PRODUCTION

Νέες οπτικές στην εφαρμογή της ανοσοπροφύλαξης στη σήψη

DIRECTOR

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CAMERA

Νεφρολόγος

athens-NEPHROLOGY

DATE

29/1/2025

SCENE

TAKE

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

Τι είναι σήψη ;

- Δεν υπάρχει ως σήμερα ένας “καλός” ορισμός για τη σήψη
- Πολλές προσπάθειες ταξινόμησης ανάλογα με τα κλινικά συμπτώματα, τη βαρύτητα, το “score” των ασθενών ή την απάντηση στη θεραπεία
- Thomas L (1972): “Κλινικό σύνδρομο που επιπλέκει τη λοίμωξη και χαρακτηρίζεται από συστηματική απορρύθμιση της φυσιολογικής φλεγμονώδους αντίδρασης”
- Pinsky M (1989): “Κακοήθης μορφή ενδαγγειακής φλεγμονής”
- Kellum J (2000): “ Διάχυτη - Τοπική φλεγμονή όπου η κυρίως διαδικασία συμβαίνει σε ιστικό επίπεδο και ό,τι υπάρχει στην κυκλοφορία είναι το αποτέλεσμα “υπερχείλισης” αυτής της φλεγμονής

Consistency in Sepsis Definitions

Pathogen Removal by Haemadsorption

1991	2001	2016
Sepsis 1	**Sepsis 2**	**Sepsis 3**
Sepsis is the systemic response to ***infection***, manifested by two or more of the SIRS criteria as a result of infection	Sepsis = the systemic response to ***infection***, manifested by two or more of the SIRS criteria as a result of infection, and some of the following: • Fever or hypothermia • Tachycardia • Tachypnea • Altered mental status • Significant fluid imbalance • Hyperglycemia • Inflammation • Altered hemodynamics • Organ dysfunction • …	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to ***infection***

Infection is Key

Pathogen Removal by Haemadsorption

Treatment?

• Empirical Antibiotic Therapy

- Antibiotics are the standard of care for bloodstream infections, but inappropriate empirical administration occurs in 37% of those cases [1]
  - Mortality is 62% for BSI patients who receive inappropriate antibiotic therapy, vs 28.4% for patients who receive early, appropriate therapy.[2]

- Rapid *effective* treatment is essential, but there is a delay while pathogens are identified.

1) Byl, Baudouin, et al. "Impact of infectious diseases specialists and microbiological data on the appropriateness of antimicrobial therapy for bacteremia." *Clinical infectious diseases* 29.1 (1999): 60-66.
2) Ibrahim, Emad H., et al. "The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting." Chest Journal 118.1 (2000): 146-155.

Pathogen Removal by Haemadsorption

Problems With Treatment?

• Antibiotic Resistance

Rates of antimicrobial resistance in European Union countries (date from European Centre for Disease Prevention ad Control, 2016[2]).

Pathogen	Resistance Rate
ESBL-producing *Escherichia coli*	12%
MDR *Escherichia coli*	5%
ESBL-producing *Klebsiella pneumoniae*	26%
CR *Klebsiella pneumoniae*	6%
MDR *Klebsiella pneumoniae*	16%
CR *Pseudomonas aeruginosa*	15%
CR *Acinetobacter* spp.	35%
Methicillin-resistant *Staphylococcus aureus*	14%
Vancomycin-resistant *Enterococcus faecium*	12%

ESBL, extended-spectrum beta-lactamase; CR, carbapenem-resistant;
MDR, multi-drug-resistant (resistant to third-generation cephalosporins, fluroquinolones and aminoglycosides).

- It is estimated that, in 2018, at least 700000 people die of antibiotic-resistant infections every year globally, and 10 million lives/year could be lost due to antimicrobial resistance by 2050

Νεότερη ταξινόμηση του συνδρόμου της σήψης

PIRO staging system

Predisposition: προδιάθεση του ξενιστή - γενετικοί παράγοντες

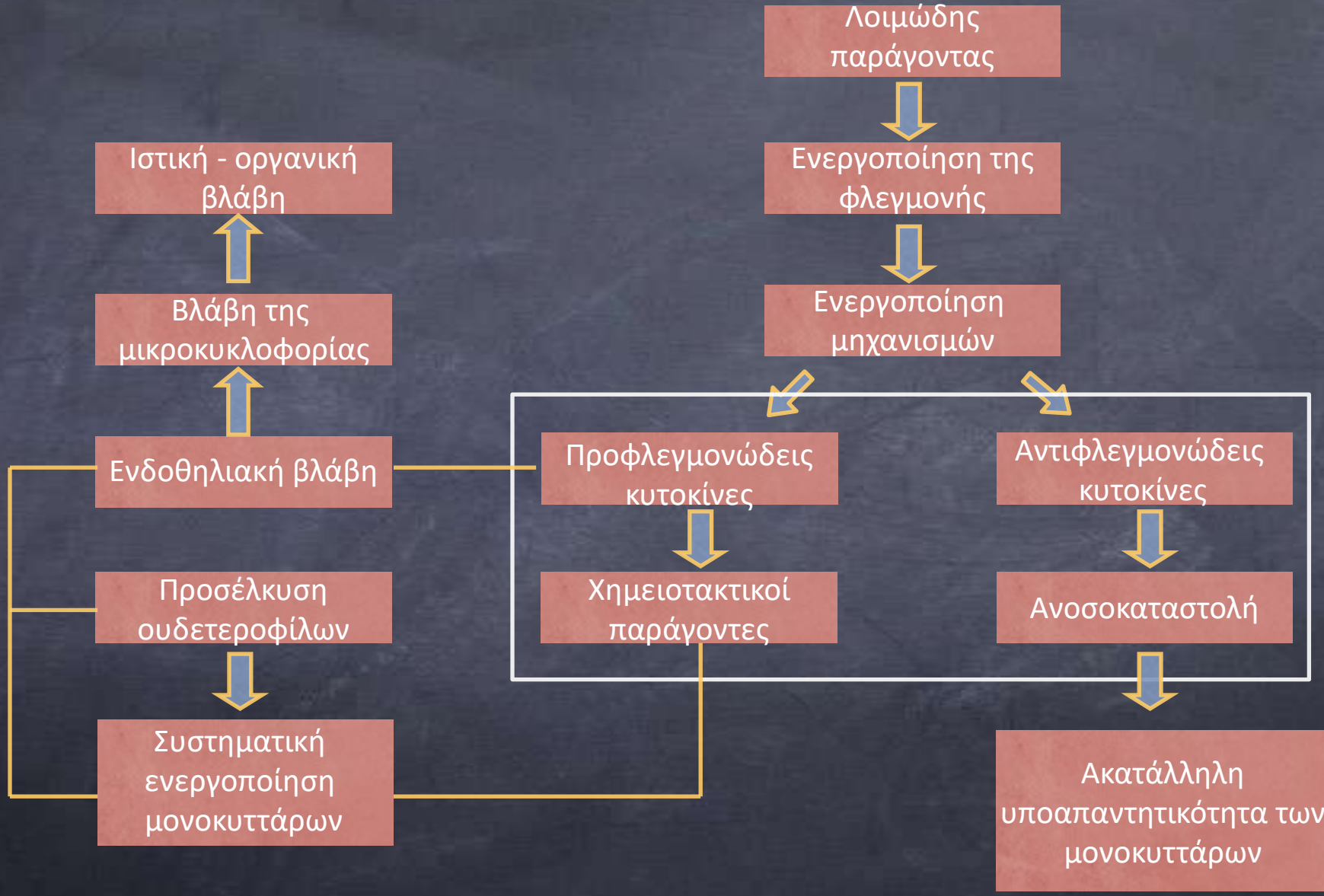
Infection insult: είδος του μικροοργανισμού - εστία λοίμωξης

Response: ανοσιακή απάντηση - επίπεδα μεσολαβητών

Organ dysfunction: συμμετοχή διαφόρων οργάνων στην κλινική εικόνα

Levy MM et al, International Sepsis Definitions Conference, Crit Care Med 1992

Διαφορετικά στάδια στην εξέλιξη της σήψης



Editorials

November 30, 1964

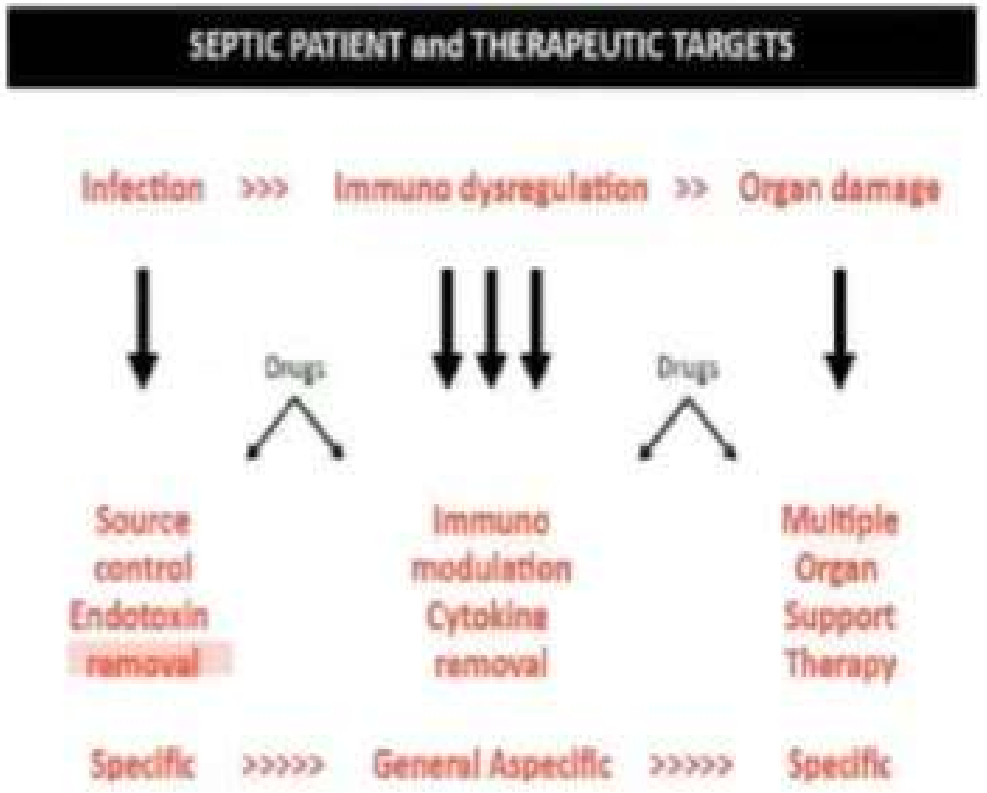
"ENDOTOXIN SHOCK"

JAMA. 1964;190(9):847-848.
doi:10.1001/jama.1964.03070220053016

Abstract

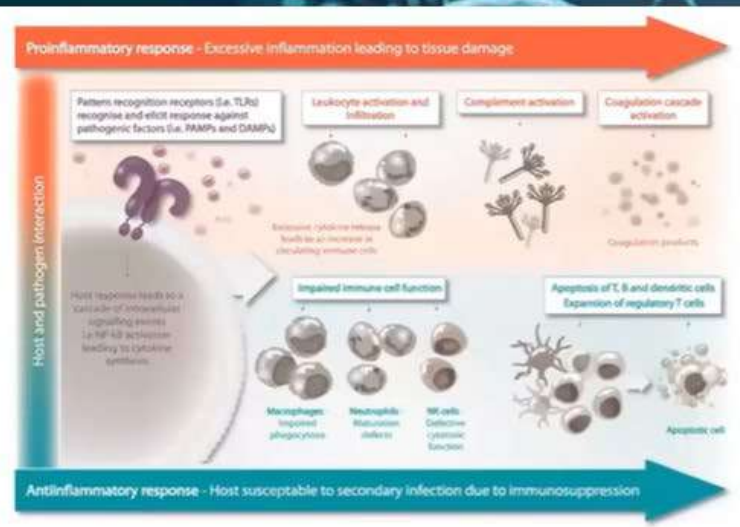
Endotoxin shock," so called because it is assumed to be caused by the release of toxin from gram-negative bacteria, presents the clinician with a therapeutic dilemma. Despite a variety of available procedures, no technique exists for removal or inactivation of the causative agent once it enters the circulation. Consequently the only successful treatment is symptomatic. In a recent evaluation of current management, Weil et al[1] indicate that none of the available therapeutic methods has been successful when used alone; however, used in judicious combi-

2020



De Rosa S. et al. Purif. 2019

4:59:39



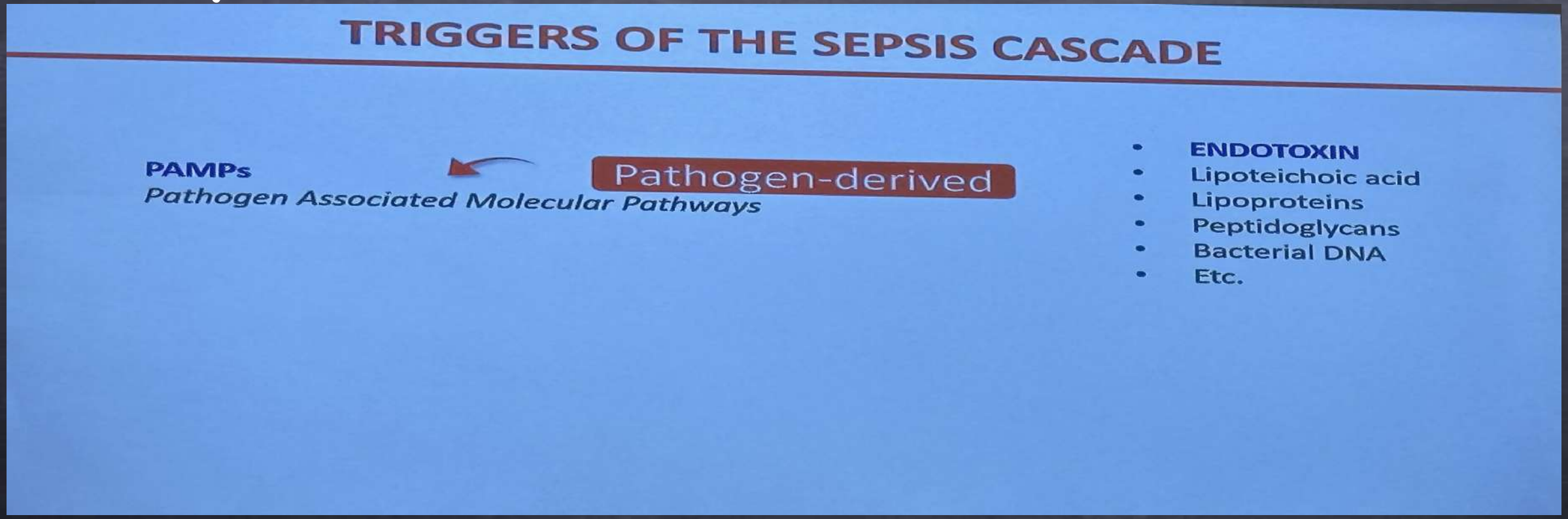
"Inflammation is a NECESSARY EVIL"

Nedeva C, Menassa J, Puthalakath H. Front Cell Dev Biol. 2019

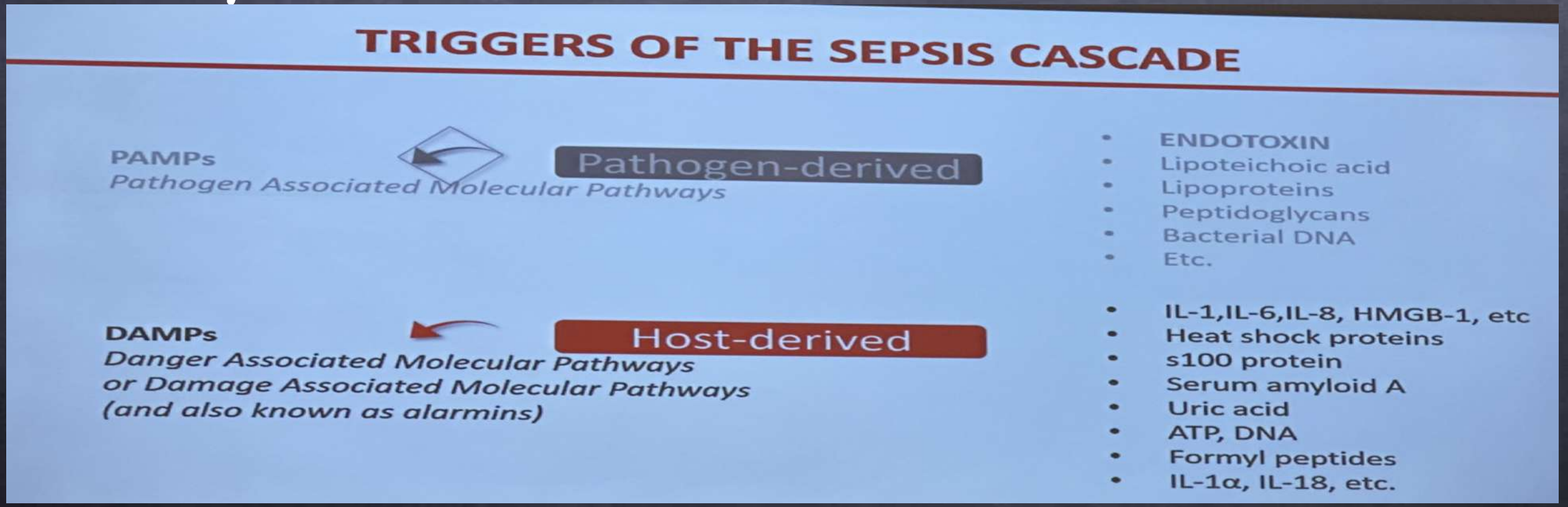
Event	Year(s)	Major Findings
Discovery of microorganisms	1676	Robert Hooke and Antoni van Leeuwenhoek independently discover living microorganisms by careful microscopy using lenses to identify microbes.
Proving the germ theory of disease	1860s	Louis Pasteur (1822–1864) and Robert Koch (1843–1910) demonstrate that microorganisms in infected tissues directly cause tissue injury. Organisms can be transmitted between animals and humans.
Ignas Semmelweis	1850s	Semmelweis (1818–1865) proves in 1847 that microbial pathogens can be transmitted by the hands of doctors and cause potentially lethal puerperal fever; hand hygiene prevents this from happening.
Discovery of Endotoxin	1892	Robert Koch and his colleague Richard Pfeiffer first prove that about 70% of the cell wall of Gram-negative bacteria is protease resistant and lipid sensitive material. They demonstrate that purified endotoxin injected intravenously is lethal to laboratory animals, forming Koch's Postulates.
Gram's stain aids to detect and define bacteria	1884	Hans Christian Gram (1853–1938) first develops a method to rapidly classify and identify bacteria as either Gram-positive or Gram-negative by differential staining and microscopy.
Polymyxin B bound hemofilters remove endotoxin	1994	Tohru Tani and Hisataka Shoji, et al. develop the cationic filters which will bind to circulating endotoxin and remove endotoxin from the circulation and can rescue patients from endotoxemia.

Shoji H, Opal SM. . Int J Mol Sci. 2021

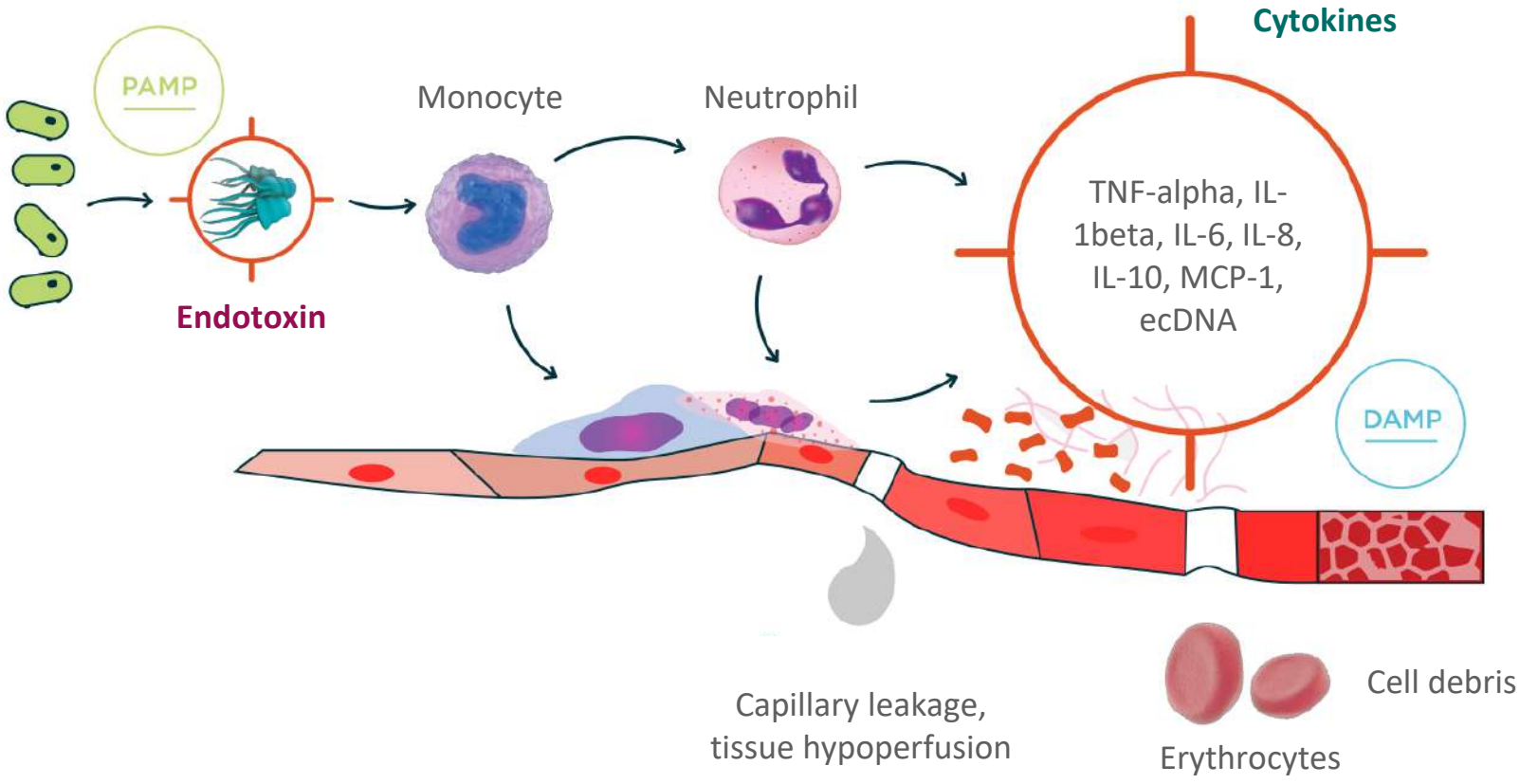
Did you know?


TRIGGERS OF THE SEPSIS CASCADE
PAMPs
Pathogen Associated Molecular Pathways
Pathogen-derived
ENDOTOXIN
Lipoteichoic acid
Lipoproteins
Peptidoglycans
Bacterial DNA
Etc.

Did you know?


TRIGGERS OF THE SEPSIS CASCADE
PAMPs
Pathogen Associated Molecular Pathways
Pathogen-derived
ENDOTOXIN
Lipoteichoic acid
Lipoproteins
Peptidoglycans
Bacterial DNA
Etc.
DAMPs
Danger Associated Molecular Pathways
or Damage Associated Molecular Pathways
(and also known as alarmins)
Host-derived
IL-1,IL-6,IL-8, HMGB-1, etc
Heat shock proteins
s100 protein
Serum amyloid A
Uric acid
ATP, DNA
Formyl peptides
IL-1α, IL-18, etc.

