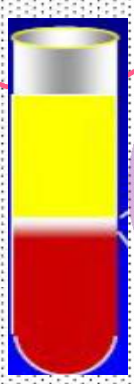
POWER

Ανάγκη ύπαρξης θεραπευτικών πρωτοκόλλων και επιστημονικής τεκμηρίωσης της αποτελεσματικότητας



Ιωάννης Γ. Γριβέας, MD, PhD
Νεφρολόγος

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MARKETING

WEB DESIGN

SUPPORT

DEVELOP

IDEAS

TEAM CPO

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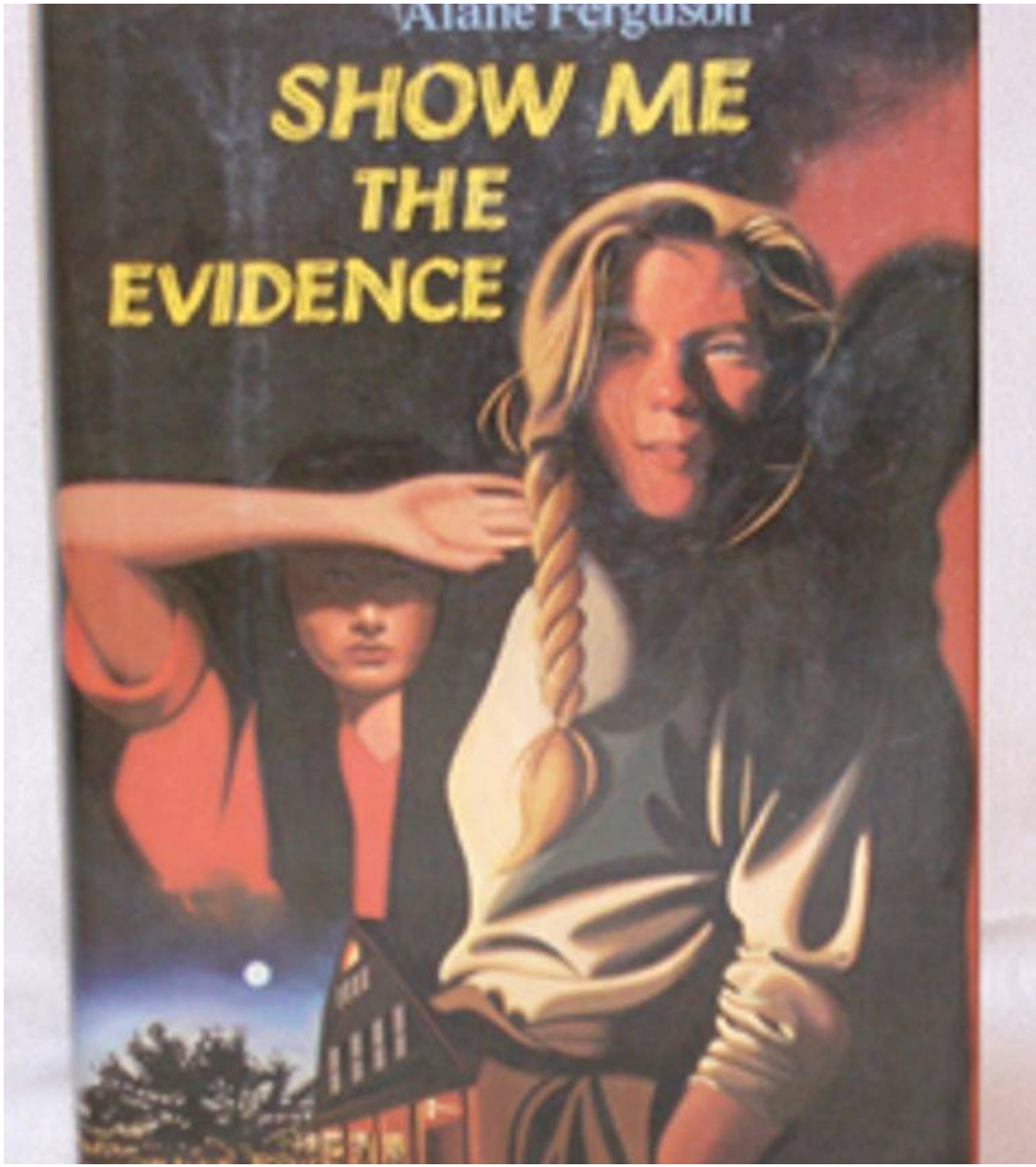
Various types of apheresis procedures have been performed on a clinical basis for many years, but the number of patients and types of diseases treated have risen significantly in the last 5 years. This increase is partially due to increased understanding of the disease and partially due to engineering advances in equipment technologies. By almost any standard, treatment by apheresis is still in relatively early stages of development—there are no ideal protocols based on a thorough understanding of reasons for its efficacy. Nevertheless, there is an increasing flow of clinical data, sometimes describing dramatic patient improvement, supporting the view that apheresis is a rapidly emerging technology with significant promise (117). Such evidence of treatment effec-



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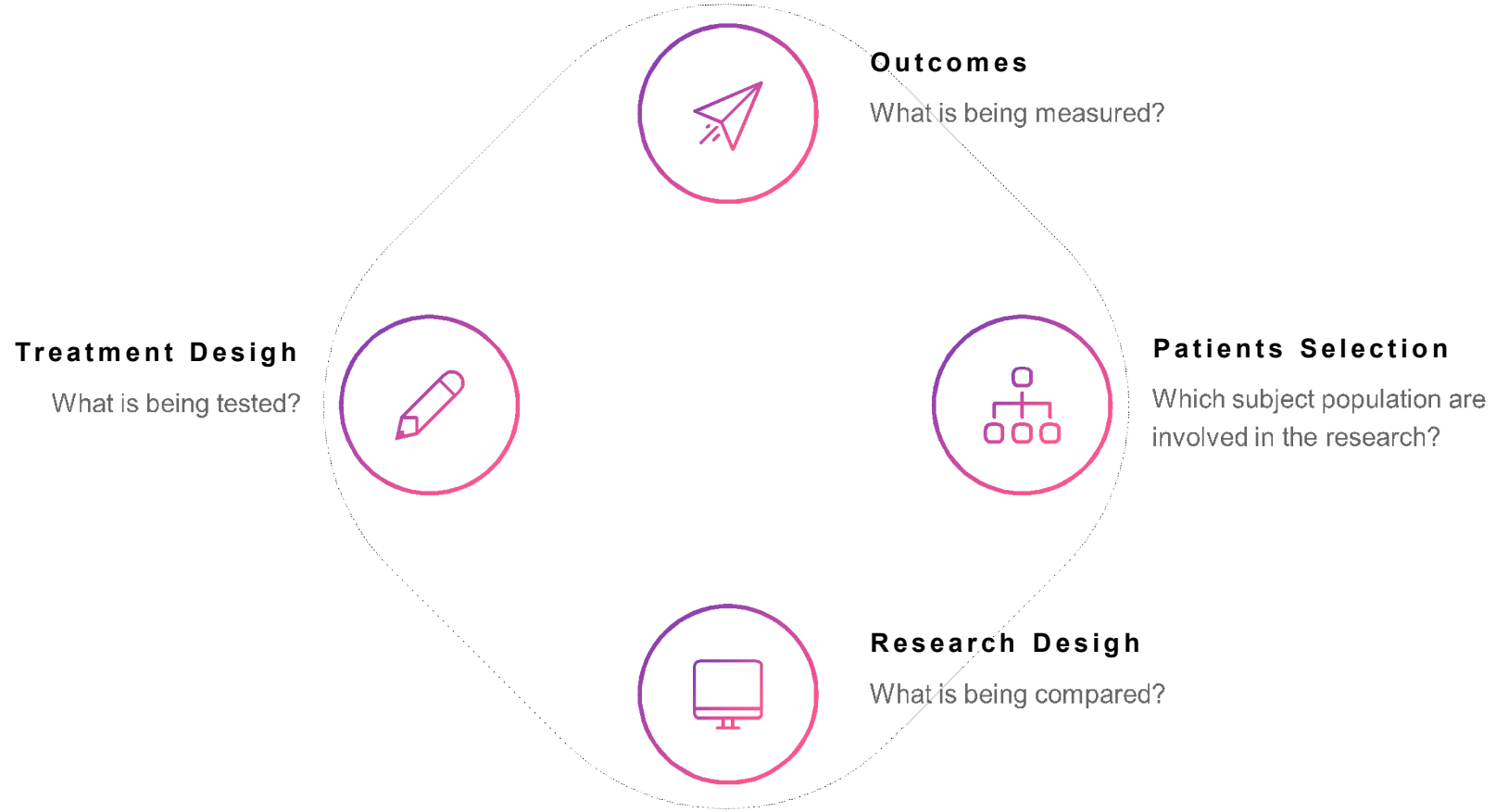
1981

