

Potenziale effetto protettivo della CPFA sul danno tubulare in corso di sepsi e bile cast nephropathy?

Vincenzo Cantaluppi

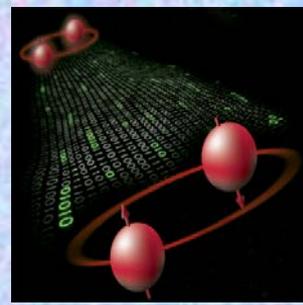
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Azienda Ospedaliera Universitaria “Città della Salute e della Scienza di Torino-Molinette”**



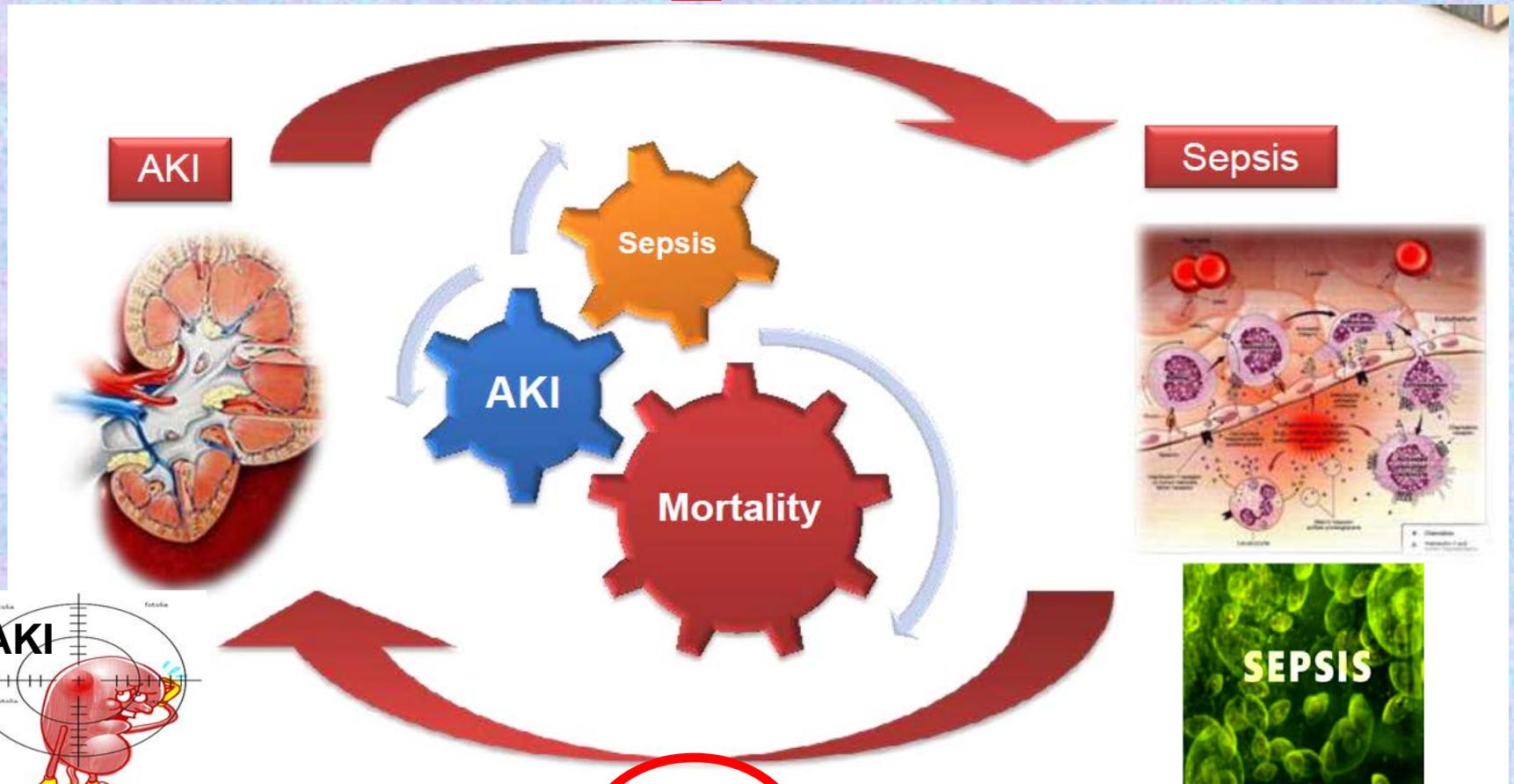
Università di Torino

*Centro Ricerca in
Medicina Sperimentale*

SEPSI E AKI: ENTANGLEMENT E BIDIREZIONALITA'



2



1

Acute Renal Failure in Critically Ill Patients

A Multinational, Multicenter Study Uchino S et al.

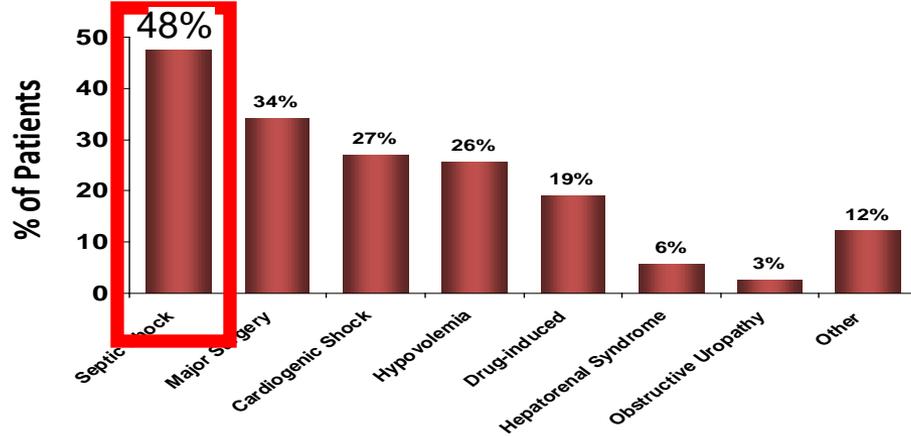


**SEPSIS AND AKI:
INCIDENCE**

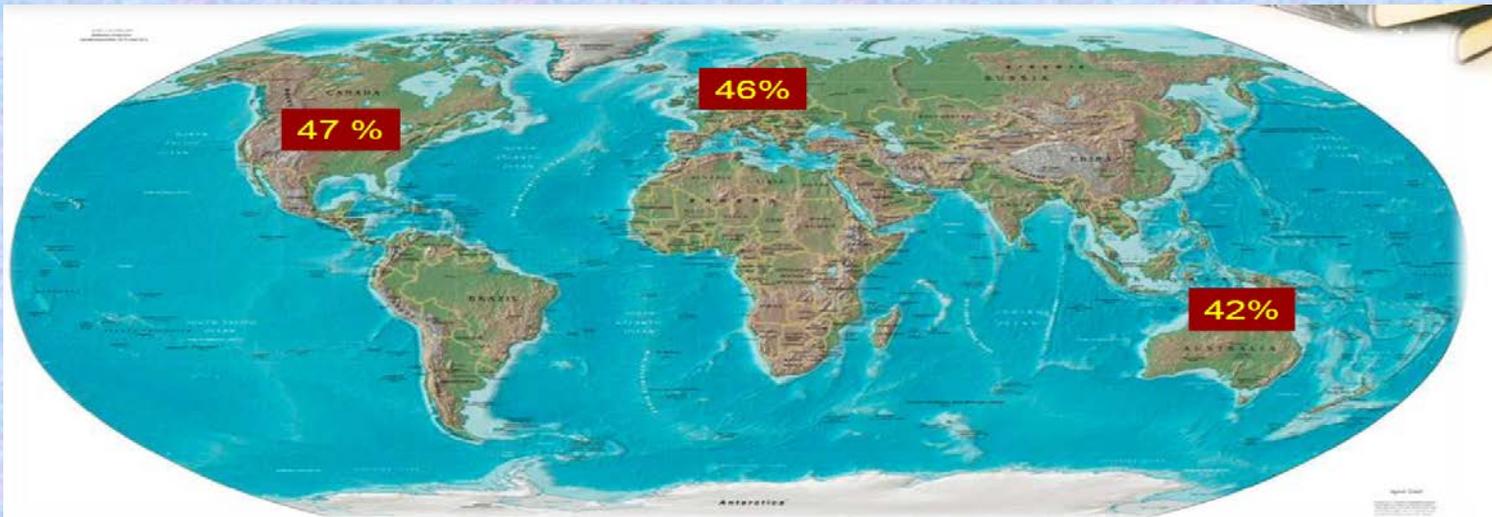
**AKI RAPPRESENTA UNA
COMPLICANZA
NEL 48% DEI PAZIENTI
AFFETTI DA SEPSI
PRESENTI NELLE ICUs.**

AKI Etiology

From an international study including >29,000 critically ill patients

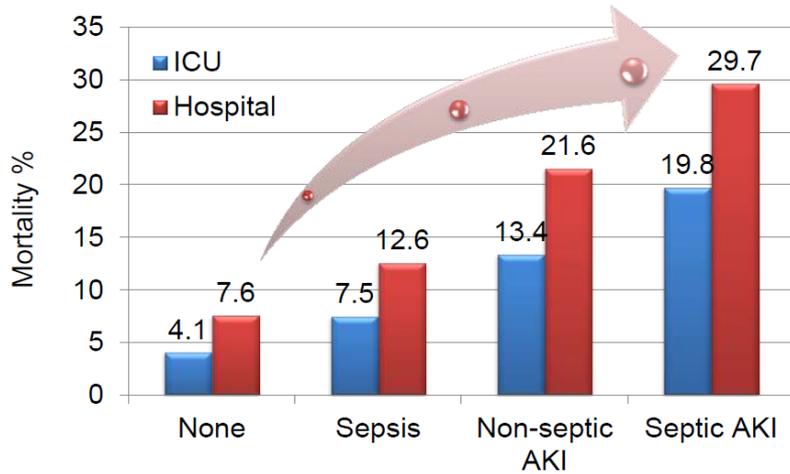
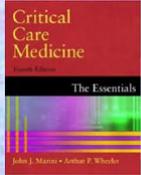


Uchino S, et al. *JAMA*. 2005;294:813-818.



Early acute kidney injury and sepsis: a multicentre evaluation

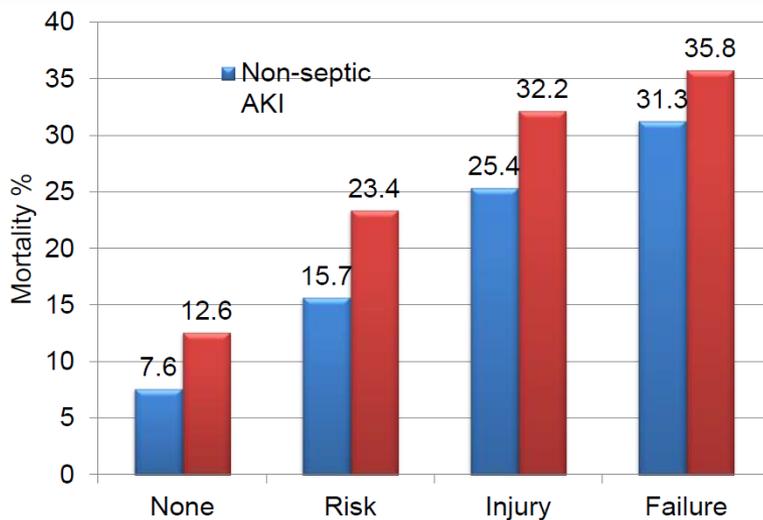
Sean M Bagshaw^{1,2}, Carol George³, Rinaldo Bellomo^{2,4} for the ANZICS Database Management Committee



CONDOTTO STUDIO PER VALUTARE INCIDENZA, FATTORI DI RISCHIO ED OUTCOME ASSOCIATI A AKI PRECOCE IN CORSO DI SEPSI.

AKI SETTICA E' COMUNE NELLE PRIME 24 ORE DAL RICOVERO IN ICU.

AKI IN CORSO DI SEPSI CORRELA CON MAGGIORE MORTALITA' E TEMPI DI OSPEDALIZZAZIONE PIU' LUNGI.



AOU San Giovanni Battista Molinette Turin: AKI in ICU

TOTALE
1584 PAZIENTI
13210 RRT

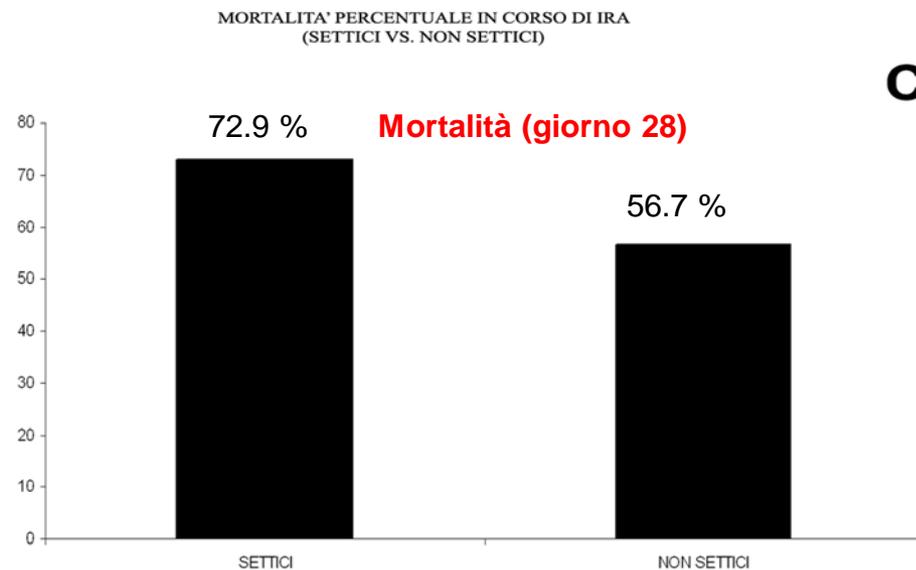
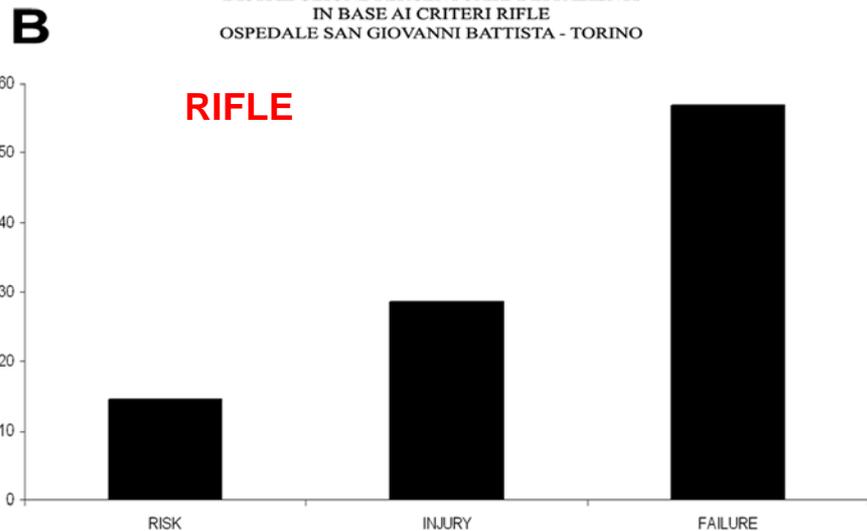
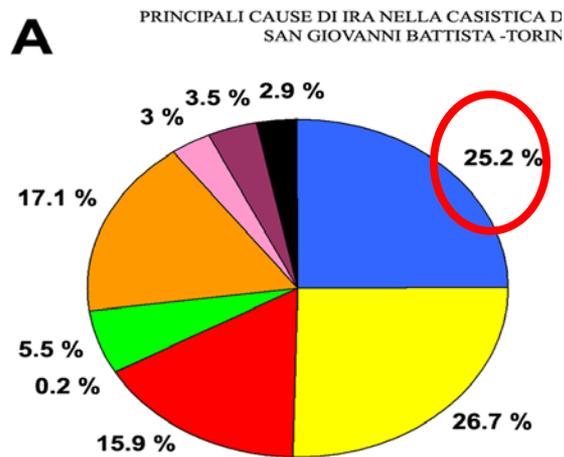
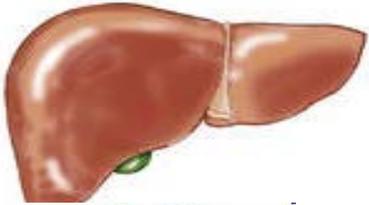
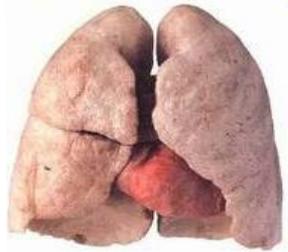


Fig.1

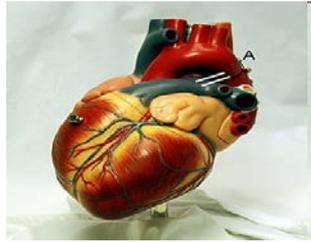
- Tra i pz con AKI l'11% erano riceventi di trapianto d'organo non renale (NRSOT)
- Causa prevalente di AKI in NRSOT : sepsi (44%)



Incidenza AKI 10,4% su tutti i pazienti con Tx fegato
Mortalità AKI in Tx fegato 42,5%



Incidenza AKI 29.4% su tutti i pazienti con Tx polmone
Mortalità AKI in Tx polmone 41.2%



Incidenza AKI 26,2 % su tutti i pazienti con Tx cardiaco
Mortalità AKI in Tx cardiaco 49.4%

La mortalità globale in NRSOT
trattati con RRT: 44.3%

Crs a fine osservazione: 2,37 +/- 0,82 mg/dL.