Therapeutic targets in sepsis

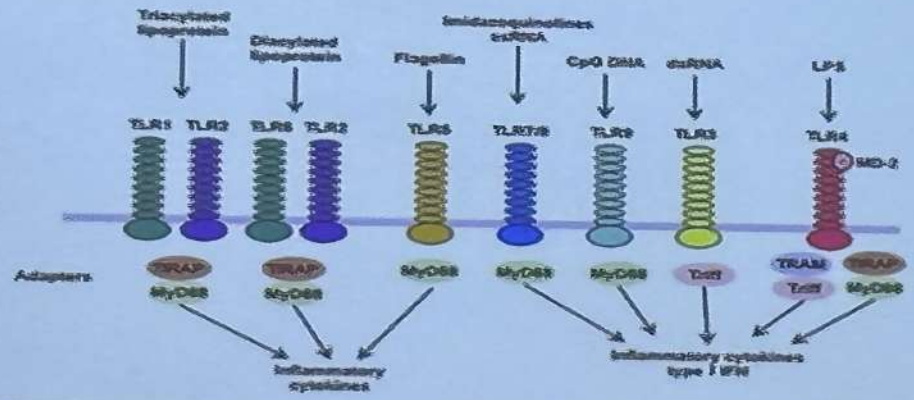


PAMP - Pathogen-Associated Molecular Pattern

DAMP - Damage-Associated Molecular Pattern

Environment: DAMPs and PAMPs

- Damage-Associated Molecular Patterns
  - HMGB1
  - Heat-shock Proteins
  - Hyaluronan fragments
  - Uric acid
  - Heparin sulfate
  - DNA

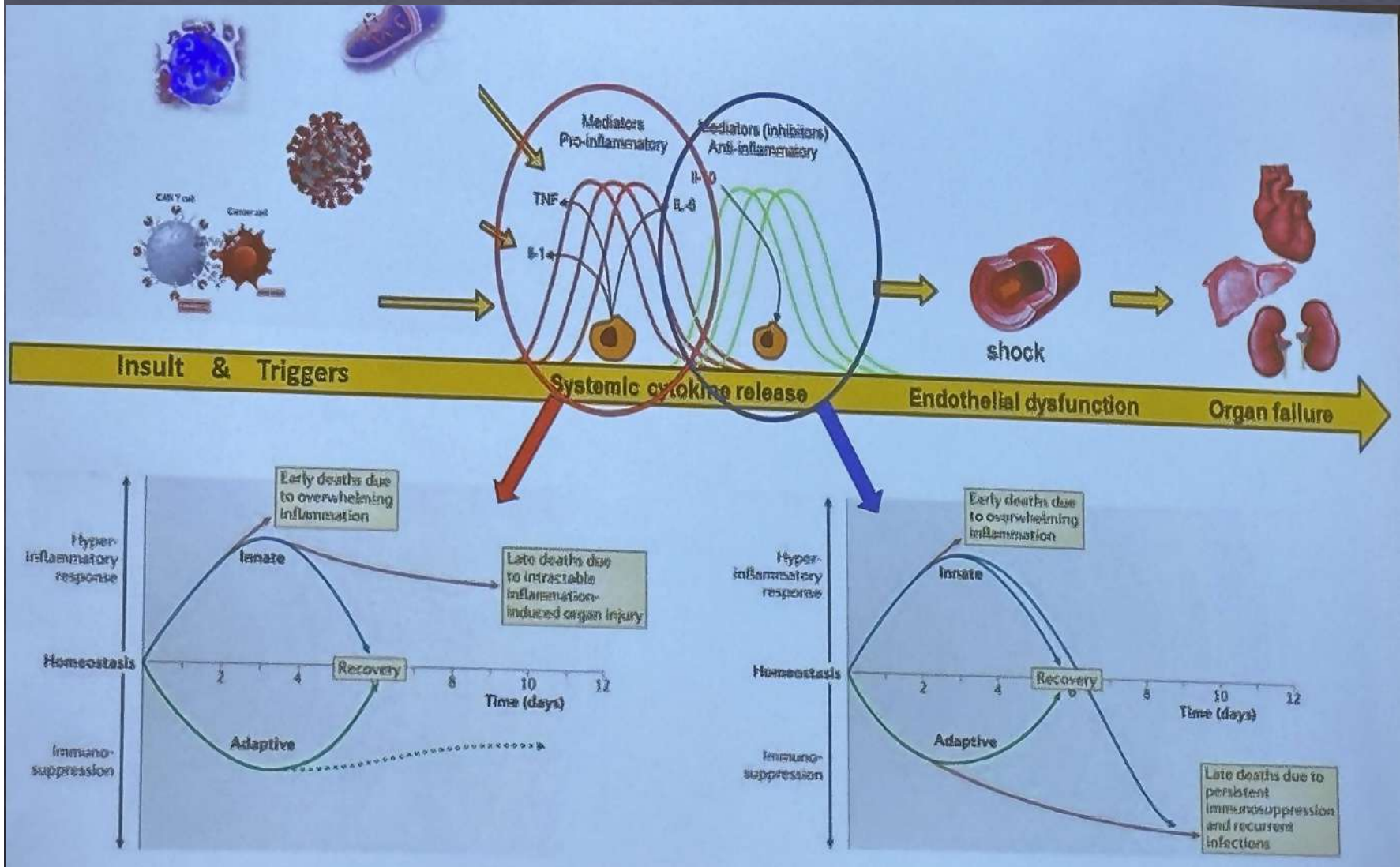


- Pathogen-Associated Molecular Patterns
  - Endotoxin
  - Flagellin
  - Lipoteichoic acid (gram-positive bacteria)
  - Peptidoglycan
  - Nucleic acid variants (viruses) e.g. double-stranded RNA (dsRNA), unmethylated CpG motifs

Τι τελικά “μεσολαβεί” στη διαδικασία της σήψης;

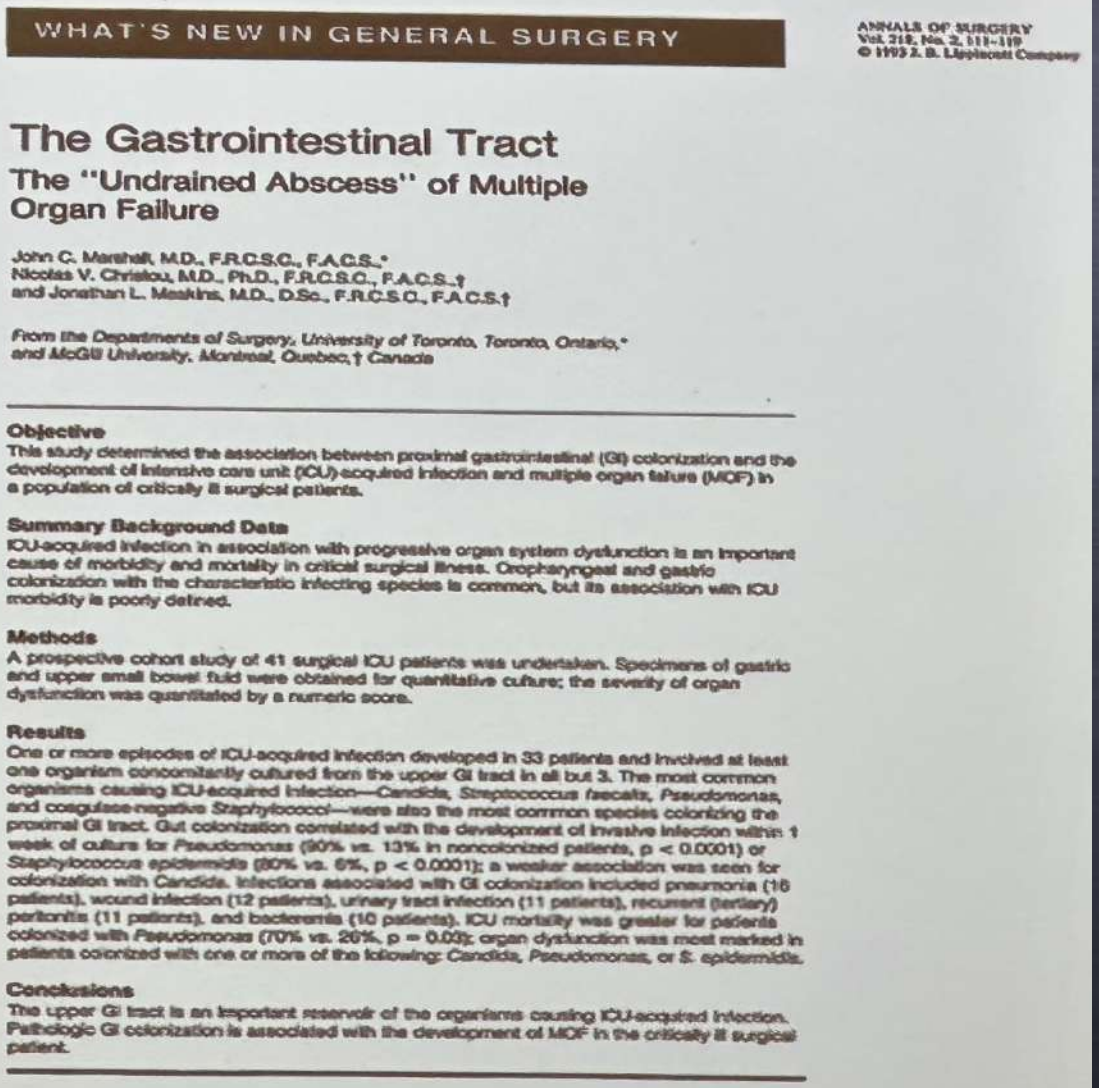
- Συστατικά του κυτταρικού τοιχώματος των gram(-) και των gram(+) μικροβίων
- Υποδοχέας των μονοκυττάρων (Toll-like receptor, CD14)
- Σύστημα μεταγραφικού παράγοντα NF-kB
- Σύστημα κυτοκινών: TNF-a, IL-1, IL-6, IL-8, IL-10, IL-4 κά
- Προϊόντα αραχιδονικού οξέος: PAF, λευκοτριένια, προσταγλανδίνες, θρομβοξάνες
- Ενεργοποιημένα προϊόντα συμπληρώματος: C3a, C5a
- Οξειδωτικές ουσίες
- Διαλυτά και επιφανειακά μόρια προσκόλλησης, κινίνες, θρομβίνη, ουσίες κατασταλτικές του μυοκαρδίου, ενδορφίνες
- Νεότερα μόρια που οδηγούν σε κυτταροπαθητική υποξία

Did you know?


Mediators Pro-inflammatory
Mediators (inhibitors) Anti-inflammatory
TNF
IL-1
IL-6
IL-10
shock
Insult & Triggers
Systemic cytokine release
Endothelial dysfunction
Organ failure
Hyper-inflammatory response
Homeostasis
Immuno-suppression
Early deaths due to overwhelming inflammation
Innate
Late deaths due to intractable inflammation-induced organ injury
Recovery
Adaptive
Time (days)
Late deaths due to persistent immunosuppression and recurrent infections

Where this endotoxin comes from?

- Human microbiome is a “bottomless” reservoir of endotoxin.
- Healthy person can maintain intestine barrier properties and keep this gut-deriven endotoxin away from the bloodstream.
- Patients in critical conditions suffer from endothelial damage and gut hypoperfusion.
- **Translocation** of endotoxin from intestine into bloodstream becomes inevitable in sepsis and ischemia-reperfusion injury.



WHAT'S NEW IN GENERAL SURGERY

ANNALS OF SURGERY
Vol. 218, No. 2, 111–119

The Gastrointestinal Tract

The "Undrained Abscess" of Multiple Organ Failure

John C. Marshall, M.D., F.R.C.S.C., F.A.C.S.*
Nicolas V. Christou, M.D., Ph.D., F.R.C.S.C., F.A.C.S.†
and Jonathan L. Meakins, M.D., D.Sc., F.R.C.S.C., F.A.C.S.†

From the Departments of Surgery, University of Toronto, Toronto, Ontario, and McGill University, Montreal, Quebec,† Canada*

Objective
This study determined the association between proximal gastrointestinal (GI) colonization and the development of intensive care unit (ICU)-acquired infection and multiple organ failure (MOF) in a population of critically ill surgical patients.

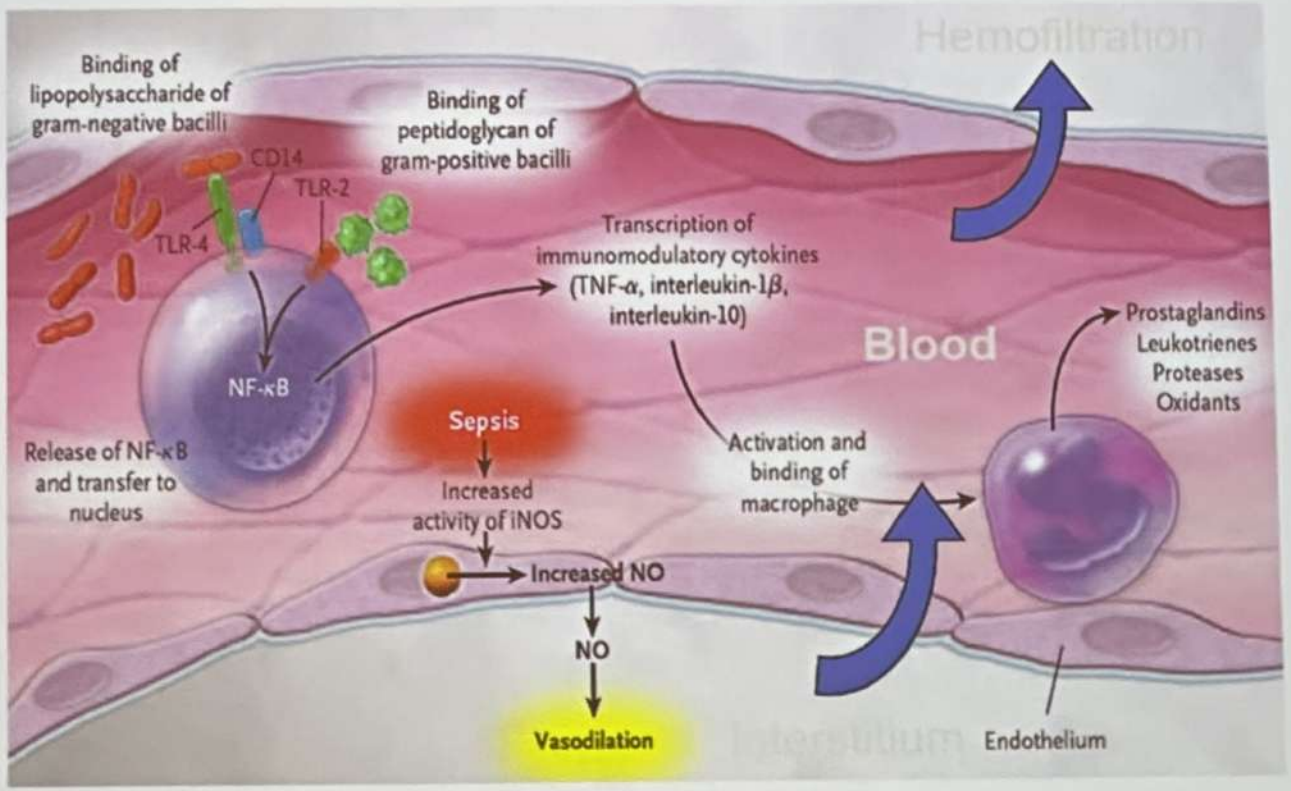
Summary Background Data
ICU-acquired infection in association with progressive organ system dysfunction is an important cause of morbidity and mortality in critical surgical illness. Oropharyngeal and gastric colonization with the characteristic infecting species is common, but its association with ICU morbidity is poorly defined.

Methods
A prospective cohort study of 41 surgical ICU patients was undertaken. Specimens of gastric and upper small bowel fluid were obtained for quantitative culture; the severity of organ dysfunction was quantitated by a numeric score.

Results
One or more episodes of ICU-acquired infection developed in 33 patients and involved at least one organism concomitantly cultured from the upper GI tract in all but 3. The most common organisms causing ICU-acquired infection—*Candida*, *Streptococcus faecalis*, *Pseudomonas*, and coagulase-negative *Staphylococci*—were also the most common species colonizing the proximal GI tract. Gut colonization correlated with the development of invasive infection within 1 week of culture for *Pseudomonas* (90% vs. 13% in noncolonized patients, $p < 0.0001$) or *Staphylococcus epidermidis* (80% vs. 6%, $p < 0.0001$); a weaker association was seen for colonization with *Candida*. Infections associated with GI colonization included pneumonia (16 patients), wound infection (12 patients), urinary tract infection (11 patients), recurrent (tertiary) peritonitis (11 patients), and bacteremia (10 patients). ICU mortality was greater for patients colonized with *Pseudomonas* (70% vs. 26%, $p = 0.03$); organ dysfunction was most marked in patients colonized with one or more of the following: *Candida*, *Pseudomonas*, or *S. epidermidis*.

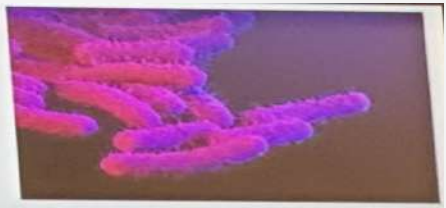
Conclusions
The upper GI tract is an important reservoir of the organisms causing ICU-acquired infection. Pathologic GI colonization is associated with the development of MOF in the critically ill surgical patient.

The "Threshold Immunomodulation" hypothesis



In spite the clinical effectiveness of extracorporeal therapies is likely to be only at the blood level, a possible effect is envisaged at tissue level. The model hypothesizes that mediator removal from blood is coupled to changes in tissues.

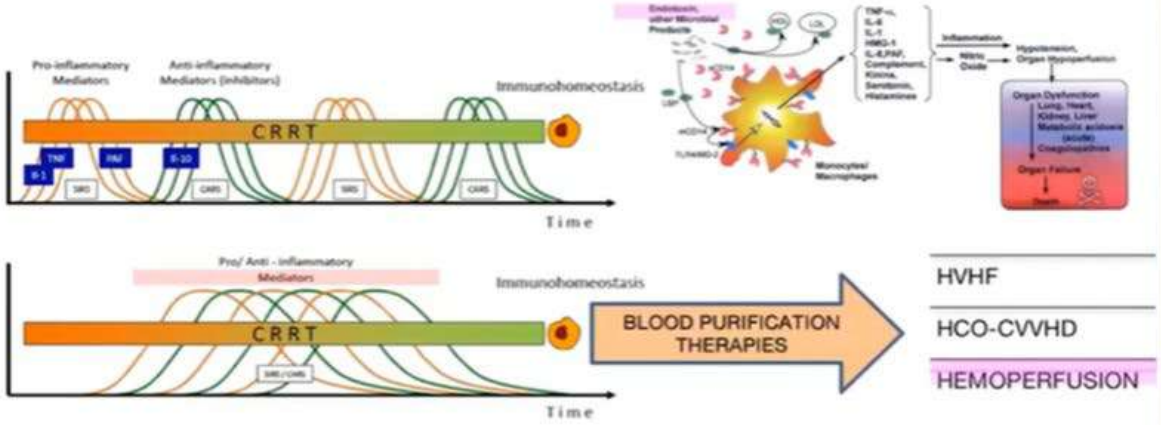
Endotoxemia ≠ bacteremia



- Endotoxin in bloodstream does not equate to primary or secondary blood stream infections.
- >70% of patients with sepsis with high endotoxin activity have negative blood cultures.[1]
- Endotoxemia can result from...
  - Active infections gram negative bacteria
  - Infections with various types of organisms (including COVID-19) that compromise gut barrier function (resulting in translocation of endotoxin)[2]
  - Antibiotics can release endotoxin as they kill bacteria[3]

[1]Dellinger RP et al. JAMA. 2018;320(14):1455-1463
[2]Sirivongrangson P et al. Intensive Care Med Exp. 2020;8(1):72.
[3]Dofferhoff AS et al. *Scand. J. Infect. Dis. 1991;*23, 745–754.

Antibiotic-induced liberation of the bacterial endotoxin LPS may have immediate adverse effects promoting septic shock in patients



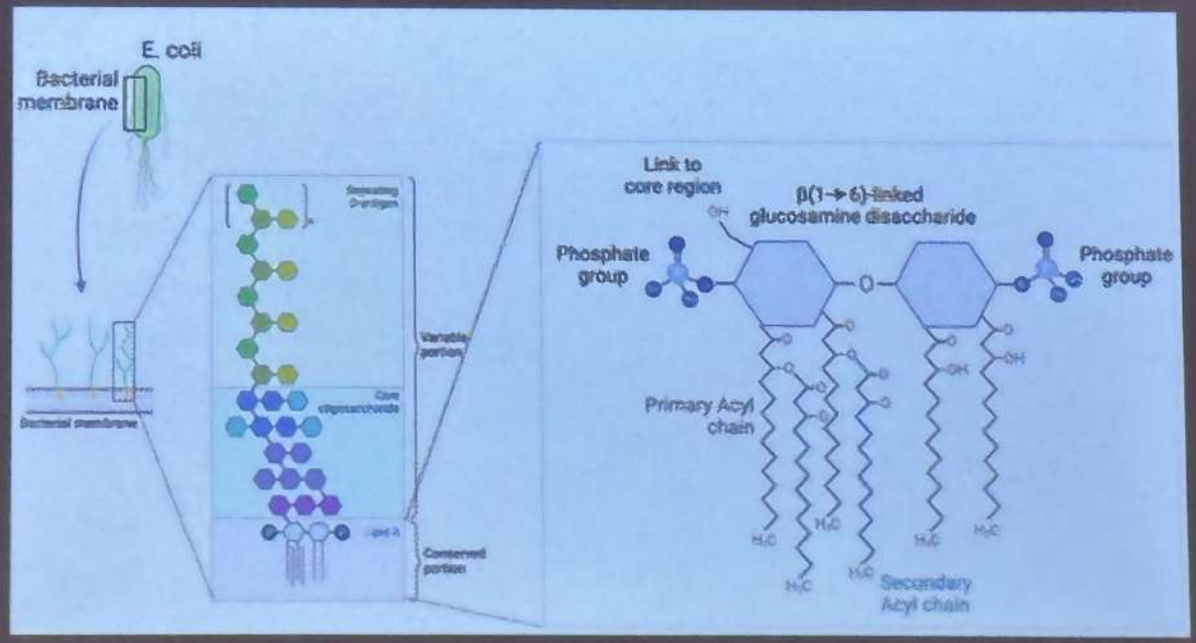
Endotoxin has a well defined mechanism of action

Richard Pfeiffer

Robert Koch

Endotoxin

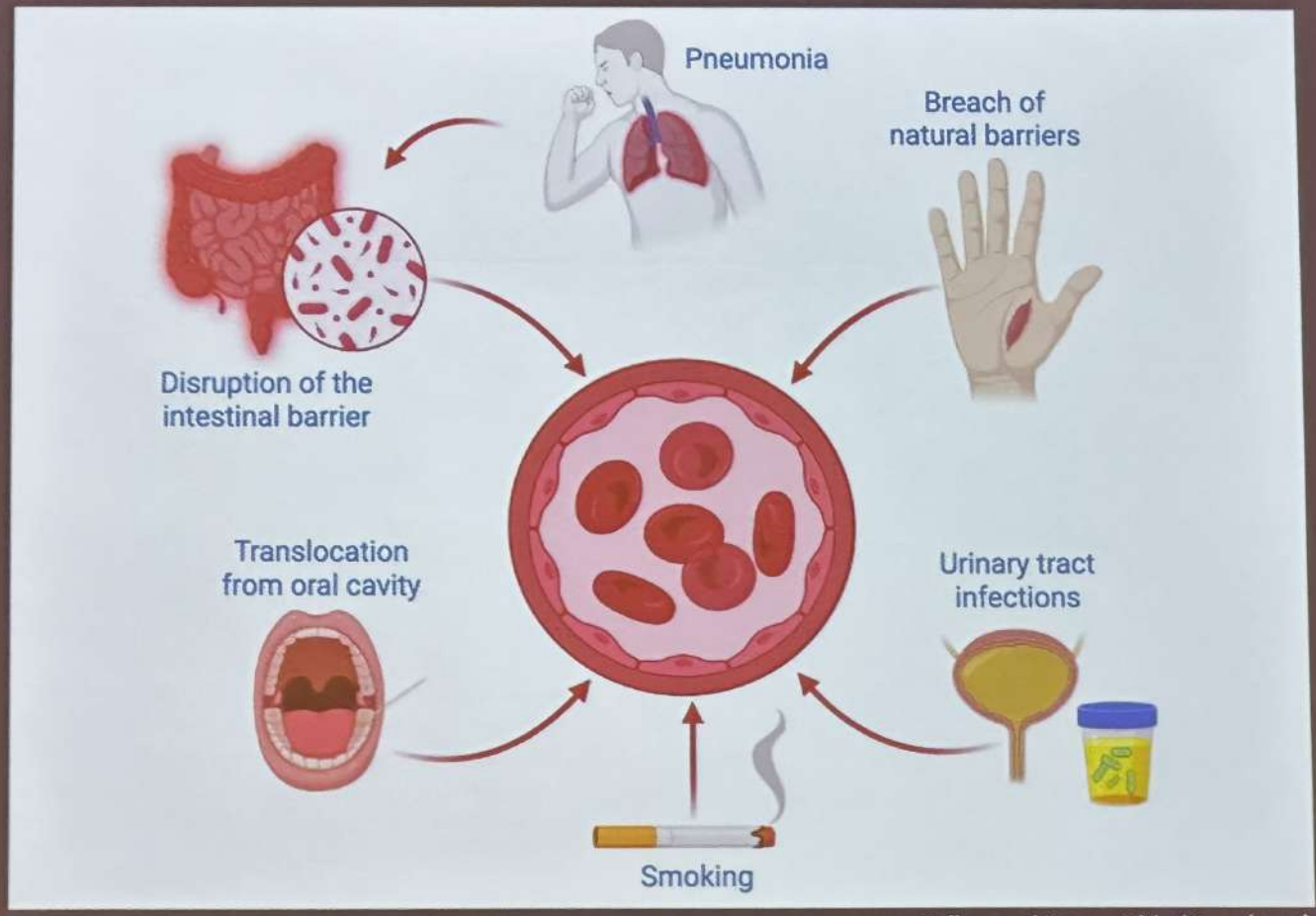
Endo = within (Greek) + Toxin (Brieger)



Program for Critical Care Nephrology · University of Pittsburgh · CRITICAL CARE MEDICINE · CRISMA · ACOMEC

Kellum and Ronco Critical Care (2023) 27:400; Adamzak et al. Medicine 94(27):e1078; Gómez. Endotoxin – The TLR4 pathway and alternatives in Endotoxin in Critical Illness (under review)

Endotoxin can gain access to the circulation



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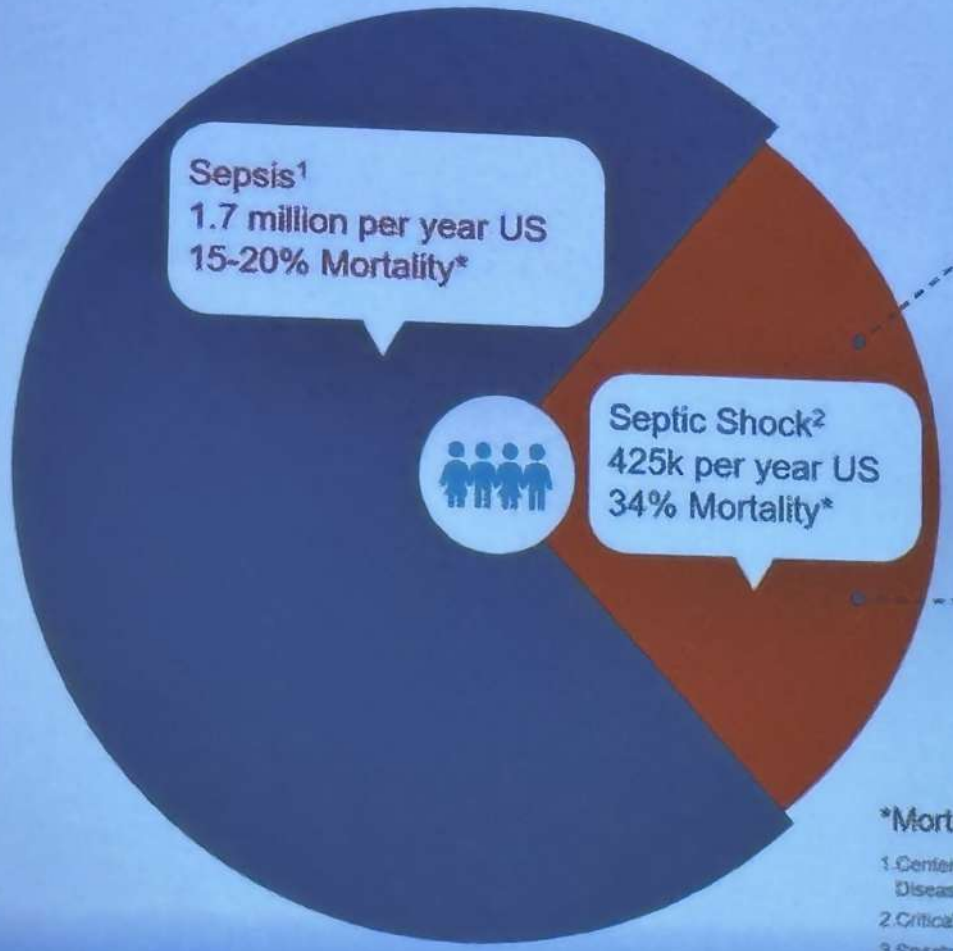
Kellum and Ronco Critical Care (2023) 27:400;
Adamiak et al. Medicine 94(27):e1085