L. F. Rothschild, Unterberg, Towbin, "Therapeutic Apheresis," unpublished, New York, Sept. 11, 1981.

*Effectiveness is the health benefit as measured under average conditions of use. *Efficacy* is the health benefit as measured under controlled conditions such as those in a randomized clinical trial (104).


Outcomes
What is being measured?
Treatment Desigh
What is being tested?
Patients Selection
Which subject population are involved in the research?
Research Desigh
What is being compared?

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Treatment Desigh
?Σαφήνεια σε σχέση με τα «ενεργά συστατικά»?

01 | Procedure involves a single treatment?

02 | Combination of treatments?

03 | Combination of treatment and non-treatments factors?

04 | Multivariant

05 | The extent to which researchers can measure the impact of any one component of the procedure

06 | Clarity of design

Varied Protocols

Type of replacement fluid

Patients selection criteria

Medications

Intensive care

Intensity of therapy

Variation of procedures

Variation in results

Difficult to compare

Normal glomerulus
ANCA glomerulonephritis
Diagram of glomerular inflammation (glomerulonephritis)
Glomerular inflammation (glomerulonephritis) in a kidney biopsy from a patient with ANCA vasculitis

Current management/treatment

Without treatment, GPA/MPA frequently progresses to ESRD over months. Symptoms include malaise, intermittent fever, weight loss, respiratory distress, and diffuse pain in joints and can culminate in mortality. The current management is combination therapy consisting of high-dose corticosteroids and cytotoxic immunosuppressive drugs (cyclophosphamide and rituximab). Two randomized trials indicate that rituximab is an effective alternative to cyclophosphamide in new or relapsing patients. Other drugs that have been used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors, mycophenolate mofetil, and antibodies against T-cells. Overall, existing controlled trials suggest no benefit of TPE for many cases with kidney involvement. Important exceptions are: Patients with (1) severe active kidney disease, i.e., requiring dialysis therapy or with serum creatinine concentration above 6 mg/dL; (2) severe pulmonary hemorrhage; and (3) anti-GBM disease who are also ANCA-positive.

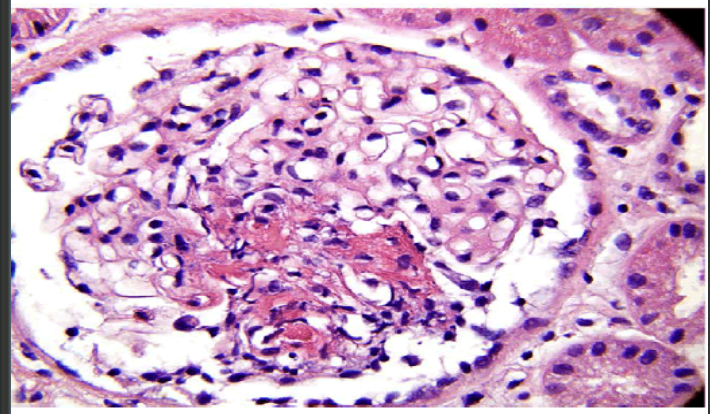

Figure 2: ANCA Vasculitis- Fibrinoid necrosis.

Incidence: 8.5/1,000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Dialysis dependence[a]	TPE	Grade 1A	I
	DAH	TPE	Grade 1C	I
	Dialysis independence[a]	TPE	Grade 2C	III
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	8(296)	1(26)	22(347)	NA

[a]At presentation, defined as Cr >6 mg/dL. DAH = diffuse alveolar hemorrhage.

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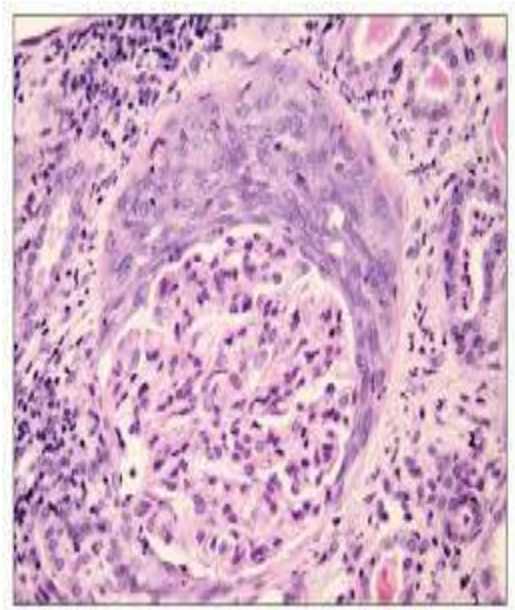
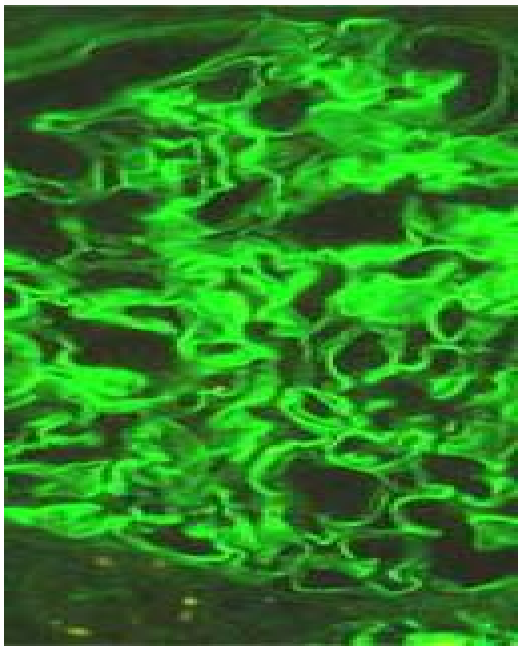
Even if standardized protocols could be developed, however, it maybe difficult or undesirable to administer them.