MORTALITA'

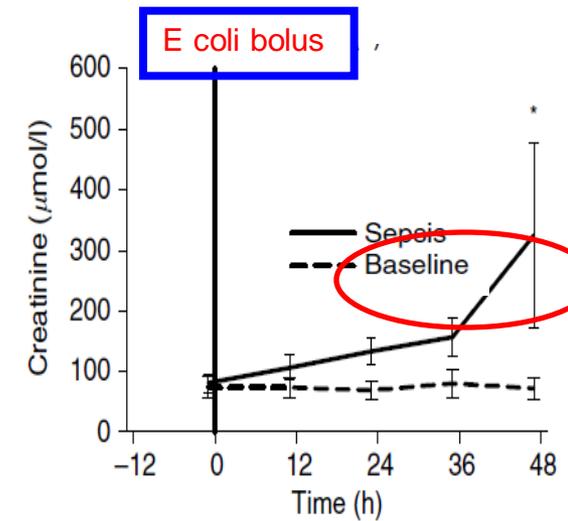
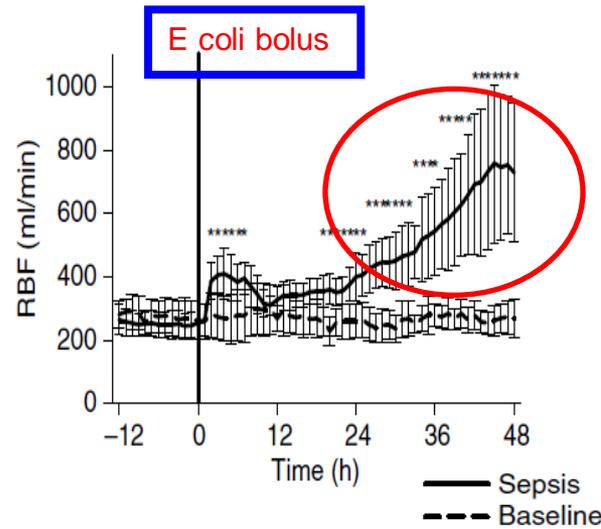
AKI

PROGRESSIONE CKD

Renal blood flow in experimental septic acute renal failure

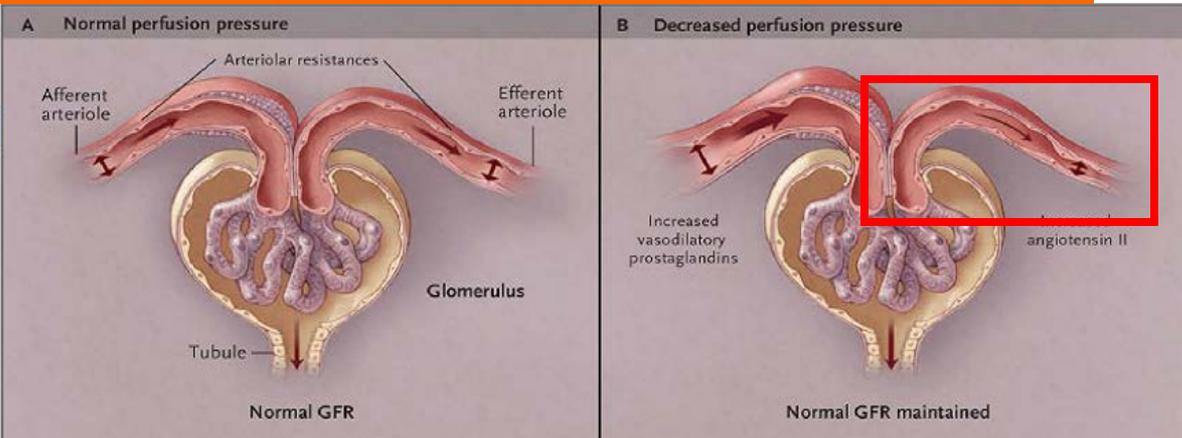


C Langenberg¹, L Wan², M Egi², CN May³ and R Bellomo²



Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: A pilot investigation

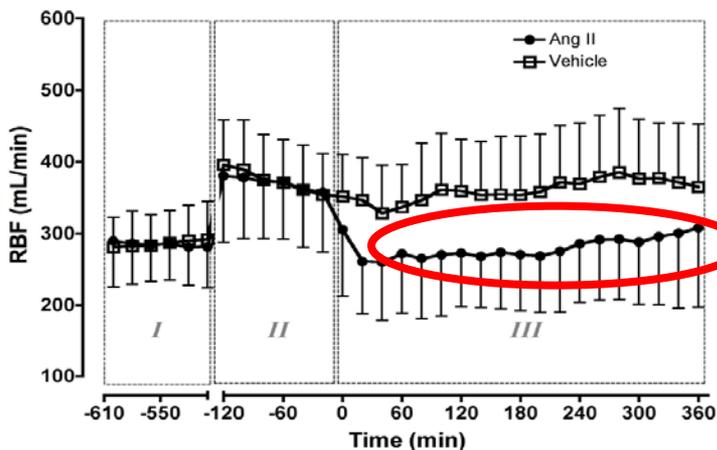
John R. Prowle, MB, BChir, MRCP, FFICM; Maurice P. Molan, MBBS, FRACR; Emma Hornsey, BSc; Rinaldo Bellomo, MD, FCICM



LA VASODILATAZIONE DELLA ARTERIOLA EFFERENTE CAUSA PERDITA DEL GFR

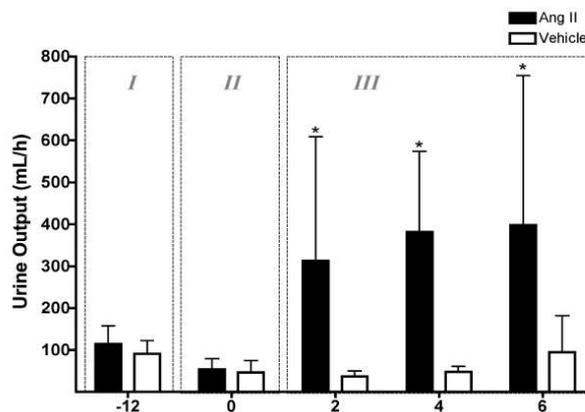
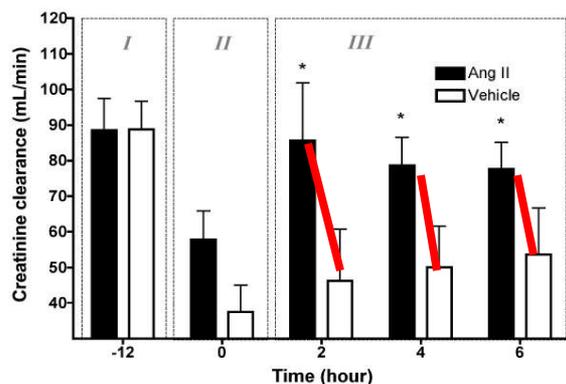
Angiotensin II in experimental hyperdynamic sepsis

Li Wan^{1,2,3,4}, Christoph Langenberg¹, Rinaldo Bellomo^{2,3} and Clive N May¹



**RIDUZIONE
DEL FLUSSO**

**NONOSTANTE IPERAFFLUSSO
PERDITA DELL'OUTPUT URINARIO
: FUNZIONE RENALE DISSOCIATA
DAL FLUSSO PLASMATICO
RENALE**

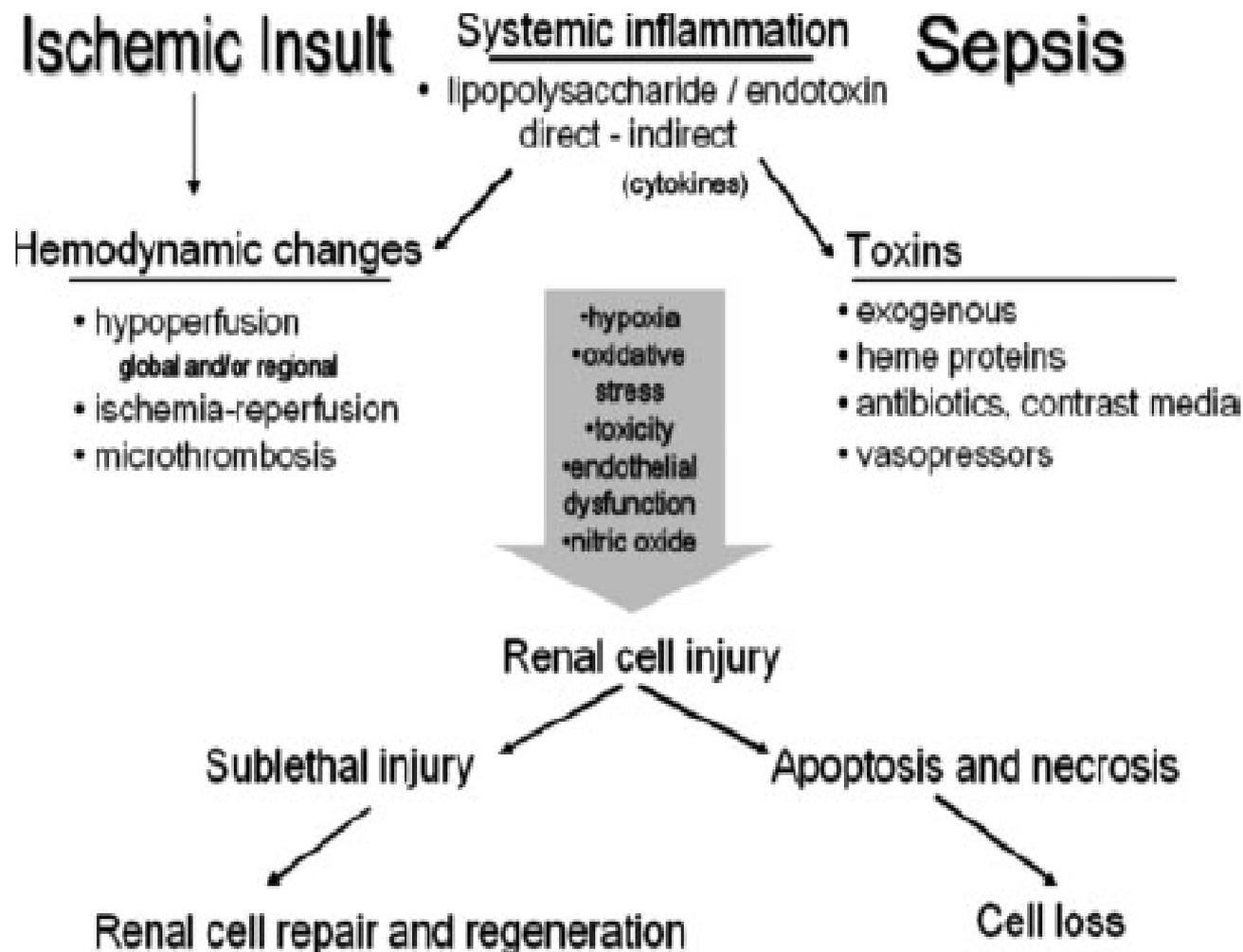


DISSOCIAZIONE FLUSSO – FUNZIONE RENALE IN CORSO DI SEPSI

**Insufficienza renale acuta può complicare la sepsi anche in presenza di una
flusso renale normale, se non addirittura aumentato**

Potential Interventions in Sepsis-Related Acute Kidney Injury

Claudio Ronco,* John A. Kellum,[†] Rinaldo Bellomo,[‡] and Andrew A. House[§]



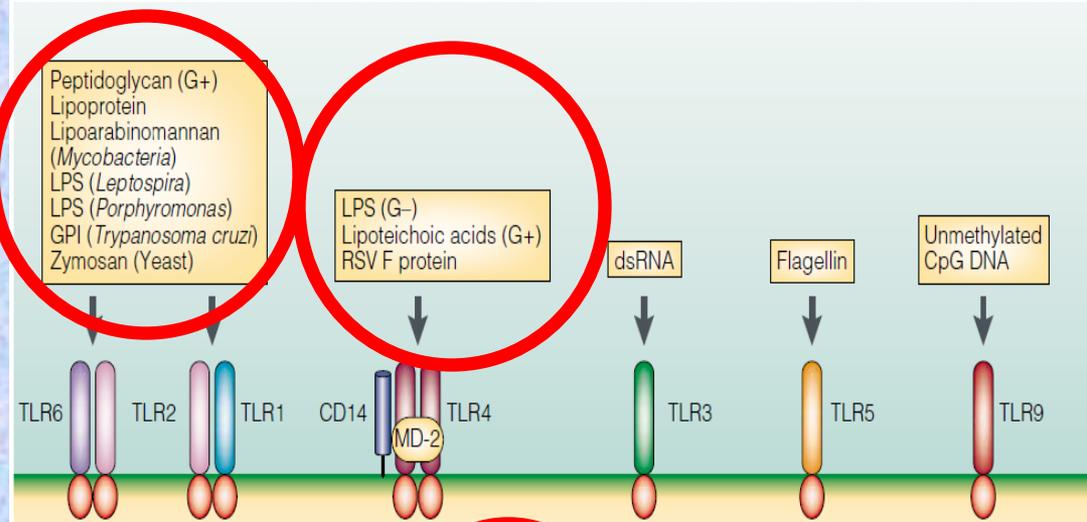
La sepsi è una causa importante di morbilità e mortalità.

Il danno renale acuto spesso complica sepsi, portando ad una maggiore complessità clinica, costo delle cure, e peggioramento prognostico.

Riconoscimento precoce: essenziale per prevenzione e trattamento con buon esito. Importante il ruolo di nuovi biomarkers in grado di identificare precocemente la patologia.

RUOLO DEI PAMPs NELLA SEPSI

PAMPS (PATHOGEN-ASSOCIATED MOLECULAR PATTERNS): MOLECOLE ASSOCIATE AD AGENTI PATOGENI IN GRADO DI ATTIVARE NELL'UOMO LA RISPOSTA IMMUNITARIA INNATA ATTRAVERSO UN PATTERN DI APPROPRIATI RECETTORI CHIAMATI TOLL-LIKE RECEPTORS (TLRs).



TOLL-LIKE RECEPTORS AND INNATE IMMUNITY

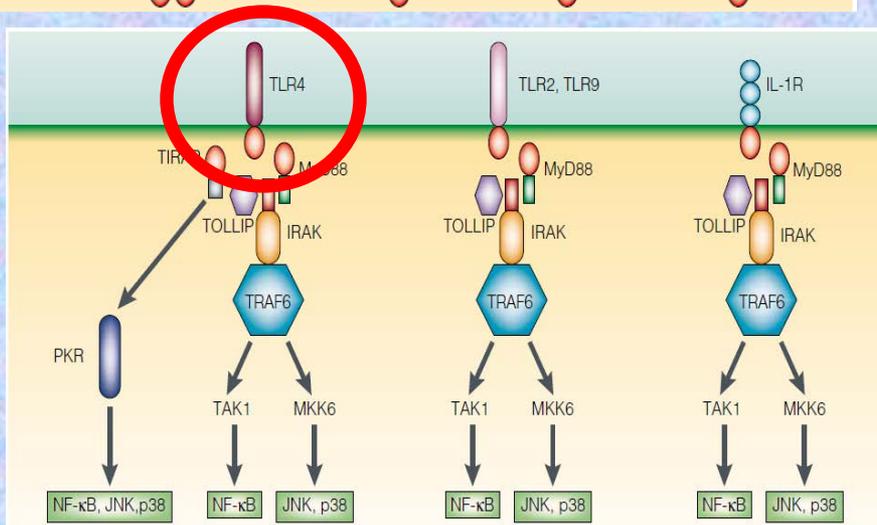
Ruslan Medzhitov



PAMPs: MOLECOLE ASSOCIATE A MICROORGANISMI PATOGENI RICONOSCIUTE DAL SISTEMA IMMUNITARIO, RICONOSCIUTE DAI TOLL-LIKE RECEPTORS.

TLRs: RUOLO CRUCIALE NELLE INFEZIONI,

NEI MAMMIFERI ATTIVANO LA RISPOSTA INFIAMMATORIA CON SUCCESSIVA RISPOSTA IMMUNITARIA ADATTATIVA ANTIGENE SPECIFICA.



RUOLO DEI DAMPs NELLA SEPSI

DAMAGE-ASSOCIATED MOLECULAR PATTERN MOLECULES (DAMPs) : MOLECOLE ENDOGENE CHE POSSONO VENIRE RILASCIATE IN SEGUITO AL DANNO CELLULARE E CHE POSSONO ATTIVARE L'IMMUNITA' INNATA

DAMPening Inflammation by Modulating TLR Signalling

A. M. Piccinini and K. S. Midwood

Circulating Mitochondrial DAMPs Cause Inflammatory Responses to Injury

Qin Zhang, Mustafa Raoof, Yu Chen, Yuka Sumi, Tolga Sursal, Wolfgang Junger, Karim Brohi, Kiyoshi Itagaki, and Carl J. Hauser

Proteins, peptides

- TLR1 β -defensin-3 [28]
- TLR2 HSP60, 70, Gp96 [15, 17, 74]
HMGB1 [20–22]
HMGB1-nucleosome complexes [89]
 β -defensin-3 [28]
Surfactant protein A, D [73, 79]
Eosinophil-derived neurotoxin [209]
Antiphospholipid antibodies [34]
- TLR4 HMGB1 [20–22]
Fibronectin EDA [81]
Fibrinogen [200]
Tenascin-C (FBG) [24]
Surfactant protein A, D [78, 79]
 β -defensin-2 [204]
HSP60, 70, 72, 22, Gp96 [12, 15–19, 74]
S100A8 (MRP8) [120, 143]
S100A9 (MRP14) [120, 143]
Neutrophil elastase [205]
Antiphospholipid antibodies [35, 36]
Lactoferrin [80]
- TLR7 Antiphospholipid antibodies [32]
- TLR8 Antiphospholipid antibodies [32, 33]

Fatty acids, lipoproteins

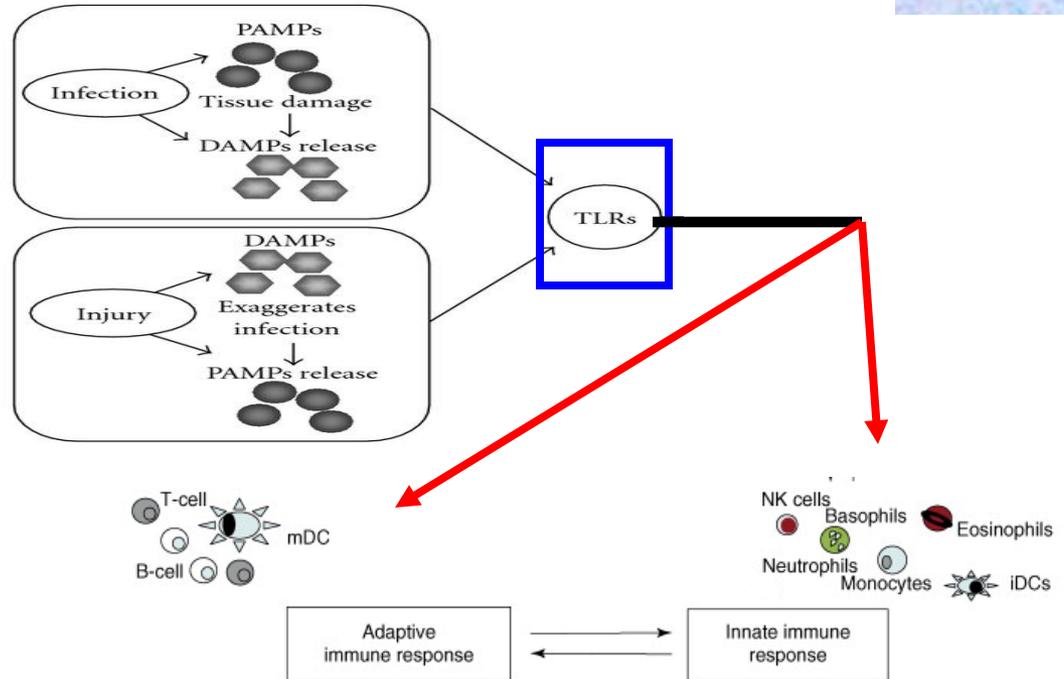
- TLR2 Serum amyloid A [201, 203]
- TLR4 Serum amyloid A [202, 169]
Oxidised LDL [206, 76, 207]
Saturated fatty acids [82, 208]

Proteoglycans, glycosaminoglycans

- TLR2 Biglycan [23]
Versican [25]
Hyaluronic acid fragments [26]
- TLR4 Biglycan [23]
Heparan sulfate fragments [27]
Hyaluronic acid fragments [26]

Nucleic acids, protein-nucleic acids complexes

- TLR3 mRNA [29]
- TLR7 ssRNA [30]
- TLR8 ssRNA [30]
- TLR9 IgG-chromatin complexes [31]



DAMPs: MOLECOLE CHE AVVIANO E PERPETUANO LA RISPOSTA IMMUNITARIA NELLA RISPOSTA INFIAMMATORIA NON SU BASE INFETTIVA (A DIFFERENZA DEI PAMPs CHE FANNO LO STESSO IN SEGUITO A INFEZIONI)

