión de plasma (PF/IP)
- El SHUa puede tener una evolución con daño progresivo que puede llevar a la muerte del paciente.
  - **79%** de los pacientes de SHUa mueren , necesitan diálisis o sufren daño renal permanente en el lapso de 3 años[1]
  - **33 a 40%** de los pacientes muere o progresa a enfermedad renal en etapa terminal a la primera manifestación clínica a pesar de PF/IP[1,2]

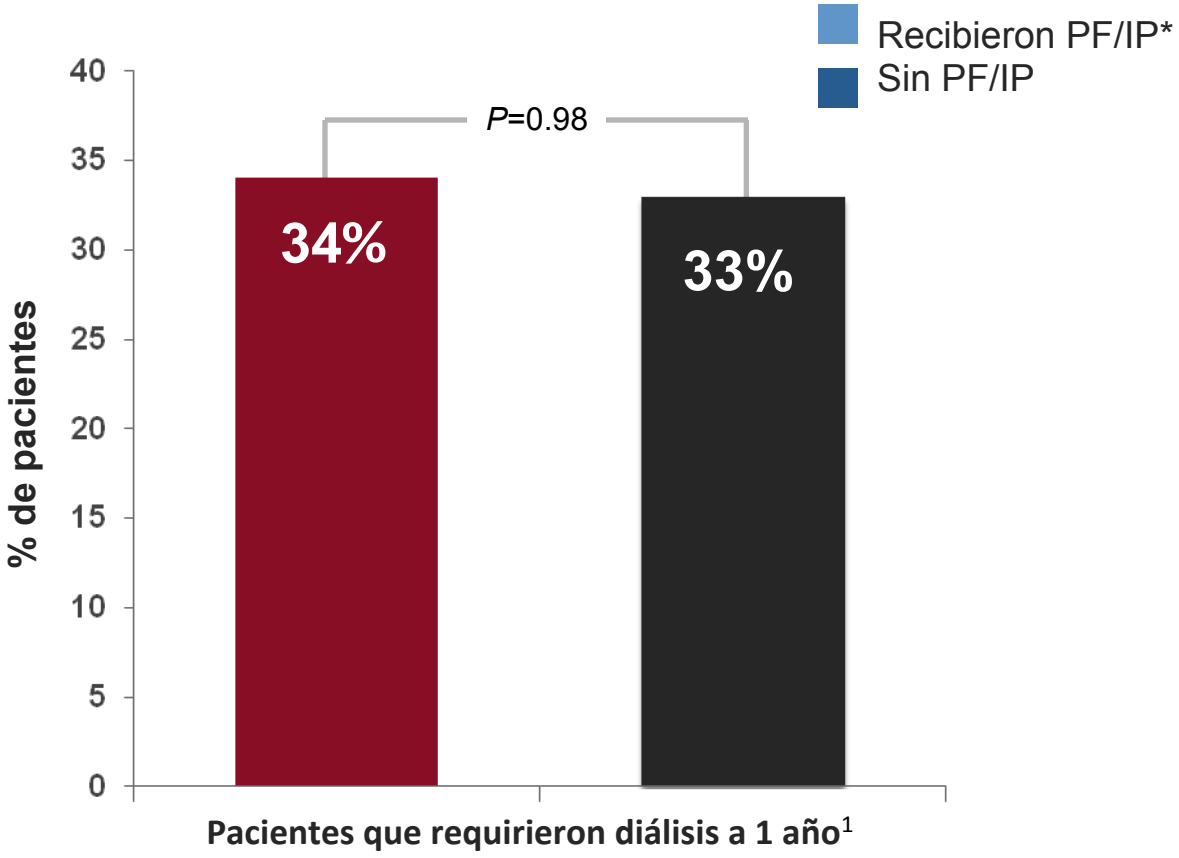


Modificado de Caprioli J et al. *Blood*. 2006. CFH mutation depicted.

Referencias: 1. Noris M, Caprioli J, Bresin E, et al. *Clin J Am Soc Nephrol*. 2010;5:1844-1859. **2.** Caprioli J, Noris M, Brioschi S, et al; for the International Registry of Recurrent and Familial HUS/TTP. *Blood*. 2006;108:1267-1279.