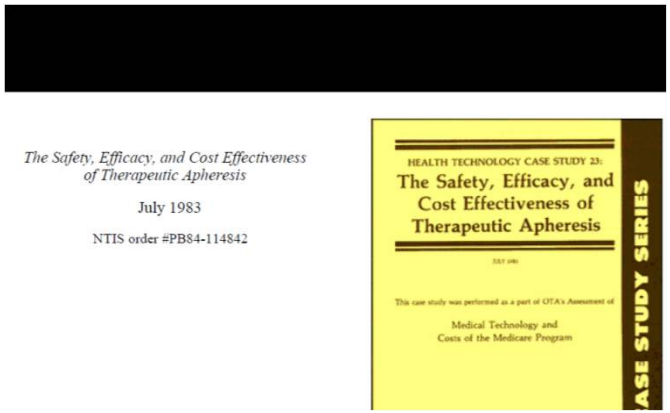
This is particularly problematic
if, for research purposes, assignment to one group or another is required.

Another obvious ethical concern is whether treatment can be denied patients in near-fatal, disease states in which apheresis has served as the treatment of last resort.





A last treatment design problem has to do with possible placebo effects of the therapy itself.



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Systematic Comparison-RCT

Case reports

A small sample size for RCTS

Related to the issue of appropriate research design is that multivariate analyses (useful for examining differences by such factors as age, sex, disease state, and levels of disability) are largely unavailable.

Studies which statistically control outcome data not easily conducted because such analyses require large patient populations and present difficulties both in data collection and analysis.

Apheresis researchers, however, seek to generate systematic experimental designs with comparison group information and multiple, longitudinal outcome measures.

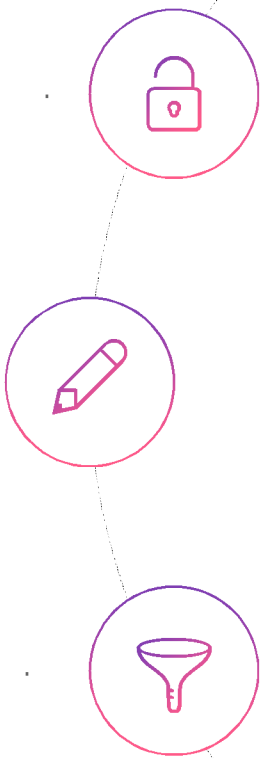
Patient Selection Criteria

Perhaps the most severe sampling problem in apheresis studies stems from the use of the therapy as a last resort, i.e., for the “worst cases.”

Eligibility for treatment

Selection for participation in research

Availability for follow-up research



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Where patients and their physicians are highly motivated to try any promising therapy because continued painful symptoms or death is the likely outcome without the therapy and there is no effective alternative treatment available.

High motivation can likely play an important role in the patient's response to a number of subjectively determined outcome criteria, producing overly optimistic results .

13

A "Desperation-Reaction" Model of Medical Diffusion

by Kenneth E. Warner

Knowledge about the adoption and diffusion of innovations is briefly reviewed. A model is then proposed to explain how certain innovations, intended to address dire medical problems, might diffuse in a manner not previously reported, with extensive diffusion occurring during what would be a period of small-scale experimentation and limited adoption in the conventional innovation-diffusion environment. The model is illustrated with findings from a case study of the diffusion of drug therapies for four types of leukemia. Possible implications of "desperation-reaction" diffusion are suggested.

New technology and new techniques in medicine have eased suffering, prolonged survival, and produced cures that would have been impossible a decade ago. At the same time, technical change in medicine has contributed to resource wastage and inflation. The profound and pervasive effects of technical change extend to the organization of medical care delivery, to increasing specialization among health professionals, and to societal expectations about the role and potential of modern medicine [1,2].

Despite their interest and importance, processes of technical change in medicine are only poorly understood. Relatively little of the research on the stages of technical change [3,4] has focused on medical care; and, as Kaluzny observed in this journal [5], "There is a need for caution in making generalizations about the health system based on innovation studies in other areas." In fact, recognizing the economic idiosyncrasies of medical care—the unorthodox nature of both supply and demand—one might expect some of the processes of technical change in medicine to differ from their counterparts in more conventional economic settings.

Through theoretical consideration and through discussion of some findings from an empirical study, this article focuses on diffusion of medical innovations—the final stage of medical technical change—in a specific context: namely, the introduction of an innovation, relatively inexpensive and easy to adopt, that is designed to address a dire medical problem, for example a terminal illness. Diffusion has not been studied in this context before, and

Address communications and requests for reprints to Kenneth E. Warner, Ph.D., Department of Health Planning and Administration, School of Public Health, University of Michigan, Ann Arbor, MI 48104.

Strategies for Medical Technology Assessment

September 1982

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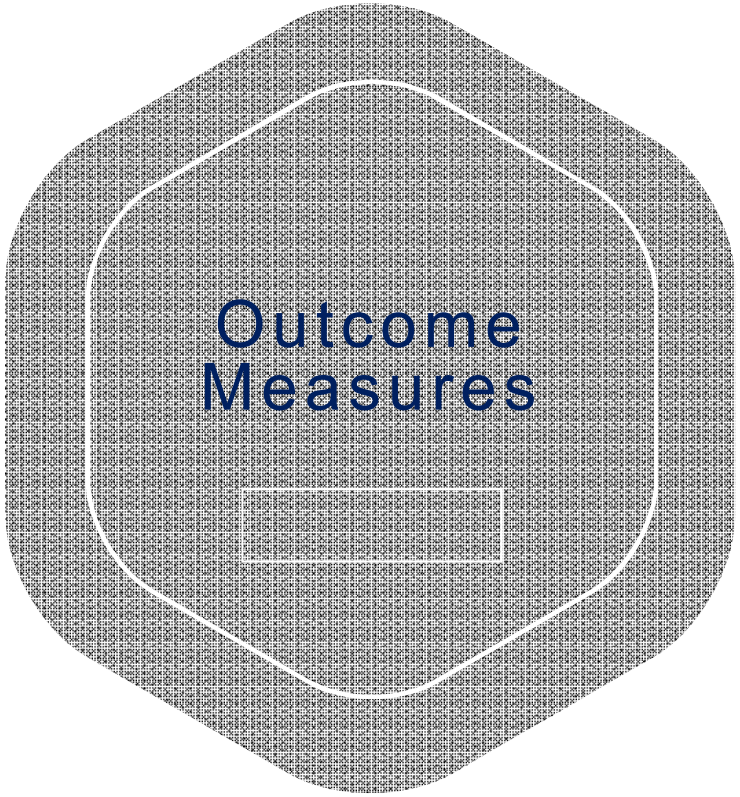
Statistical regression arises when patients are chosen because of their extreme value on a laboratory test or other measure relevant to treatments.