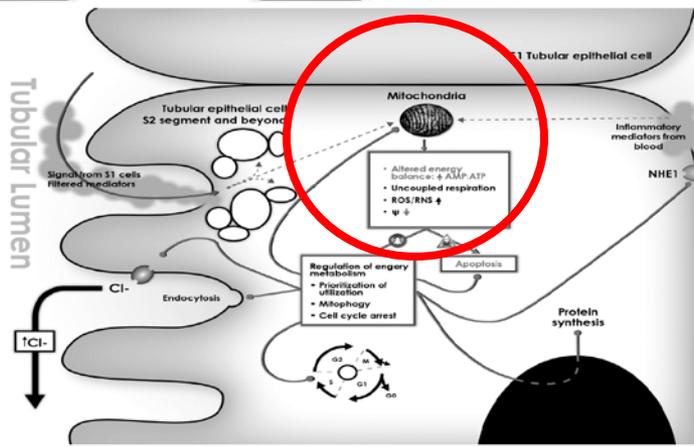
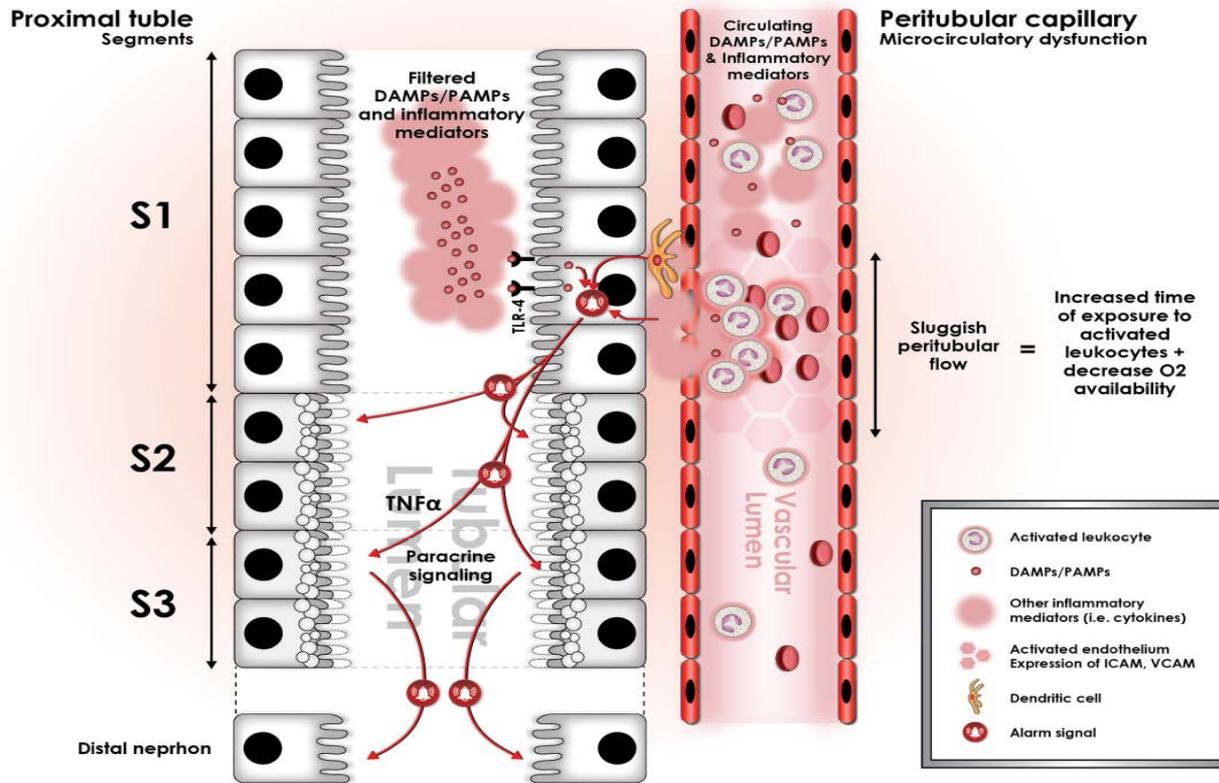
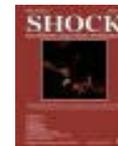
MOLTI DAMPs SONO PROTEINE DEL NUCLEO (ANCHE DNA CELLULARE) O DEL CITOSOL CHE, ESPOSTE ALL'ESTERNO O ALLA SUPERFICIE DELLA CELLULA (AD ES. PER NECROSI), SI DENATURANO A CAUSA DELL'AMBIENTE OSSIDANTE.

ATTIVAZIONE DA PARTE DEI DAMPs DEI TLR: ESPRESSIONE DEI GENI DELL'INFIAMMAZIONE PER MEDIARE LA RIPARAZIONE DEL DANNO.

DAMPs IMPLICATI IN MALATTIE INFIAMMATORIE CRONICHE , NEOPLASIE ED ATEROSCLEROSI.

A UNIFIED THEORY OF SEPSIS-INDUCED ACUTE KIDNEY INJURY: INFLAMMATION, MICROCIRCULATORY DYSFUNCTION, BIOENERGETICS, AND THE TUBULAR CELL ADAPTATION TO INJURY

Hernando Gomez,^{*†} Can Ince,[‡] Daniel De Backer,[§] Peter Pickkers,^{||} Didier Payen,^{||} John Hotchkiss,^{*†} and John A. Kellum^{*†}



AKI su base settica: può verificarsi in assenza di ipoperfusione renale.

Sepsi: alterazioni del microcircolo, incremento del flusso ematico peritubulare e aumento quota capillari con flusso rallentato.

Aumentato tempo di transito di leucociti attivati e rilascio di citochine, presenza di stress ossidativo (soprattutto apicale) con formazione di vacuoli.

LPS riconosciuto da TEC S1 attraverso TLR-4 ed interiorizzato tramite endocitosi, attiva stress ossidativo (soprattutto in S2).

L'espressione di recettori del TNF in S2 ha portato a ipotizzare un meccanismo paracrino di secrezione del TNF e di mediatori di arresto del ciclo cellulare (TIMP-2, IGFBP-7).

Teoria "unificante": spiega l'interazione tra l'infiammazione e lo stress ossidativo, la disfunzione del microcircolo e la risposta adattativa cellulare tubulare all'insulto settico.

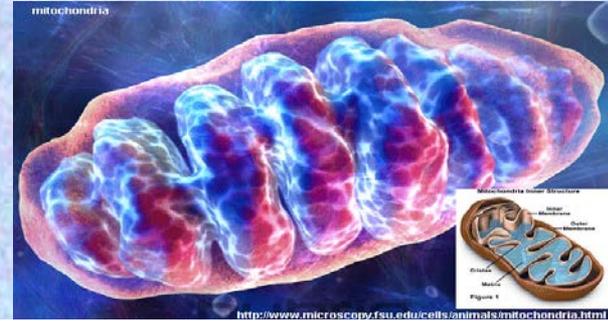
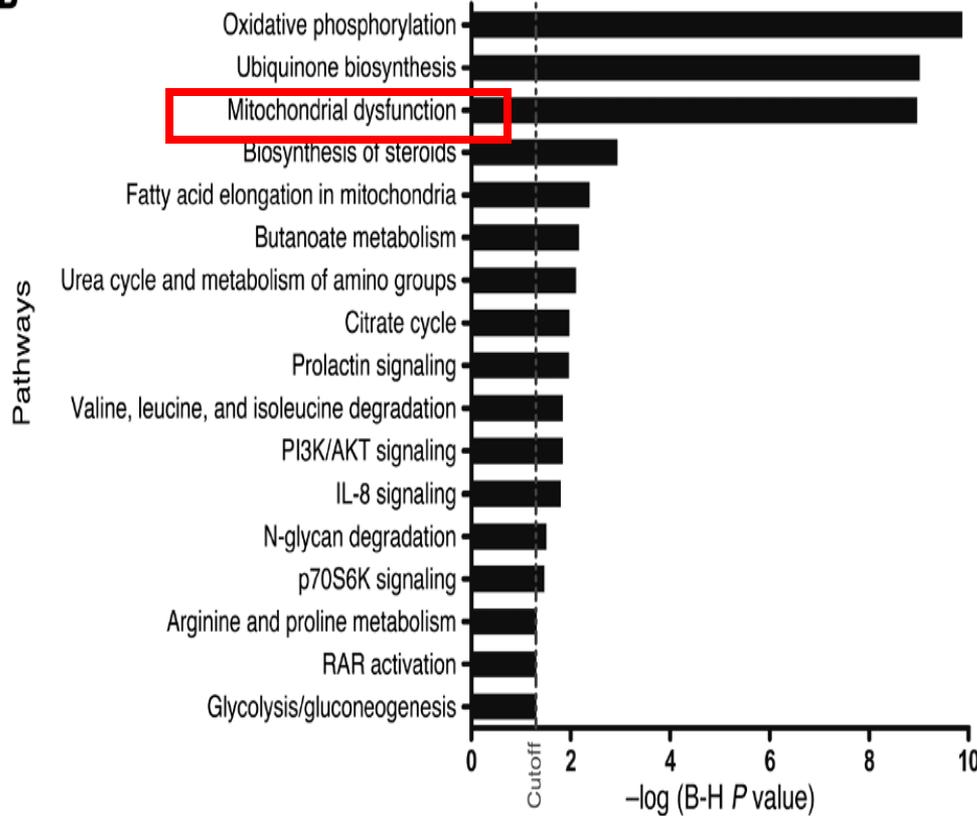
Risposta di tipo adattativo con ruolo fondamentale del mitocondrio.

PGC-1 α promotes recovery after acute kidney injury during systemic inflammation in mice

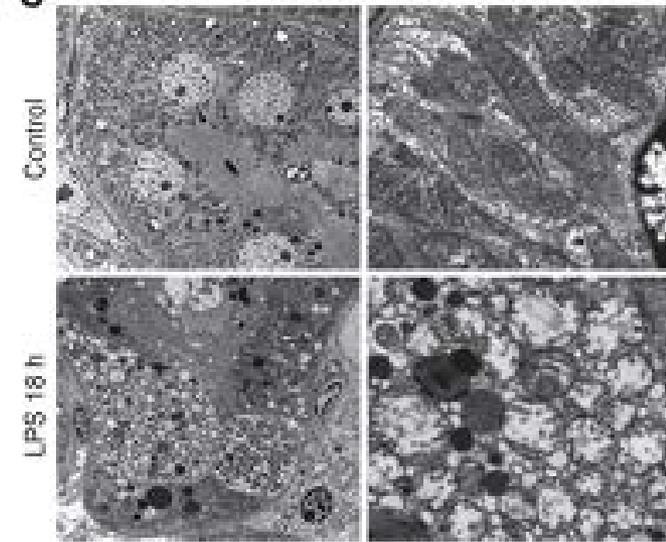
Mei Tran,¹ Denise Tam,¹ Amit Bardia,¹ Manoj Bhasin,² Glenn C. Rowe,³ Ajay Kher,¹ Szusanna K. Zsengeller,⁴ M. Reza Akhavan-Sharif,⁵ Eliyahu V. Khankin,¹ Magali Saintgeniez,⁶ Sascha David,¹ Deborah Burstein,⁶ S. Ananth Karumanchi,^{1,7,8} Isaac E. Stillman,⁴ Zoltan Arany,^{3,8} and Samir M. Parikh^{1,8}



B



C



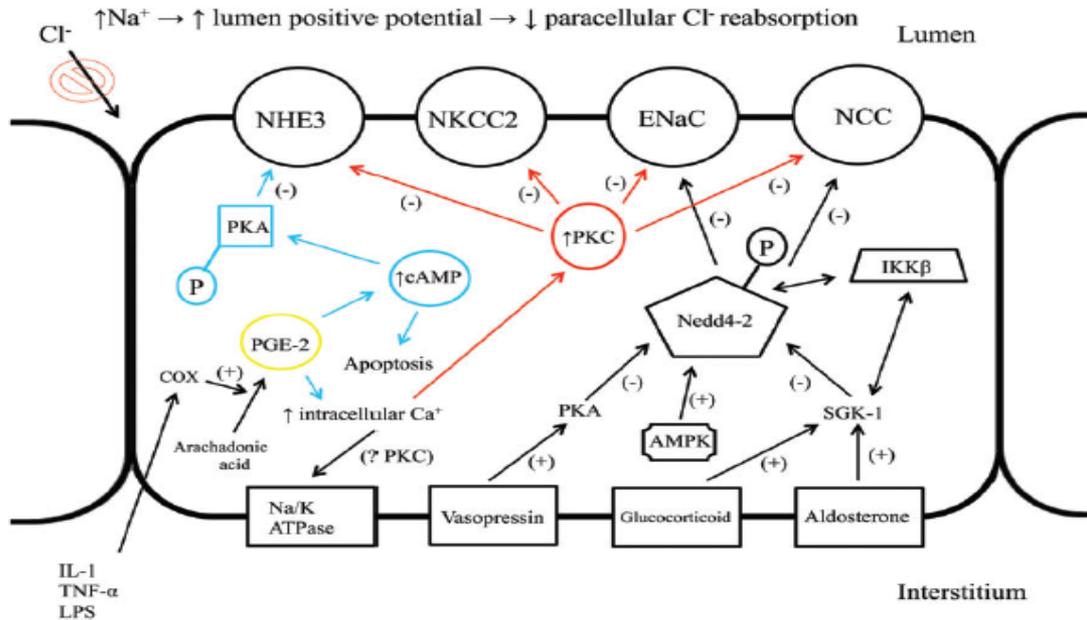
ENDOTOSSINE CIRCOLANTI RIDUCONO OSSIGENAZIONE RENALE CON MINOR CONSUMO DI OSSIGENO DA PARTE DELLE CELLULE RENALI E FUNZIONE DEI MITOCONDRI ALTERATA.

PGC-1 alfa RAPPRESENTA UNO DEI PRINCIPALI REGOLATORI DELLA BIOGENESI MITOCONDRIALE E DEL METABOLISMO, E LA SUA ESPRESSIONE E' SOPPRESSA IN MODO PROPORZIONALE AL GRADO DI COINVOLGIMENTO RENALE.

LIVELLI PGC-1 alfa RIDOTTI IN CORRELAZIONE ANCHE CON AZIONE DI TNF-alfa.

Epithelial transport during septic acute kidney injury

Eric D. Morrell¹, John A. Kellum^{2,3,4}, Kenneth R. Hallows^{1,2,5} and Núria M. Pastor-Soler^{1,2,5}

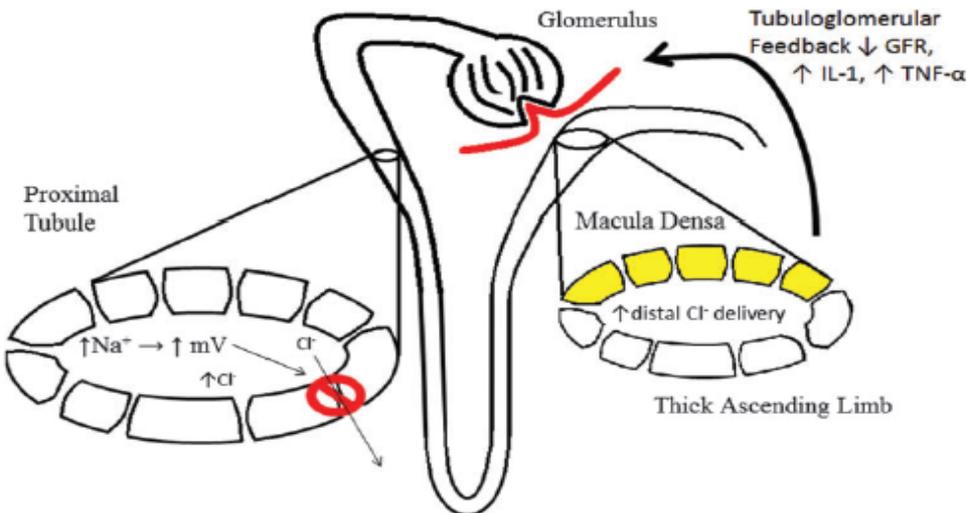


The tubuloglomerular feedback mechanism reduces the GFR to a level compatible with the decreased reabsorptive capacity.

The glomeruli takes over the volume-conserving function normally exercised by the tubules.

Hypovolemia is averted at the expense of the regulation of body fluid composition.

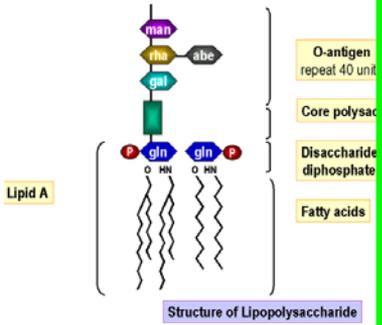
It provides time to repair structure and function of the damaged tubules.



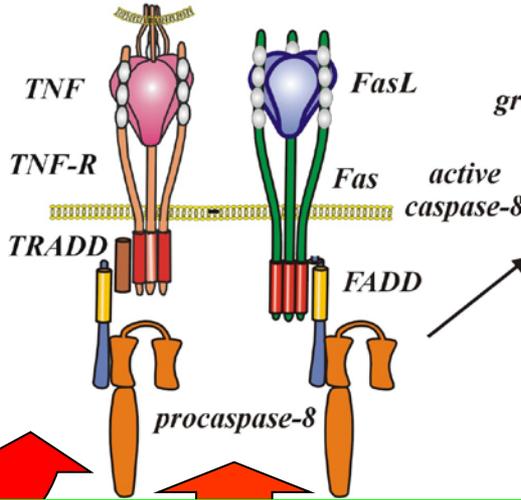
Disfunzione tubulare in corso di sepsi conduce a incrementato arrivo di sodio e cloro al tubulo distale ed alla macula densa contribuendo al tubulo-glomerular feedback e alla contrazione funzionale

APOPTOSIS: A KEY MECHANISM IN SEPSIS

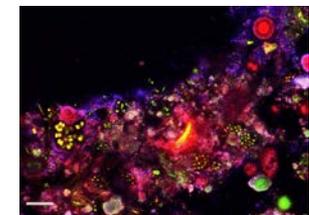
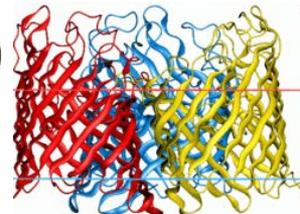
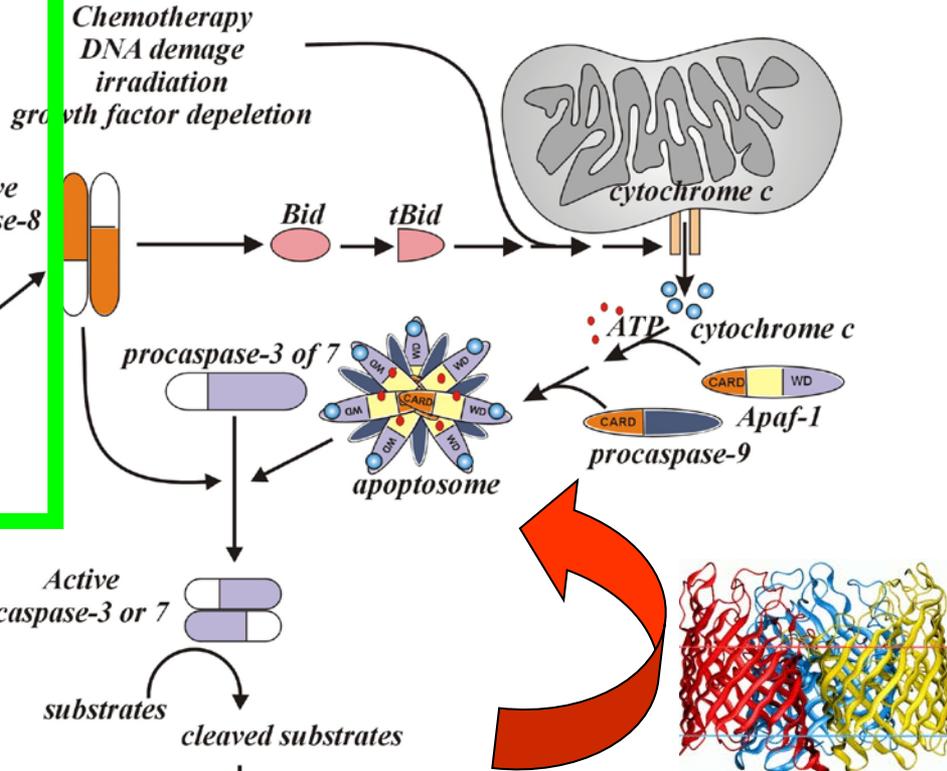
Death receptor pathway