Sepsis Epidemiology



Endotoxic Septic Shock (ESS)[3]
140k per year US (3-4 million worldwide)
>50% mortality

<10% of sepsis **but**
>25% of deaths

Other forms of Septic Shock
285k per year US (6-7 million worldwide)
25-30% mortality

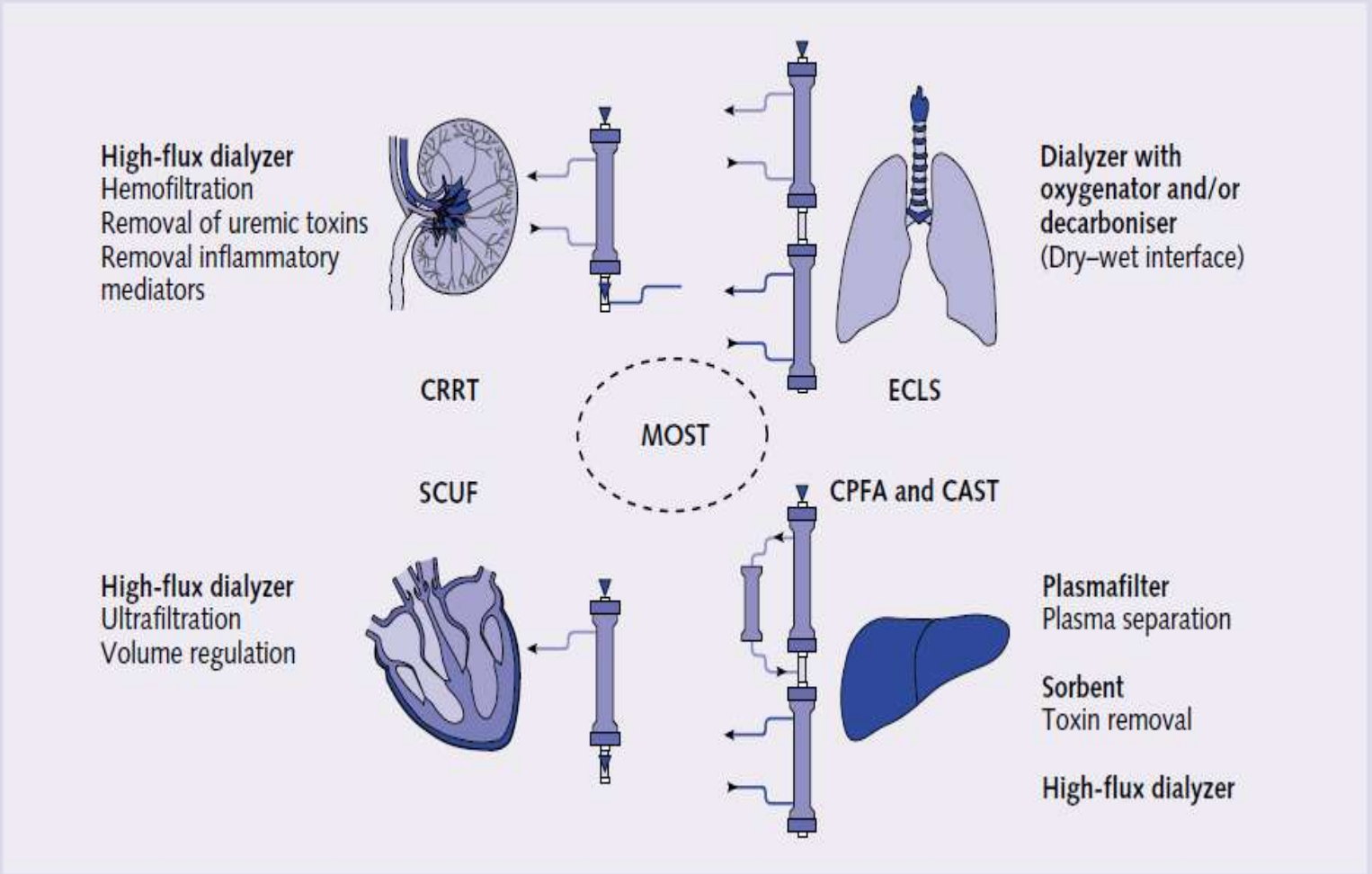
*Mortality attributed to sepsis. Usually measured within 30-60 days.

1. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP) August 9, 2022
2. Critical Care Medicine 46(12):p 1889-1897, December 2018
3. Spectral Management estimates, based on Euphrates trial data

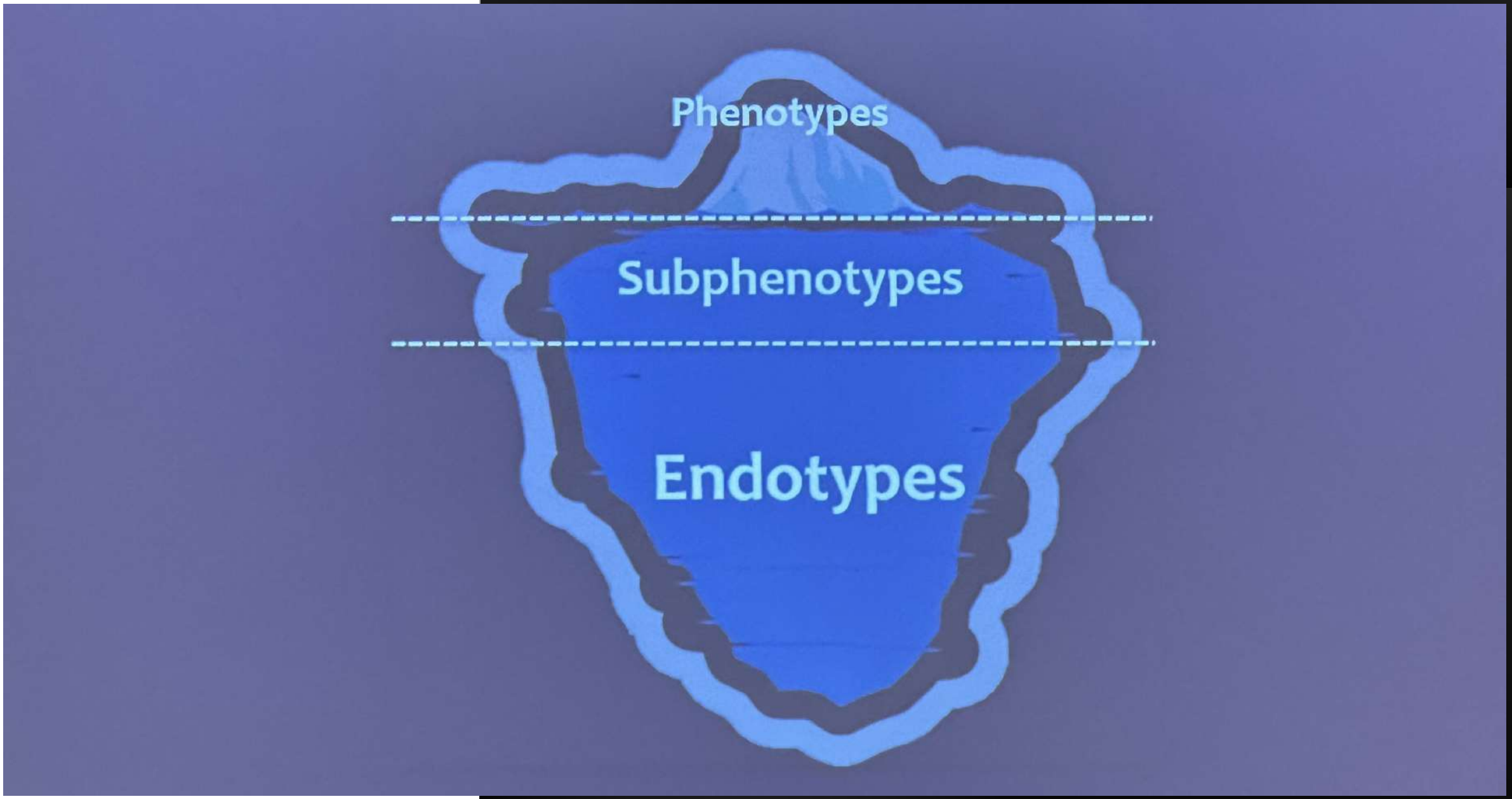
Βασικοί άξονες αντιμετώπισης του συνδρόμου της σήψης

- Αντιμικροβιακή θεραπεία
- Υποστήριξη των ζωτικών λειτουργιών
- Αντιφλεγμονώδης αγωγή: μικρές δόσεις κορτικοστεροειδών, ενεργοποιημένη πρωτεΐνη C, μονοκλωνικό αντίσωμα έναντι του TNF-α (afelimomab), έναντι της IL-1, IL-6, CD14, TLR
- Εντατική ινσουλινοθεραπεία
- Αντιαποπτωτική αγωγή
- Μέθοδοι εξωσωματικής - εξωνεφρικής κάθαρσης

Figure 4. The concept of MOST. Different organs can be supported by special modifications to the extracorporeal circuit. The kidney is supported by dialysis, the lung by extracorporeal CO_2 removal, the heart by optimal ultrafiltration and fluid balance, and the liver by specific filters and sorbents to remove liposoluble toxins.



CAST: counter anti-inflammatory support therapy; CPFA: coupled plasmafiltration–absorption; CRRT: continuous renal replacement therapy; ECLS: extracorporeal life support; MOST: multiorgan support therapy; SCUF: slow continuous ultrafiltration.

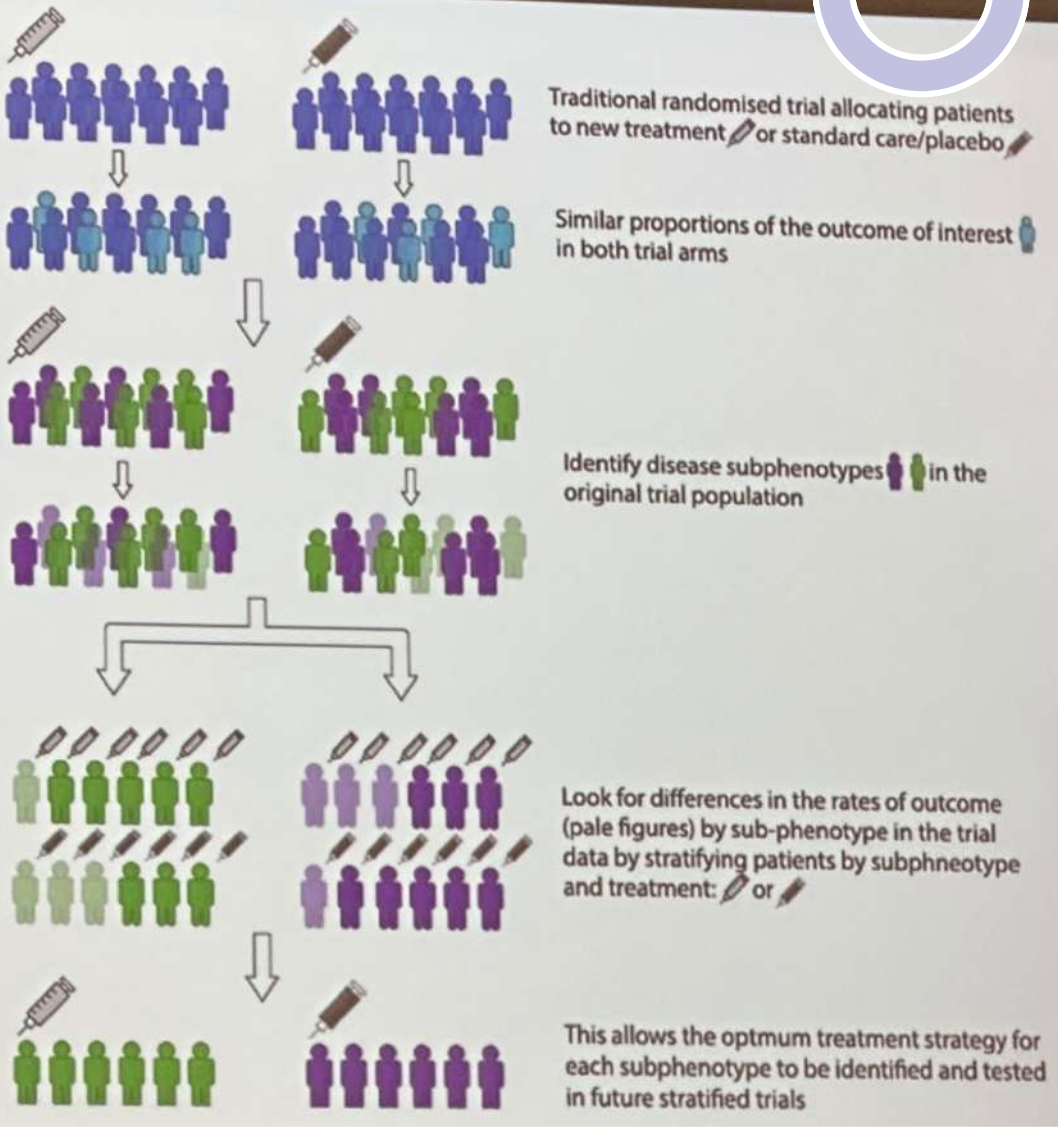

Phenotypes
Subphenotypes
Endotypes

Intensive Care Med
https://doi.org/10.1007/s00134-025-07873-6

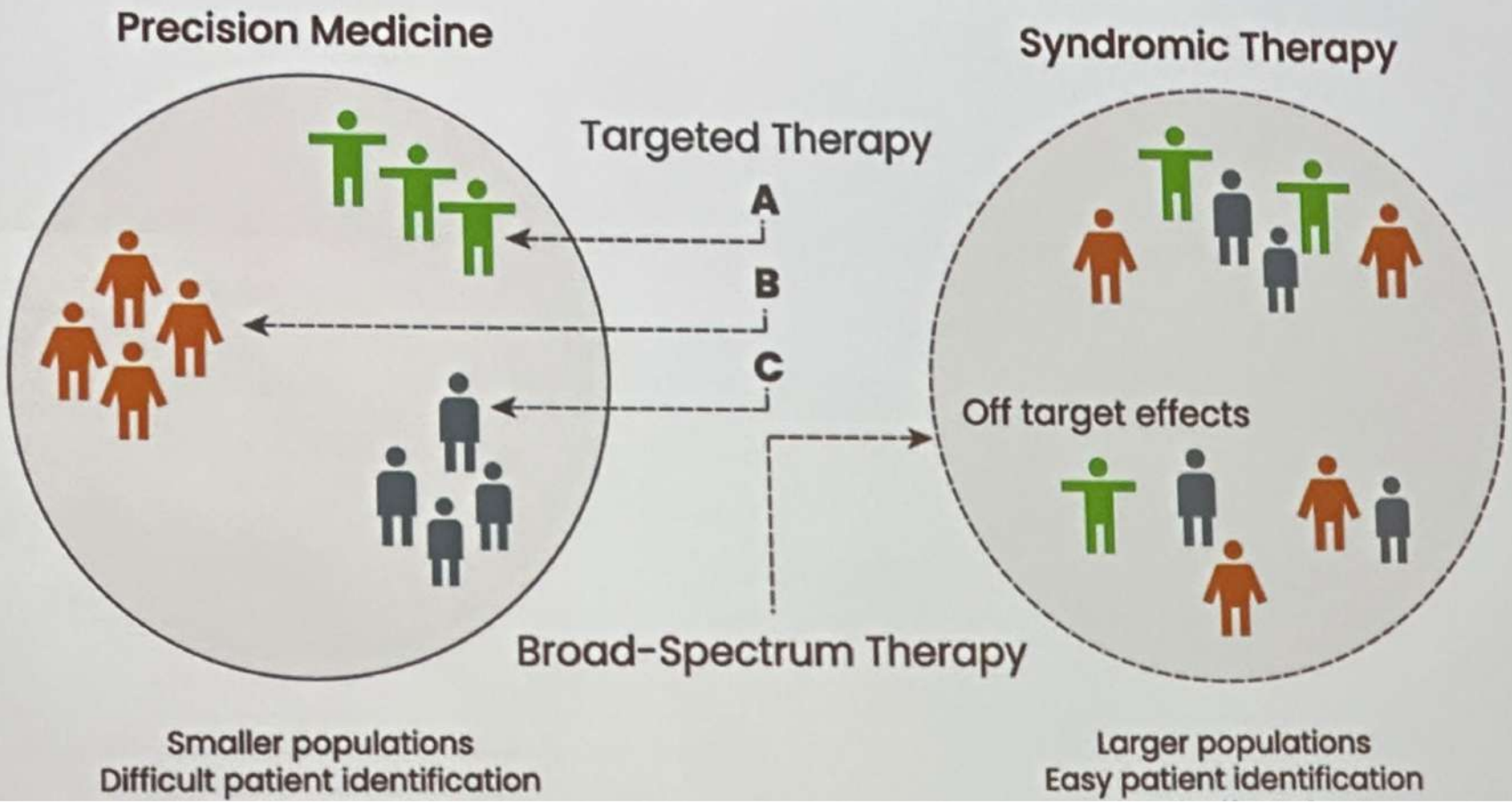
Sepsis subphenotypes, theragnostics and personalized sepsis care

David B. Antcliffe[1,5*], Aidan Burrell[2], Andrew J. Boyle[3,4], Anthony C. Gordon[1], Daniel F. McAuley[3,4] and Jon Silversides[3,4*]

Heterogeneity between critically ill patients with sepsis is a major barrier to the discovery of effective therapies. The use of machine learning techniques, coupled with improved understanding of sepsis biology, has led to the identification of patient sub-phenotypes. This exciting development may help overcome the problem of patient heterogeneity and lead to the identification of patient subgroups with treatable traits



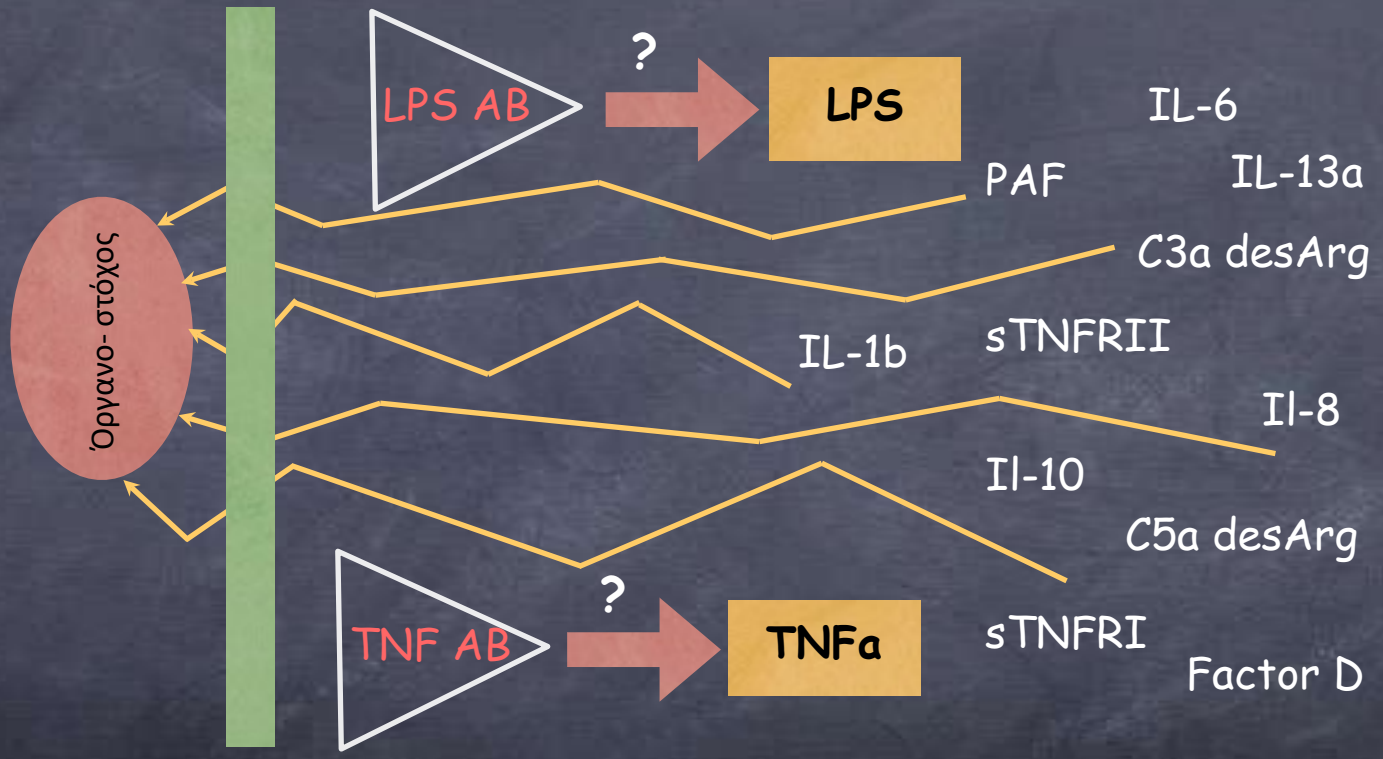
Precision medicine vs Syndromic therapy



Εφαρμογή θεραπευτικής αφαίρεσης στη σήψη
Μια ιδέα που έφτασε η ώρα της εφαρμογής της

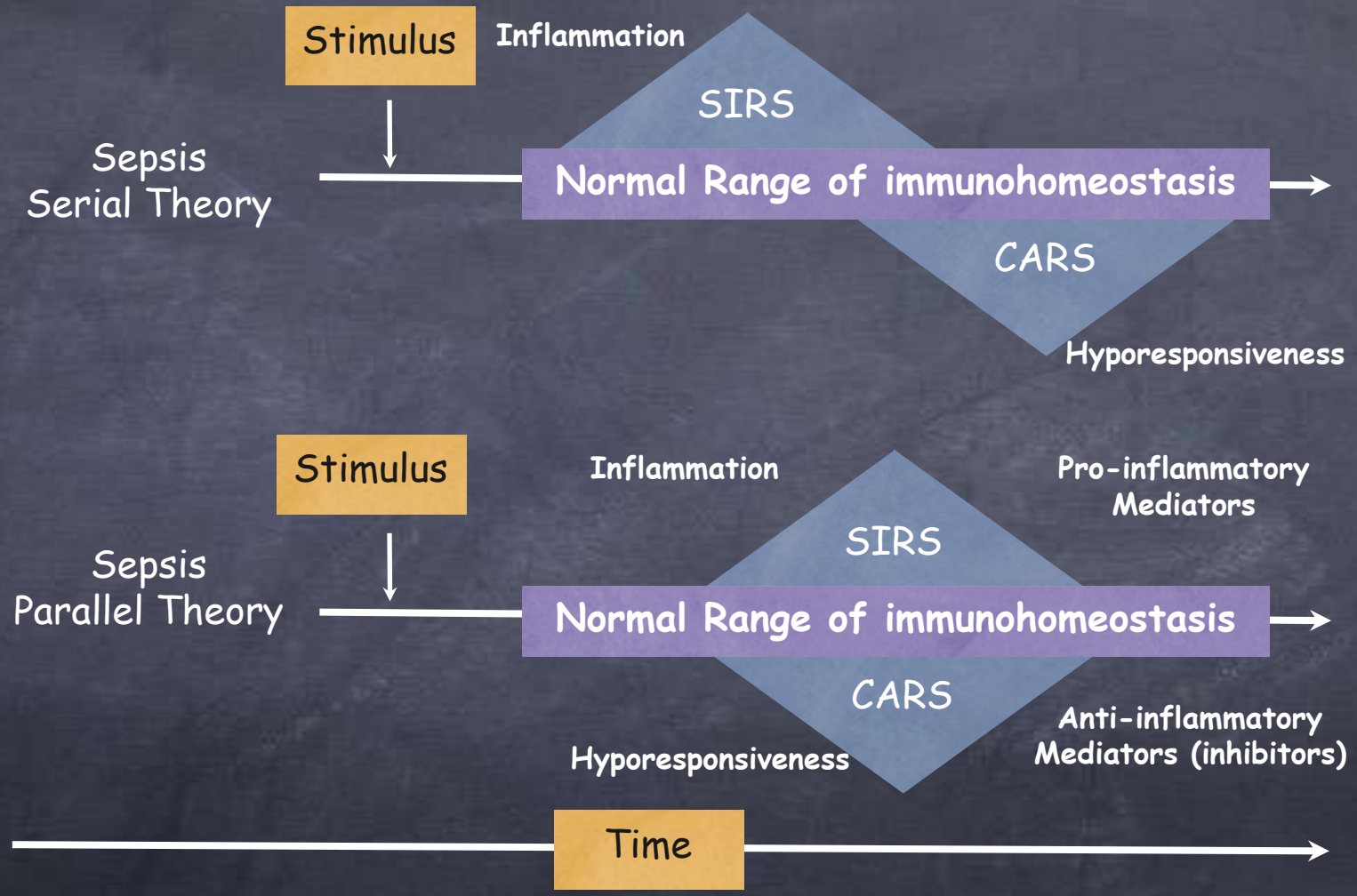
- Καλύτερη κατανόηση της σήψης και γνώση όλο και περισσότερων μεσολαβητών - παραγόντων που συμμετέχουν ενεργά στην παθοφυσιολογία του συνδρόμου
- Ποικίλλες θεραπευτικές προσεγγίσεις: “Μαγική σφαίρα” εναντίον συγκεκριμένου παράγοντα ή “μαγική ασπίδα” που προστατεύει από πολλαπλές ουσίες που ενέχονται στην εκδήλωση του συνδρόμου
- Η ιδέα της “αποτοξίνωσης” του αίματος σε ασθενείς με σήψη είναι ήδη παλιά