Investigators have found that subjects with high pretreatment measures tend to have lower scores after the treatment-when, in fact, no change has taken place.

This is the statistical regression effect and it can deceive clinicians into believing that apheresis has been effective when it really has not.



A recurring critical issue in any attempt to analyze the effectiveness of a medical technology is the selection **of appropriate endpoints for evaluating the success or failure of the intervention.**

The way in which outcomes of apheresis therapies are measured significantly affects interpretation of apheresis therapy research.

Haemolytic uraemic syndrome

Syndrome comprising

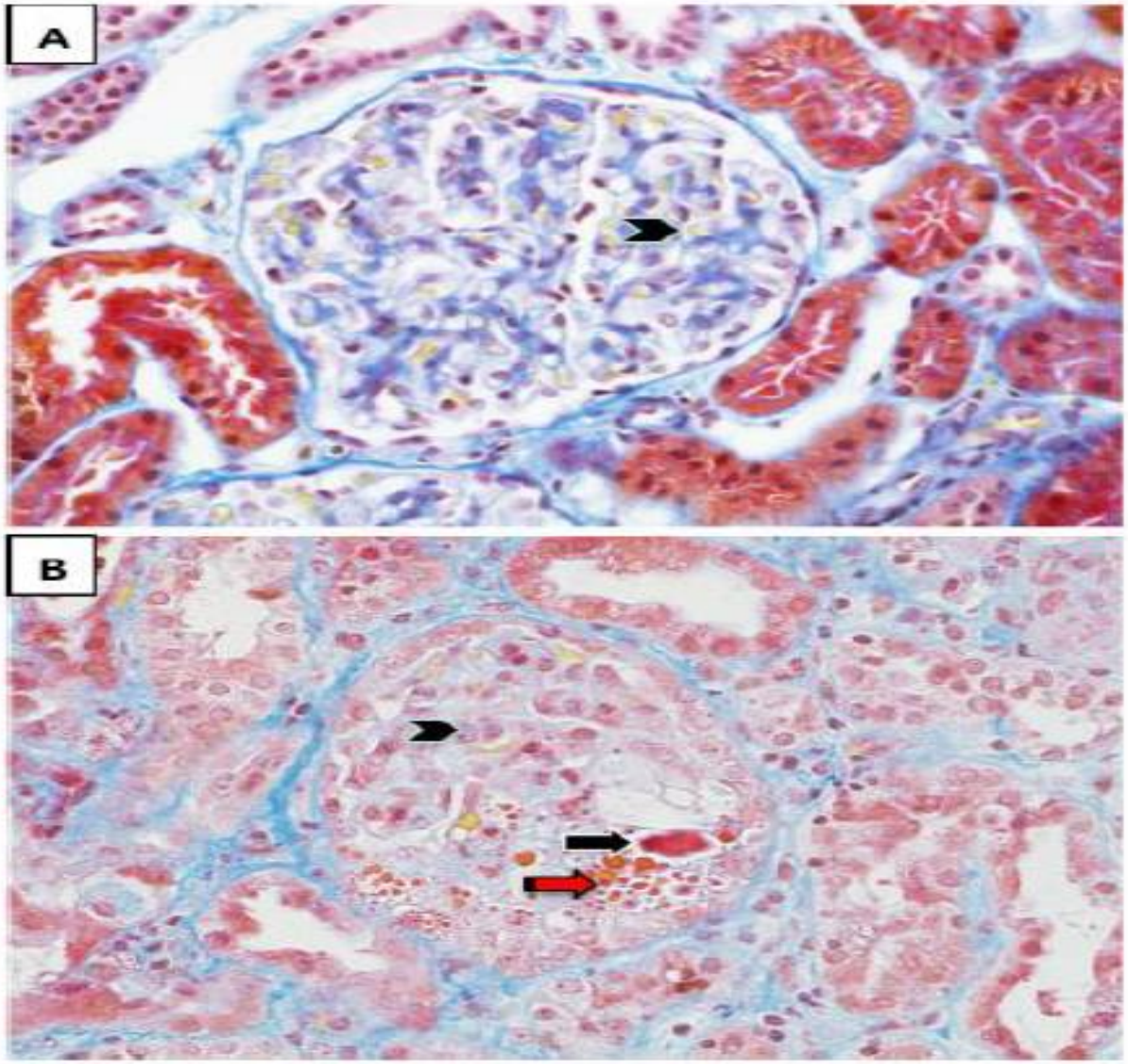
acute renal failure of varying severity
microangiopathic anaemia
thrombocytopenia of varying severity

Multiple aetiologies

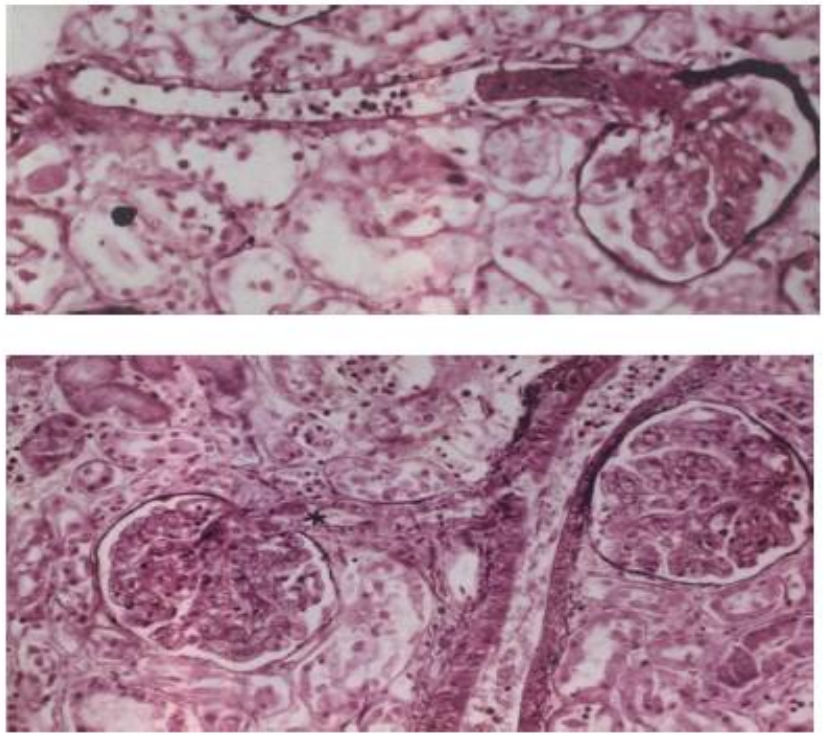
- Fibrin thrombi
- Endothelial cell swelling
- Red cell fragmentation

athens-NEPHROLOGY

Figure 1. Glomerular pathology in hemolytic uremic syndrome



Acute Kidney Injury



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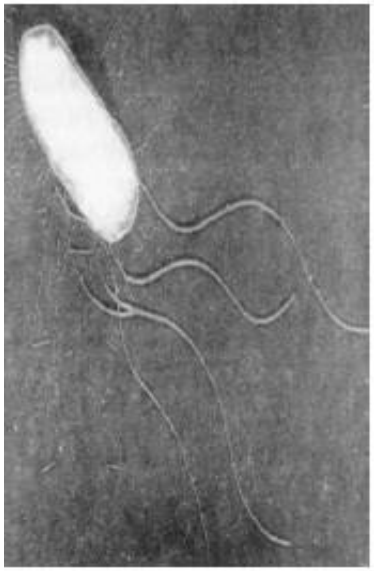
REVIEW