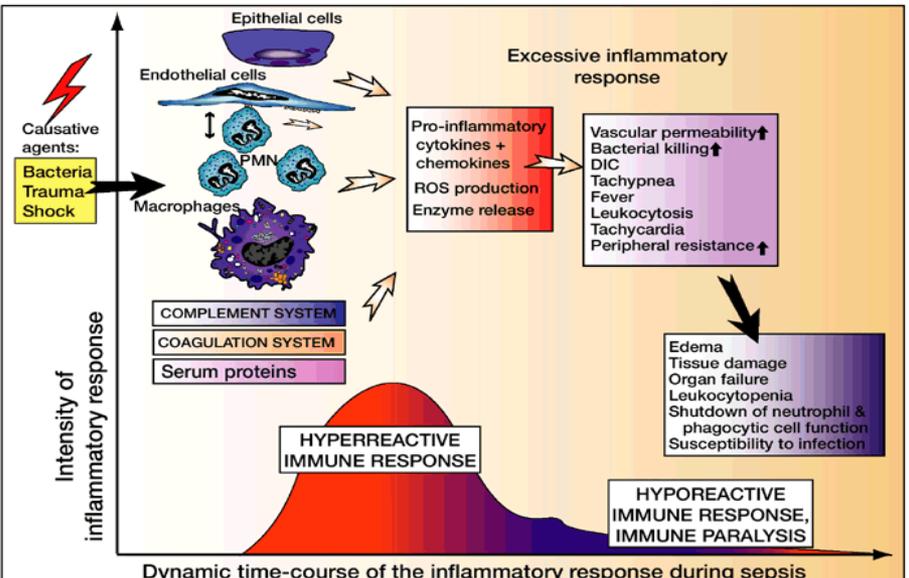
LPS



Mitochondrial pathway



Fattori pro-apoptotici circolanti plasmatici

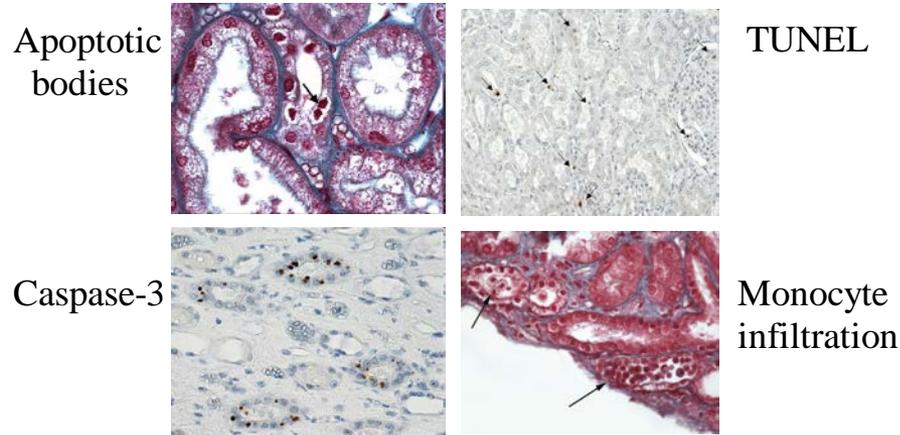


Acute Renal Failure in Endotoxemia Is Caused by TNF Acting Directly on TNF Receptor-1 in Kidney¹

Patrick N. Cunningham,^{2*} Hristem M. Dyanov,^{*} Pierce Park,^{*} Jun Wang,[†] Kenneth A. Newell,[†] and Richard J. Quigg^{*}

Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration

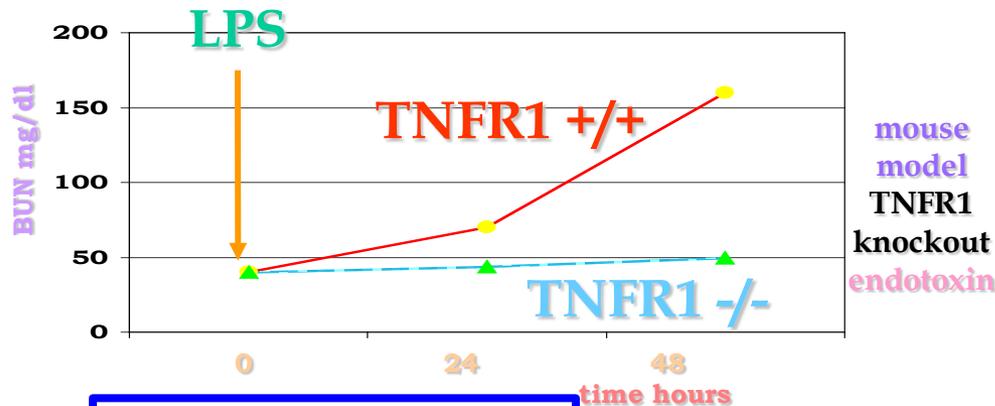
Nicolas Lerolle
Dominique Nochy
Emmanuel Guérot
Patrick Bruneval
Jean-Yves Fagon
Jean-Luc Diehl
Gary Hill



Acute Renal Failure in Endotoxemia Is Caused by TNF Acting Directly on TNF Receptor-1 in Kidney¹



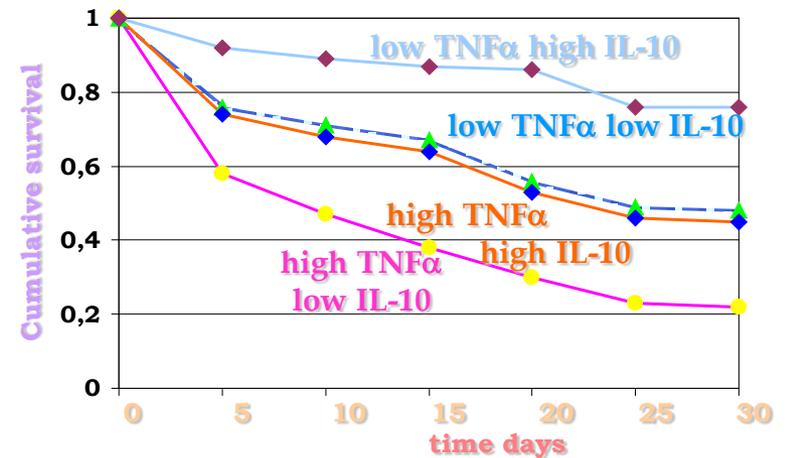
Patrick N. Cunningham,^{2*} Hristem M. Dyanov,^{*} Pierce Park,^{*} Jun Wang,[†] Kenneth A. Newell,[†] and Richard J. Quigg^{*}



Effect of TNF-alfa in ARF

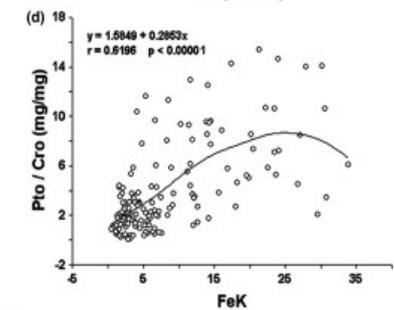
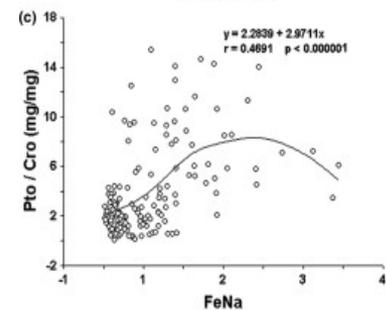
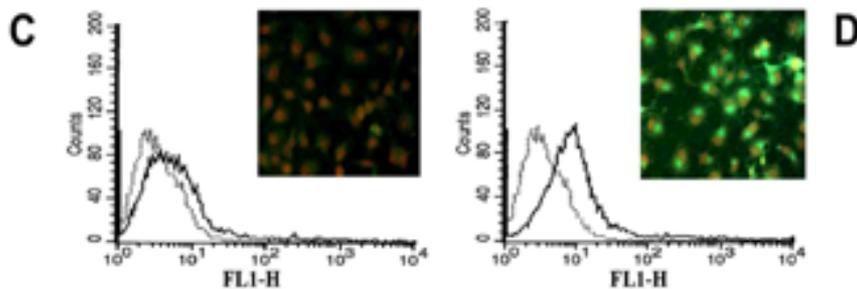
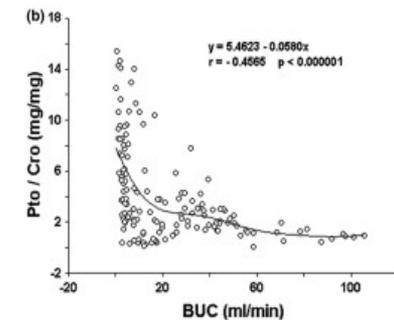
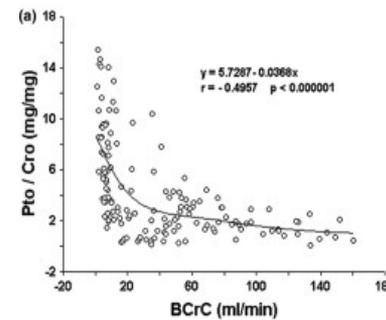
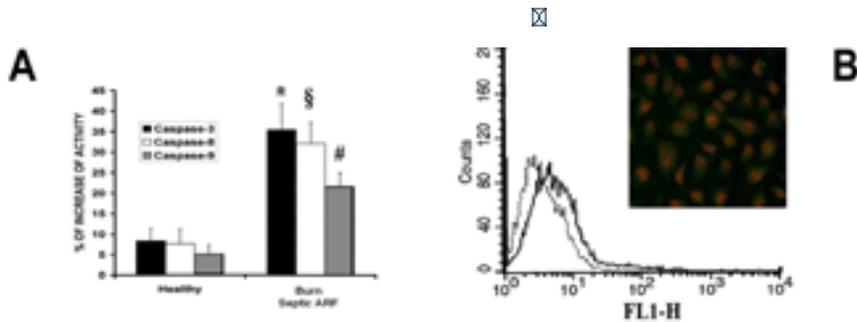
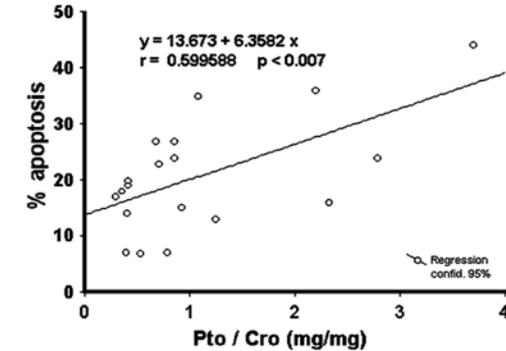
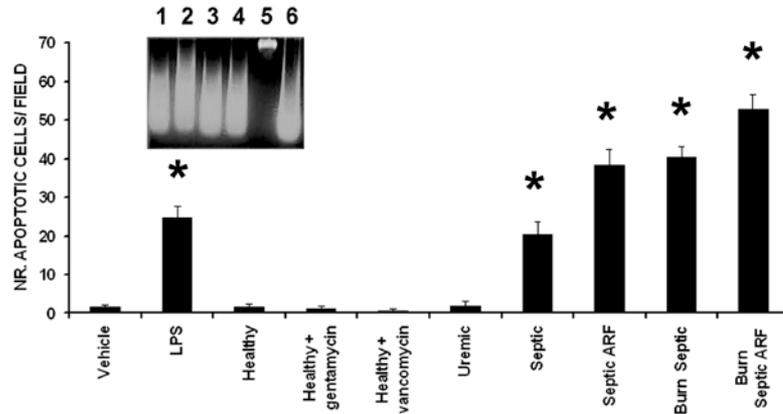
Polymorphism of immunomodulatory cytokine genes: implications in acute renal failure.

Adjusted survival by genotypes

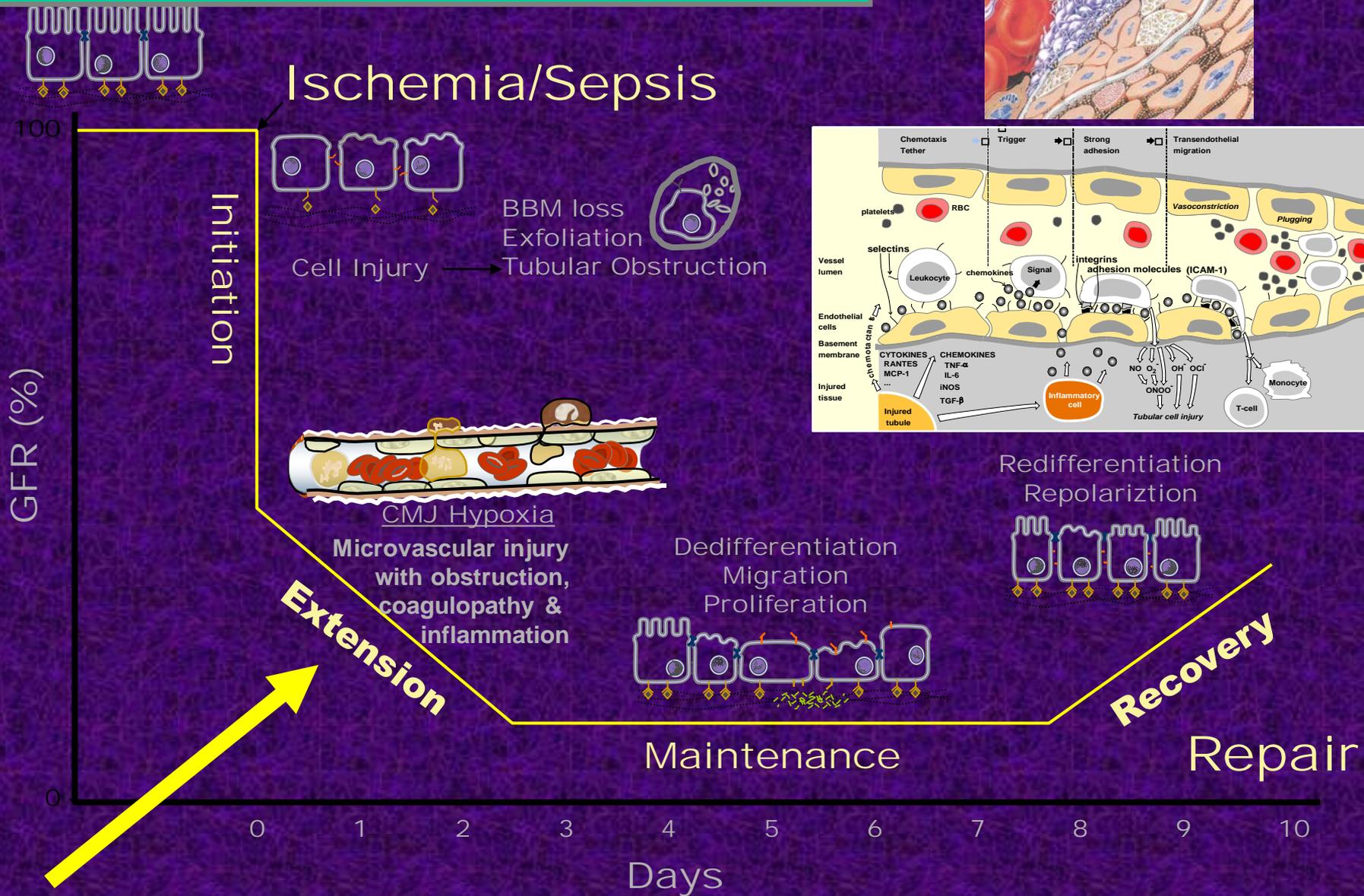


Circulating plasma factors induce tubular and glomerular alterations in septic burns patients

Filippo Mariano,[#] Vincenzo Cantaluppi,[#] Maurizio Stella, Giuseppe Mauriello Romanazzi, Barbara Assenzio, Monica Cairo, Luigi Biancone, Giorgio Triolo, V Marco Ranieri, and Giovanni Camussi

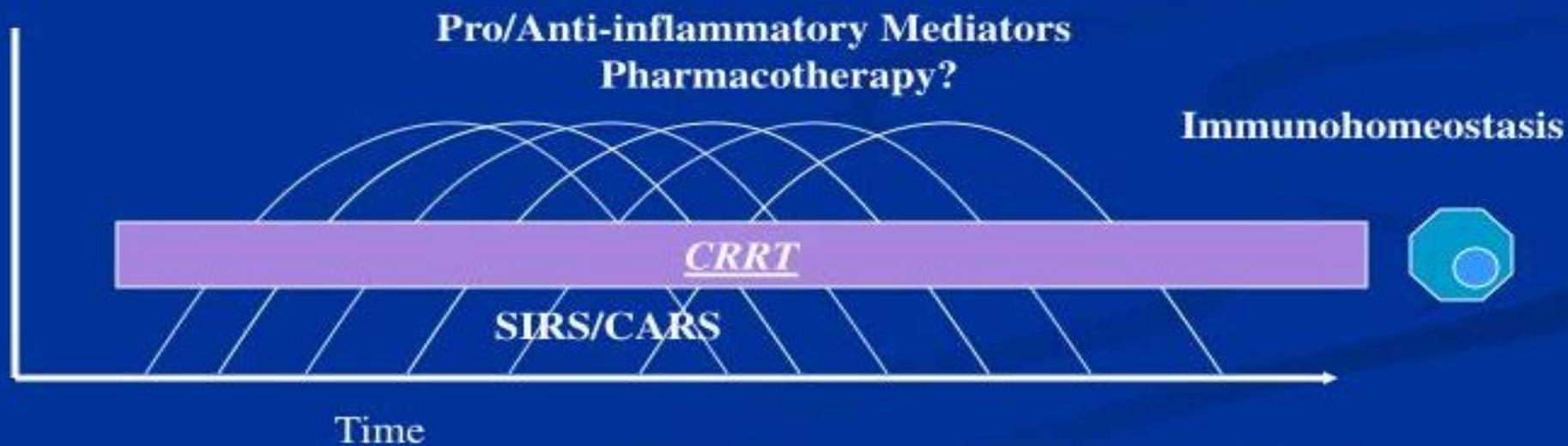
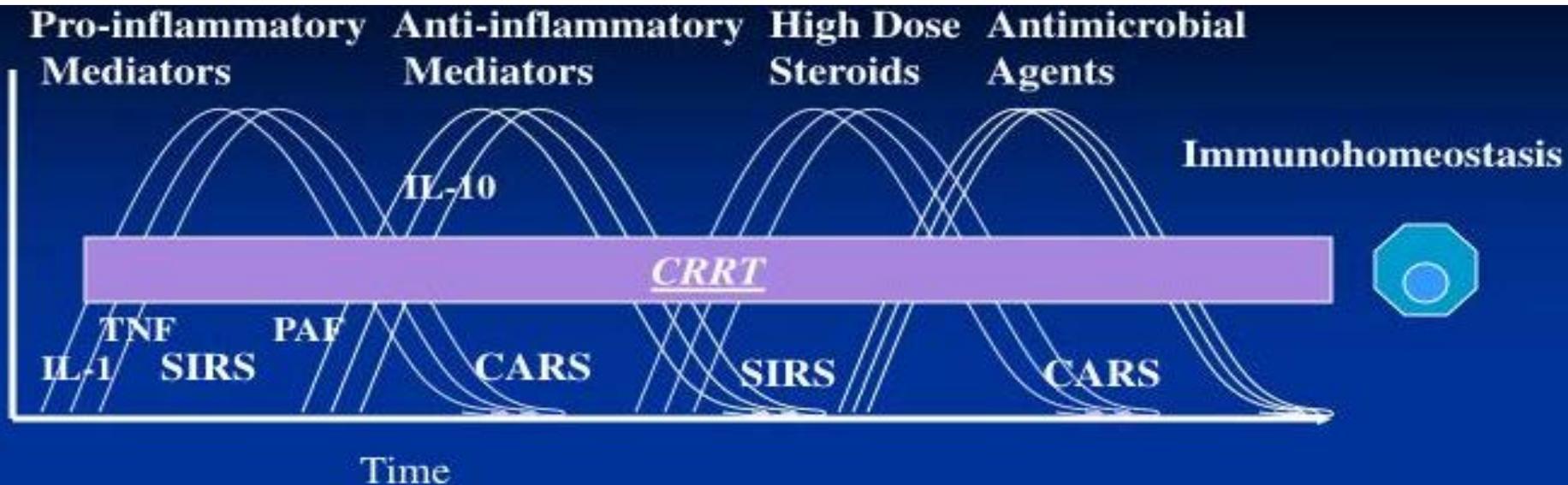