“Καταιγίδα κυταροκινών” στη διαδικασία της σήψης: “μαγική σφαίρα” ή “μαγική ασπίδα”



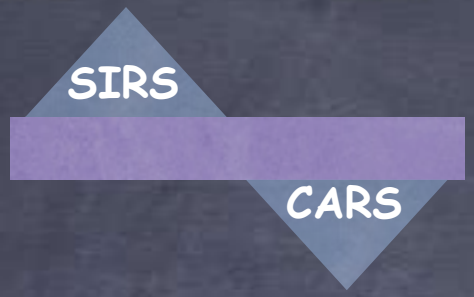
Ciro Tetta et al, Ther Apher, 2002

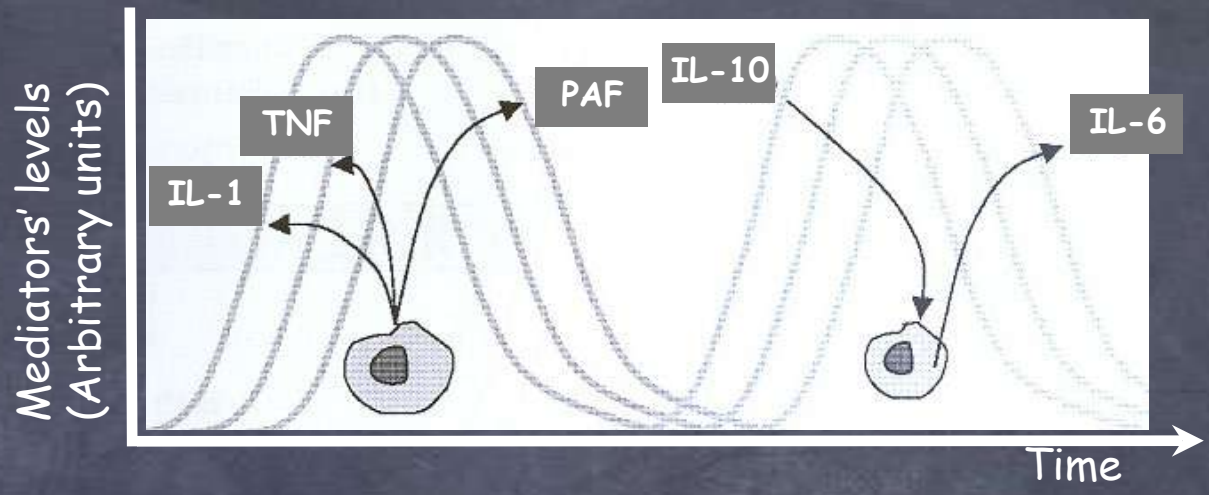
“Κατά σειρά” και “παράλληλη” θεωρία της σήψης

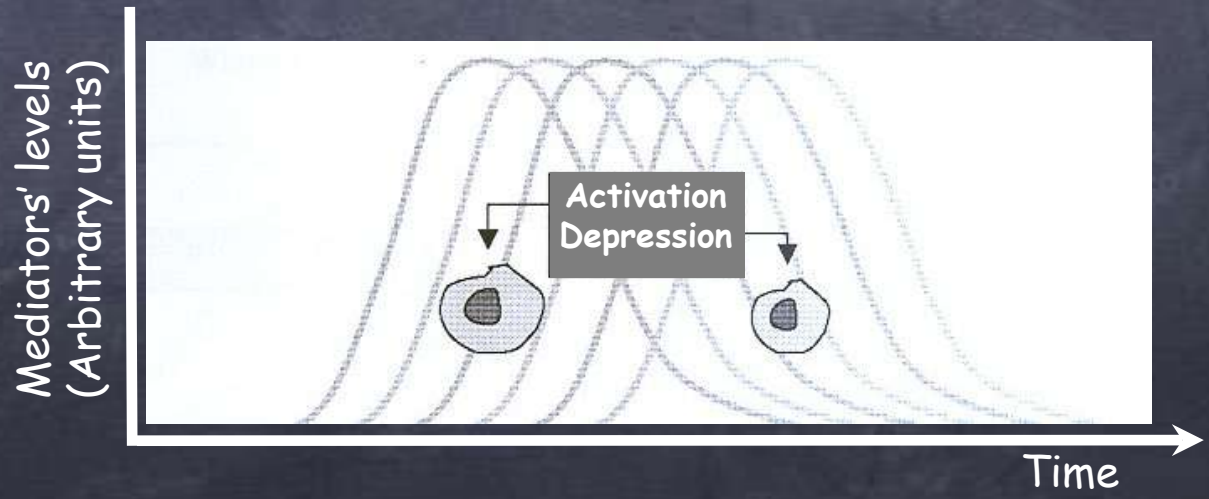


C. Ronco et al, Artif organs, 2003

The Peak Concentration Hypothesis

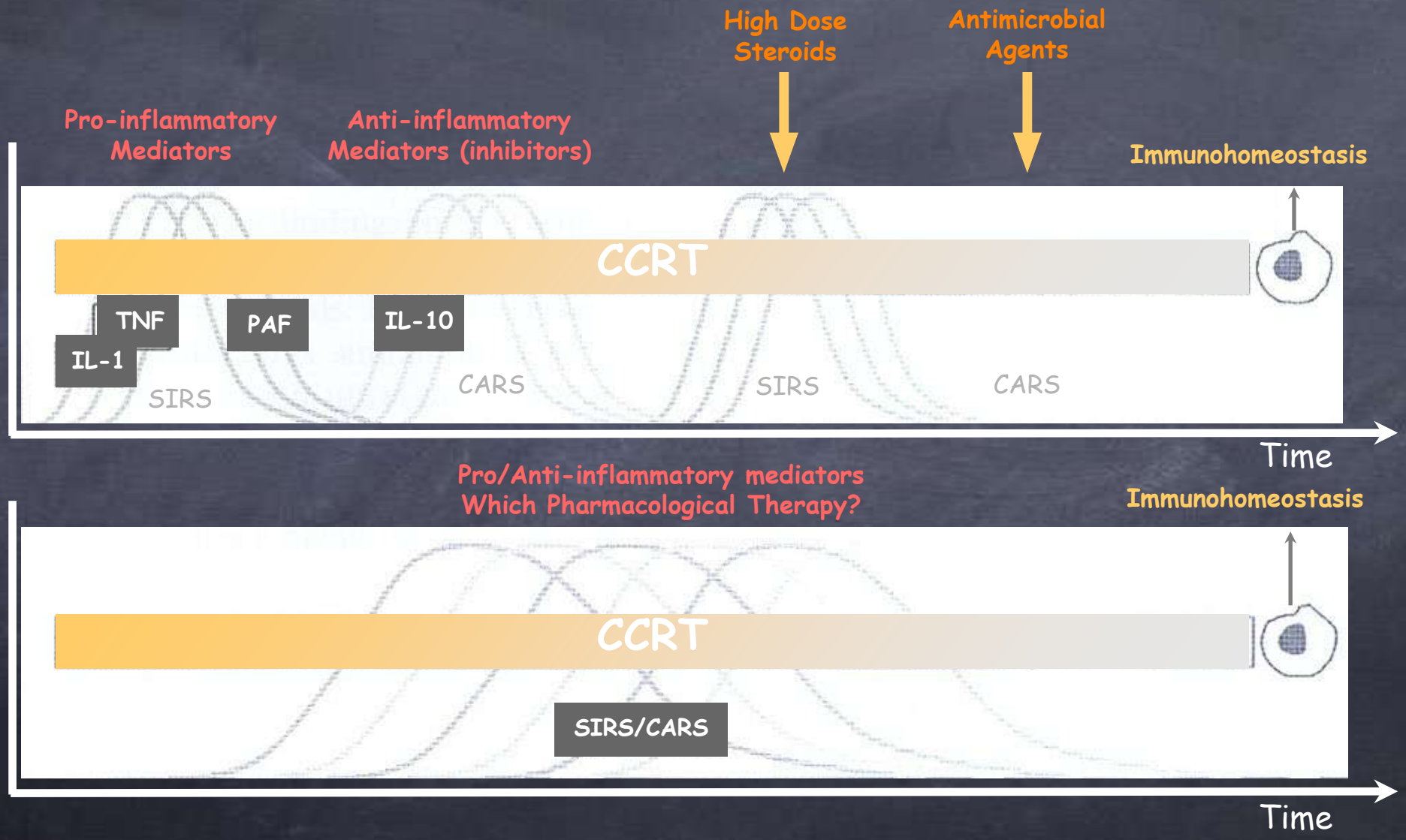






C. Ronco et al, Artif organs, 2003

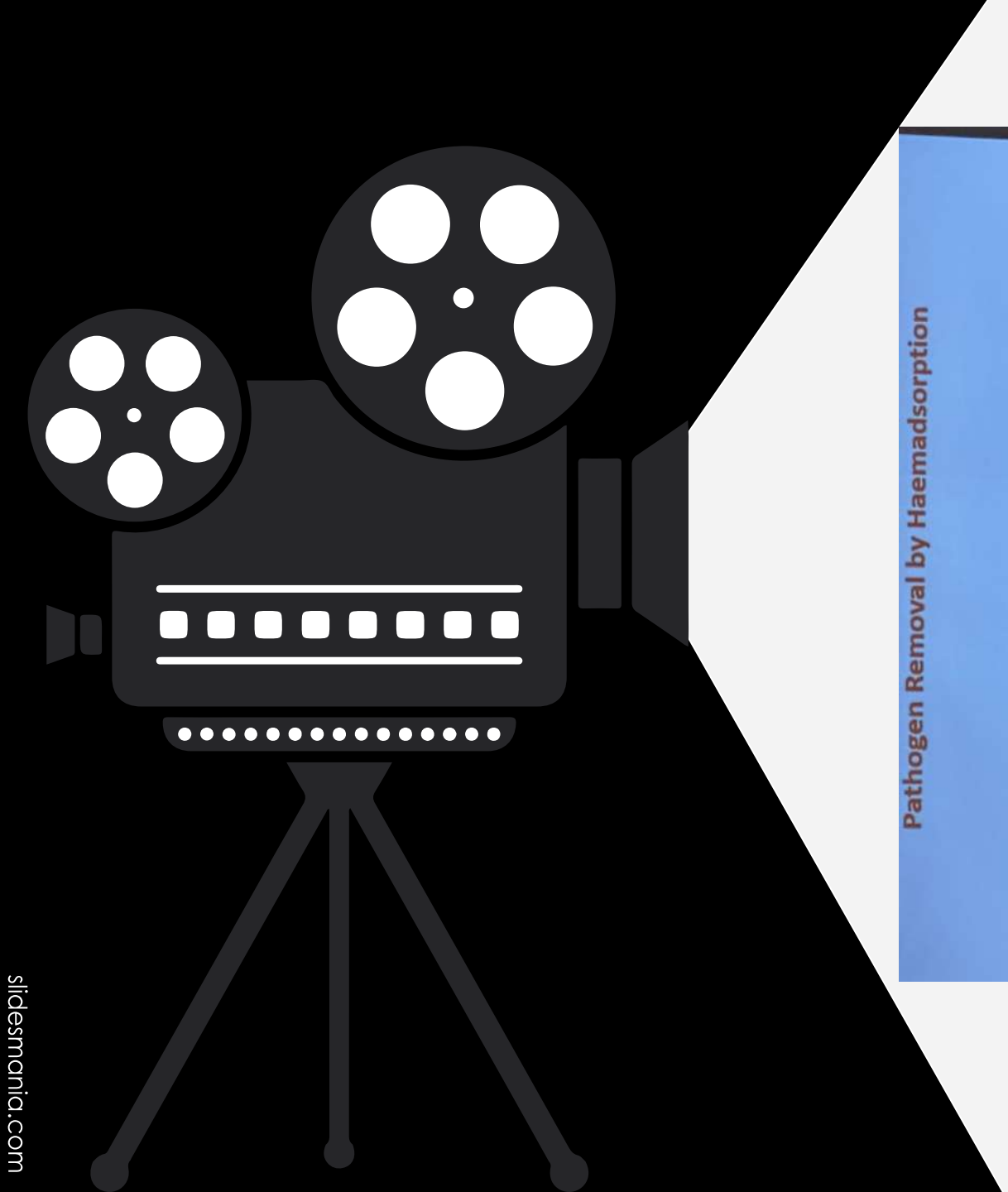
Σήψη και συνεχής υποκατάσταση της νεφρικής λειτουργίας (CRRT)



C. Ronco et al, Artif organs, 2003

“Νεφρική” και “σηπτική” δόση κάθαρσης στην οξεία νεφρική ανεπάρκεια στα πλαίσια της σήψης

- Εφαρμογή μεθόδων υψηλής διήθησης (high convection) στην αντιμετώπιση ΟΝΑ σηπτικής αιτιολογίας
- Γραμμική βελτίωση ανάλογη της αυξανόμενης δόσης κάθαρσης: “σηπτική δόση”, χωρίς την εμφάνιση ορίου (plateau)
- Αποβολή ουραιμικών τοξινών και μεσολαβητών της φλεγμονώδους διαδικασίας καθώς και τροποποίηση του ανοσολογικού περιβάλλοντος
- Ronco C. et al (2000): 425 ασθ. με ΟΝΑ, “σηπτική δόση” κάθαρσης αναλόγως του σωματικού βάρους με ρυθμό υπερδιήθησης (UFR) 35ml/Kg/h ή >3L/h - 72L/24h
- Χρήση συνθετικών μεμβρανών με υψηλό cut off >70Kd - αναλογία με μεμβράνες πλασμαφαίρεσης



Clinical trials of biologic response modifiers in sepsis

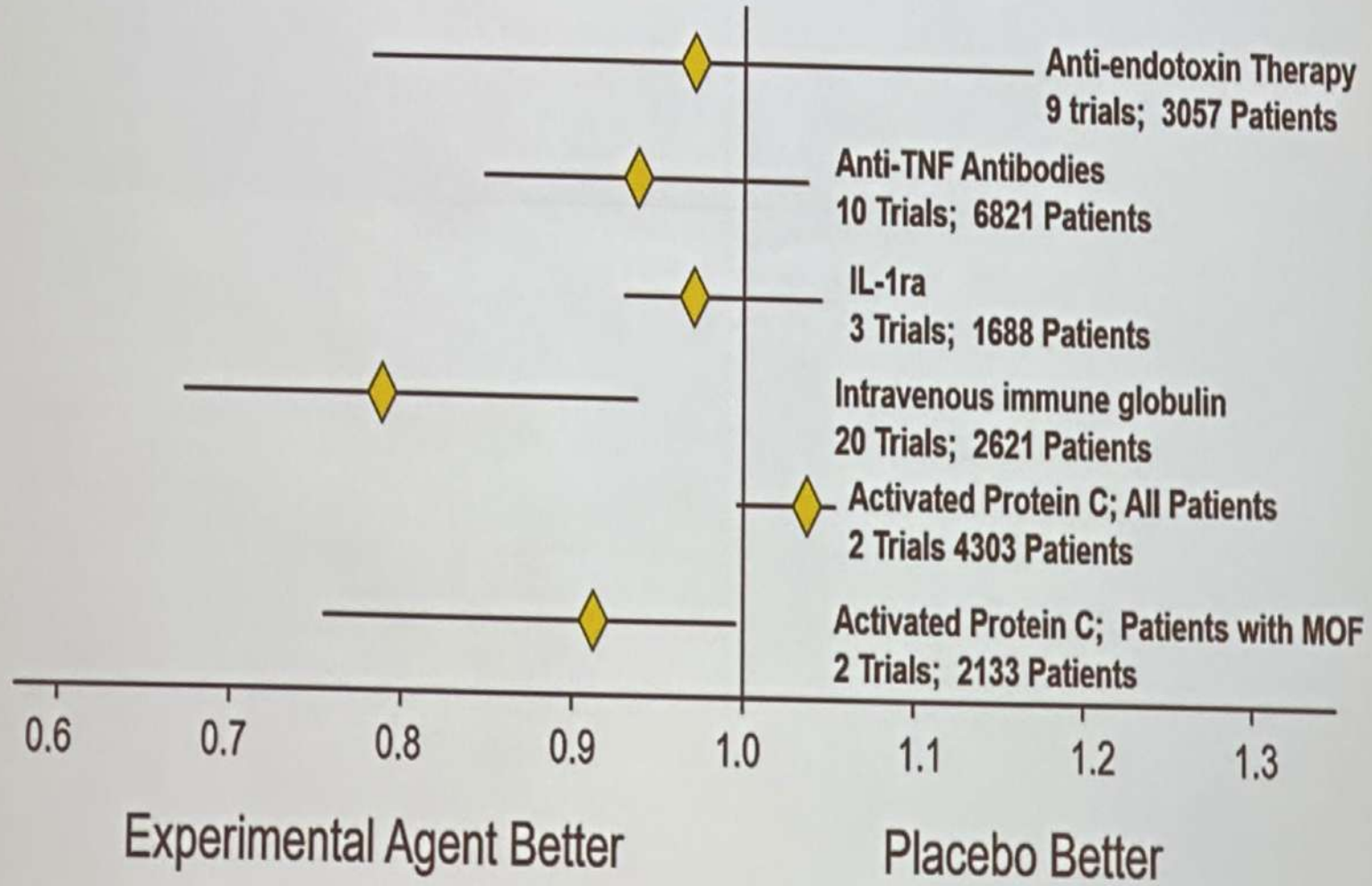
Pathogen Removal by Haemadsorption

Target	Strategies
Endotoxin (LPS)	Monoclonal antibodies
	LPS: HA-1A, E5
	Enterobacterial common antigen
	Toll-like receptor 4 (TLR4) antagonists
	Eritoran
	TAK-242
	Anti-CD14
	Bactericidal permeability increasing protein
	Taurolidine
	Alkaline phosphatase
	Polymyxin B
	Conjugate
	Extracorporeal column
	Lipid emulsion
Tumor necrosis factor (TNF)	Monoclonal or polyclonal antibodies
	Soluble receptor constructs
Interleukin-1 (IL-1)	Recombinant IL-1 receptor antagonist

Target	Strategies
Platelet activating factor (PAF)	Small molecule inhibitors
	PAF acetylhydrolase
Eicosanoids	Ibuprofen
	Soluble phospholipase A2 (sPLA2) inhibitor
Nitric oxide	L-NMMA
	Methylene blue
Hypercoagulability/disseminated intravascular coagulation (DIC)	APC, Protein C concentrate
	TFPI
	Antithrombin
	Anti-tissue factor antibody
	Heparin
	Thrombomodulin
Immune suppression	Intravenous immunoglobulin
	G-CSF, GM-CSF
	Interferon γ
Endocrinopathy	Corticosteroids
	Vasopressin
Others	Selenium
	Lactoferrin
	Bradykinin antagonists
	Statins
	Extracorporeal hemoperfusion

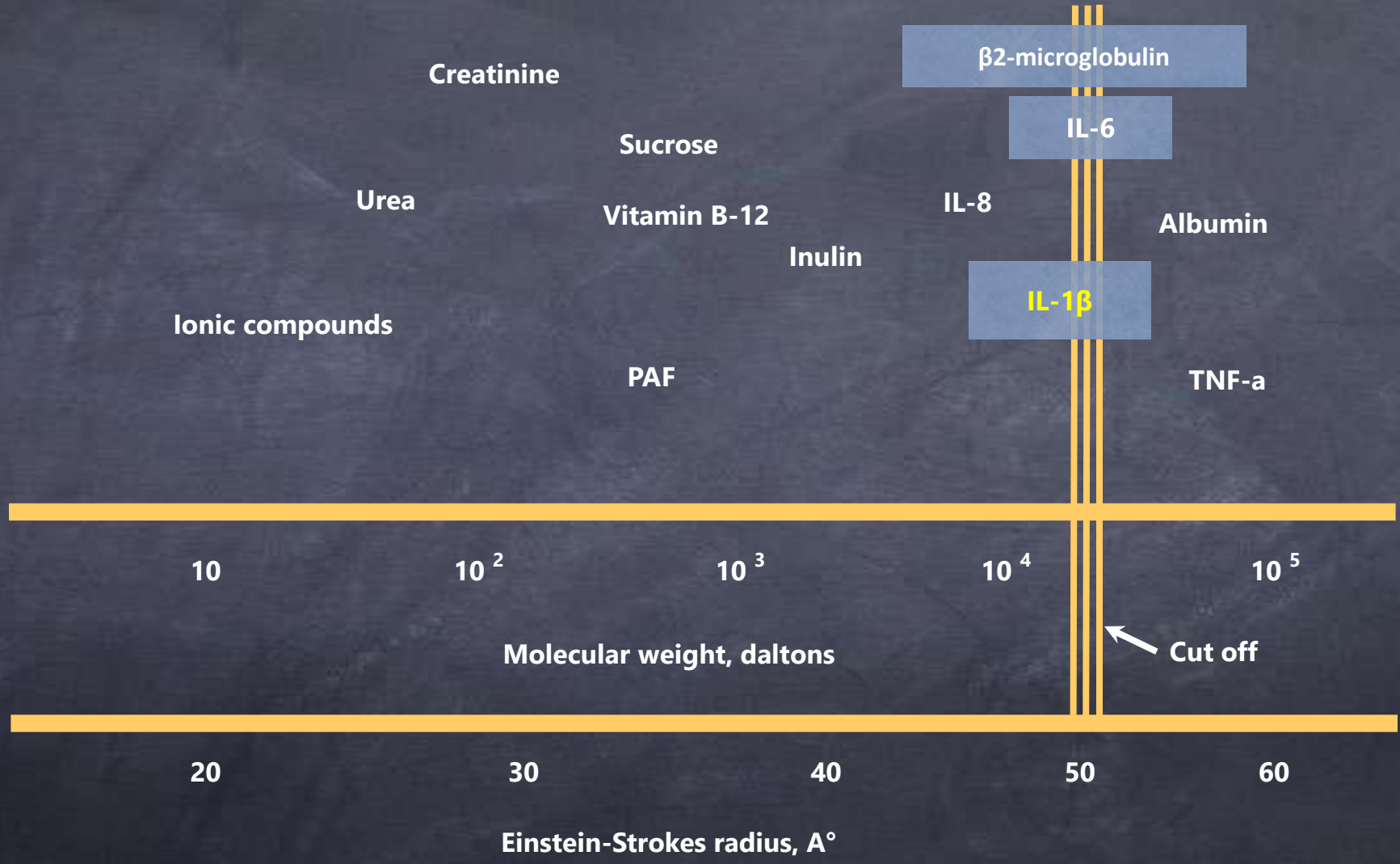
Trends in Molecular Medicine April 2014, Vol. 20, No. 4

Adjuvant Therapy in Sepsis

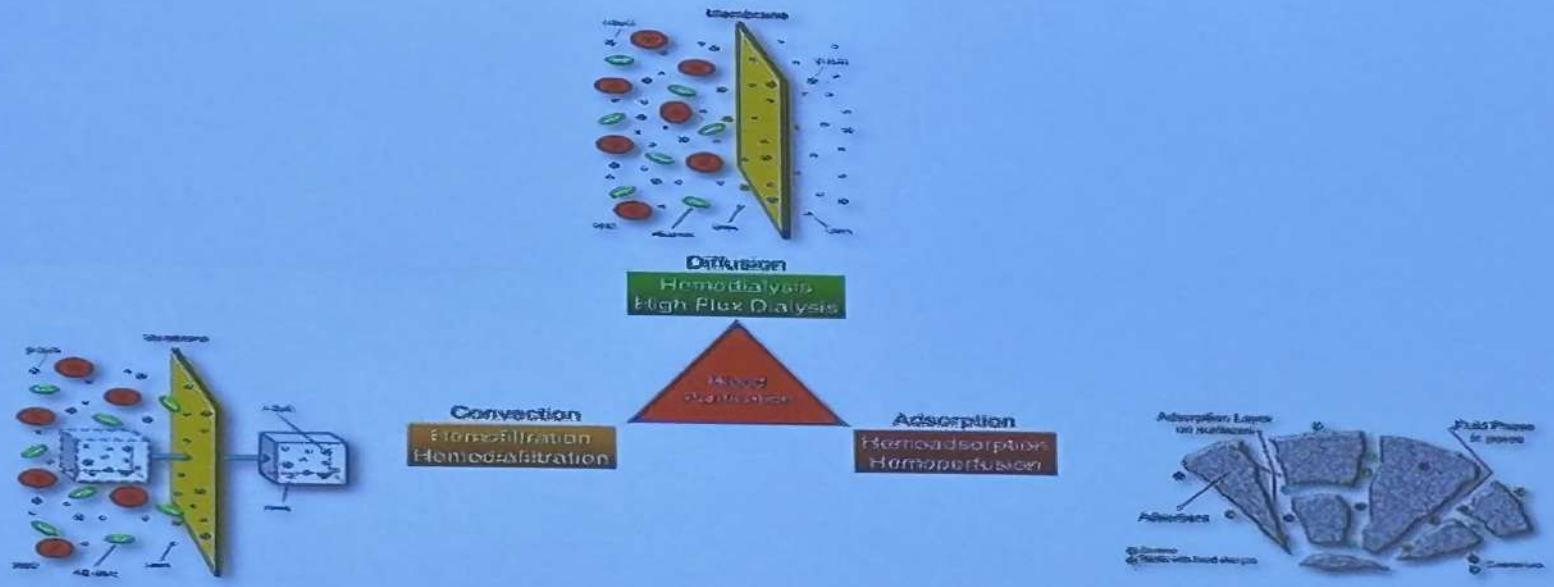


- Marshall, *J Leukoc Biol* 83:471, 2008

Μοριακά βάρη μεσολαβητών στη σήψη συγκριτικά με το cut off των μεμβρανών υψηλής διαπερατότητας