Update on hemolytic uremic syndrome: Diagnostic and therapeutic recommendations

Maurizio Salvadori, Elisabetta Bertoni



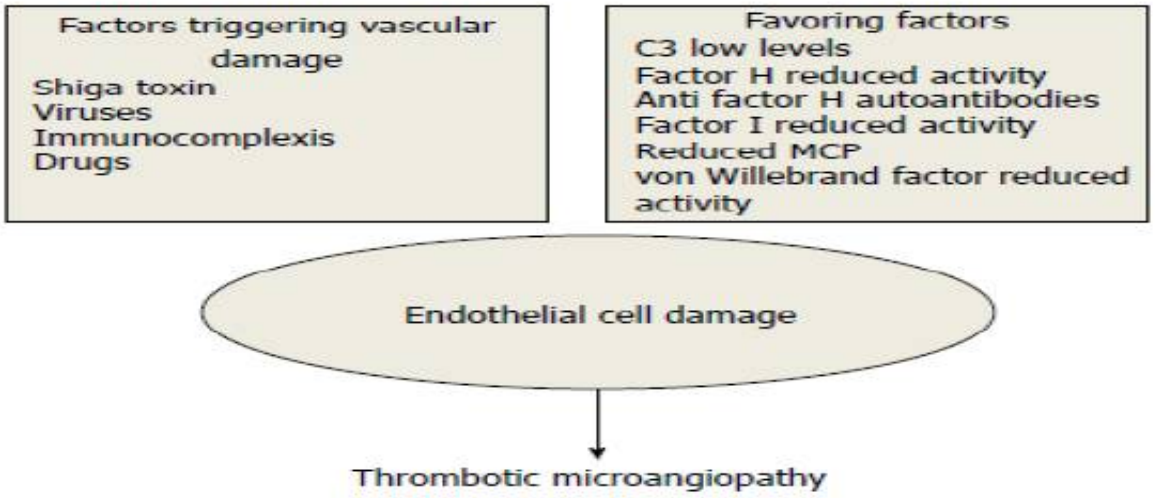


Figure 1 Pathogenetic mechanisms of thrombotic microangiopathy. MCP: Membrane cofactor protein.

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HEMOLYTIC UREMIC SYNDROME, ATYPICAL

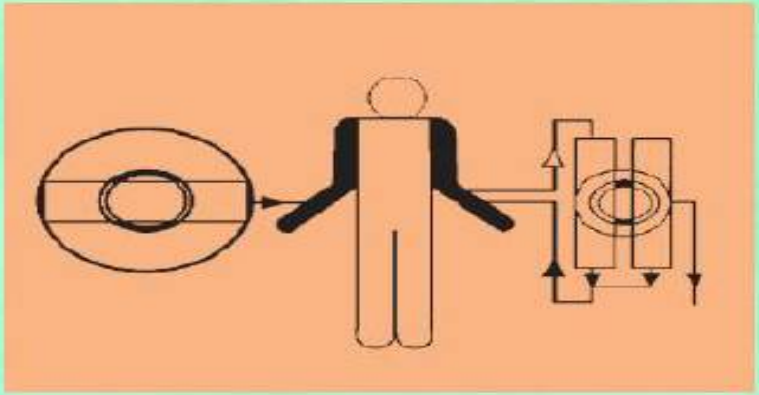
Incidence: 3.3/1,000,000/yr (<18 yo); 7/1,000,000/yr (children in European community)

Condition	Procedure	Recommendation	Category
Complement factor gene mutations	TPE	Grade 2C	II
Factor H autoantibodies	TPE	Grade 2C	I
MCP mutations	TPE	Grade 1C	IV

# of reported patients*: >300

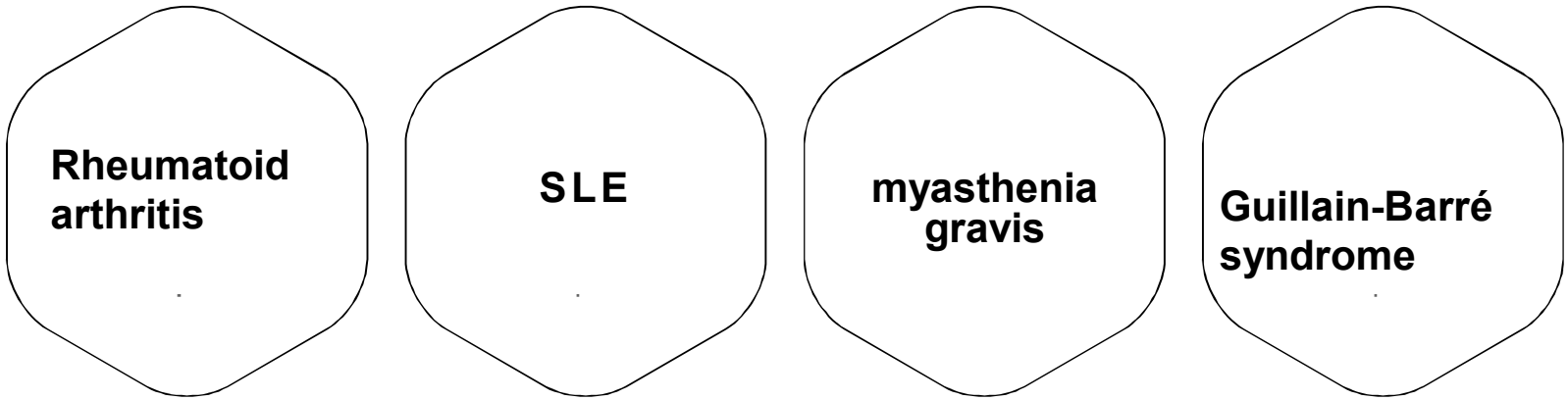
	RCT	CT	CS	CR
Complement factor gene mutations	0	0	4(23)	21(26)
Factor H autoantibody	0	0	2(6)	2(2)