Phases of AKI



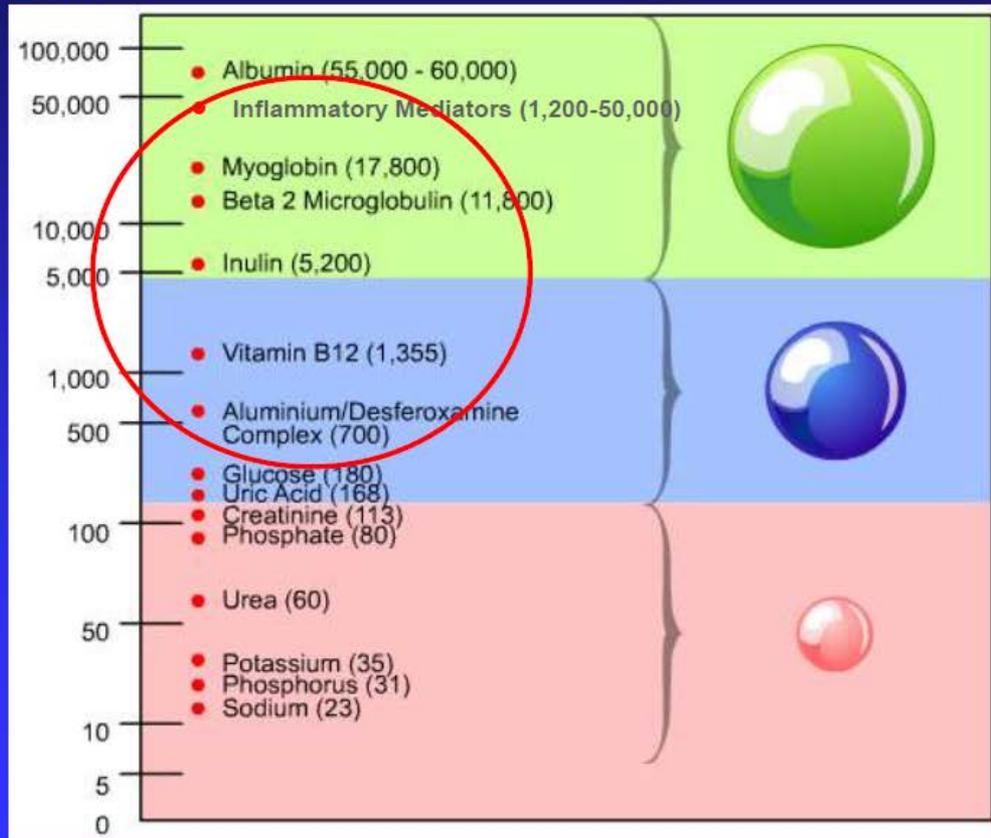
Potential Interventions in Sepsis-Related Acute Kidney Injury

Claudio Ronco,* John A. Kellum,[†] Rinaldo Bellomo,[‡] and Andrew A. House[§]



Solute Classes by Molecular Weight

Daltons



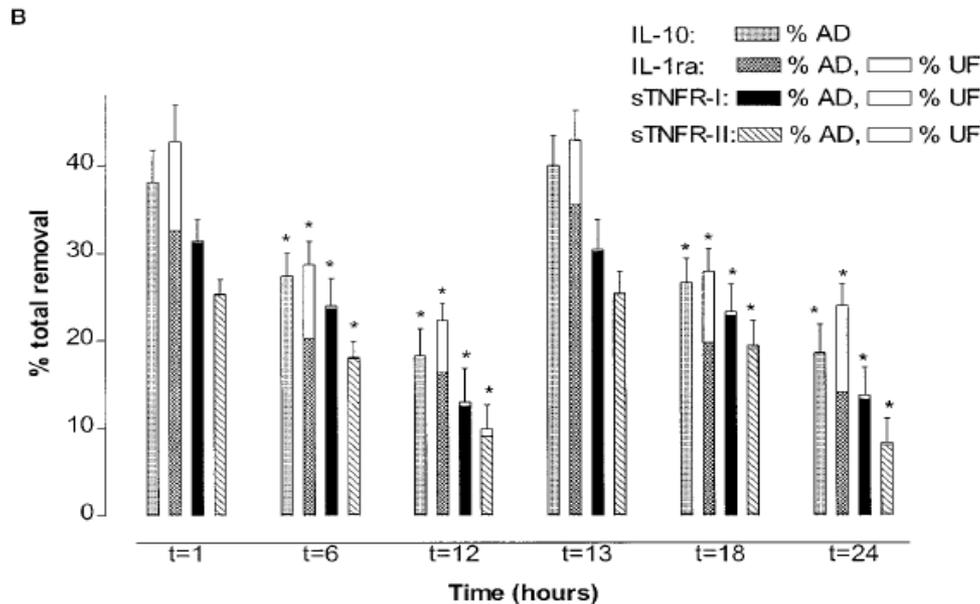
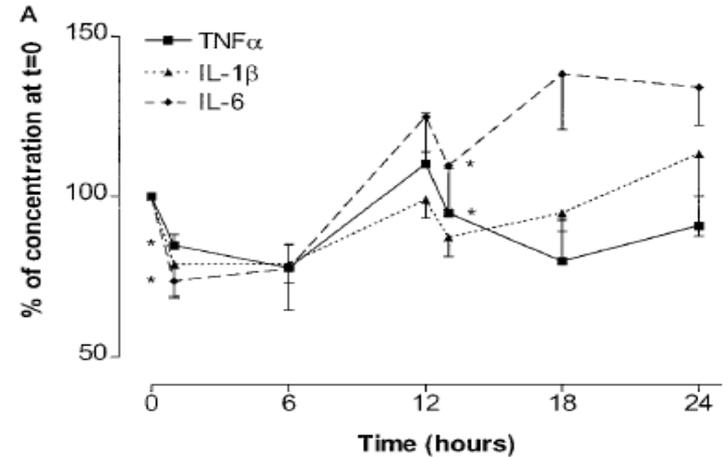
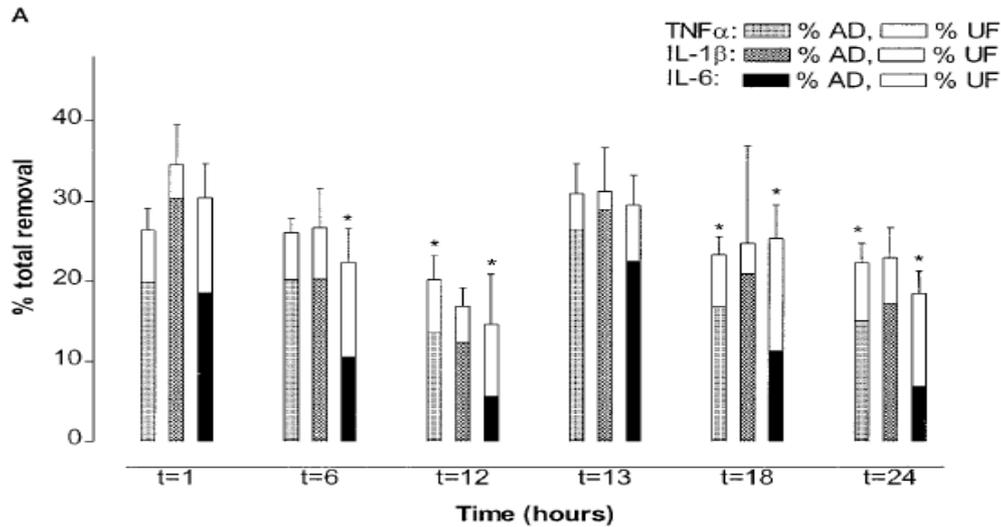
“large”

“middle”

“small”

Cytokine Removal during Continuous Hemofiltration in Septic Patients

AN S. DE VRIESE,* FRANCIS A. COLARDYN,† JAN J. PHILIPPÉ,‡
 RAYMOND C. VANHOLDER,* JOHAN H. DE SUTTER,† and
 NORBERT H. LAMEIRE*



IL BILANCIO DI MASSA DELLE CITOCHINE VIENE CALCOLATO IN QUESTO MODO:

$$Q_I = Q_B(1 - \text{hematocrit}), Q_O = Q_I - Q_{UF}$$

$$M_I = Q_I \times C_I, M_O = Q_O \times C_O$$

$$M_{TR} = M_I - M_O, M_{UF} = Q_{UF} \times C_{UF}, M_{AD} = M_{TR} - M_{UF}$$

$$SC = 2 \times C_{UF}/C_I + C_O$$



ADSORBIMENTO

Attacco aspecifico di sostanze solubili alla superficie di cellule o di particelle inerti.

Alcuni gruppi di piante sono stati testati dalla NASA (l'agenzia spaziale USA) nell'ambito di studi sulla purificazione dell'aria nelle basi lunari

Un gruppo di **ricercatori giapponesi** ha proposto una **soluzione ecologica** volta ad assorbire il cesio radioattivo: piantare **girasoli** a perdita d'occhio. Sembrerebbe infatti che questa particolare tipologia di fiore sia in grado di **ripulire il suolo** contaminato, assorbendo le sostanze letali. L'idea è venuta ad un team di scienziati specializzati in **agricoltura spaziale**, gruppo che ha preso esempio dai risultati riscontrati nel precedente **disastro nucleare di Chernobyl**.



Ficus Benjamin



Marijuana

ADSORBENTS

NATURAL

Zeolites (Alumino silicates)

Inorganic Porous Polymers with porosity deriving from their crystal structure (today synthetically made to control the structure of the internal pore system)

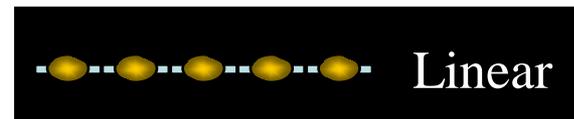
Porous Carbons

Cellulose-derived organic polymers prepared by controlled thermal oxidation

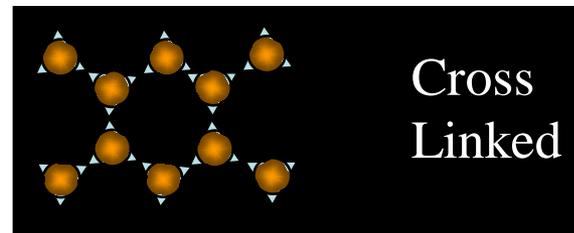
SYNTHETIC

Almost all polymerizable monomers can be built up into large molecules via a multitude of reactions.

Difunctional Monomers

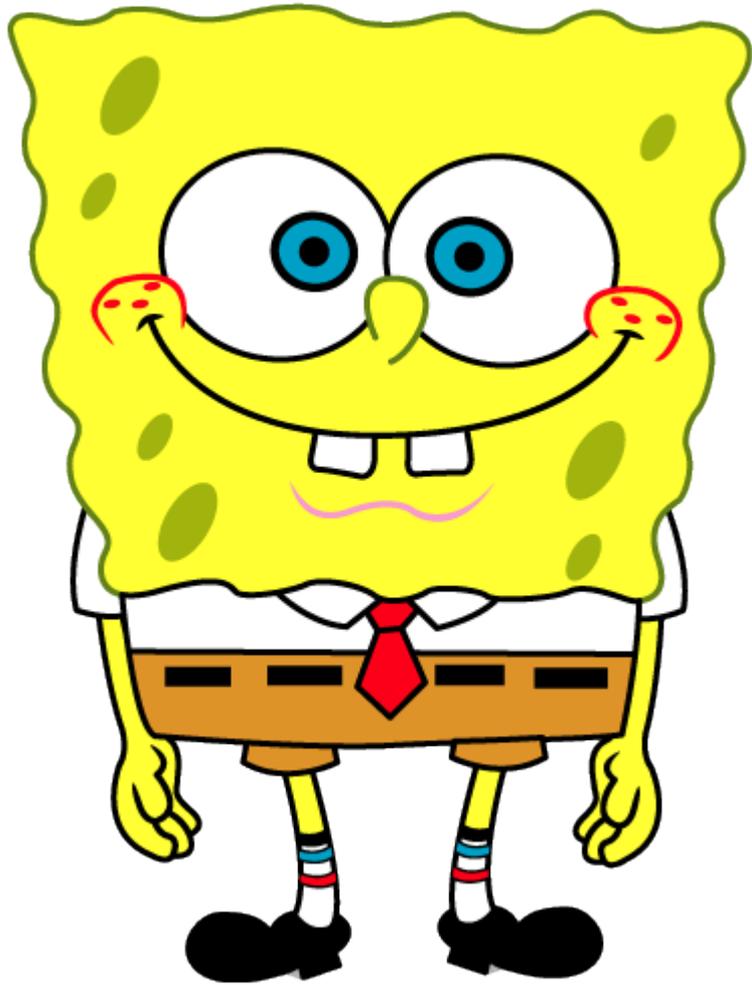


High functional Monomers



Divinylbenzene (potent crosslinker)

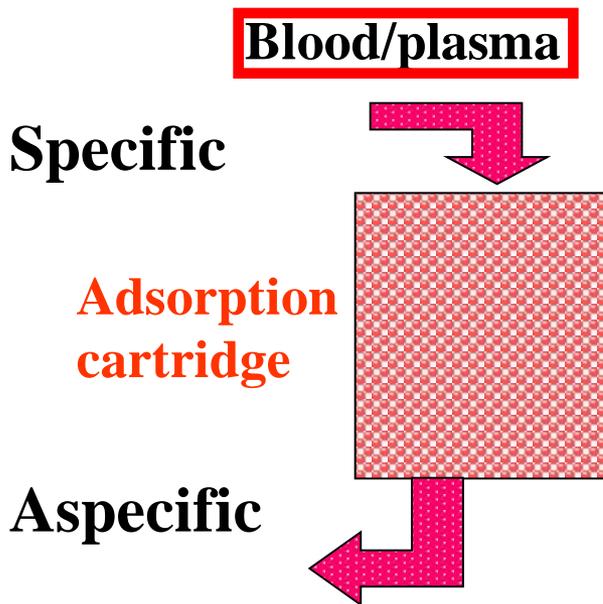




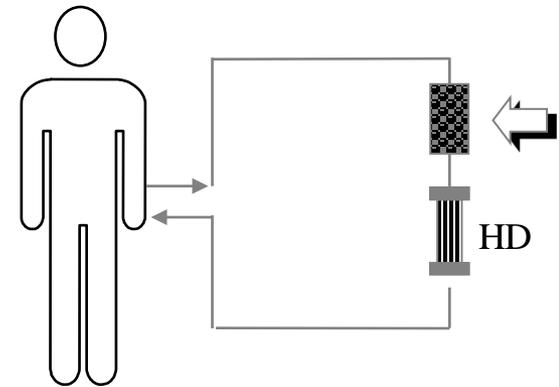
Spongebob Squarepants

Adsorption

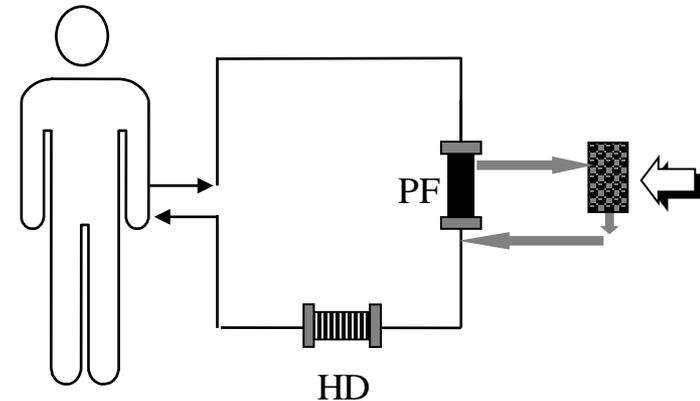
Adsorption = Chemical attachment of a specific element at the surface of another element with a molecular structure prepared to be complementary



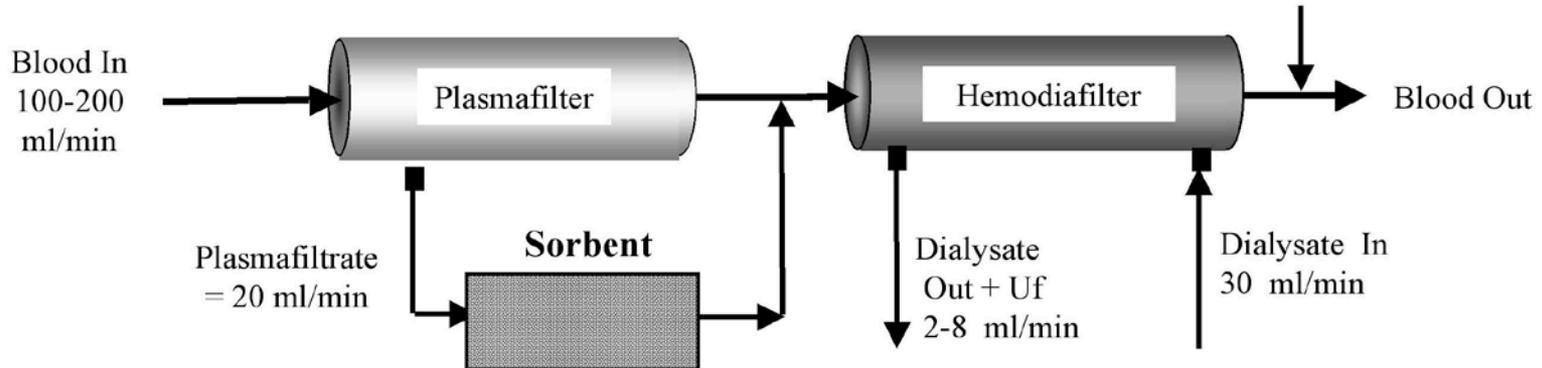
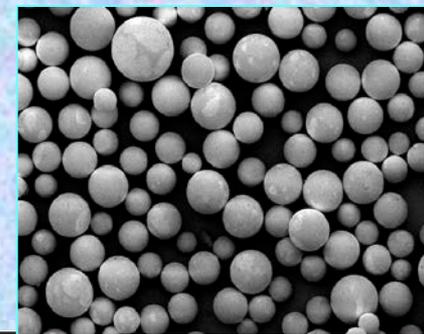
Hemoperfusion