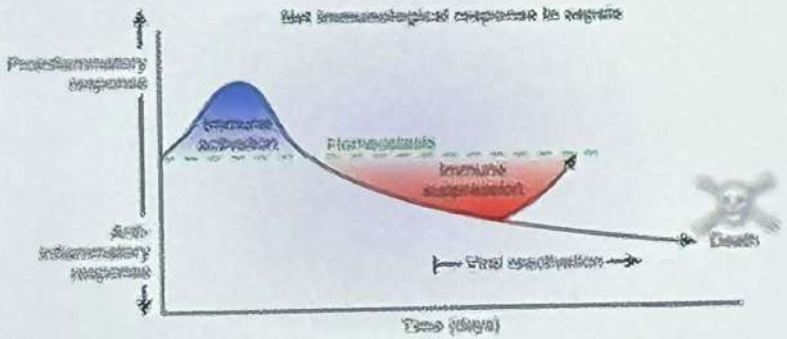
Mass Separation Process



a) **Separation by barrier** (CRRT: CVVH-CVVHD-CVVHDF)

b) **Separation by solid agent** (Hemoadsorption)

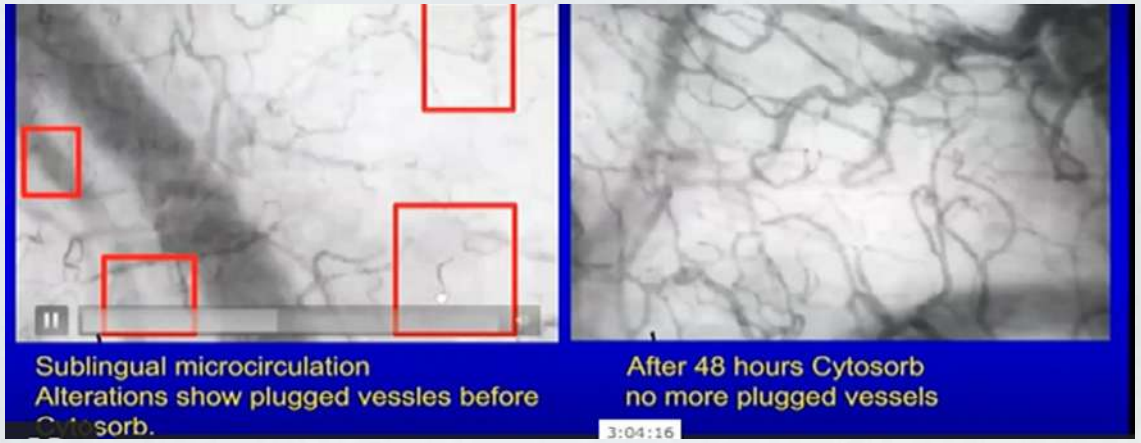
The extracorporeal blood purification concept in sepsis

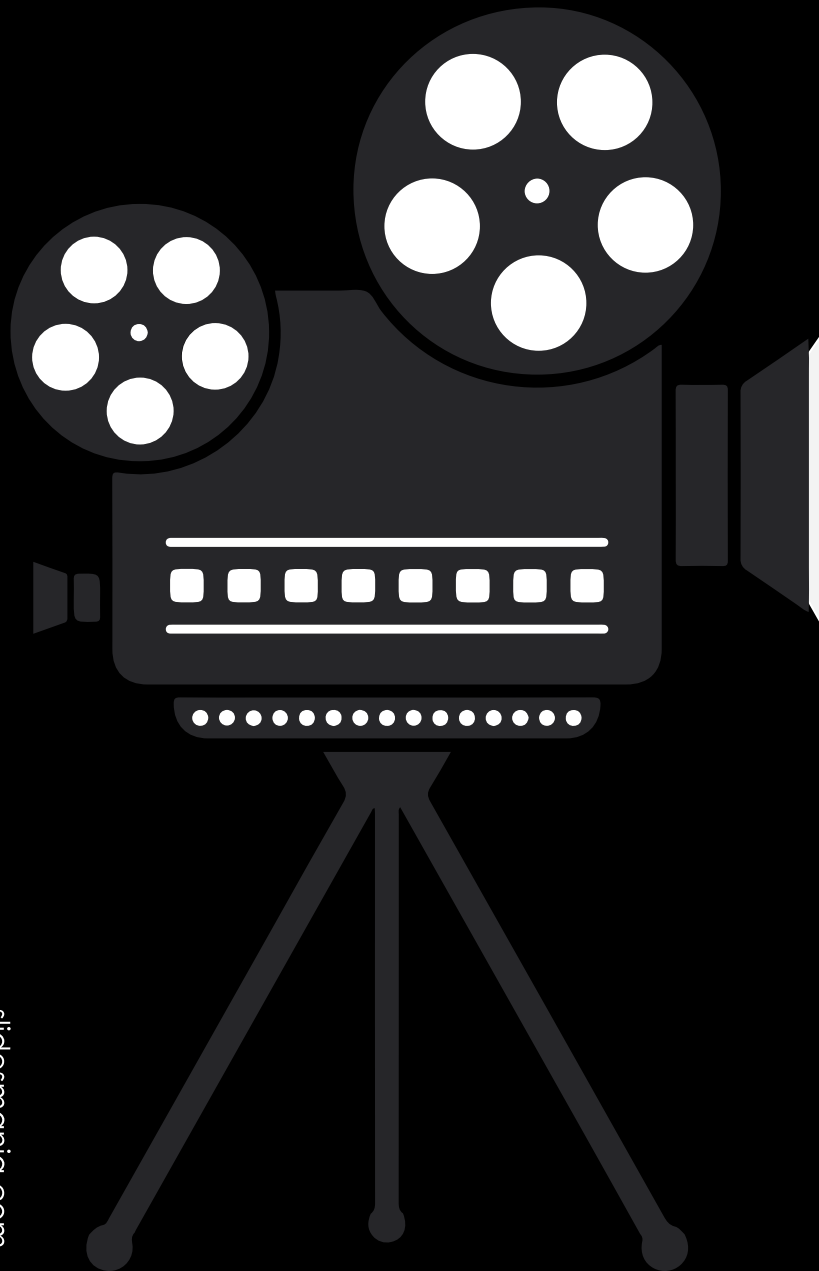


+

=

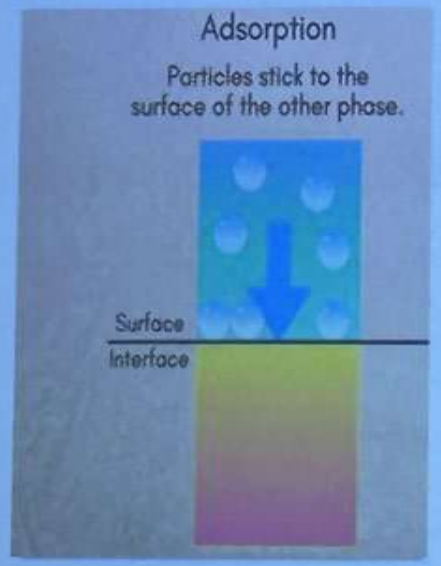
Improved
patient outcomes ?

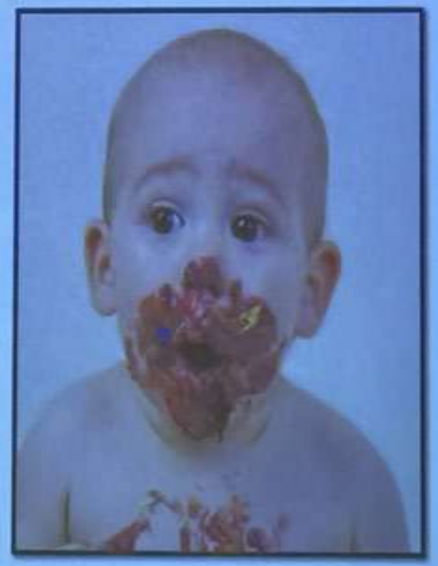




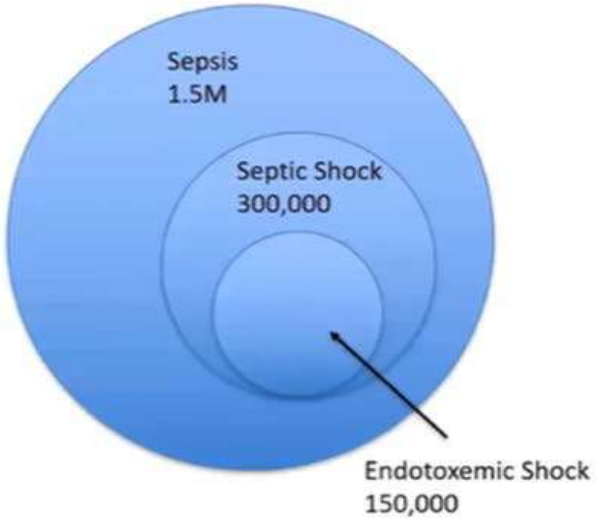
Before I start....

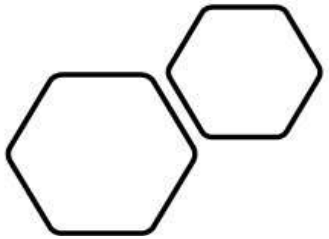
Nomenclature that regularly goes wrong … Adsorption vs Absorption



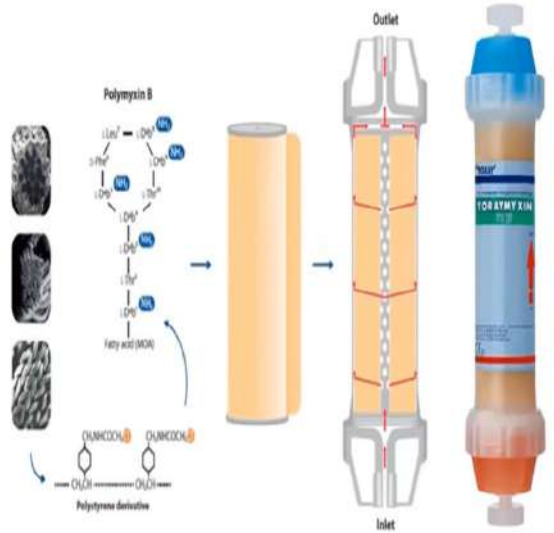


Endotoxin and Endotoxemia





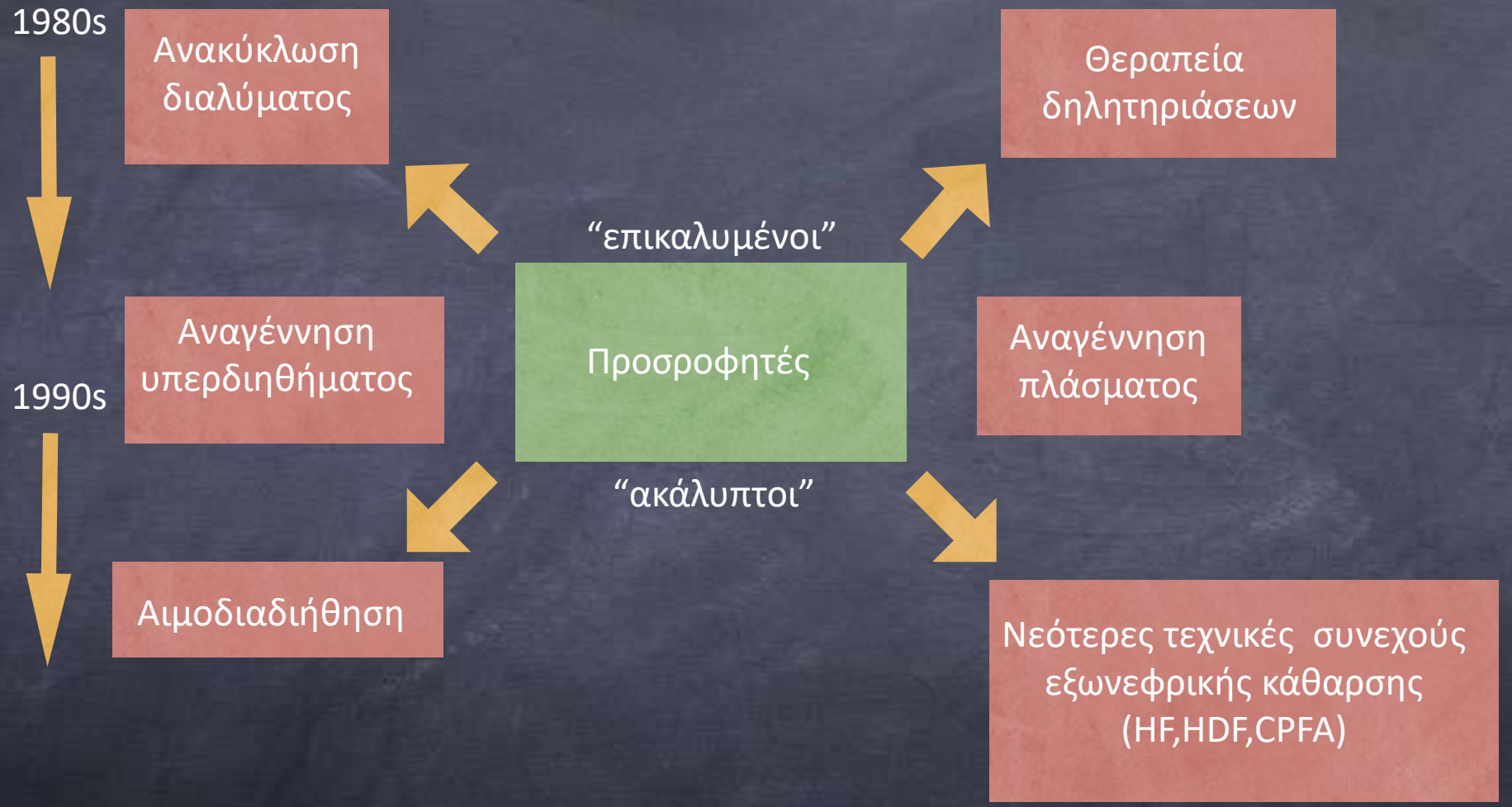
In the mid-1970s, polymyxin B was discovered to be protective against endotoxin-induced hemodynamic shock b
time, was demonstrated to be extremely toxic for the kidney and central nervous system, which precludes its systemic use



PMX is composed of polymyxin B (PL-B) covalently bonded to polystyrene-derivative fibers.

Since 1994, polymyxin B has been bound and immobilized to polystyrene fibers

Η χρήση των προσροφητών στις θεραπείες εξωσωματικής κάθαρσης



Προβλήματα βιοασυμβατότητας, απελευθέρωση μετάλλων, έκλυση μικροσωματιδίων, χαμηλή ομογενοποίηση, πυρετογόνες αντιδράσεις, ηλεκτρολυτικές δχ, αιμόλυση

Ronco C et al, Kid Int, 2000

Αιμοπροσρόφηση με τη χρήση πολυμυξίνης Β (PL-Β)

- Πολυκατιονικό αντιβιοτικό που συνδέει την ενδοτοξίνη και την αδρανοποιεί. Αντεδείκνυται η ενδοφλέβια χορήγηση λόγω νεφρο- και νευροτοξικότητας

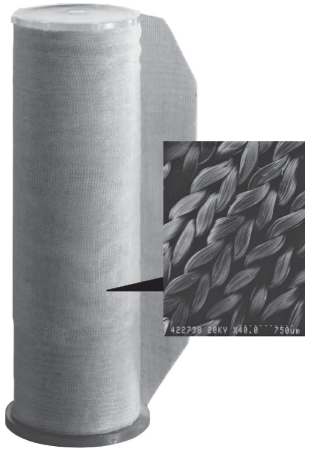
- Συνδεδεμένα ινίδια πολυστερένιου και πολυπροπυλένιου: υλικό - φορέας που συνδέει και ακινητοποίει την PL-Β προσδίδοντας μεγαλύτερη σταθερότητα

- 30.000 ασθενείς έχουν υποβληθεί σε αιμοπροσρόφηση με PL-Β από το 1994 στην Ιαπωνία

- Χωρίς ιδιαίτερες παρενέργειες εκτός από υποτασικά επεισόδια και θρομβοπενία

Toraymyxin PMX 20-R

First-generation anti-LPS adsorber



~1 m2
No micro- and meso pores -> no middle-sized molecules adsorption

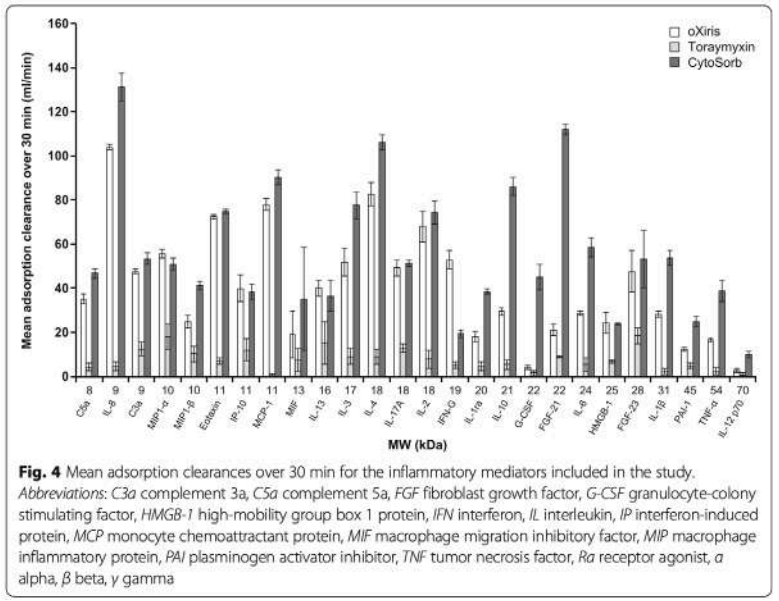


Fig. 4 Mean adsorption clearances over 30 min for the inflammatory mediators included in the study. *Abbreviations*: *C3a* complement 3a, *C5a* complement 5a, *FGF* fibroblast growth factor, *G-CSF* granulocyte-colony stimulating factor, *HMGB-1* high-mobility group box 1 protein, *IFN* interferon, *IL* interleukin, *IP* interferon-induced protein, *MCP* monocyte chemoattractant protein, *MIF* macrophage migration inhibitory factor, *MIP* macrophage inflammatory protein, *PAI* plasminogen activator inhibitor, *TNF* tumor necrosis factor, *Ra* receptor agonist, *α* alpha, *β* beta, *γ* gamma

https://doi.org/10.1186/s40635-018-0177-2

<u>Endotoxemia validation problems:</u>

If this approach removes only endotoxin,

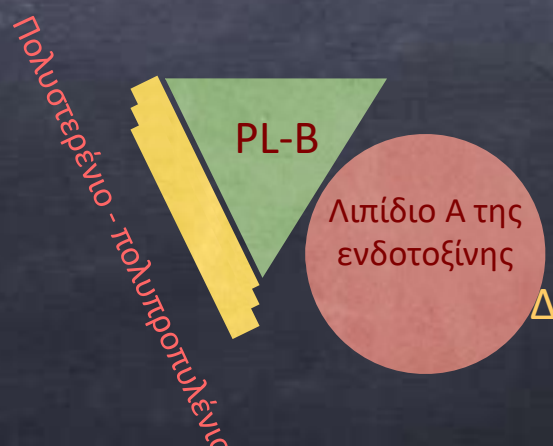
should we confirm its presence in the bloodstream prior hemoperfusion

and is this confirmation even possible?

59. For adults with sepsis or septic shock we suggest against using polymyxin B hemoperfusion.	***Weak,*** *low quality of evidence*	**NEW from previous:** "We make no recommendation regarding the use of blood purification techniques"
60. There is insufficient evidence to make a recommendation on the use of other blood purification techniques.	***No recommendation***	

Χαρακτηριστικά των φίλτρων πολυμυξίνης Β

PL-B: πολυανιονικό αντιβιοτικό	Μήκος σε mm 225
	Διάμετρος σε mm 49
Αποστείρωση με ατμό	Priming volume: 135 ml



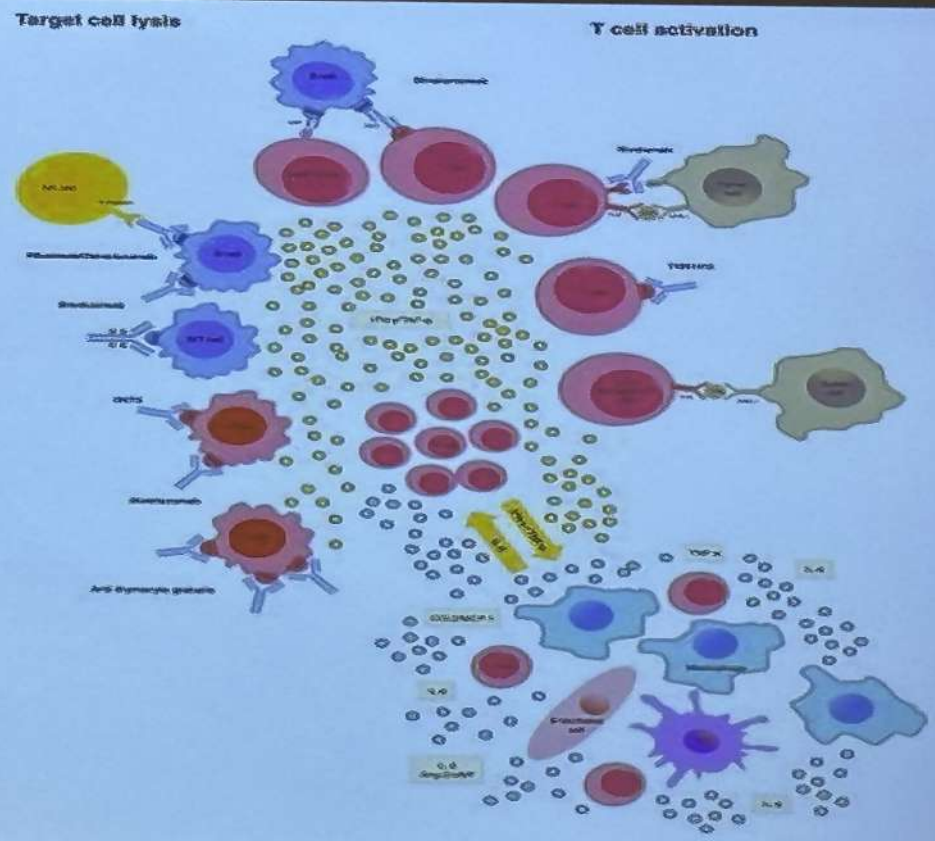
Διάρκεια 2h με ροή αίματος συνήθως 80-100ml/min

Menu

Modality

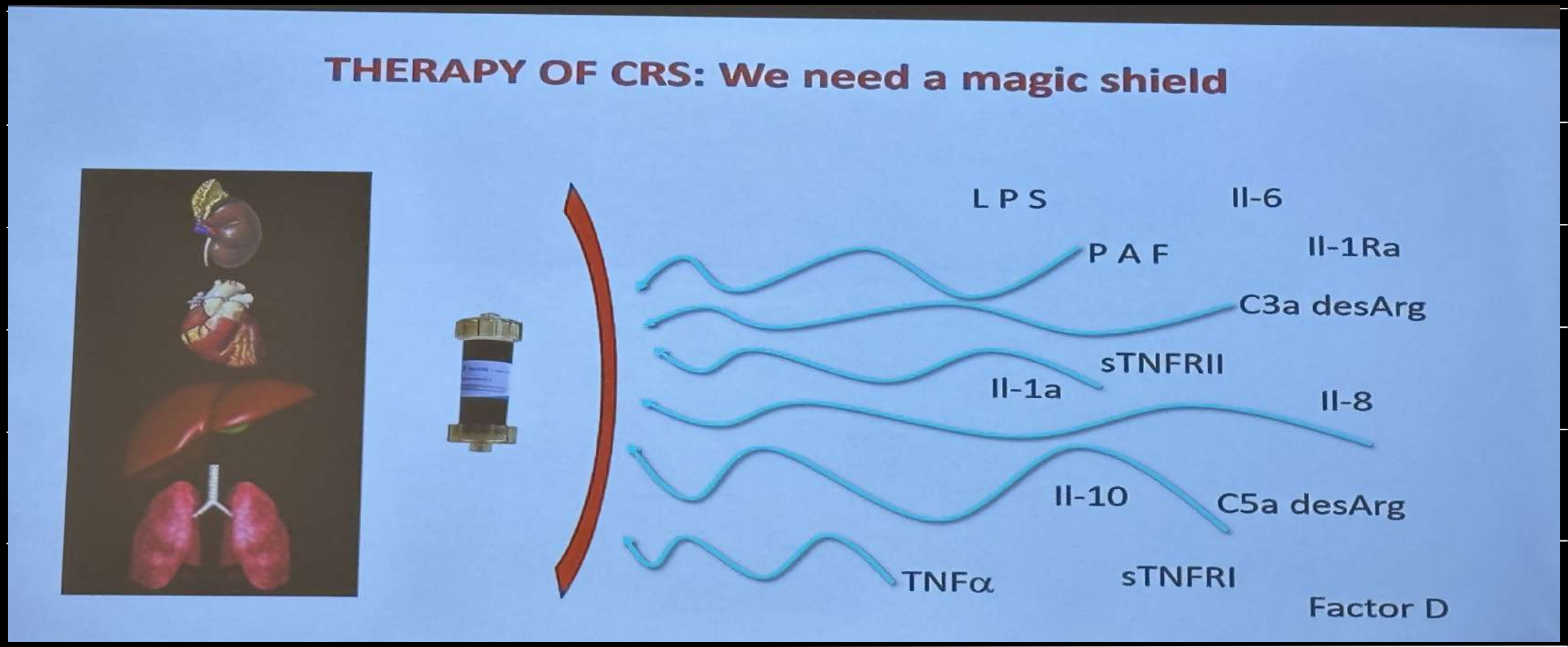
CRS:
Triggers and Mechanisms

CRS can be induced by direct target cell lysis with consecutive release of cytokines like IFN-γ or TNF-α) or by activation of T cells due to therapeutic stimuli with subsequent cytokine release. These cytokines trigger a chain reaction due to the activation of innate immune cells like macrophages and endothelial cells with further cytokine release.