La PF/IP no reduce la morbilidad en el SHUa

- A pesar de la PF/IP, el resultado renal para los pacientes con SHUa sigue siendo desfavorable[2]
- El impacto renal un año posterior al diagnóstico de SHUa fue comparable entre pacientes que recibieron PF/IP y os que no recibieron PF/IP[1]

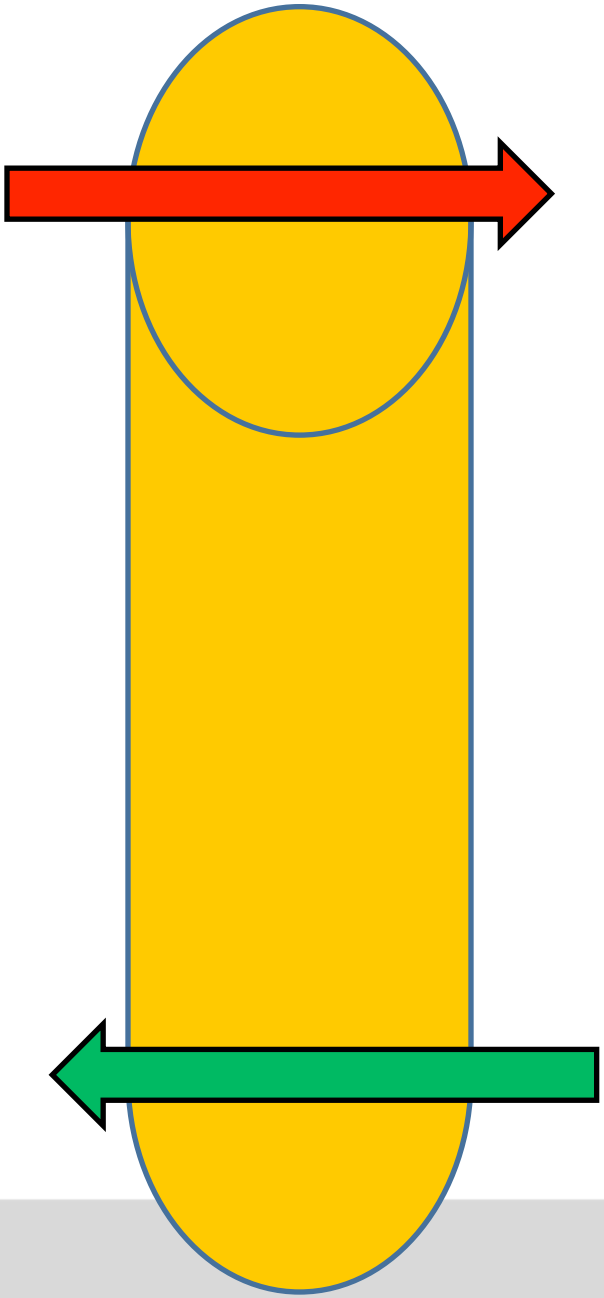


Descripción del estudio: Análisis de los pacientes del registro SHUa del GPN (Grupo de Nefrología Pediátrica). 141 pacientes estaban incluidos en el registro al momento de este análisis. Los datos del tratamiento sobre las manifestaciones iniciales estaban disponibles para 99 pacientes.

Pie de página: *Cuarenta y dos por ciento (38/89) de los pacientes recibieron PE. 48% (45/93) recibieron PI, y 22 pacientes recibieron tanto PF como IP.

Referencias: 1. Riedl M, Hofer J, A Rosales, et al. Initial plasma therapy in patients with atypical HUS: No negative predictive value for the outcome after one year. *Klin Padiatr*. 2011;223-P031. **2.** Fakhouri F et al. Am J Kidney Dis. 2013;1:40-8.