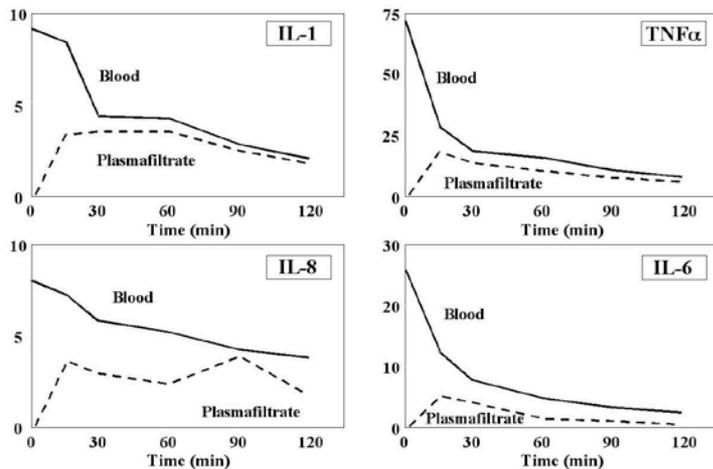
Plasma Filtration Adsorption



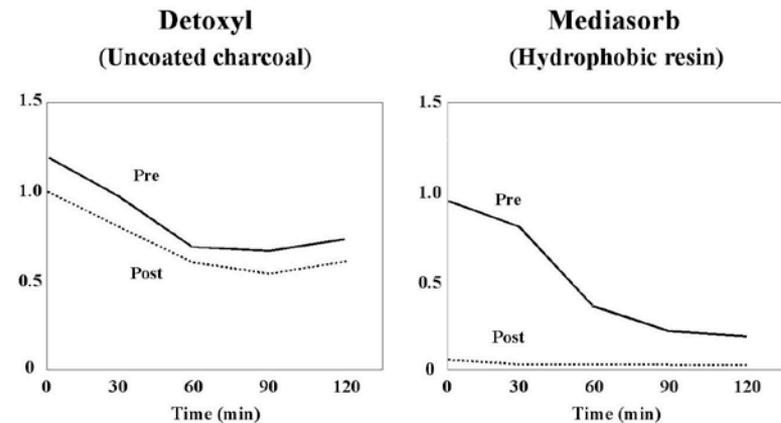
Coupled Plasma-Filtration Adsorption (CPFA)



CYTOKINES CONCENTRATION IN BLOOD AND UF

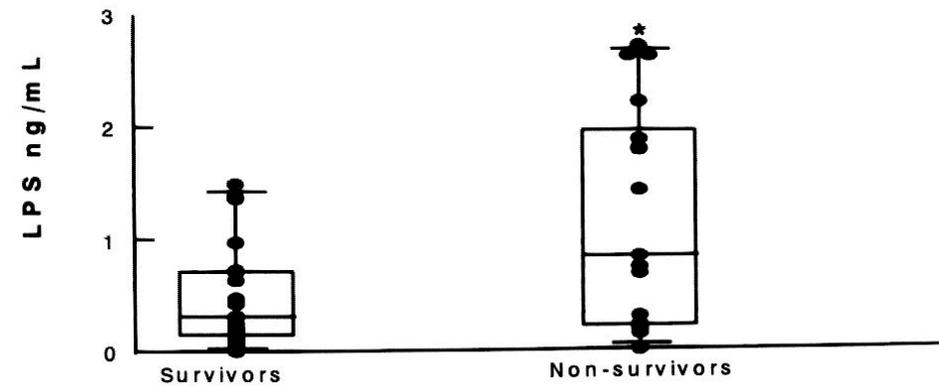
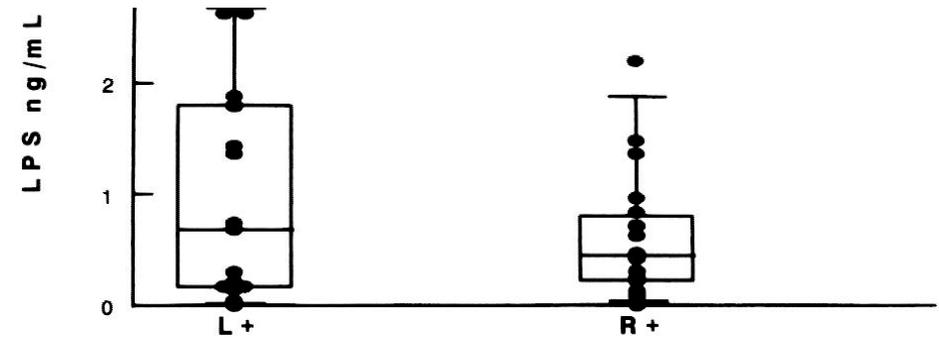
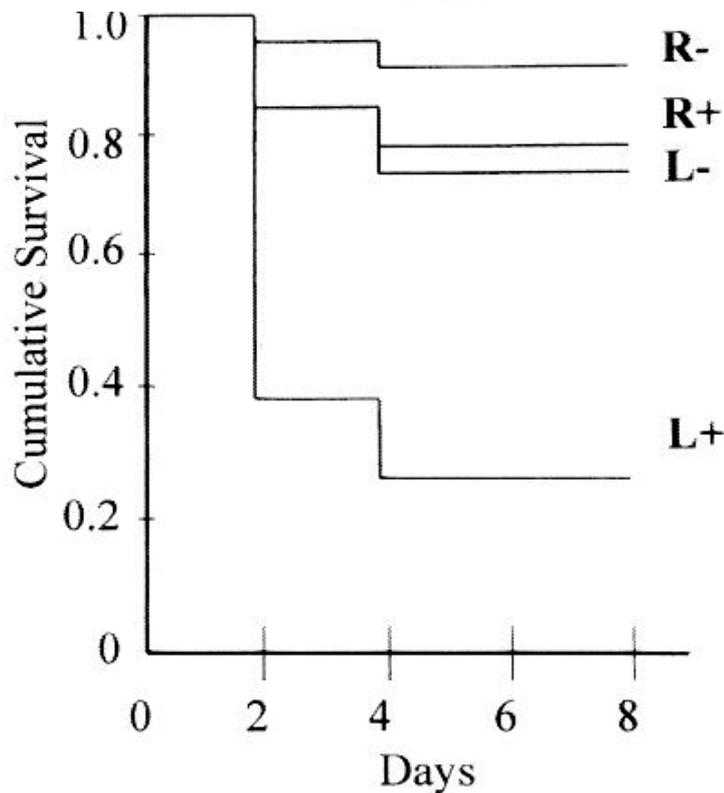
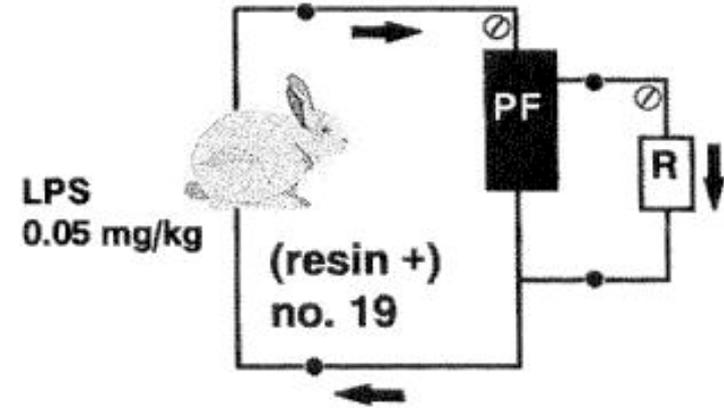
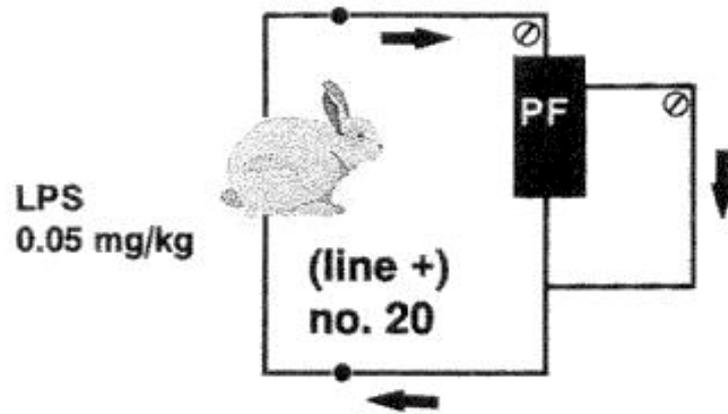


Adsorption capacity for TNF α of two sorbent materials



Coupled plasma filtration-adsorption in a rabbit model of endotoxic shock

Tetta C et al



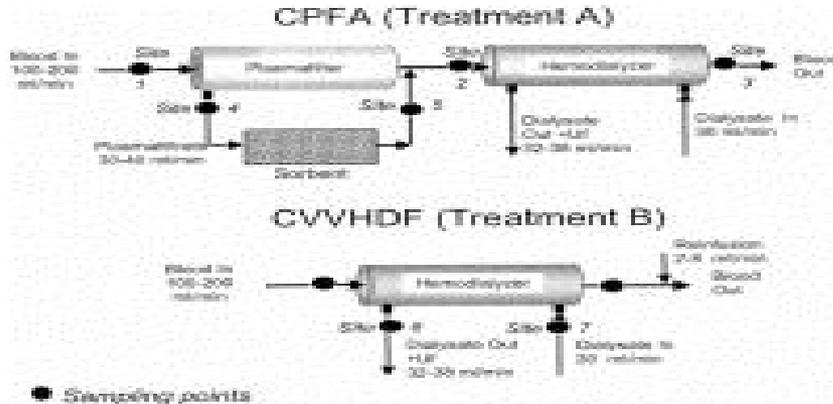
A pilot study of coupled plasma filtration with adsorption in septic shock

Ronco C et al

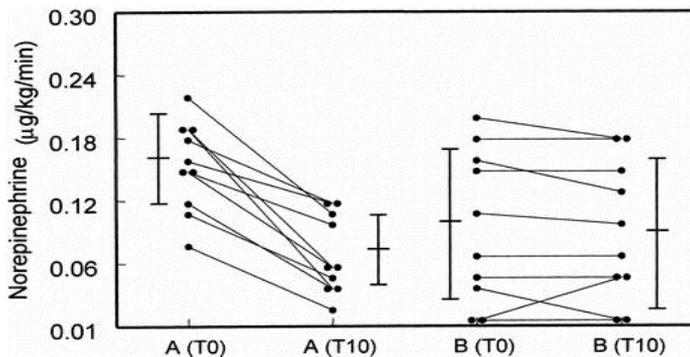
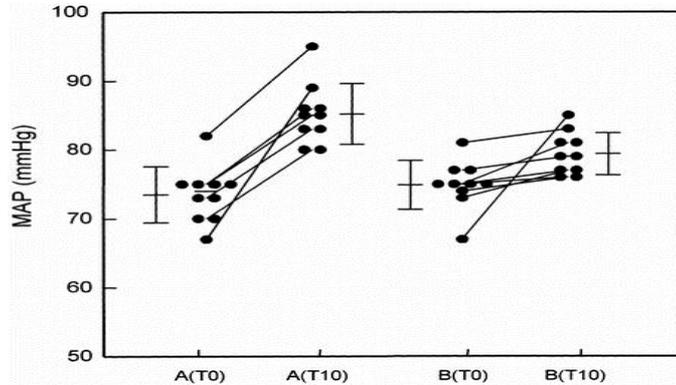
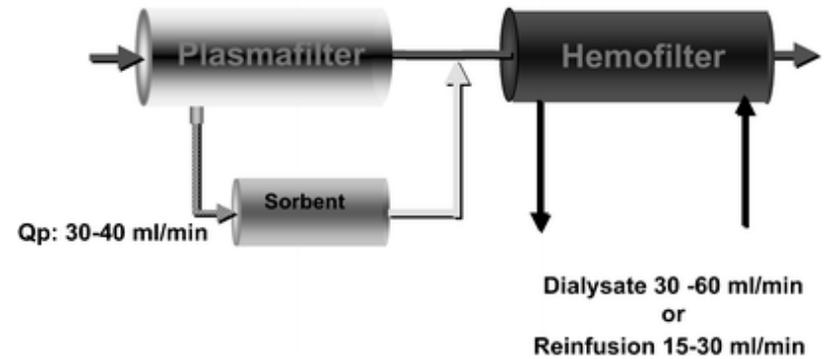


Hemodynamic response to CPFA in human septic shock

Formica M et al.



Qb: 150-180 ml/min



Safe use of CPFA in ICU-hospitalized patients with septic shock independently of the presence of concomitant ARF. In this long-term study, we showed CPFA to be a safe and feasible treatment with significant improvement in hemodynamic stability, vasopressor requirement, pulmonary function, and 28- and 90-day survival. The 28 days survival rate was 90%, which was quite unexpected considering an Apache II-predicted mortality for these patients of about 40%.

Conclusion Coupled plasmafiltration-adsorption was a feasible and safe extracorporeal treatment and exerted a remarkable improvement in the hemodynamics, the pulmonary function, and the outcome in septic shock patients with or without concomitant ARF.

COMPACT

(COMbining Plasmafiltration and Adsorption Clinical Trial)

Efficacia e sicurezza della CPFA
(plasmafiltrazione associata ad adsorbimento)
nello shock settico in Terapia Intensiva

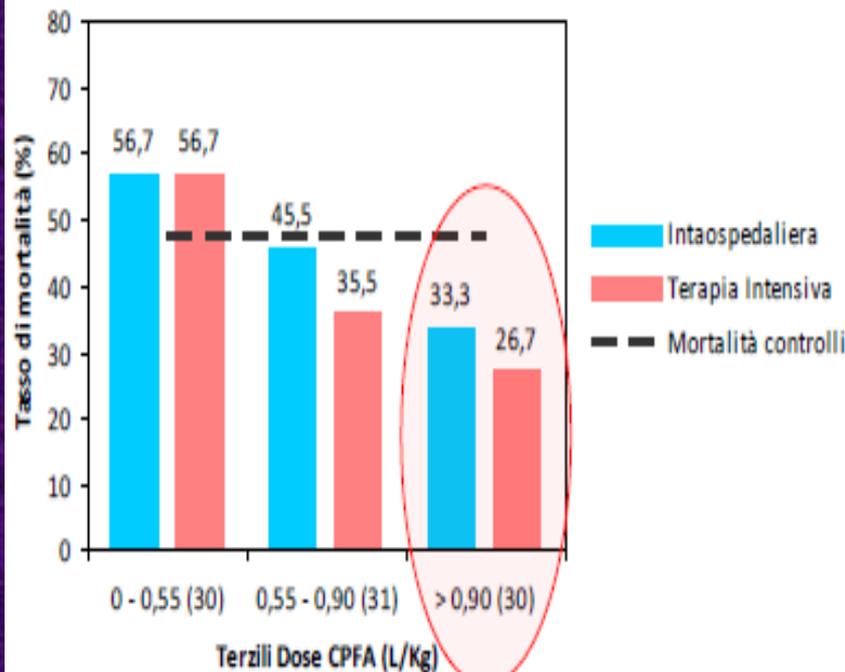
CODICE: ISRCTN24534559, NCT003323

progetto sperimentale
GiViTI

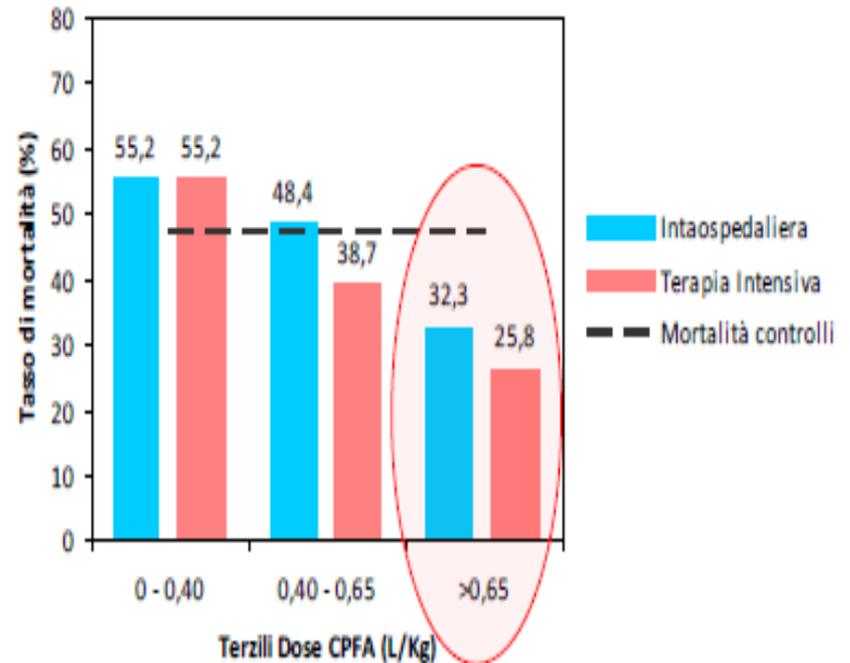
(Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva)

Mortalità per volume di plasma pro-Kg trattato

nei primi 5 giorni

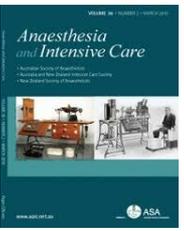


nei primi 3 giorni

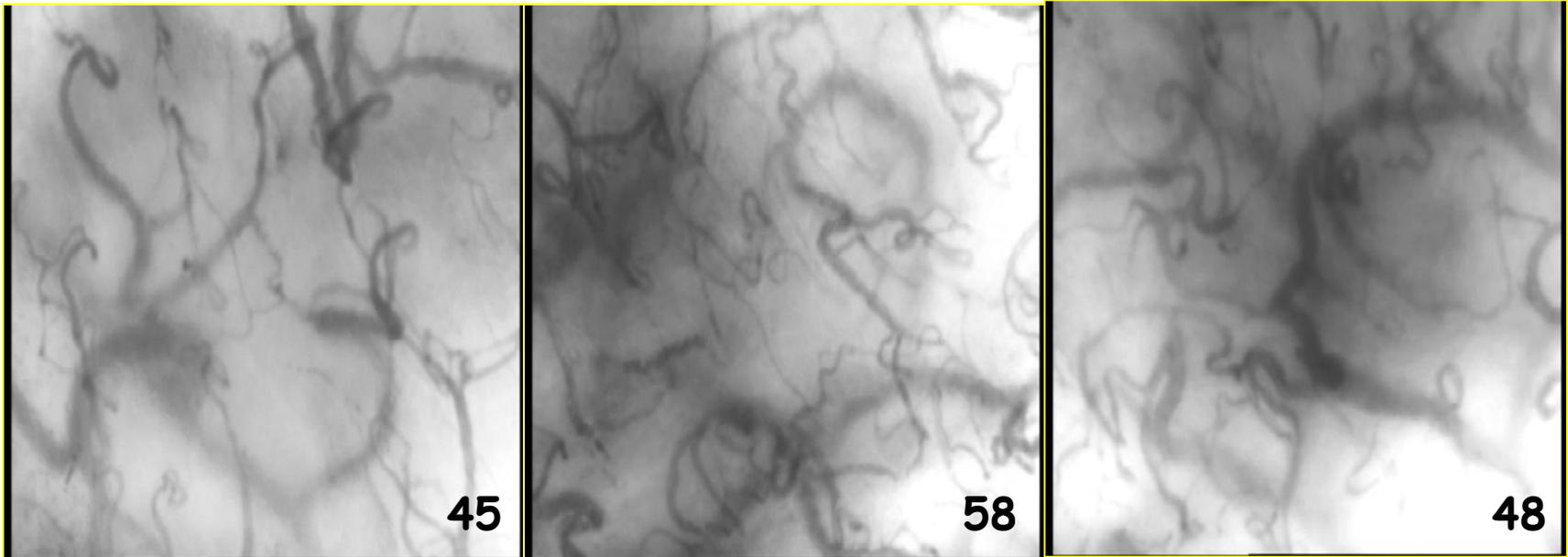


Changes in microvascular blood flow during coupled plasma filtration and adsorption

Berlot G et al.