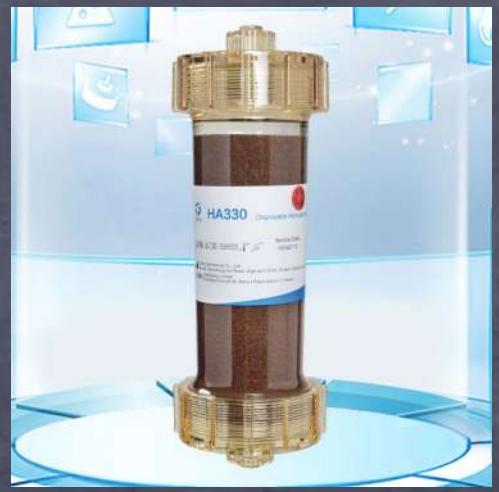
Menu

Modality



CytoSorb and Jafron

Second generation “anti-cytokine” adsorbers



500-1000 m2/g
Lots of micro- and meso pores -> efficient middle-sized molecules adsorption

Possible reasons for these negative results?

Spectrum of pessimistic and optimistic explanations

“Better ways to look for responding patients are warranted”	It’s not possible to help these patients without removing the primary trigger - endotoxin

- There is subpopulation of sepsis patients who are benefitting from “anticytokine” hemoperfusion, we just have to look for them.
- Certain levels of certain biomarkers?
- Certain sepsis endotype?
- Hyper- or hypoimmune subtype?
- Certain degree of multiple organ failure?
- Certain stage of sepsis?
- Certain locus of infection?

- Past-generation “anticytokine” adsorbers do not remove the primary trigger of sepsis - endotoxin molecule.
- “Removing smoke without extingushing fire”.
- This is inherent limitation of technology and therefore it will always have subpar clinical efficacy in sepsis patients.

Two approaches to hemoperfusion in sepsis

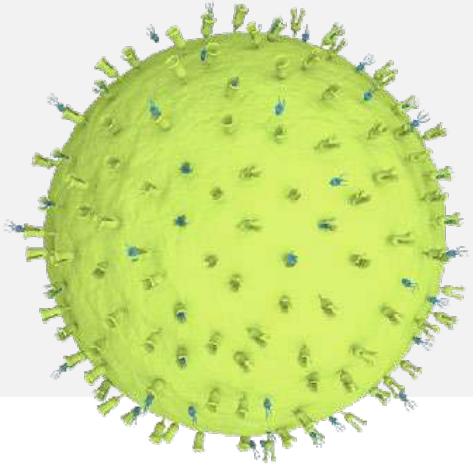
1st gen

Toraymyxin, Alteco LPS Adsorber

2nd gen

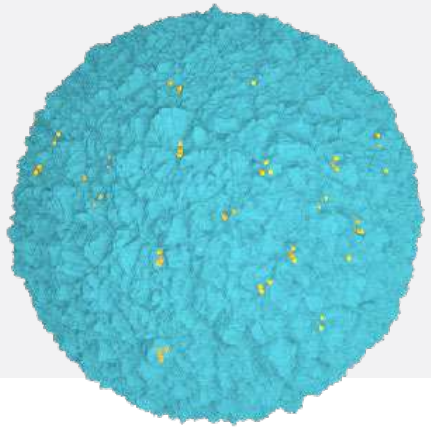
CytoSorb, Jafron HA 330

Two sets of strong and weak points



LPS-selective adsorbents don’t possess internal structure to effectively remove cytokines, cytolysis products and other inflammatory mediators (DAMP molecules)

Affinity ligand



Non-selective mesoporous adsorbents can’t remove primary trigger of sepsis - endotoxin (PAMP molecules) - as in blood it exists as supramolecular structures of alternating size and composition

Porous matrix

Extracorporeal blood purification techniques available in 2024

HEMOADSORPTION (Sorbents)

PMX-B (Toray/Estor)
Cytosorb (Cytosorbents)
LPS adsorber (Alteco)
HA330, HA380 (Jafron)
MG350 (Biosun)

CRRT filters (kidney support + blood purification)

high adsorptive hemofiltration (oXiris, Baxter – PMMA, Toray)

high cut-off membranes (Emic2, Fresenius Medical Care)

MISCELLANEOUS, OTHER TECHNIQUES

High-volume hemofiltration/Cascade hemofiltration

Plasma exchanges

Coupled Plasma Filtration Adsorption

NEW BLOOD PURIFICATION THERAPIES

(capable of leukocyte or bacteria or virus removal)

Seraph® (Exthera Medical)

FcMBL protein (Opsonix)
Hemopurifier® (Aethlon Medical)
other selective cytapheresis technology...

Pathogen Removal by Haemadsorption

Ankawi et al. Critical Care (2018) 22:262
https://doi.org/10.1186/s13054-018-2181-z

Critical Care

REVIEW

Open Access

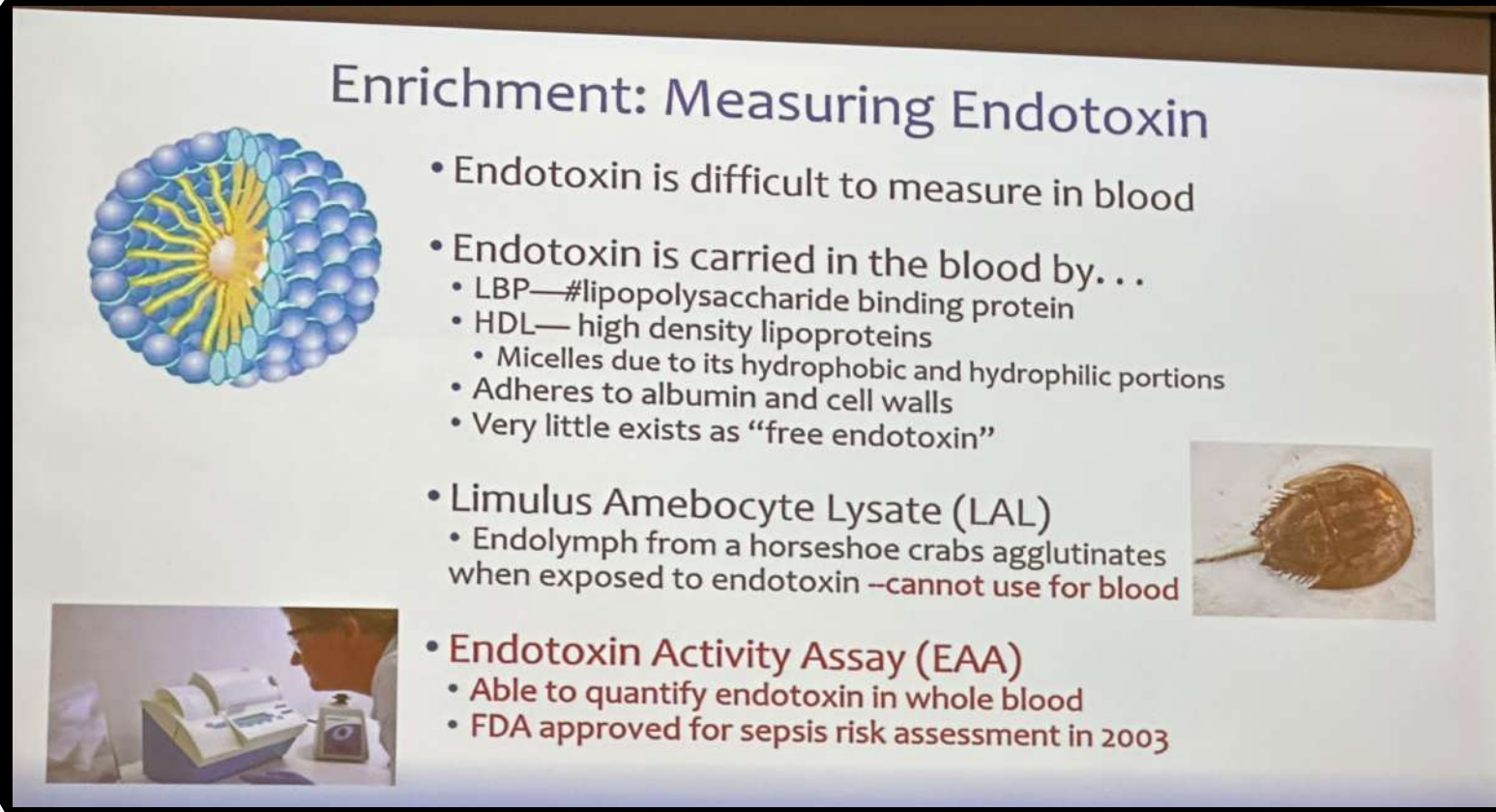
Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls

Ghada Ankawi[1,2*], Mauro Neri[2,3], Jingxiao Zhang[2,4], Andrea Breglia[2,5], Zaccaria Ricci[6] and Claudio Ronco[2,3]

Table 3 The commonly used adsorption cartridges and their prescriptions

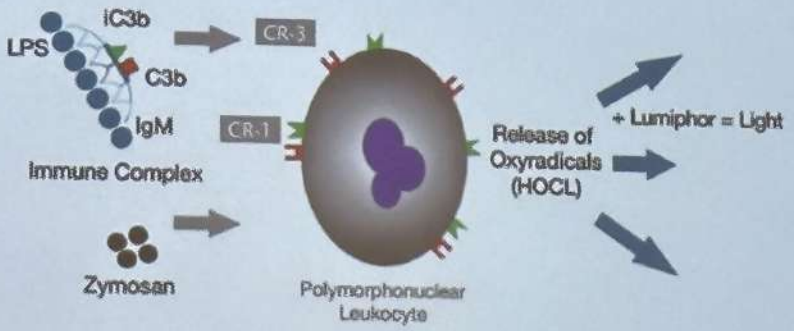
	Toraymyxin	Cytosorb	Oxiris	LPS adsorber	HA 330
Composition	Polymyxin B-immobilized fiber blood-purification column	Porous polymer beads	AN69-based membrane, surface treated with PEI and grafted with heparin	Synthetic polypeptide bound to porous polyethylene discs	Styrene divinylbenzene copolymers
Indication	Severe sepsis and septic shock	Severe sepsis and septic shock Cardiac surgery with SIRS	Severe sepsis and septic shock	Severe sepsis and septic shock	Severe sepsis and septic shock
Toxins removed	Endotoxins	Cytokines/chemokines Anaphylatoxins Myoglobin Free hemoglobin Bilirubin/bile acids Toxins/metals Drugs	Endotoxin Cytokines	Endotoxins	Cytokines Complements Free hemoglobin
Prescription	2-h session daily for 2 consecutive days	Up to 24-h therapy daily for 2–7 consecutive days	Prescribed dose > 35 ml/kg/h (60% convective). Filter replacement after 24 h or if there is no reduction in VP dose by 50%. Treatment should be stopped if VP are reduced by > 50% or after 3 days of treatment in case of non-response	2–6 h. One session is usually sufficient to achieve improvement. Repeated procedures can be performed	2–6 h daily for 2 days
Blood flow rate (ml/min)	80–120	150–700	100–450	150 ± 50	100–300
Anticoagulation	Heparin	Heparin or citrate	Heparin	Heparin	Heparin or citrate
Additional features	Polymyxin B antimicrobial effect	Largest surface area	Lower risk of thrombogenicity by adsorbing antithrombin-III from the blood		

CRRT continuous renal replacement therapy, *LPS* lipopolysaccharides, *PEI* polyethyleneimine, *SIRS* systemic inflammatory response syndrome, *VP* vasopressors



Endotoxin Activity Assay (EAA)

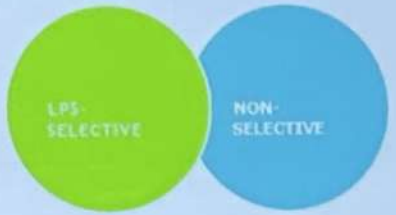
- EAA is a Chemiluminescent assay based on the oxidative burst reaction of neutrophils in combination with a complement coated antibody-antigen (LPS-IgM) complex.
- The antibody is specific for the Lipid A portion of endotoxin (LPS). This portion was selected due to the highly conserved nature of the structure allowing for the robust response across Gram Negative endotoxins.



Very interesting facts!

Unified approach - third generation

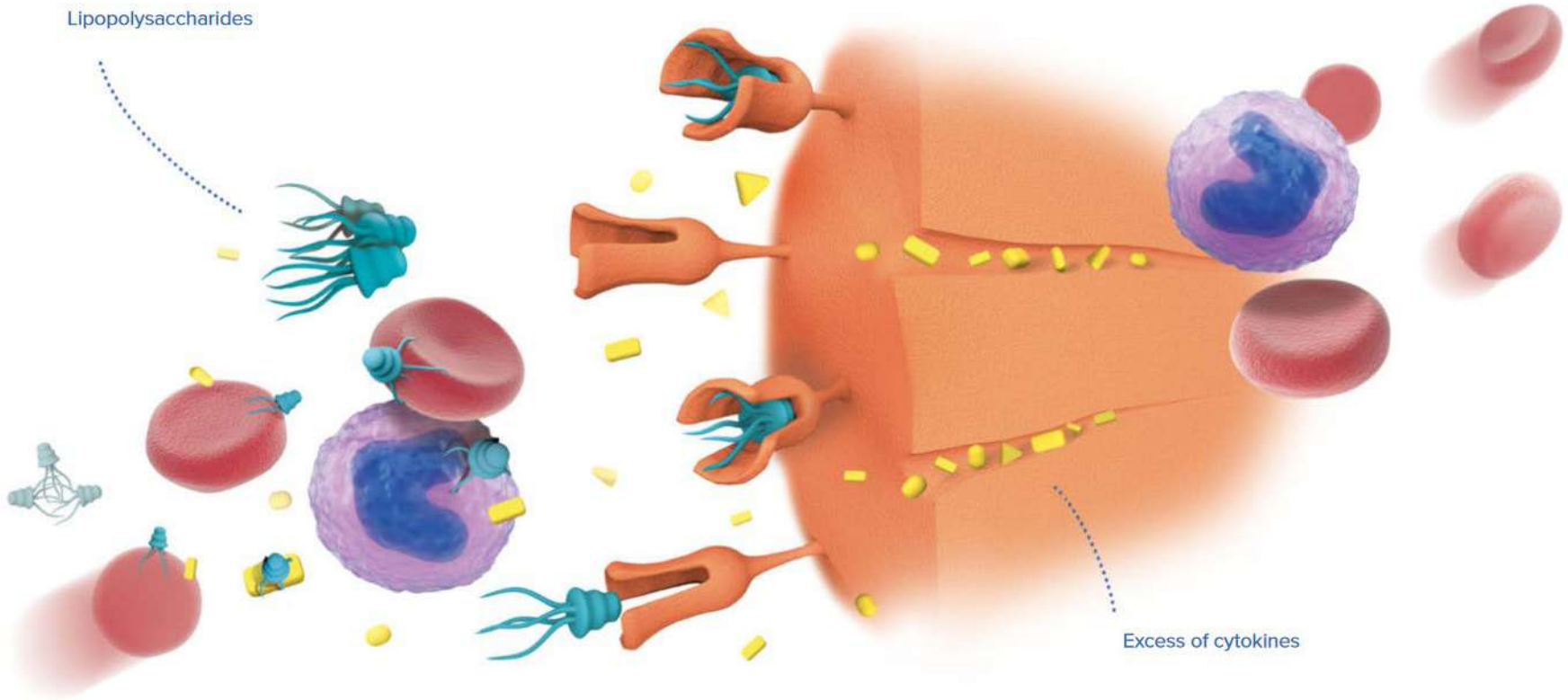
Is it possible to integrate these two sets of benefits in one single material?



EFFERON LPS IS THE FIRST PRODUCT OF SUCH KIND

Polymeric adsorbent with multimodal distribution of target sorbates selectively binds two dissimilar kinds of therapeutic targets

How Efferon LPS works? What does “multimodal” mean?



Endotoxin is bound due to interaction with surface-immobilized LPS-selective ligand

Cytokines are bound by intrinsic porosity of polymeric scaffold

ADQI

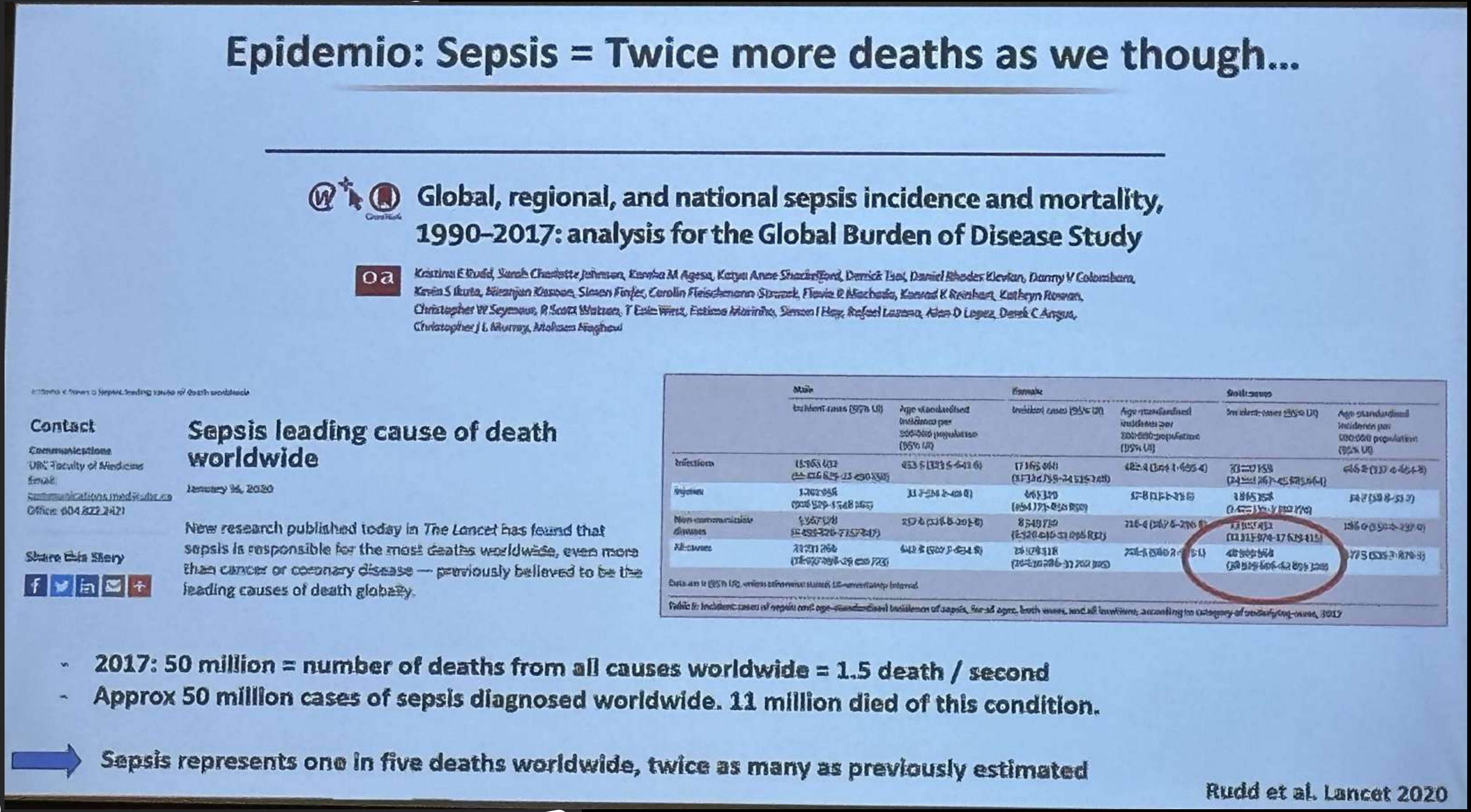
Extracorporeal Therapies for the critically ill patient

Consensus statement 5a

Extracorporeal blood purification (EBP) techniques can be used to remove pathogens, microbial toxins, inflammatory mediators and toxic metabolites from the blood as well as replenish solutes (grade 1A).

Consensus statement 5d

Initiation of EBP in sepsis might be considered for immunomodulatory molecular patterns and pathogen-associated molecular patterns, as well as other targets of systemic inflammation (not graded).



We should be careful of the increasing gap between technological progres and medical knowledge!

Medical knowledge

Increasing gap!

EBP device

Technological progress

Past

Future

FOUR IMPORTANT UNANSWERED QUESTIONS :

a- How do these therapies exactly interfere with sepsis pathophysiology?
b- Which patients exactly?
c- Which timing?
d- What to ultimately remove?

Extracorporeal blood purification techniques available in 2025

HEMOADSORPTION (Sorbents)

PMX-B (Toray/Estor)
Cytosorb (Cytosorbents)
LPS adsorber (Alteco)
HA330, HA380 (Jafron)
Efferon LPS and Efferon CT (Efferon)

CRRT filters

high adsorptive hemofiltration (oXiris, Baxter – PMMA, Toray)

high cut-off membranes (Emic2, Fresenius Medical Care)

NEW BLOOD PURIFICATION THERAPIES

(capable of leukocyte or bacteria or virus removal)

Seraph® (Exthera Medical)
FcMBL protein (Opsonix)
Hemopurifier® (Aethlon Medical)
other selective cytapheresis technology...

MISCELLANEOUS, OTHER TECHNIQUES

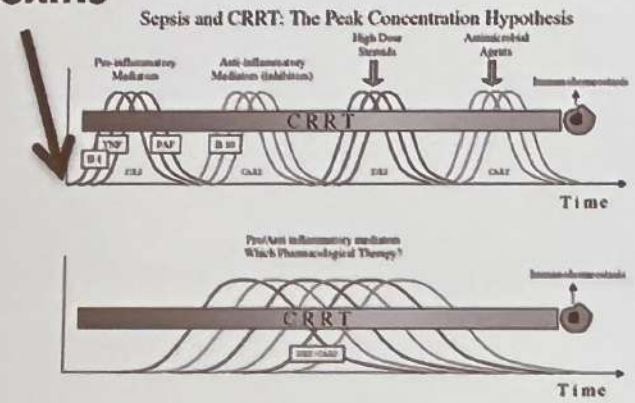
High-volume hemofiltration/Cascade hemofiltration

Plasma exchanges

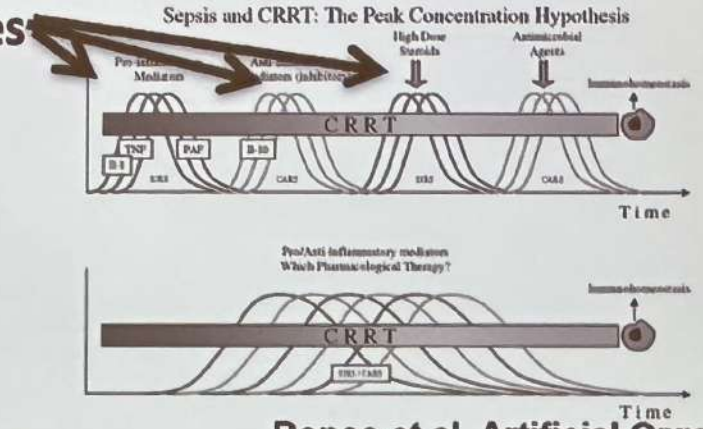
Coupled Plasma Filtration Adsorption

HEMOADSORPTION: Possible mechanisms of action in sepsis

Endotoxins

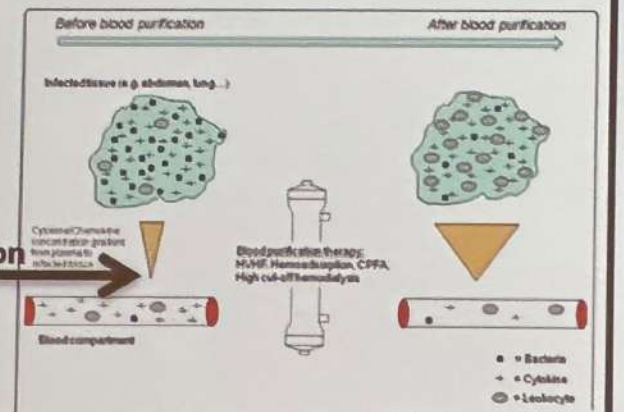


Cytokines



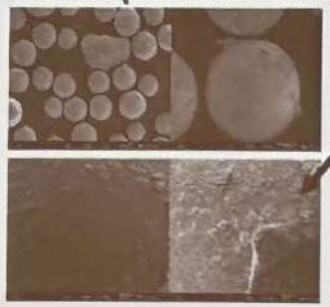
Ronco et al. Artificial Organs 2003

Chemokine concentration gradient



Peng et al. Critical Care 2014
Rimmelé et al. Anesthesiology 2012

- Direct removal of activated leucocytes through adsorption
- Interaction sorbent-leucocyte leading to a modification of expression of leucocyte surface markers (ex: HLA-DR increase)