MCP = membrane cofactor protein

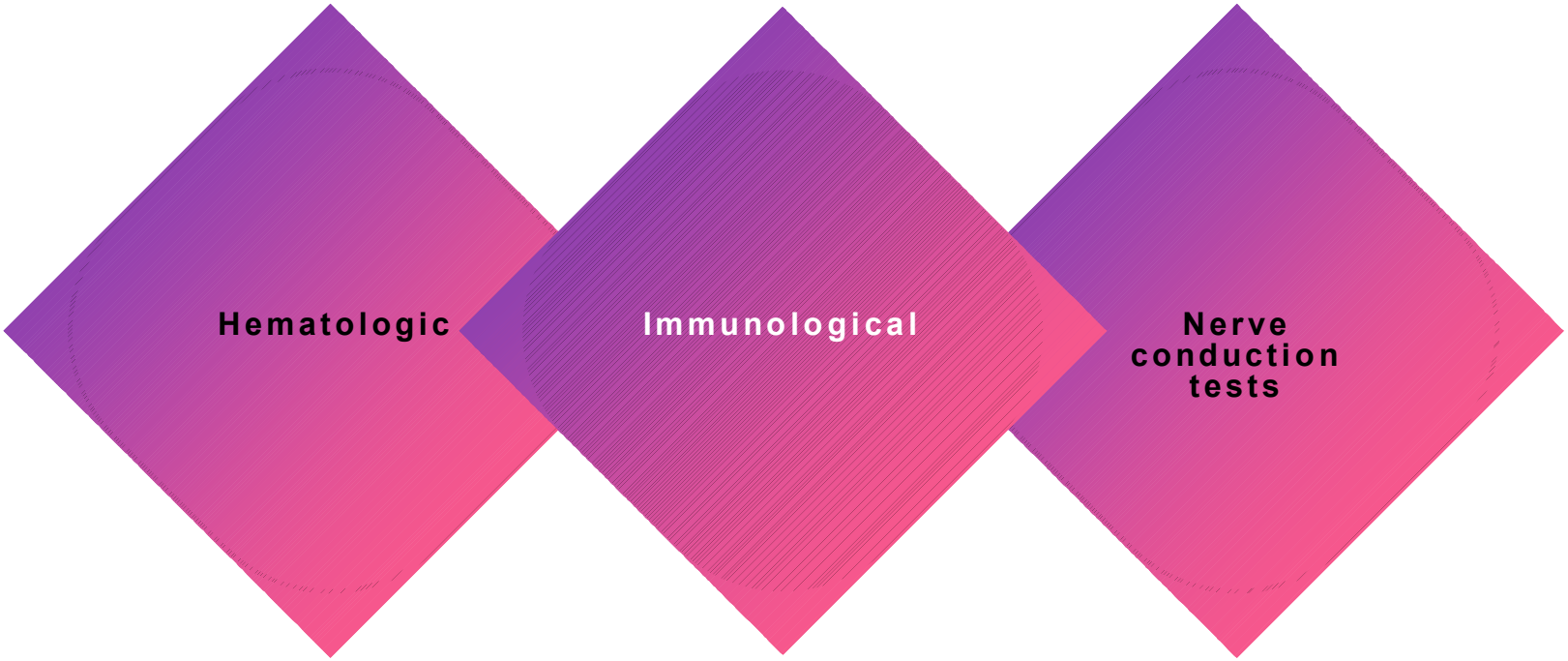


athens-NEPHROLOGY

Interpretation of clinical improvement for many diseases treated by apheresis is further confounded by the variability produced by a basic "remitting exacerbating" nature of the illness.



Clinical outcomes



Finally, outcome measures probably suffer from the lack of systematic documentation of adverse effects.
As a new technology is developed, used, and reported, researchers and practitioners may also champion the technology for a variety of personal and professional reasons .

Apheresis therapy reporting may have been biased by the tendency to report the more successful uses of the new therapy.

What is Apheresis?

- **Apheresis** is Greek for "to take away" or "subtract"
- **Plasmapheresis** – remove plasma
- **Cytapheresis** – remove cells
  - **Leukopheresis** – remove white blood cells
  - **Erythropheresis** – remove red blood cells
  - **Plateletpheresis** – remove platelets
- Originally performed discontinuously
- Now performed with continuous removal and separation of blood components

Cell therapy companies & their products

~300 therapeutic companies with ~250 cell-based therapies in the market or in some stage of clinical development. These therapies can be roughly broken down into the following stages*:

~110 Phase I
~70 Phase II
~30Phase III
~40 Commercial (marketed in at least one country)

Only ~1/3 of the therapies currently marketed (~13) required and received regulatory approval. In contrast, an estimated 90% of the therapies in development are "products" requiring pre-market approval.

* Note that these numbers are limited to industry-sponsored trials and may not capture fully products in early-stage trials where industry "sponsorship" is less than transparent.

Have the fundamentals changed?

- **Cell therapy is here – instances of it being routine clinical practice & commercial**
- There has been incremental success
  - CT is now very much a part of individual, corporate, academic, policy, and financial consciousness
  - CT is now part of routine clinical practice and commercial products
  - Emerging metrics of a maturing industry (e.g., players, orgs, FDA, etc.)
  - On financial sector's radar
  - Now working on second generation (not first generation) products.

- Very little of this was true 10 year's ago.

Phase III Clinical Trials

- Refractory angina and chronic myocardial ischemia
- Renal cell carcinoma
- Multiple sclerosis
- Prostate cancer
  - Similar to Provenge but with some important variations

Polymyxin B Hemoperfusion

EUPHAS Clinical Trial

- Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS)
  - Randomized 64 patients @ 10 Italian tertiary care ICUs
  - Significant improvements:
    - Cardiac index; Left ventricular stroke index; Oxygen delivery index
  - Shorter hospital stay and better 28-day survival (32% in the hemo-adsorption group compared with 53% in the control group ($P = 0.03$)).
  - Not different:
    - Endotoxin and IL-6 levels pre-post treatment
    - Organ dysfunction (SOFA) between control and treatment group
  - The study was prematurely stopped because
    - It was judged to be unethical to deprive patients of hemoadsorption
    - Inability to blind treating physicians

Polymyxin B Hemoperfusion

EUPHRATES Clinical Trial

- Evaluating the Use of Polymyxin B in Randomized controlled trial of Adults Treated for Endotoxemia and Septic Shock (EUPHRATES)
  - 360 patients in 15 centers in the United States
  - primary end point of 28-day mortality

Conclusions re Hemoperfusion with Polymyxin-B:

- "No large-scale randomized trials have been completed and lower mortality has not yet been sufficiently demonstrated." (JC Schefold).
- 3 authors conclude that single LPS adsorption did not improve morbidity or organ dysfunction (Amoureaux et al; Staubach et al; Cruz et al).