ANTICUERPOS



ANTI-MBG, ANTI-ADAMTS-13, ANTI-FACTOR H, ANTI-FACTOR-I

FACTOR H, FACTOR I

MOLÉCULAS FALTANTES

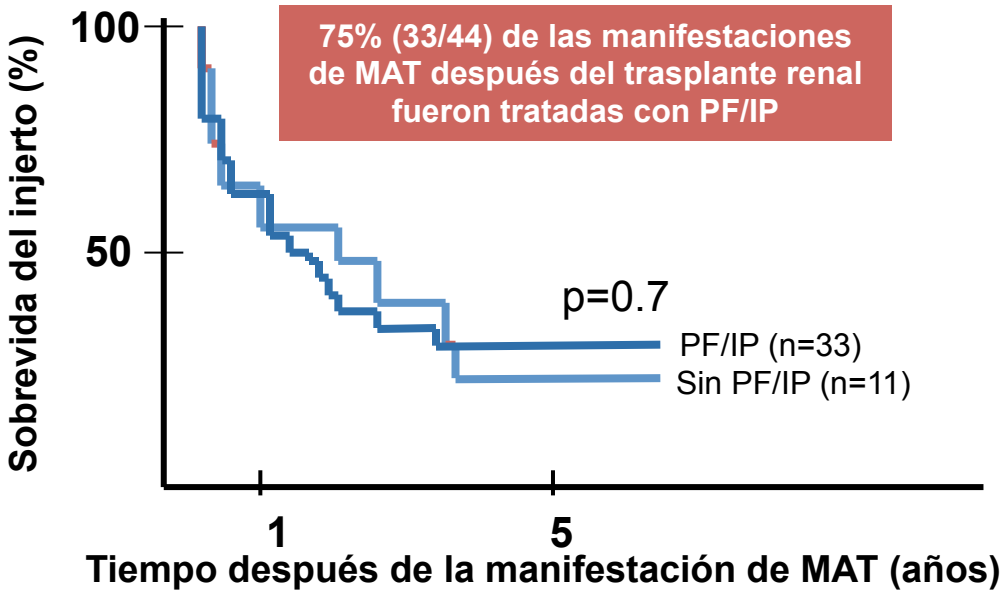
PF/IP en el SHUa ha sido clínicamente inefectivo en forma crónica, si bien es muy útil al comienzo

- La desregulación del complemento y la MAT persisten en los pacientes de SHUa en PF/IP, aún si se presenta un impacto transitorio en el recuento plaquetario y los niveles de LDH[5,12]
- La PF/IP no es suficiente para reemplazar las proteínas reguladoras del complemento deficientes o de mal funcionamiento en forma crónica[1-9]
  - Los procedimientos de aféresis por sí mismos pueden llevar también a la actividad del complemento por vía de la agregación palquetaria[10,11]
- Los biomarcadores de la actividad del complemento, inflamación, activación y daño de célula endotelial, coagulación y daño renal (p.ej., Ba, sTNFR1, sVCAM-1, Dímero-D, U-Cistatina C) se encuentran igualmente elevados entre los pacientes con SHUa reciban o no plasmaféresis o infusión de plasma[12]

Referencias: 1. Waters AM, Licht C. *Pediatr Nephrol.* 2011;26:41-57. **2.** Remuzzi G et al. *Am J Transplant*. 2005;5:1146-1150. **3.** Mache CJ et al. *Clin J Am Soc Nephrol*. 2009;4:1312-1316. **4.** Vergouwen MD et al. *AJNR Am J Neuroradiol*. 2008;29:e34. **5.** Legendre et al. *N Engl J Med.* 2013;368:2169-2181. **6.** Larakeb A et al. *Pediatr Nephrol*. 2007;22:1967-1970. **7.** Neuhaus TJ, Calonder S, Leumann EP. *Arch Dis Child*. 1997;76:518-521. **8.** Loirat C, Macher M-A et al. *Nephrol Dial Transplant.* 2010;25:3421-3425. **9.** Malina M et al. *Pediatr Nephrol*. 2011;26:1678. **10.** Boogaerts MA et al. *Transfusion.* 1986;26:82-87. **11.** Burnouf T et al. *J Clin Apheresis.* 2004;19:142-147. **12.** Cofiell R et al. Poster presented at the 55th Annual Meeting of the American Society of Hematology; December 7-10, 2013; New Orleans, LA. Abstract 2184.