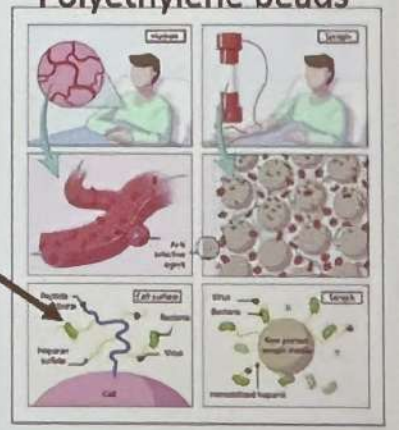


Leukocytes

Rimmelé et al. Crit Care 2013

Polyethylene beads

Pathogens

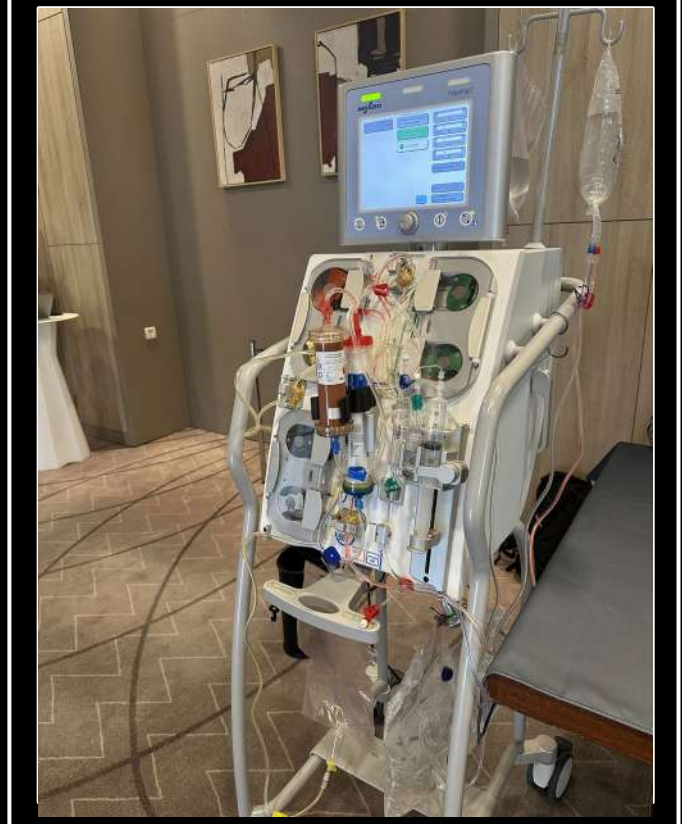


Seffer et al. Blood Purif 2021

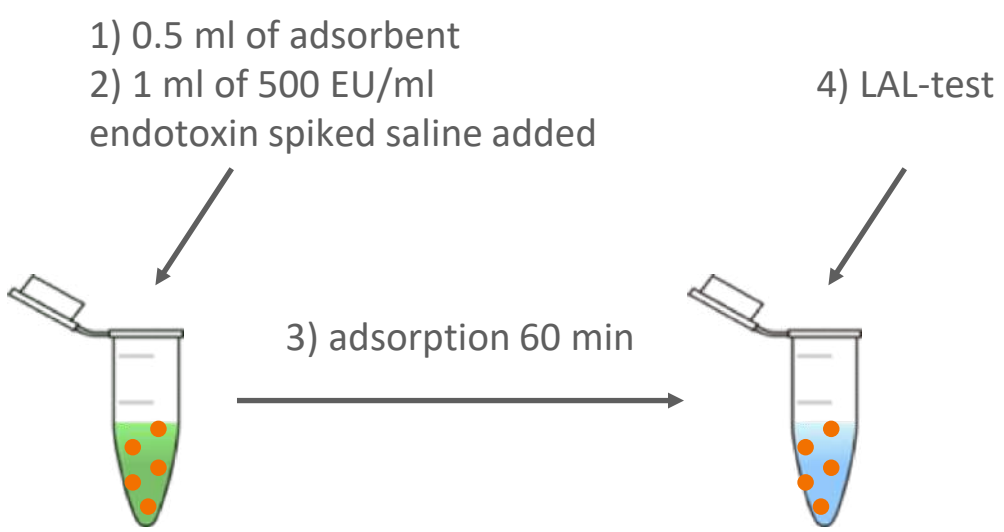
Broad-Spectrum Hemoadsorption devices also targeting Endotoxin

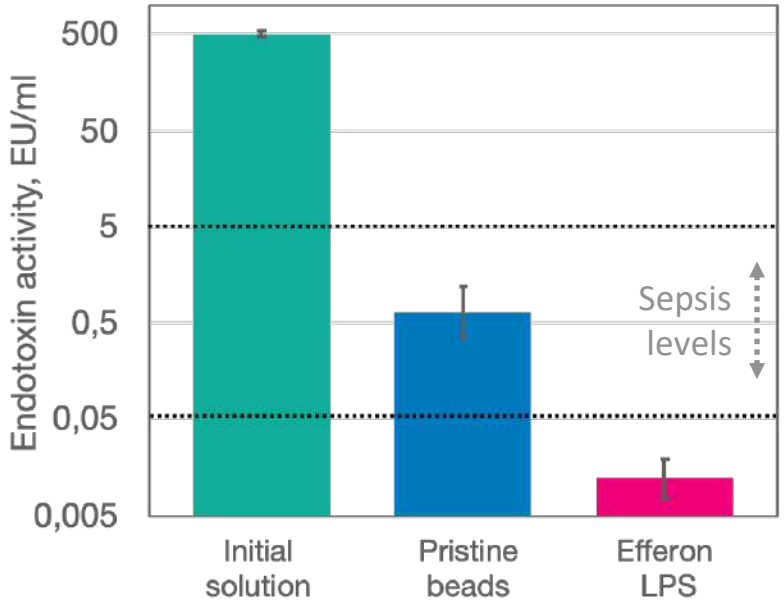
Device Name	Description	Target Solute(s)	Randomized Clinical Trials
Broad-Spectrum HA Devices Also Targeting Endotoxin			
Efferon LPS	Consists of a matrix of styrene and divinylbenzene copolymer, with synthetic LPS-selective ligands covalently grafted to its surface	Endotoxin and other pro-inflammatory immune mediators	LASSO RCT N=60; no significant improvements in 28-d mortality
oXiris	Consists of modified AN69 membrane technology modified so membrane has a positively charged polyimine ethylene layer	Inflammatory mediators, endotoxins, fluid, and uremic toxins	RCT 1 N=16; reduction in endotoxin level, reduction in TNF-α, IL-6, IL-8 and IFNγ, hemodynamic stability RCT 2 N=16; hemodynamic stability

Kellum JA, Kamaluddin E, Foster D. Blood Purif. 2025 Mar 11:1-12.



Endotoxin adsorption is drastically improved





Transfusion and Apheresis Science 64 (2025) 104232

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

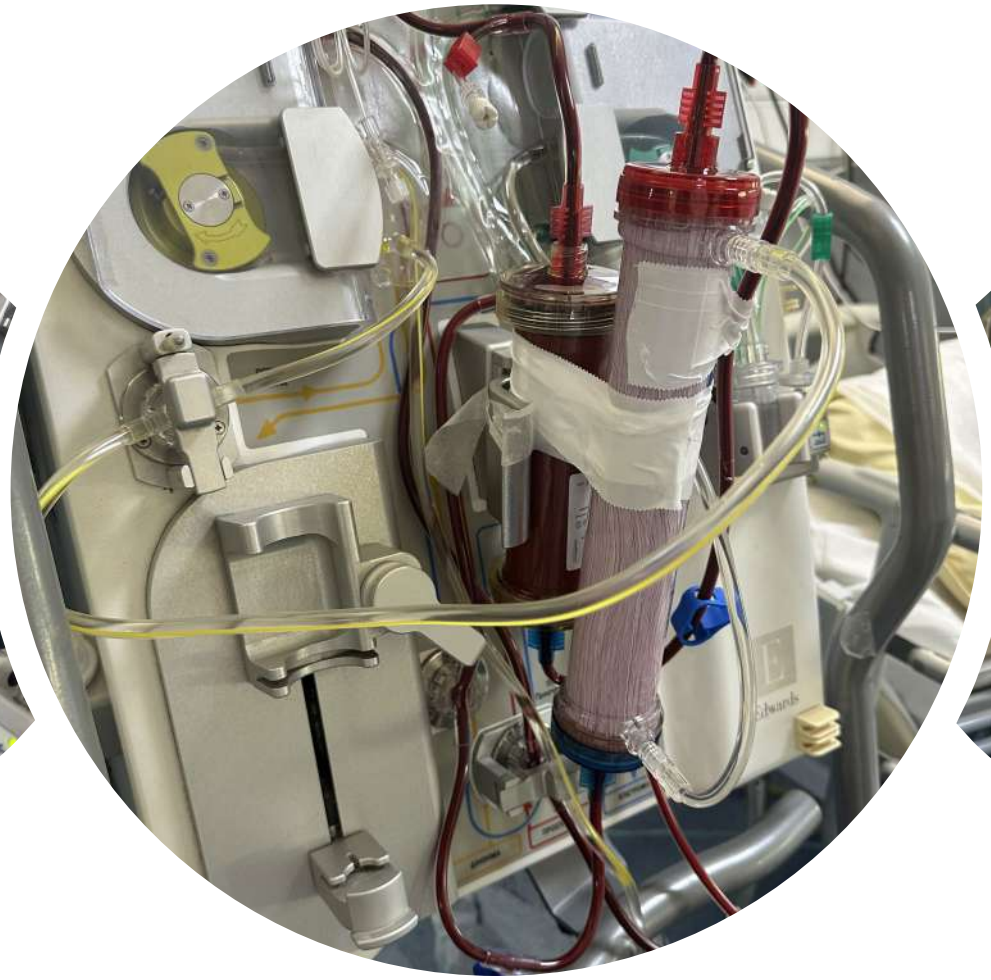
Immunoadsorption in specific conditions

Ioannis Griveas [a,b,*]

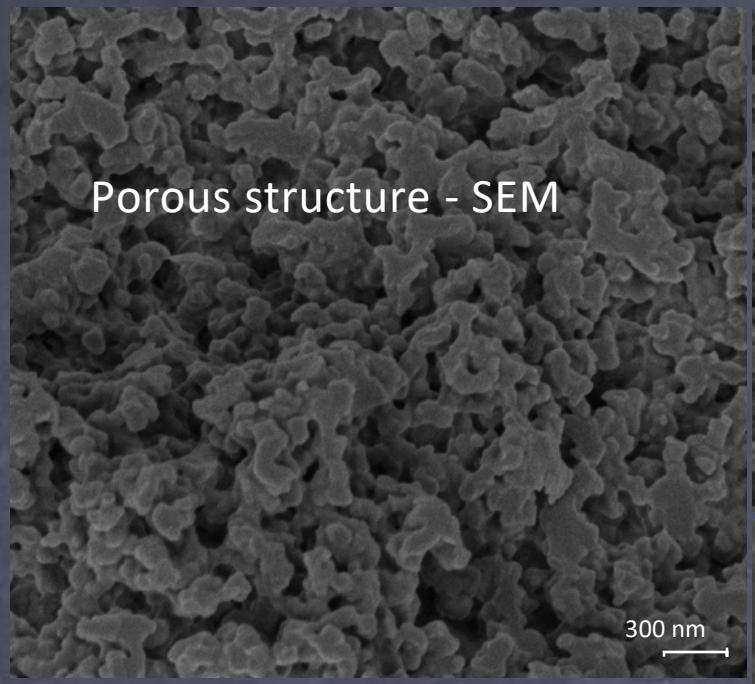
[a] Medical Director, Consultant Nephrologist, Nephrology Department, Army Share Fund Hospital of Athens, 417 NIMTS, Greece
[b] Private Dialysis Unit "Polyxenia-Renal", Athens, Greece

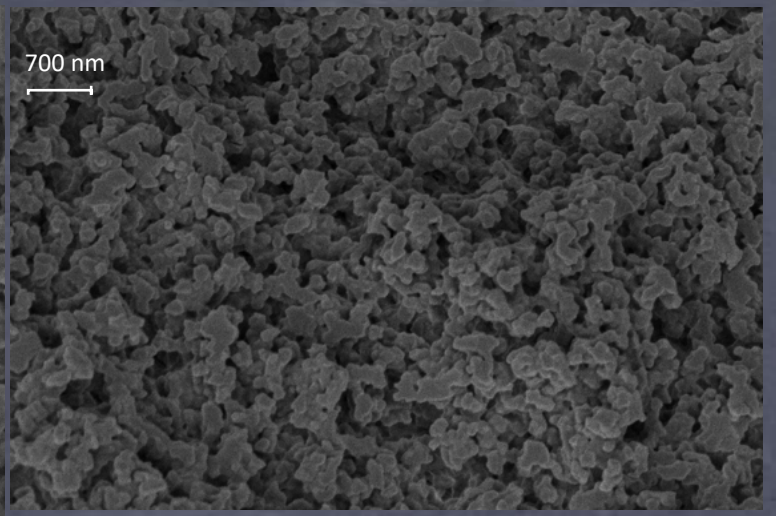
4.3. Endocarditis

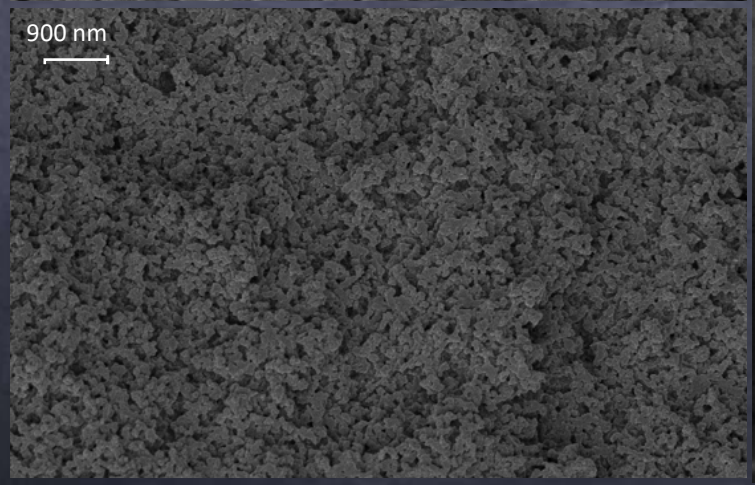
Patients with ESRD who suffer from infective endocarditis are at high risk for developing a systemic hyperinflammatory state that could lead to septic shock. IA, by removing inflammatory mediators, could be used as a means of controlling the "inflammatory" process and stabilizing the patient's clinical and hemodynamic picture.

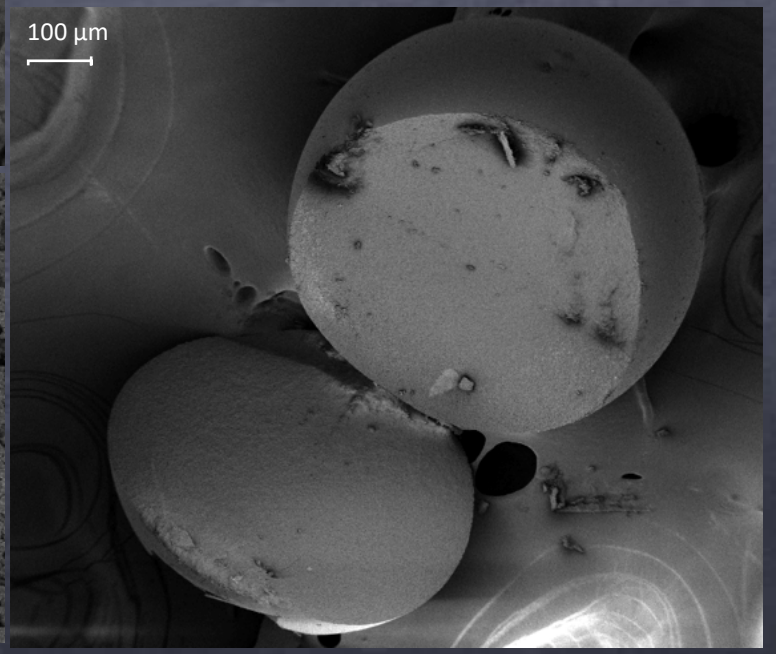


Porous structure - SEM









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Critical patients, intended to be treated with Efferon® LPS hemoperfusion, represent a highly heterogeneous population. This device has the potential to involve in 2 stages of sepsis: in elevated levels of endotoxin in blood which provokes critical endotoxemia and at the same time in elevated levels of cytokines in blood that provokes the so called "cytokine storm" syndrome. The course and outcome of the provided treatment depends on the source control of the infection, adequacy of antibiotic therapy, fluid management, respiratory support, time window of the intervention, and many other variables. A certain subpopulation of patients does not always respond to hemoperfusion therapy with expected benefits. Hemoperfusion is an adjuvant treatment. It cannot be regarded as monotherapy with independent stand-alone benefits.

Transfusion and Apheresis Science 64 (2025) 104226

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

"Green" methodology: An overview and basic principles

Ioannis Griveas *

Nephrology Department, Army Share Fund Hospital of Athens, 417 NIMTS, Greece, Private Dialysis Unit "Polyxenia-Renal", Athens, Greece

Transfusion and Apheresis Science 64 (2025) 104228

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

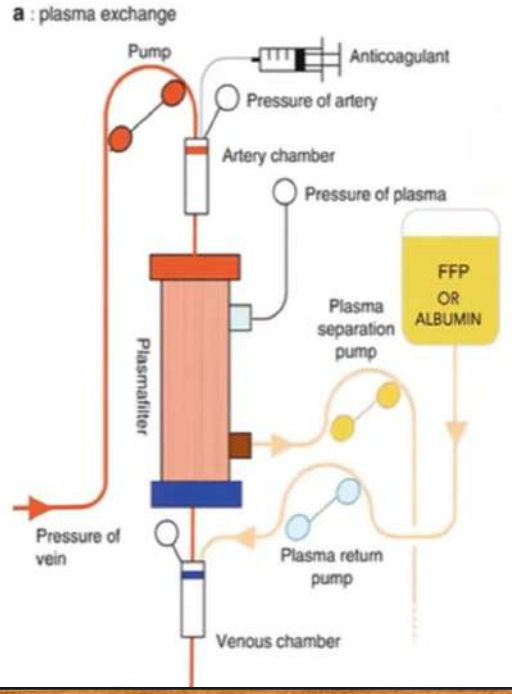
journal homepage: www.elsevier.com/locate/transci

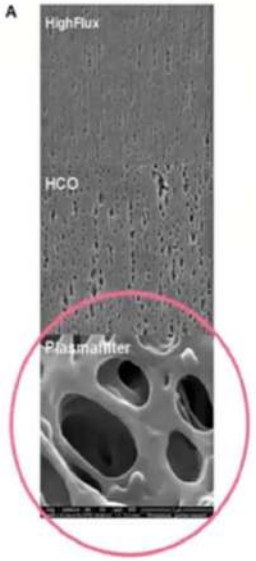
Organizing in "green" a plasmapheresis unit

Ioannis Griveas [a,*], Paraskevi Tseke [b]

[a] *Private Dialysis Unit "Polyxenia-Renal", Nephrology Department, Army Share Fund Hospital of Athens, 417 NIMTS, Greece*
[b] *Renal Unit, Department of Clinical Therapeutics UOA, General Hospital of Athens "Alexandra", Athens, Greece*

THERAPEUTIC PLASMA EXCHANGE





2. Conclusions

Surely, it is difficult to reach solid conclusions comparing TPE and IA on the basis of their environmental footprint. On the other hand, this a new era of discussion in our scientific community and who really knows how this chapter will end? TPE seems more "hostile" to the environment than IA which seems easier than plasma exchange with less equipment and consumables than TPE. However, this a new path for physicians that deal with blood purification and it seems that a lot of our decisions in the future will have the eco-footprint of each method under consideration.

Efferon LPS indications as per IFU

2. DESCRIPTION OF THE DEVICE

Efferon® LPS is a sealed polycarbonate cylinder with two dialysis-type connectors at the edges, filled with a suspension of polymeric adsorbent beads in isotonic (0,9 %) sodium chloride solution. Efferon® LPS is used in intensive care units, departments of haemodialysis and extracorporeal treatment methods.

3. INDICATIONS

- Sepsis of verified or suspected gram-negative aetiology, including septic shock.
- Elevated levels of endotoxin in blood, critical endotoxemia.
- Elevated levels of cytokines in blood, “cytokine storm” syndrome.

Administration of Therapy:

- Day 1: First treatment for 6-12 hours.
- Day 2: Second treatment for another 6-12 hours (since 24 hours after the first treatment initiation).

Clinical assessment to be made after 48 hours of use to determine if patient is receiving clinical benefit for continuation of therapy.

4. CONTRAINDICATIONS

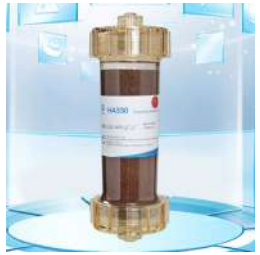
- Uncorrected hypovolemia;
- Uncontrolled bleeding;
- Anaphylactic or nonspecific reaction to the components of the extracorporeal circuit;
- Pregnancy

5. PATIENT TARGET GROUP AND INTENDED USERS

- Efferon® LPS is intended for purpose in adult patients ≥18 years old.
- Efferon® LPS should only be used by qualified intensivists, anesthesiologists, nephrologists, transfusion specialists.

Three generations. Where are we now?

2020s: “let’s extinguish fire **and** capture smoke”



2000s: “let’s capture smoke”

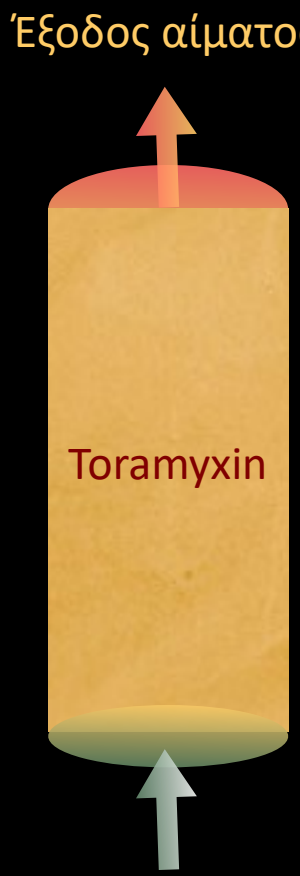
1990s: “let’s extinguish fire”

Thank you!

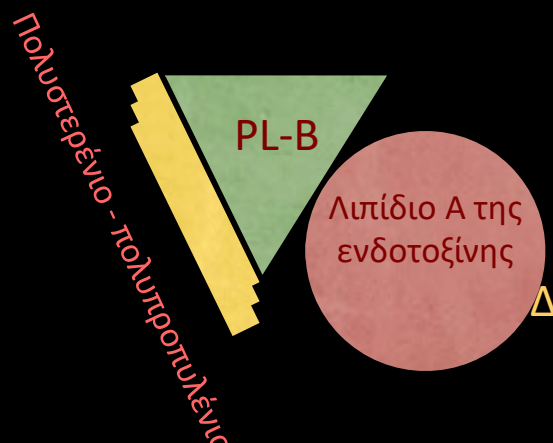
Do you have any questions?

giannigriv@hotmail.com
www.athens-nephrology.gr

Χαρακτηριστικά των φίλτρων πολυμυξίνης Β



PL-B: πολυανιονικό αντιβιοτικό	Μήκος σε mm 225
	Διάμετρος σε mm 49
Αποστείρωση με ατμό	Priming volume: 135 ml



Διάρκεια 2h με ροή αίματος συνήθως 80-100ml/min

Hello! I’m...

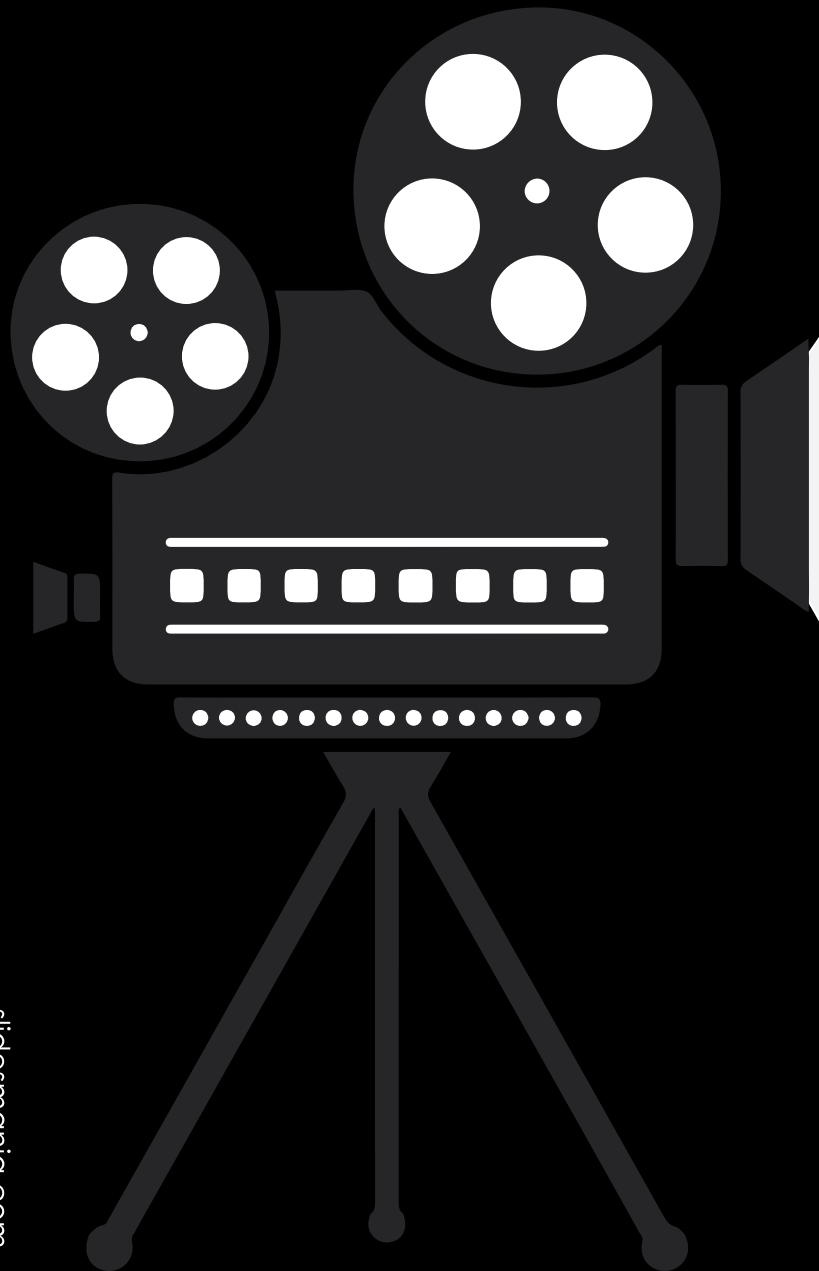
Here is where you introduce yourself.