CPFA and Sublingual Blood Flow



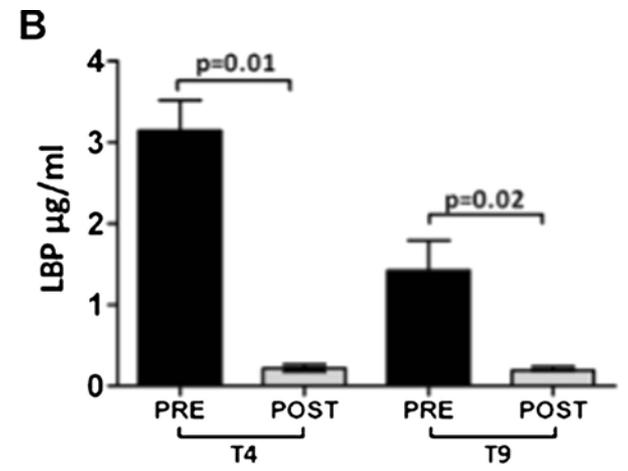
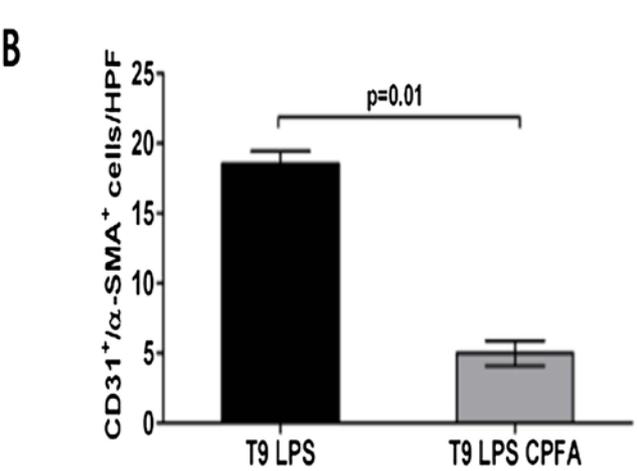
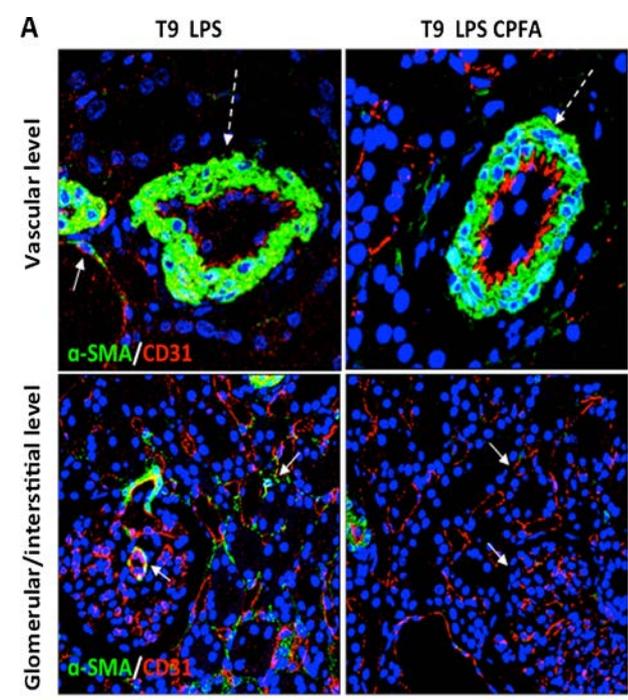
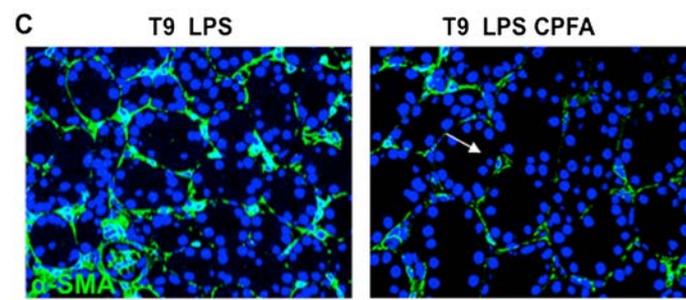
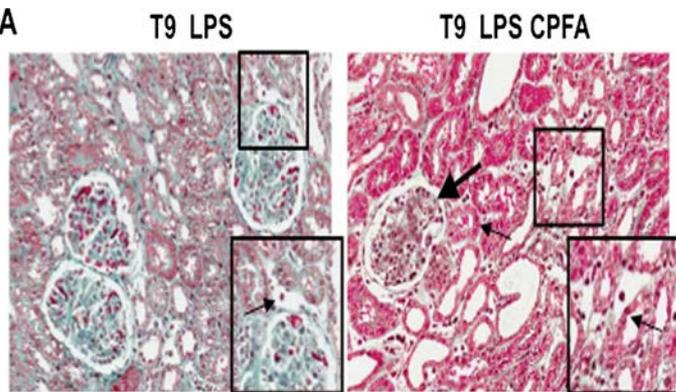
Pre CPFA

2 h after
CPFA initiation

1 after
Stop CPFA

Endothelial dysfunction and renal fibrosis in endotoxemia-induced oliguric kidney injury: possible role of LPS binding protein

Castellano G et al.



AKI indotta da sepsi: attivazione del sistema immunitario dell'ospite e delle cellule residenti renali mediante LPS e prodotti pro-infiammatori.

Fibrosi renale in questo contesto : scarsamente indagata.

Disfunzione endoteliale potrebbe avere un ruolo nello sviluppo di fibrosi tubulointerstiziale in AKI indotta da LPS.

LBP ridotta a seguito di trattamento CPFA

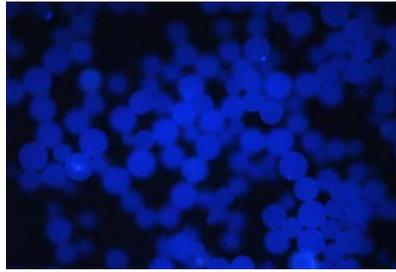
La rimozione selettiva di LPS potrebbe rappresentare una futura opzione terapeutica volta alla prevenzione della disfunzione endoteliale e della fibrosi tissutale in corso di AKI su base settica.

Protective effect of resin adsorption on septic plasma-induced tubular injury.

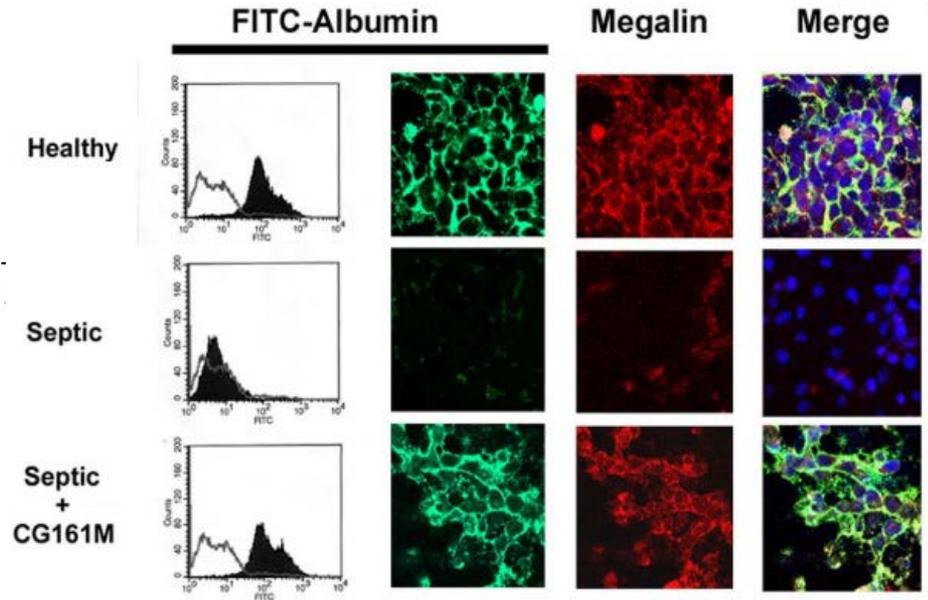
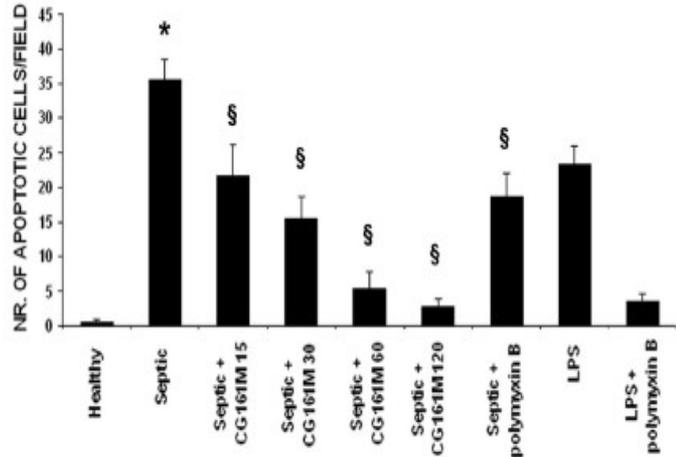
Cantaluppi V, Weber V, Lauritano C, Figliolini F, Beltramo S, Biancone L, De Cal M, Cruz D, Ronco C, Segoloni GP, Tetta C, Camussi G



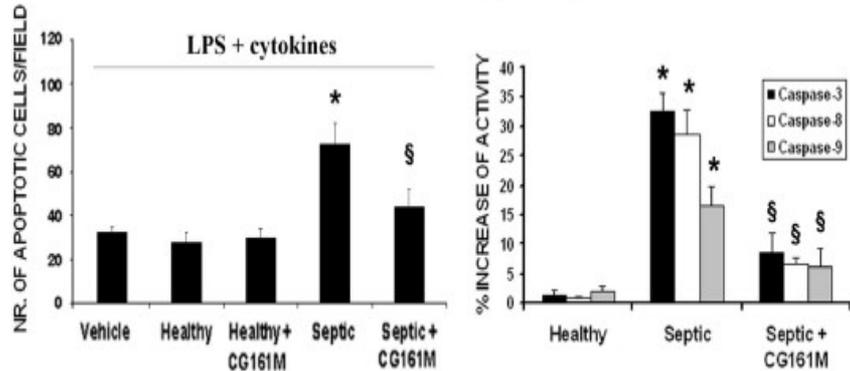
**Amberchrom
CG161M resin
(Rohm and Haas Co.
Philadelphia, PA)**



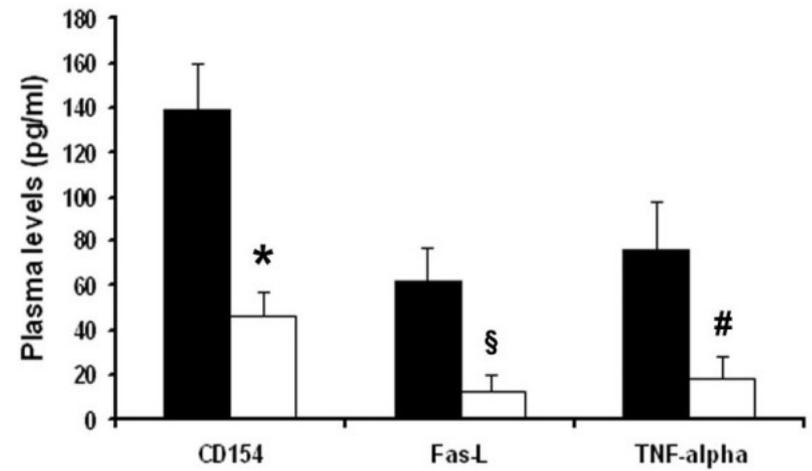
A



B



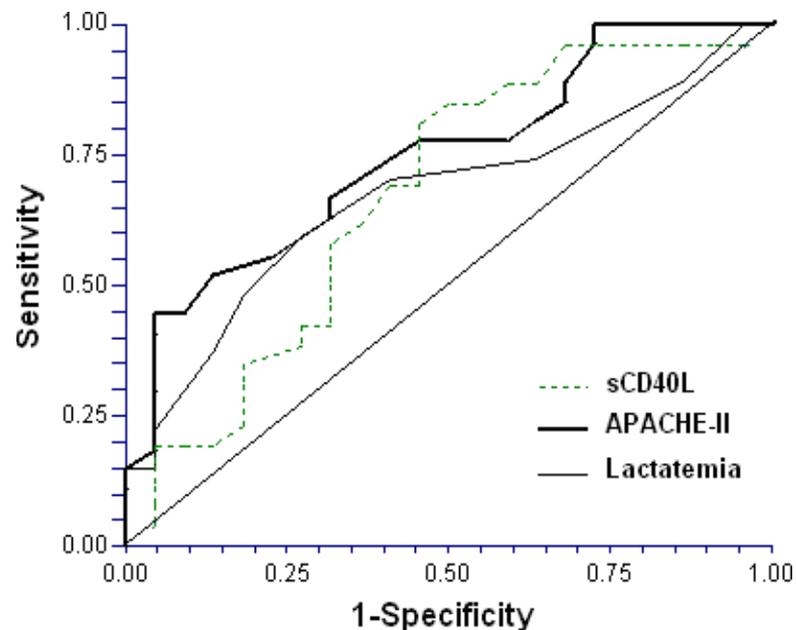
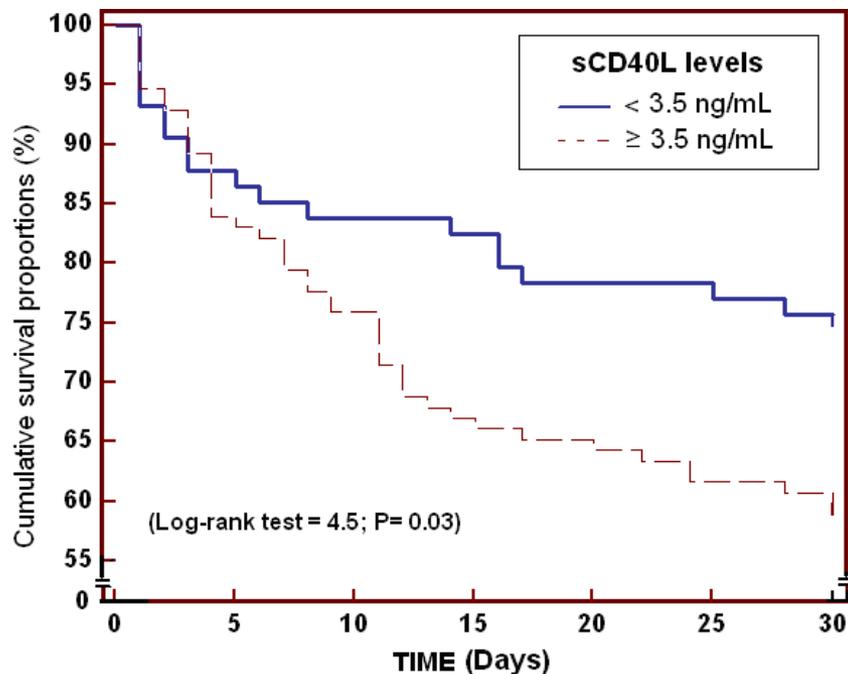
C



Association between serum soluble CD40 ligand levels and mortality in patients with severe sepsis



Leonardo Lorente^{1*}, María M Martín², Nerea Varo³, Juan María Borreguero-León⁴, Jordi Solé-Violán⁵, José Blanquer⁶, Lorenzo Labarta⁷, César Díaz⁸, Alejandro Jiménez⁹, Eduardo Pastor¹, Felipe Belmonte², Josune Orbe¹⁰, José A Rodríguez¹⁰, Eduardo Gómez-Melini⁴, José M Ferrer-Agüero⁵, José Ferreres⁶, María C LLimiana¹¹, José A Páramo¹⁰



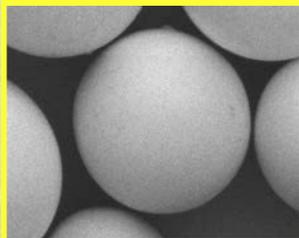
Circulating sCD40L levels are increased in septic patients and are independently associated with mortality.

The modulation of sCD40L could represent an attractive therapeutic target.

COSA ADSORBONO LE RESINE IN CPFA?