La PF/IP falló en mejorar la sobrevida del injerto en pacientes con SHUa posterior al trasplante renal[1]

- En la mayoría de los reportes, la PF/IP falló en la prevención de la pérdida del injerto[2-5]
- No hubo mejoría en la sobrevida del injerto en los pacientes con SHUa posterior al trasplante renal a pesar de PF/IP en la cohorte de Francia (N=44)[1]



Modificado de Le Quintrec et al. *AJT 2013*

Referencias: 1. Le Quintrec et al. Am J Transplant. 2013 3:663-75; **2.** Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5:1844-1859; **3.** Loirat C et al. *Semin Thromb Hemost.* 2010; 6:673-81; **4.** Loirat C, Frémeaux-Bacchi V. *Orphanet J Rare Dis.* 2011;6:60; **5.** Zuber J, Le Quintrec M, Sberro-Soussan R, et al. *Nat Rev Nephrol.* 2011;1:23-35.

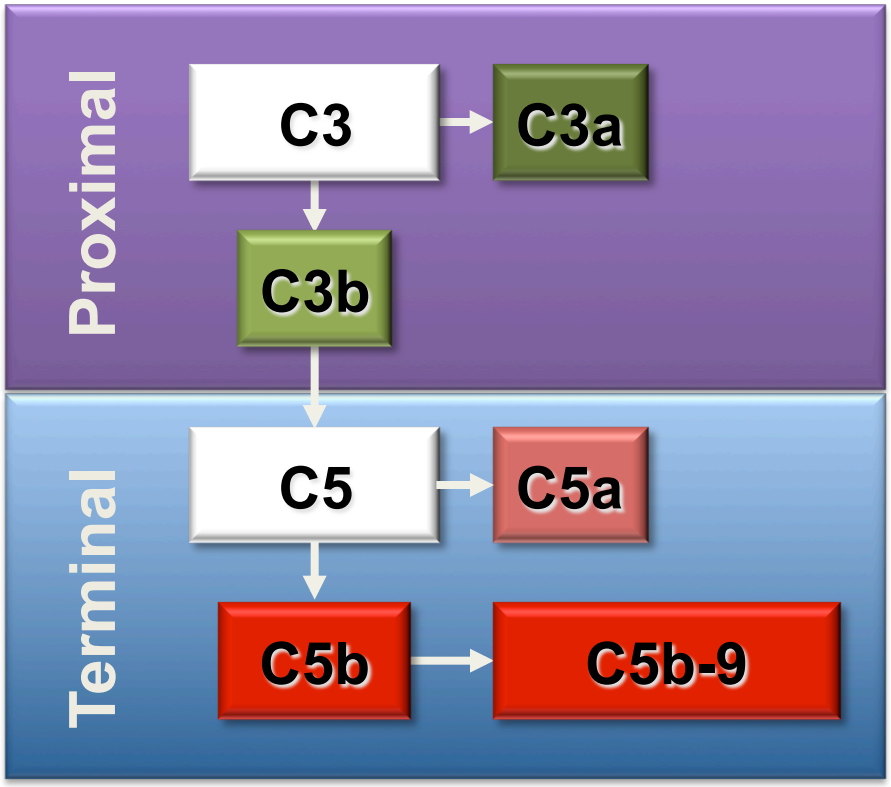
El trasplante renal no atiende la causa subyacente del SHUa

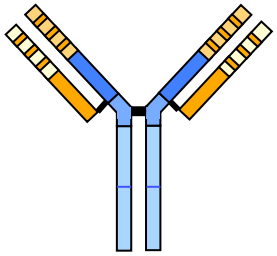
Proteína afectada	Resultado del Trasplante renal[1]
Factor H	Porcentaje de pacientes con MAT permanente: **80-90%**
CFHR1, R3	Porcentaje de pacientes con MAT permanente: **20%**
MCP	Porcentaje de pacientes con MAT permanente: **15-20%**
Factor I	Porcentaje de pacientes con MAT permanente: **70-80%**
Factor B	MAT permanente en un caso publicado
C3	Porcentaje de pacientes con MAT permanente: **40-50%**
THBD	MAT permanente en un caso publicado

Más del 90% de los pacientes con SHUa en otra cohorte experimentaron pérdida del injerto, la mayoría en el primer año[2]

Referencias: 1. Noris M et al. *N Engl J Med*. 2009;361:1676-1687. **2**. Bresin E et al. International Registry of Recurrent and Familial HUS/PTT. *Clin J Am Soc Nephrol*. 2006;1:88-99.