You can add your name, title and a little background. Right click the image and replace it with your own.

Table of Contents.

We will talk about this first.

Add a brief introduction of your section here: Let’s dive in and get to know some interesting facts about animals!



Did you know?

Elephants and storms.

Did you know that elephants can sense storms?

Elephants may be able to detect a thunderstorm from hundreds of miles away, and will head towards it, looking for water.

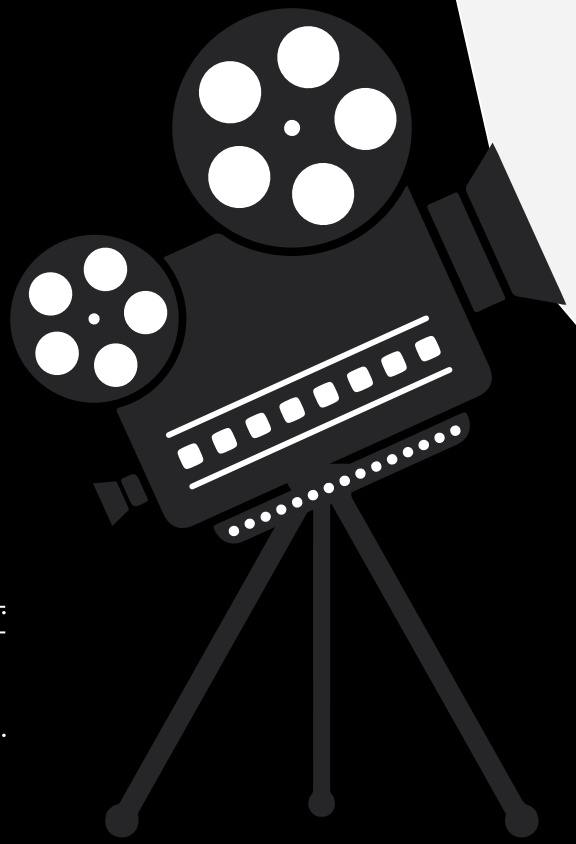
Did you know?

Did you know that dogs can smell your feelings?

Dogs can pick up on subtle changes in your scent, which can help him figure out how you are feeling, such as by smelling your perspiration when you become nervous or fearful.

Did you know that a cat uses its whiskers as feelers to determine if a space is too small to squeeze through?

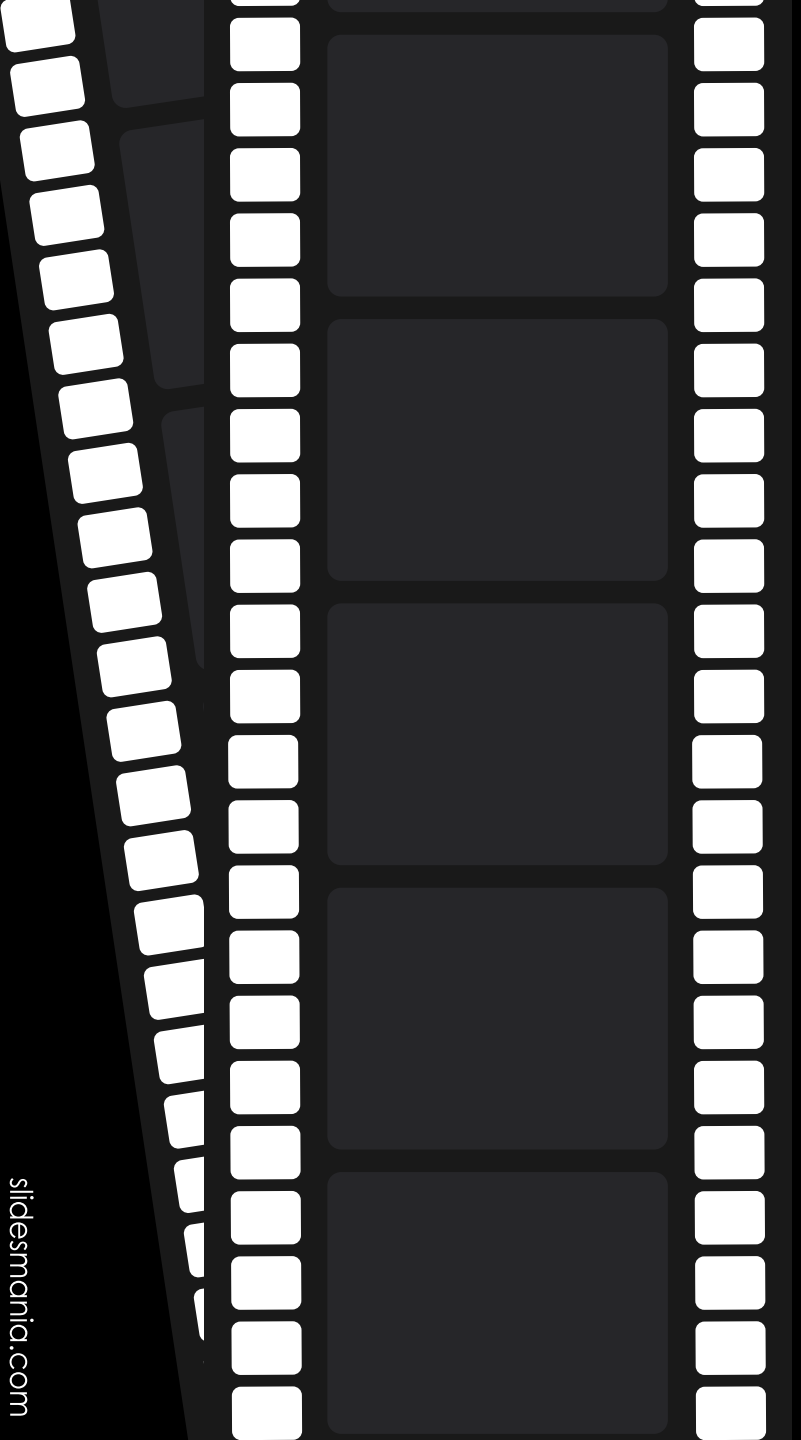
Also, cats love to sleep. A fifteen-year-old cat has probably spent ten years of its life sleeping.



“

Clearly, animals know more than we think, and think a great deal more than we know.

— Irene M. Pepperberg



Did you know?

Pandas don’t hibernate.

When winter approaches, they head lower down their mountain homes to warmer temperatures, where they continue to chomp away on bamboo!

There are more kangaroos than humans in Australia.

It is estimated that more than 50 million kangaroos live there. They are Australia’s national symbol and appear on postage stamps, coins, and airplanes.

Koalas are even more lazy than cats.

Koalas don’t have much energy and, when not feasting on leaves, they spend their time dozing in the branches. Believe it or not, they can sleep for up to 18 hours a day!

Very interesting facts!

This is where you section ends. Duplicate this set of slides as many times you need to go over all your sections.

Now we will talk about this.

Add a brief introduction of your section here: Let’s dive in and get to know some interesting facts about animals!

Dogs can smell your feelings.

Dogs can pick up on subtle changes in your scent, which can help him figure out how you are feeling, such as by smelling your perspiration when you become nervous or fearful.

Cats love to sleep.

A fifteen-year-old cat has probably spent ten years of its life sleeping.

Also, cats use their whiskers as feelers to determine if a space is too small to squeeze through.

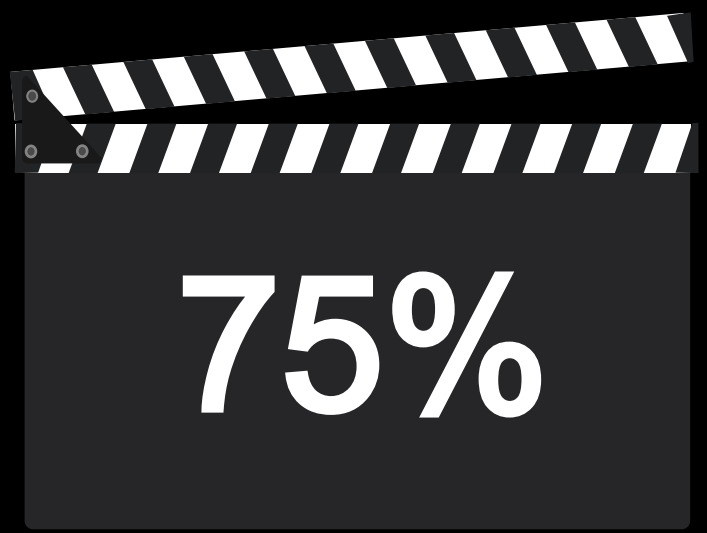
Some facts about my cats.

100%

Of my cats are adorable.

25%

Traveled by plane. Twice!



75%

Are females.

Let’s review some facts.

Elephants

Elephants can sense storms.

Pandas

Pandas don’t hibernate.

Cats

Cats use their whiskers as feelers

Dogs

Dogs can smell your feelings.

Kangaroos

There are more kangaroos than humans in Australia.

Koalas

Koalas are even more lazy than cats.

This is our team.

Erika V.

Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Aenean commodo ligula eget dolor.

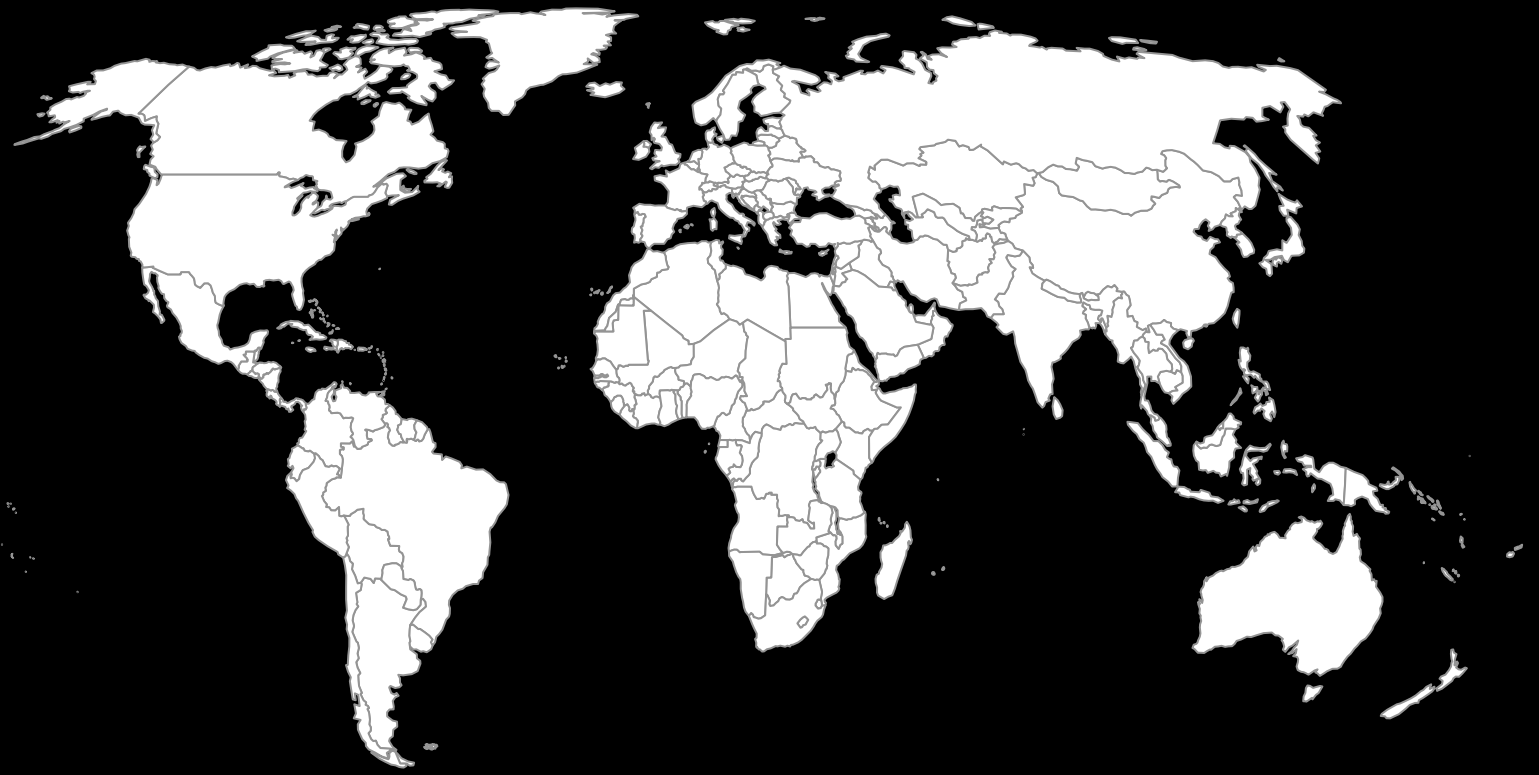
John S.

Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Aenean commodo ligula eget dolor.

Marie M.

Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Aenean commodo ligula eget dolor.

This is an editable world map.



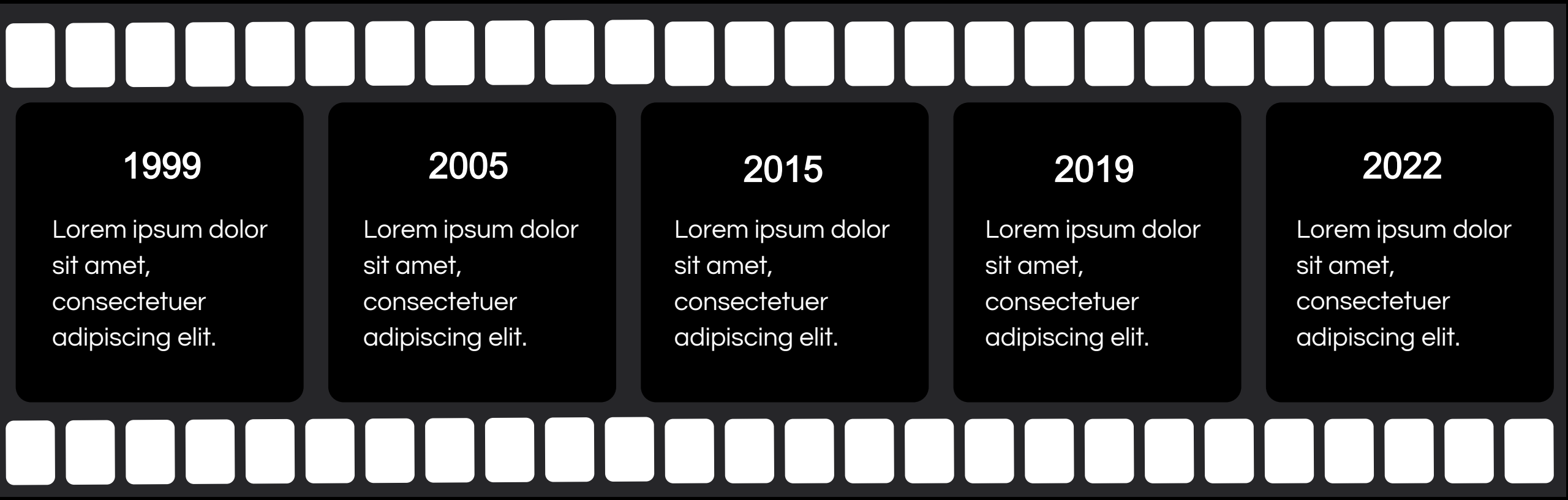
Showcase places

You can use maps to show your offices or markets. Or as charts, highlighting the countries and adding your data.

100% Editable

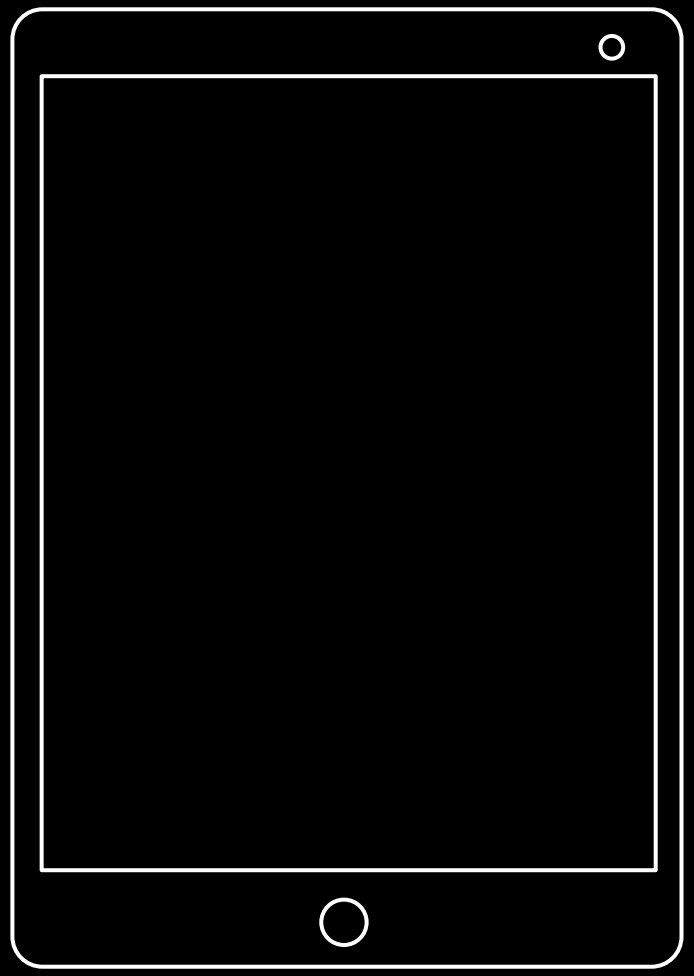
You can double click on the desired country and change fill color.

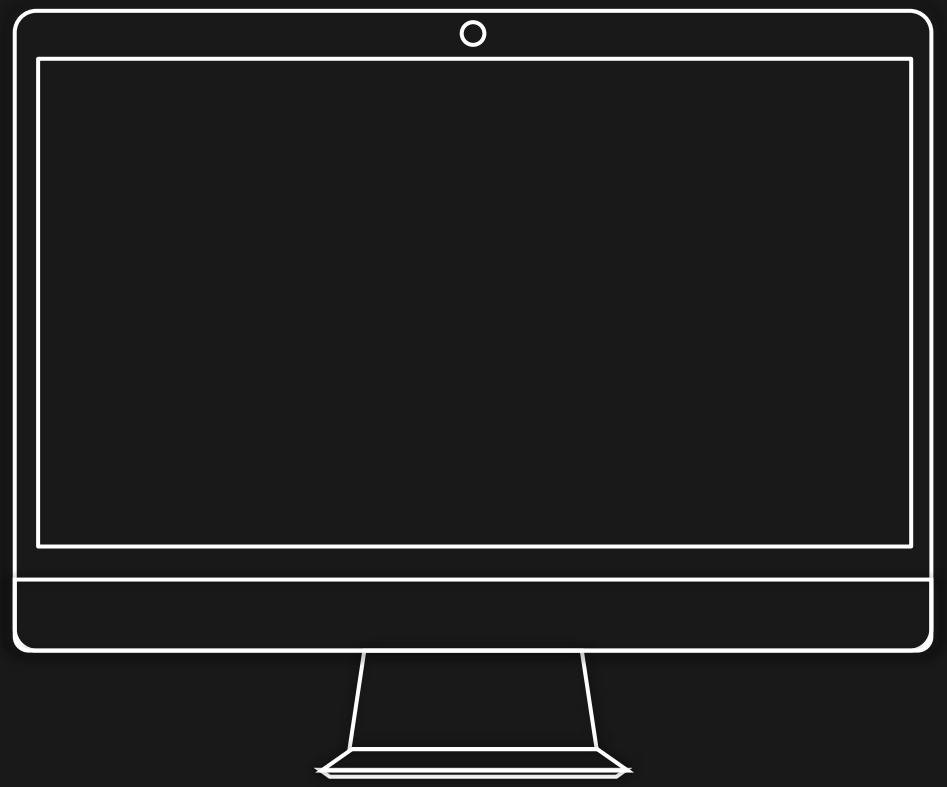
And this is a timeline.



Presenting a website or an app?

If you are presenting a website, an internet product or an app, you can place a screenshot of it here.





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Broad-Spectrum Hemoadsorption devices also targeting Endotoxin

Device Name	Description	Target Solute(s)	Randomized Clinical Trials
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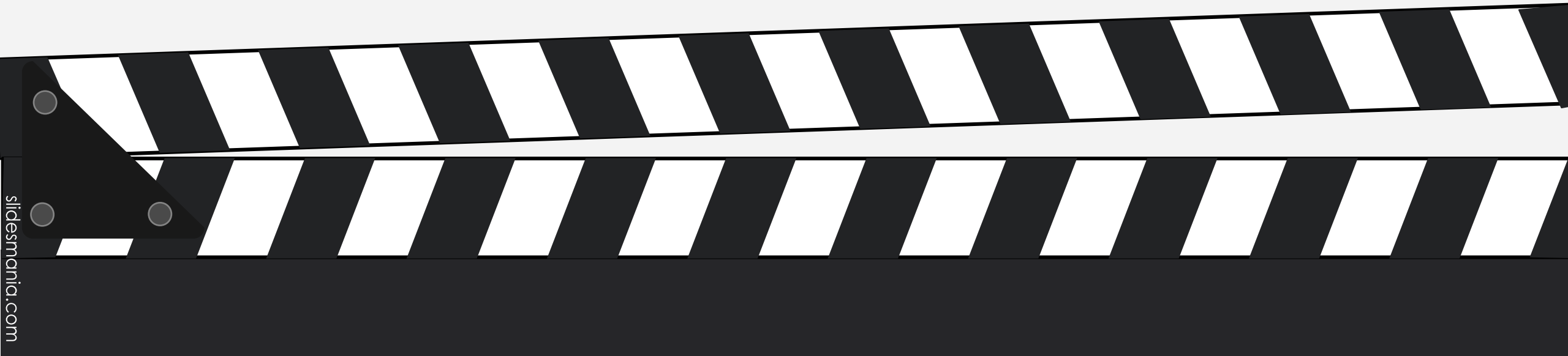

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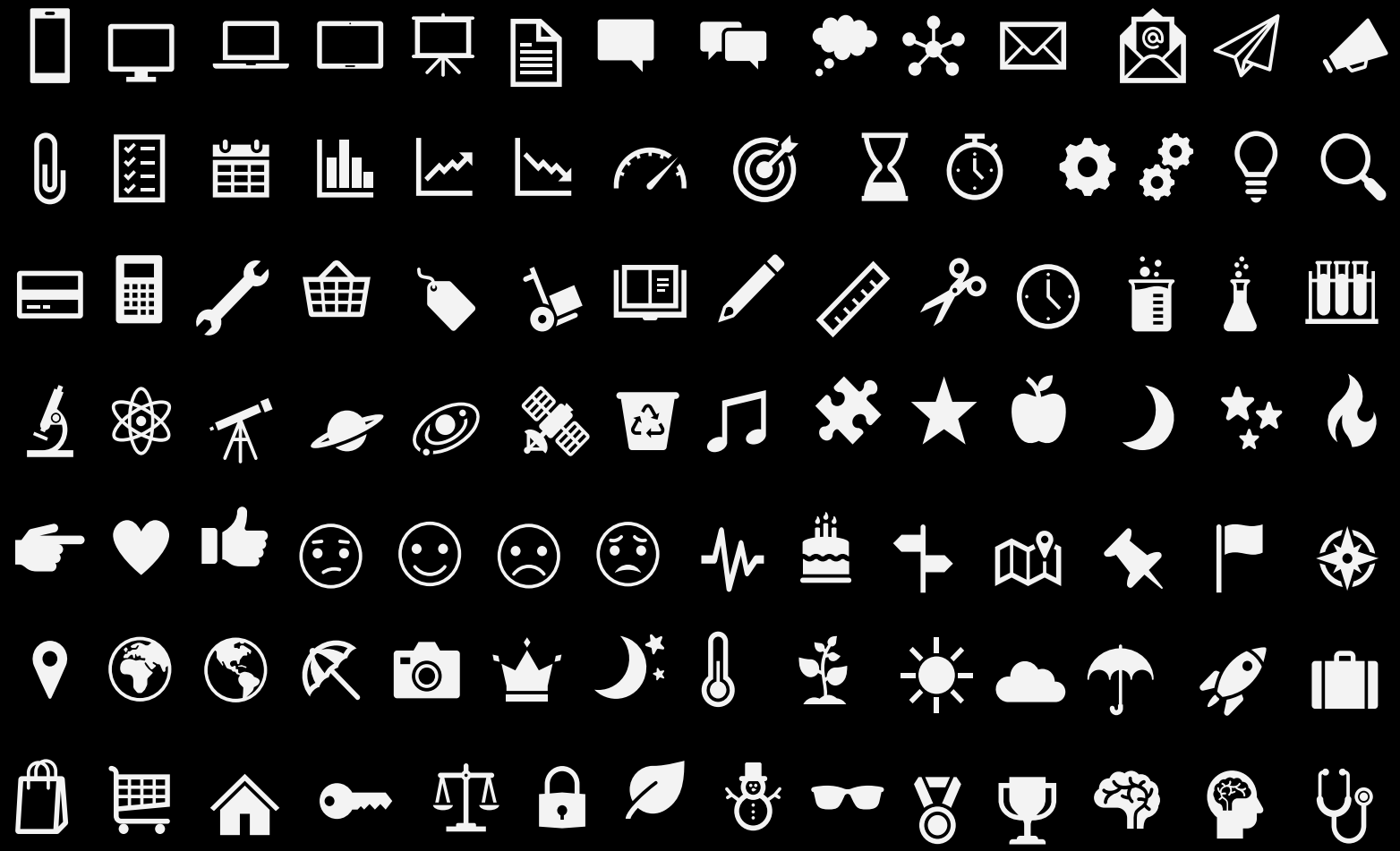

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