Cytokine Adsorbing Columns

(Non-selective)

Company	Cytosorbents	Toray	Kaneka	Kaneka
Product	Cytosorb	Cyt-860-DHP	Lixelle	CTR-001
Structure	Polystyrene divinyl co-polymer beads	Polystyrene conjugated fiber	Porous cellulose beads	Porous cellulose beads
Methods	In vitro circuit	Batch	Batch	Batch
TNF-α	<50%	20%	31.2%	53%
IL-1β		97%	98.5%	98%
IL-6	<50%	92%	82.9%	80%
IL-8		99%	99.9%	80%
Animal	Rat		Rat	Rat
Method	Endotoxin injection, CLP		Endotoxin injection	Endotoxin injection

Altrichter et al. Critical Care 2011, 15:R82
http://ccforum.com/content/15/2/R82

CRITICAL CARE

RESEARCH Open Access

Extracorporeal cell therapy of septic shock patients with donor granulocytes: a pilot study

Jens Altrichter[1], Martin Sauer[2], Katharina Kaftan[1], Thomas Birken[2], Doris Gloger[3], Martin Gloger[4], Jörg Henschel[4], Heiko Hickstein[1], Ernst Klar[3], Sebastian Koball[1], Annette Pertschy[3], Gabriele Nöldge-Schomburg[2], Dierk A Vagts[2] and Steffen R Mitzner[1*]

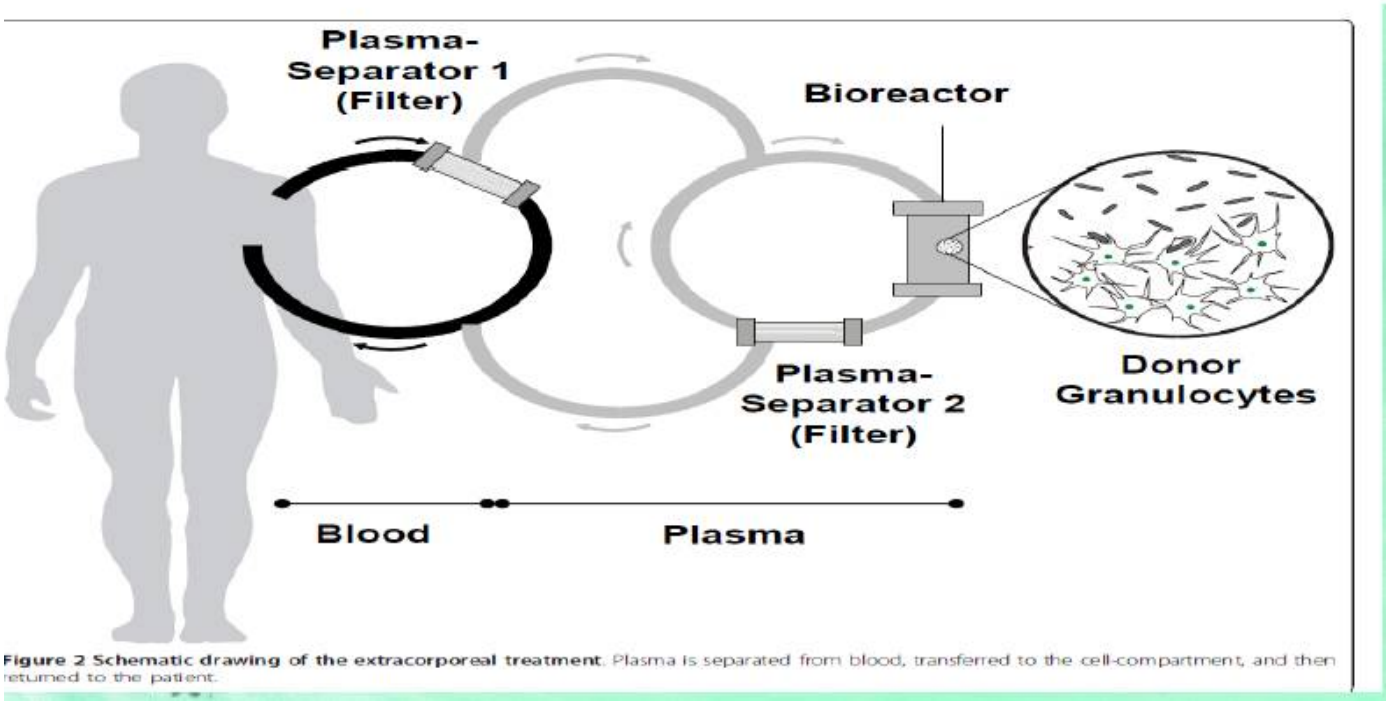
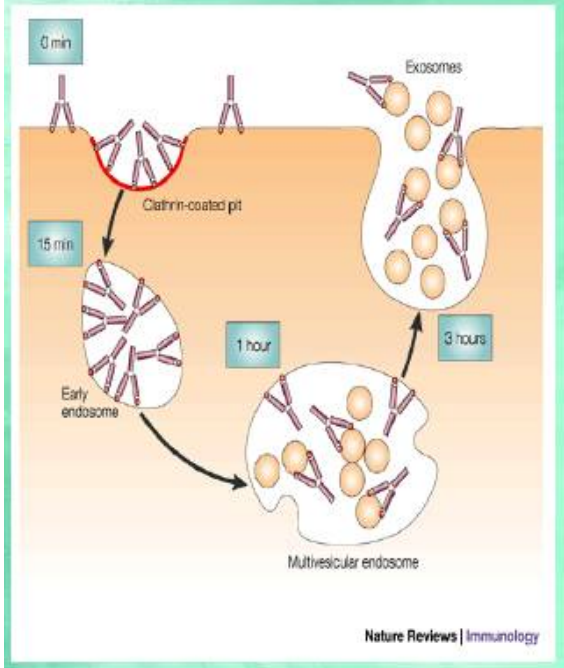


Figure 2 Schematic drawing of the extracorporeal treatment. Plasma is separated from blood, transferred to the cell-compartment, and then returned to the patient.

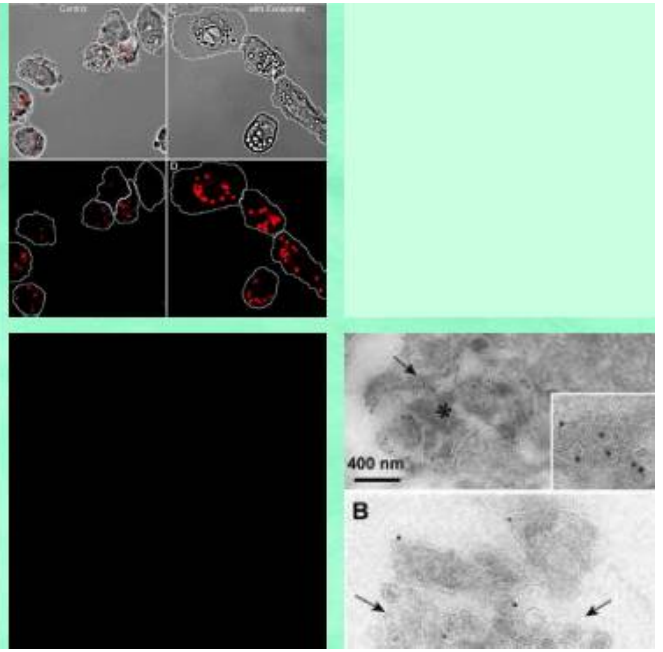


Exosomes

- A specific subset of membrane-bounded vesicles formed intracellularly within vesicular endosomes.
- Released into the extracellular environment by many cells from different tissues and organs.
- Exist in a wide range of biological fluids, including blood and urine.
- Between 30 and 100 nm in diameter.