El eculizumab bloquea la fase terminal de activación del complemento





Soliris

- Soliris binds with high affinity to C5
- Terminal complement - C5a and C5b-9 activity blocked
- Proximal functions of complement remain intact
  - Weak anaphylatoxin
  - Immune complex clearance
  - Microbial opsonization

Figueroa JE, Densen P. *Clin Microbiol Rev*. 1991;4(3):359-395. Walport MJ. *N Engl J Med*. 2001;344(14):1058-66. Soliris® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2011. Rother RP et al. *Nature Biotech*. 2007;25(11):1256-64.

Eculizumab – Approved Dosing Schedule in aHUS

For patients ≥18 years of age, eculizumab therapy consists of:

	Induction	Maintenance
	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks

For patients <18 years of age, administer Eculizumab based upon body weight, according to the following schedule:

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Novel roles of complement in renal diseases and their therapeutic consequences

Takehiko Wada[1] and Masaomi Nangaku[1]

[1]*Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, Bunkyo-ku, Tokyo, Japan*

Kidney International (2013) **84**, 441–450

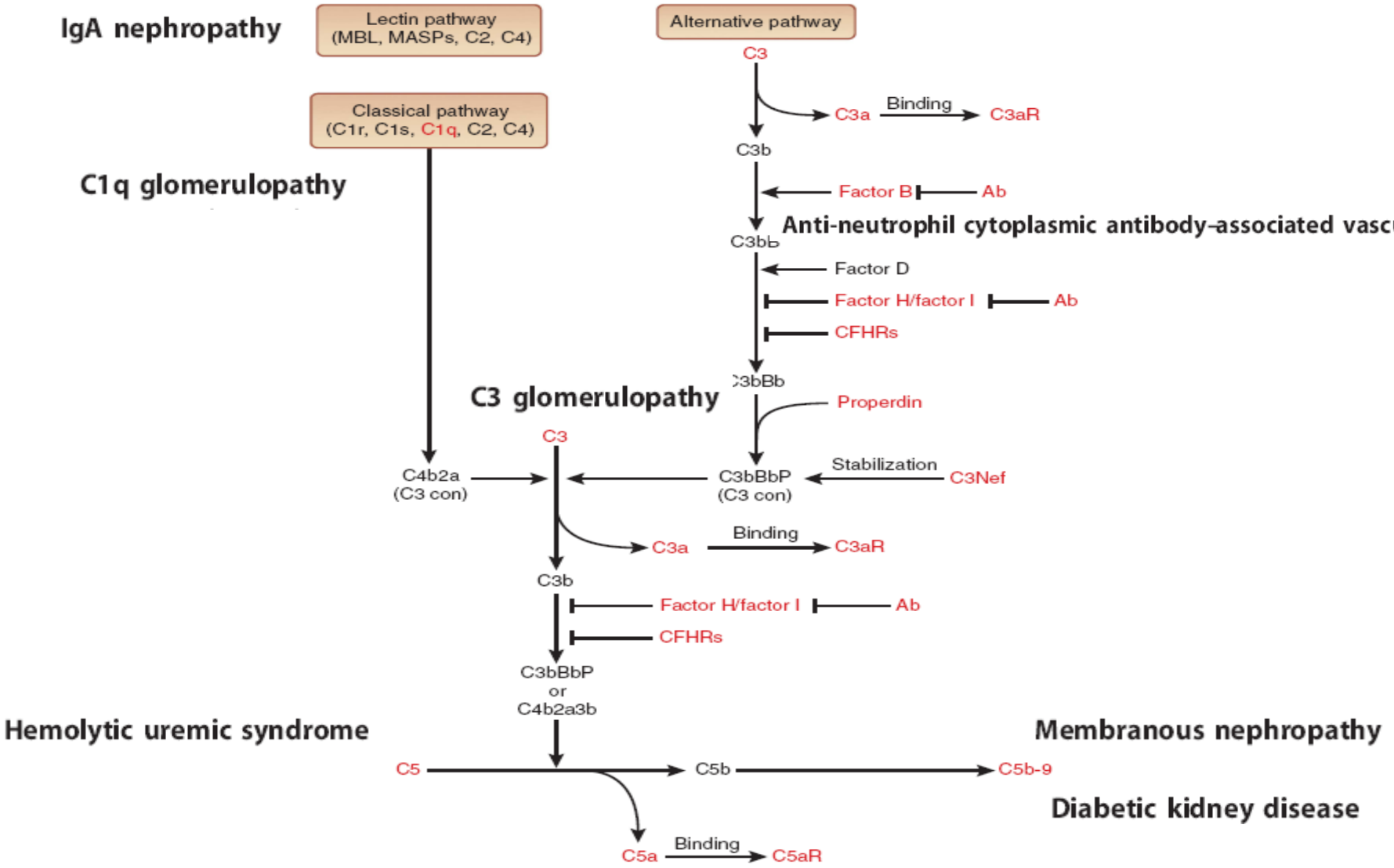
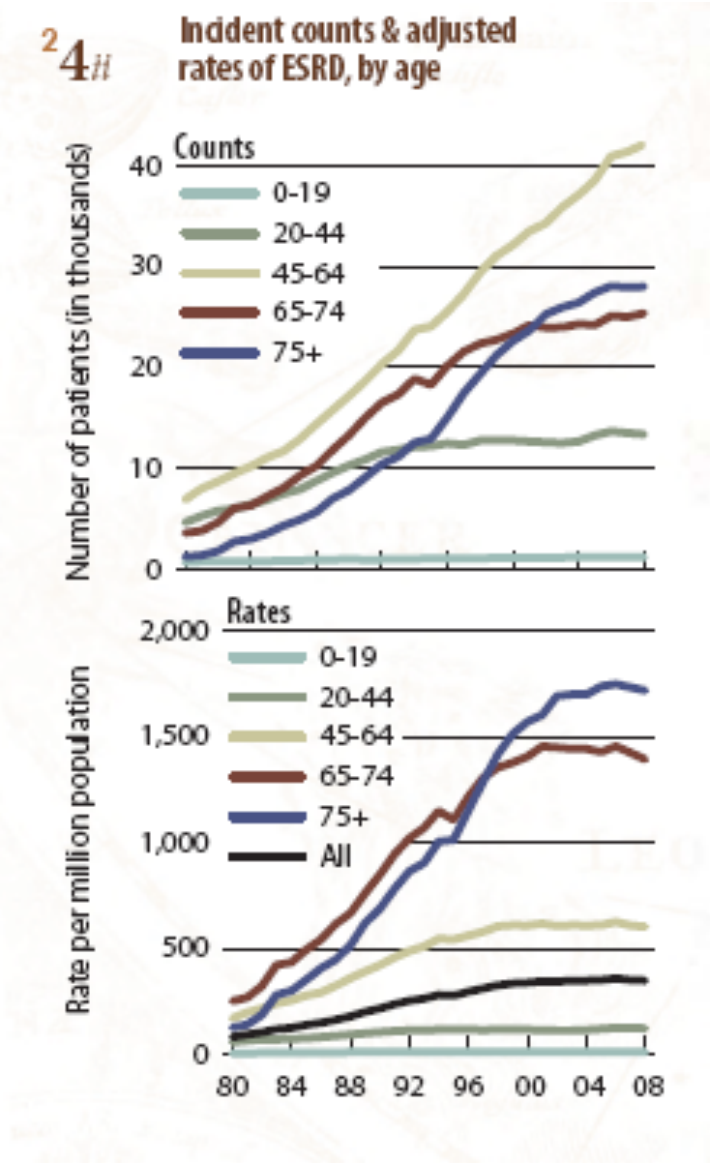
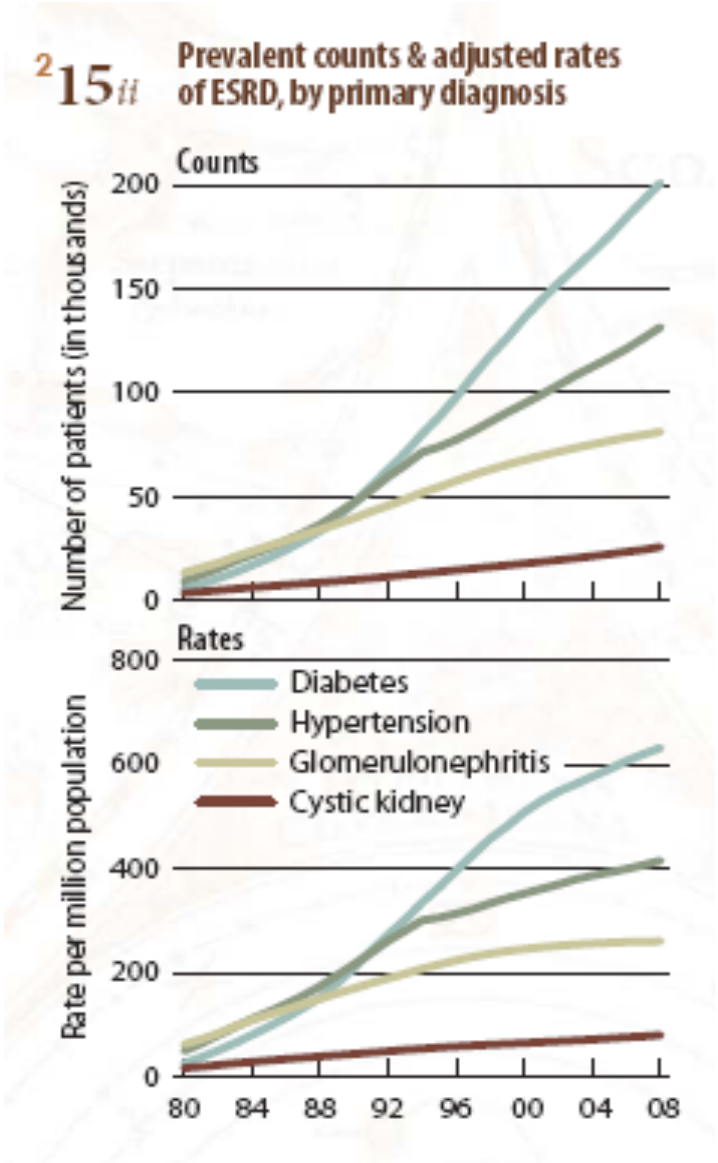


Figure 1 | Complement components and related molecules implicated in abnormal activation. The pathways of complement activation are depicted, with particular emphasis on the alternative pathway. The molecules highlighted in red are the complement components and the related molecules specifically discussed in this review. Ab, antibody; C3 con, C3 convertase; C3Nef, C3 nephritic factor; C3aR/C5aR, C3a receptor/C5a receptor; CFHRs, complement factor H–related proteins; MASPs, mannose-binding protein–associated serine proteases; MBL, mannose-binding lectin.

C + IgS	**PENSAR EN VÍA CLÁSICA**
C3	**PENSAR EN VÍA ALTERNA**
C4	**PENSAR EN VÍA DE LAS LECTINAS**





Desde el año 2000, la tasa ajustada de incidencia de la enfermedad renal terminal ha aumentado un 9.4% para sujetos >75 años, a 1.718 por millón en el año 2008

HOSPITAL BRITANICO DE BUENOS AIRES

SERVICIO DE NEFROLOGÍA

Some kind of happiness is measured out in miles

You can talk to me
If you're lonely, you can talk to me

Hey Bulldog Lennon & McCartney 1968