Exosomes

- Have a molecular envelope structure that is remarkably similar to that of viruses.
- Have a hydrophilic core containing proteins, mRNAs and microRNAs (miRNA).
- Originally thought to be "cellular trash bags"
- Now, widely believed to be involved with intercellular communications.

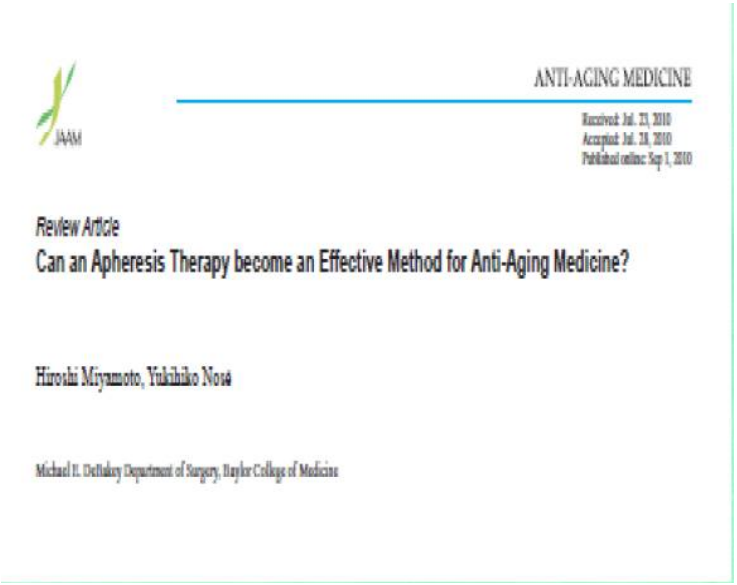


Exosomes

- Both mRNAs and miRNAs present in the exosomal fraction maintain their function when transferred to other cells demonstrating that exosomal RNA transfer may be an important route for epigenetic signaling between cells.
- Transferred RNAs can affect protein production and gene expression in target cells.
- The dissemination of pro-cancer cargo by exosomes has been identified as promoting several critical aspects of cancer pathogenesis, including:
  - signaling for tumor growth,
  - metastasis,
  - angiogenesis, and
  - resistance to chemo- and immunotherapeutic agents.

Phase III Clinical Trials

- Glioblastoma
- Recurrent glioblastoma
- Alzheimer's disease
  - Utilize plasma exchange for treatment



JAAM

ANTI-AGING MEDICINE

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Published online: Sep 1, 2010

Review Article

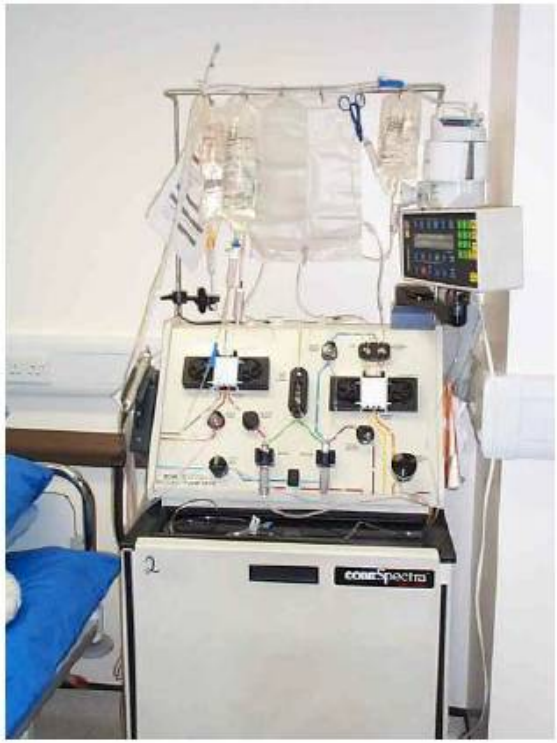
Can an Apheresis Therapy become an Effective Method for Anti-Aging Medicine?

Hiroshi Miyamoto, Yukihiko Nose

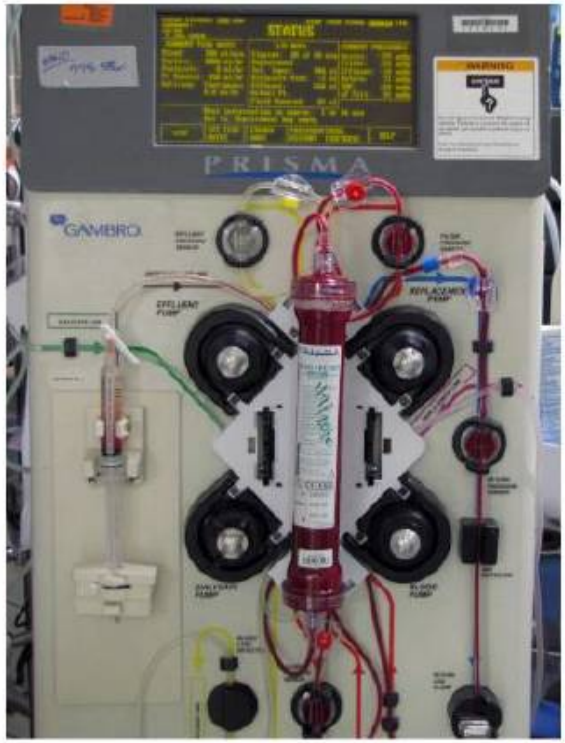
Michael E. DeBakey Department of Surgery, Baylor College of Medicine

Challenge 1: The Apheresis Modality

Cobe Spectra



Gambro Prisma



Challenge 2: Role of ADAMTS13 Removal in Thrombotic Thrombocytopenic Purpura

Challenge 3: Defining the Role of Therapeutic Plasma Exchange in Atypical Hemolytic Uremic Syndrome Treated with Eculizumab

Challenge 4: Role of Therapeutic Plasma Exchange in Multiple Myeloma

POWER

In-Depth Review

Blood Purification

Blood Purif 2016;41:1–10
DOI: 10.1159/000439238

Published online: October 20, 2015

New Options of Apheresis in Renal Diseases: How and When?

Jolanta Korsak Zofia Wańkowicz

Military Institute of Medicine, Warsaw, Poland

Conclusion

Plasmapheresis and its new options became important tools in the therapy of primary and secondary autoimmune renal diseases. Limited practical use of the method stems mainly from the lack of controlled, multicenter clinical studies as well as the disproportion between a significant technological development and still insufficient knowledge of the method's pathomechanism. It is to be hoped that this new century, thanks to increasingly applied proteomics and molecular biology achievements, will bring on the breakthrough in clinical application of apheresis and its new options, particularly in autoimmune renal diseases.

CONCLUSIONS

- The clinical application of therapeutic plasma exchange to patients with kidney disease continues to evolve
- Likely to be a growing number of potential target molecules
- Need for more information about the relationship between target removal and clinical outcomes
- TPE likely to be coupled to other therapies
- Apheresis remains a safe but crude technology