- **Interleukin 1b**
- Interleukin 5
- **Interleukin 6**
- Interleukin 7
- **Interleukin 8**
- Interleukin 10(?)
- Interleukin 12p70
- Interleukin 16
- Interleukin 18

- **Macrophage inflammatory protein-a (MIP-a)**
- **Macrophage inflammatory protein-b (MIP-b)**
- **Tumor necrosis factor-aTNF-a**
- Monocyte chemotactic protein (MCP-1)
- RANTES
- Epithelial neutrophil activating peptide 78 (ENA-78)
- Angiogenin



COSA NON ADSORBONO LE RESINE IN CPFA

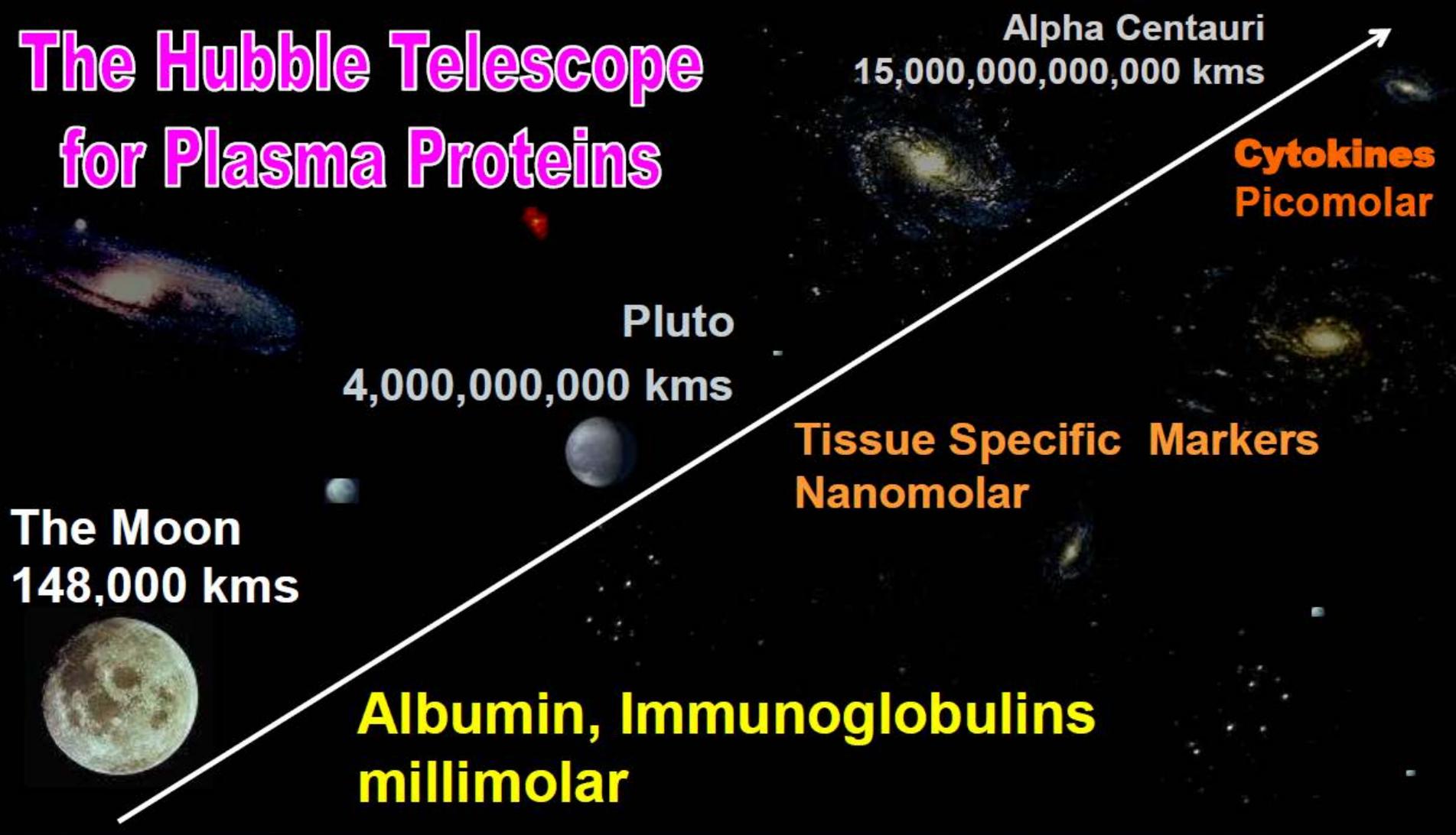
Adsorbimento non significativo

- **ALBUMINA**
- **EPARINA**
- **CITRATO**
- **ANTICORPI**
- **FERRITINA**
- **GM-CSF**
- **TIROXINE**
- **ADIPONECTINA**
- **FATTORE VON WILLEBRAND**
- **ENDOTOSSINA**

Basso adsorbimento

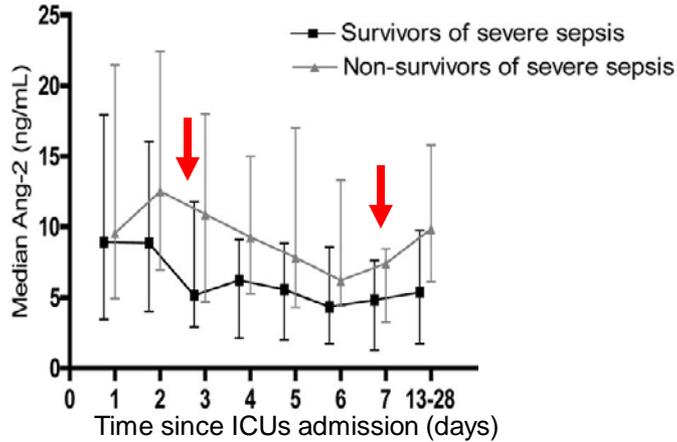
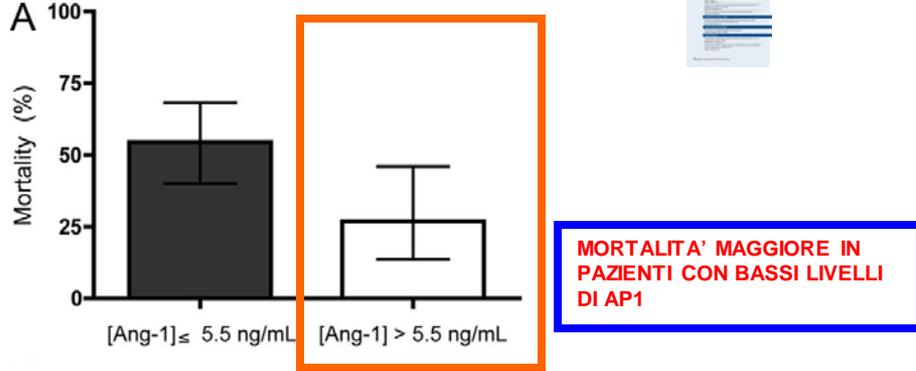
- **INSULINA (1 ORA)**
- **VEGF**
- **EGF**
- **ICAM**
- **VCAM**
- **MCP**

The Hubble Telescope for Plasma Proteins



Angiotensin-1 and angiotensin-2 as clinically informative prognostic biomarkers of morbidity and mortality in severe sepsis*

Daniel R. Ricciuto, MD; Claudia C. dos Santos, MD; Michael Hawkes, MD; Lisa J. Tolti, BSc; Andrea L. Conroy, BSc; Nimerta Rajwans, MSc; Erin I. Lafferty, BSc; Deborah J. Cook, MD; Alison Fox-Robichaud, MD; Kamyar Kahnemouli, MD, MSc; Kevin C. Kain, MD; Patricia C. Liaw, PhD; W. Conrad Liles, MD, PhD

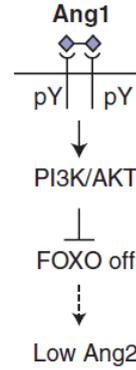


ANGIOPETINA 1 E 2 DI AP2 MISURATI IN CORSO DI RICOVERO IN PAZIENTI SETTICI CORRELANO CON LA MORTALITA' A 28 GIORNI

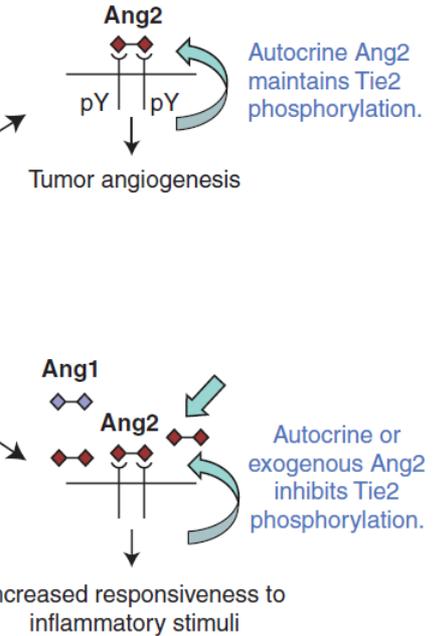
AP2 CORRELA CON DANNO MULTIORGANICO ED E' UN VALIDO SCORE CLINICO PER LA SEVERITA' DELLA SEPSI.

AP COME BIOMARCATORE DI SEVERITA' DI MALATTIA ED OUTCOME DEL PAZIENTE SETTICO.

Low Ang2 expression
Stable, quiescent endothelium



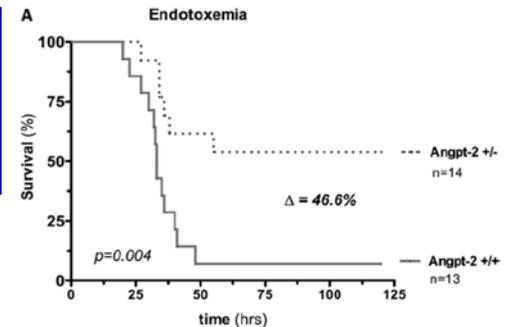
High Ang2 expression
Tumors, inflammation

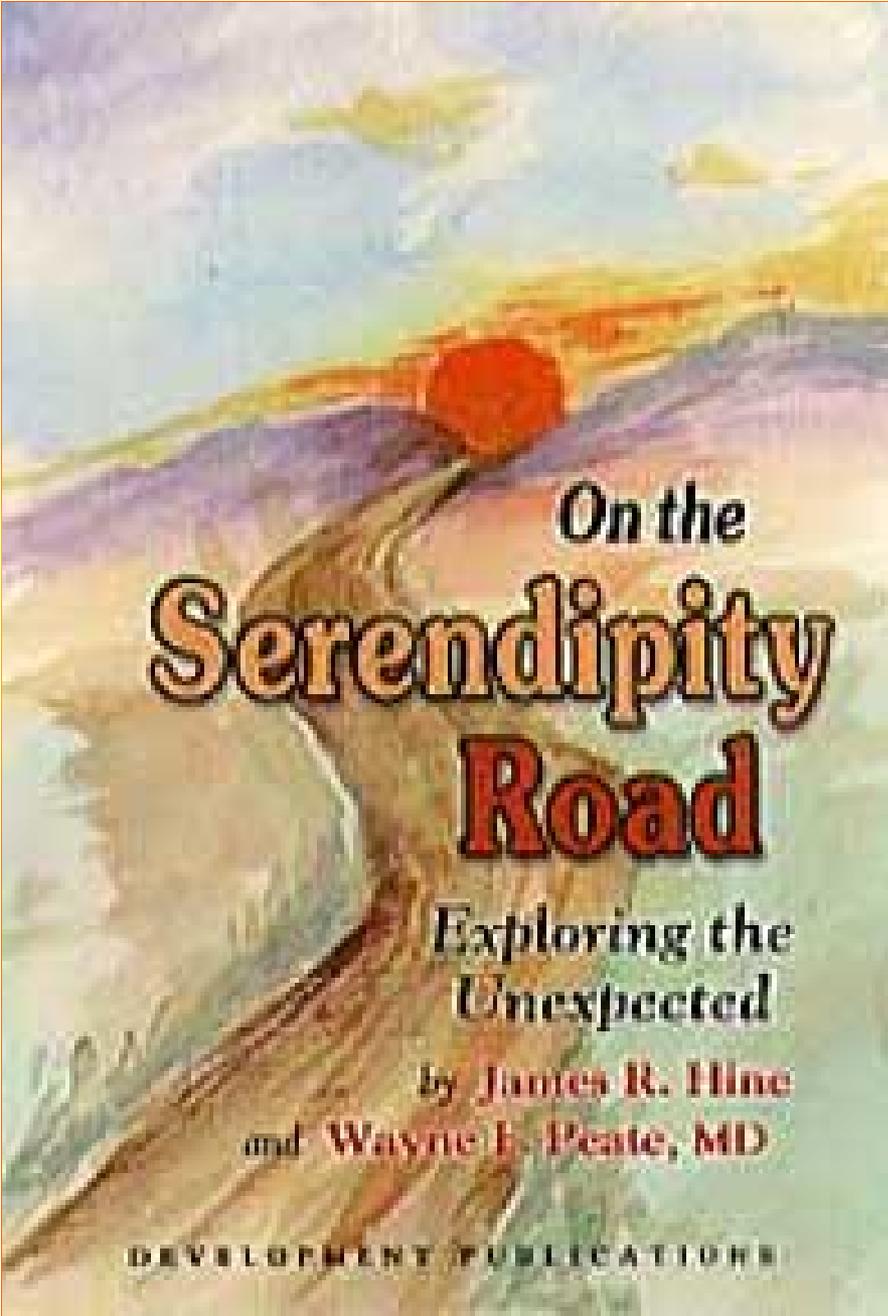


Angiotensin-2 may contribute to multiple organ dysfunction and death in sepsis*

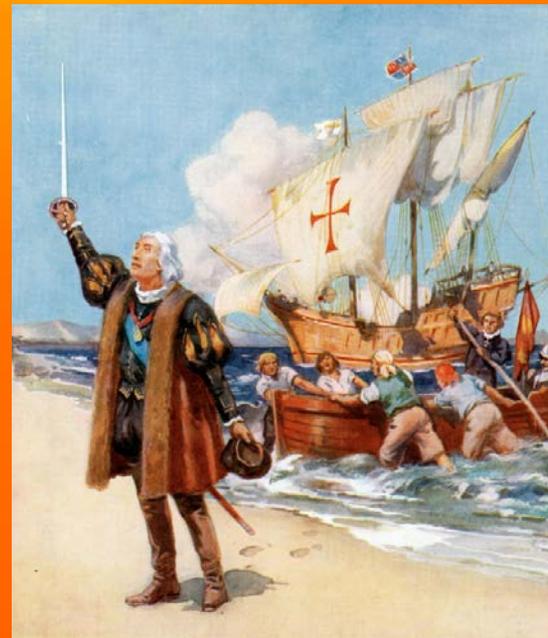
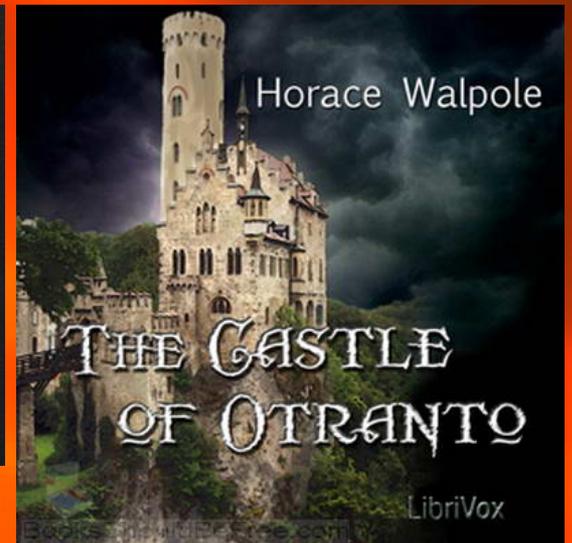
Sascha David, MD; Aditi Mukherjee, MS; Chandra C. Ghosh, PhD; Midori Yano, BS; Eliyahu V. Khankin, MD; Julia B. Wenger, MPH; S. Ananth Karumanchi, MD; Nathan I. Shapiro, MD, MPH; Samir M. Parikh, MD

TOPIETEROZIGOTI PER AP2 (Angpt-2) HANNO SOPRAVVIVENZA MAGGIORE IN UN MODELLO SETTICO SPERIMENTALE





Horace Walpole



Cristoforo Colombo

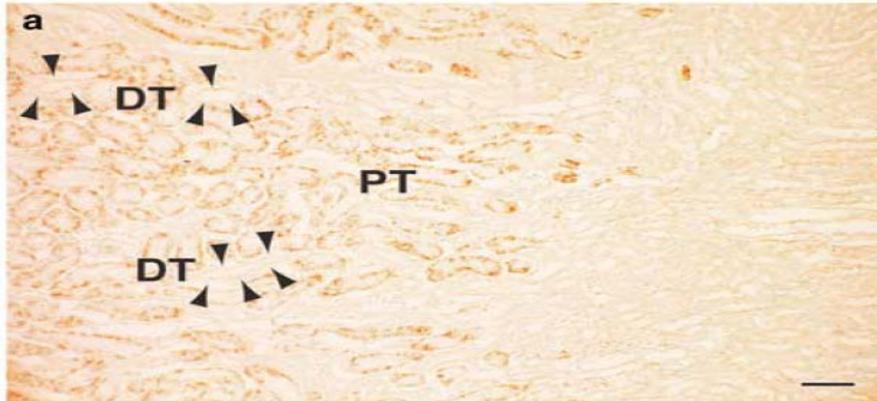


LIVER-TYPE FATTY ACID BINDING PROTEIN (L-FABP)

Evidence for megalin-mediated proximal tubular uptake of L-FABP, a carrier of potentially nephrotoxic molecules



Yuko Oyama¹, Tetsuro Takeda^{1,2}, Hitomi Hama¹, Atsuhito Tanuma¹, Noriaki Iino¹, Kiyoko Sato¹, Ryohei Kaseda¹, Meilei Ma³, Tadashi Yamamoto³, Hiroshi Fujii⁴, Junichiro J Kazama⁵, Shoji Odani⁶, Yoshio Terada⁷, Kunihiko Mizuta⁸, Fumitake Gejyo¹ and Akihiko Saito^{1,2}



- Liver-type fatty acid binding protein (L-FABP - 14 kD MW) binds with high affinity to hydrophobic molecules including free fatty acids, bile acids and bilirubin.

- First identified in hepatocytes and then in kidney proximal tubular epithelial cells.

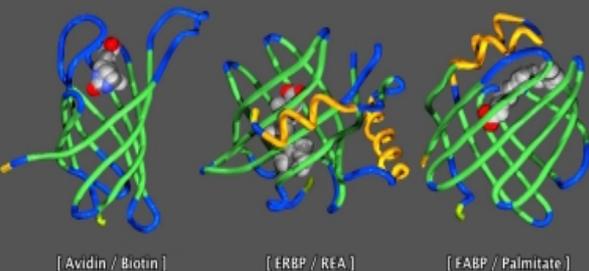
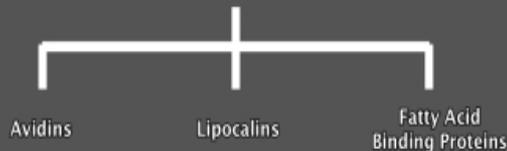
- L-FABP is released into the circulation, and patients with liver damage have an elevated plasma L-FABP level. L-FABP is also present in renal tubules; however, the precise localization of L-FABP and its potential role in the renal tubules have been only recently investigated.

- L-FABP is transported through the circulation into PTC by megalin-mediated endocytosis.

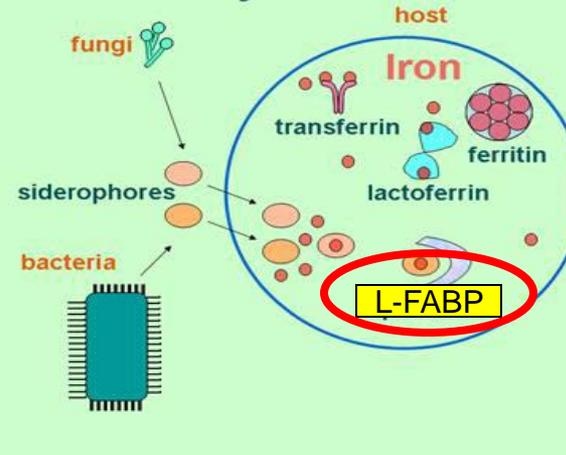
- Increase during tubular damage, obstructive disease and cisplatin nephrotoxicity.

- increased peak at 4 h after injury similar to NGAL

Calycins



Iron thievery



Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction

Charles M. van Slambrouck¹, Fadi Salem², Shane M. Meehan¹ and Anthony Chang¹



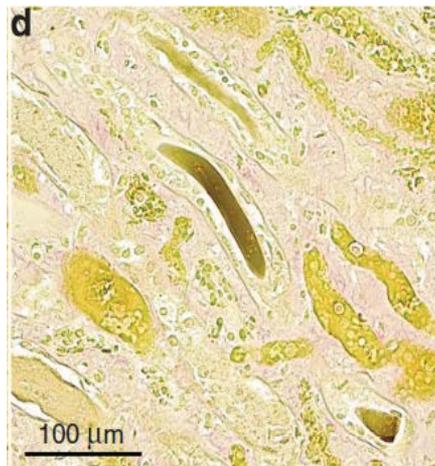
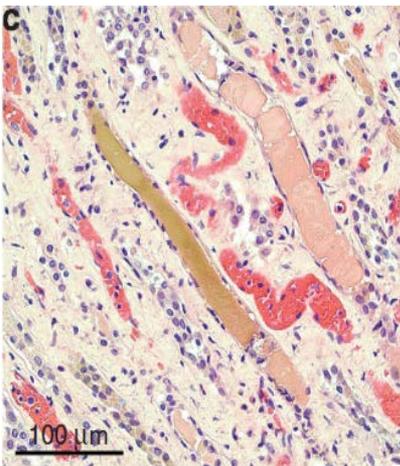
Bile-cast nephropathy: danno tubulare prossimale a seguito di formazione di cristalli biliari intrarenali riscontrati in pazienti con severa insufficienza epatica.

I cristalli biliari possono contribuire al danno renale di pazienti con severo ittero per tossicità diretta da parte di bile e bilirubina e per ostruzione tubulare.

Entrambi i meccanismi di danno sono analoghi a quelli riscontrati nel danno da catene leggere nel mieloma o della mioglobina in pazienti con rhabdomiolisi.

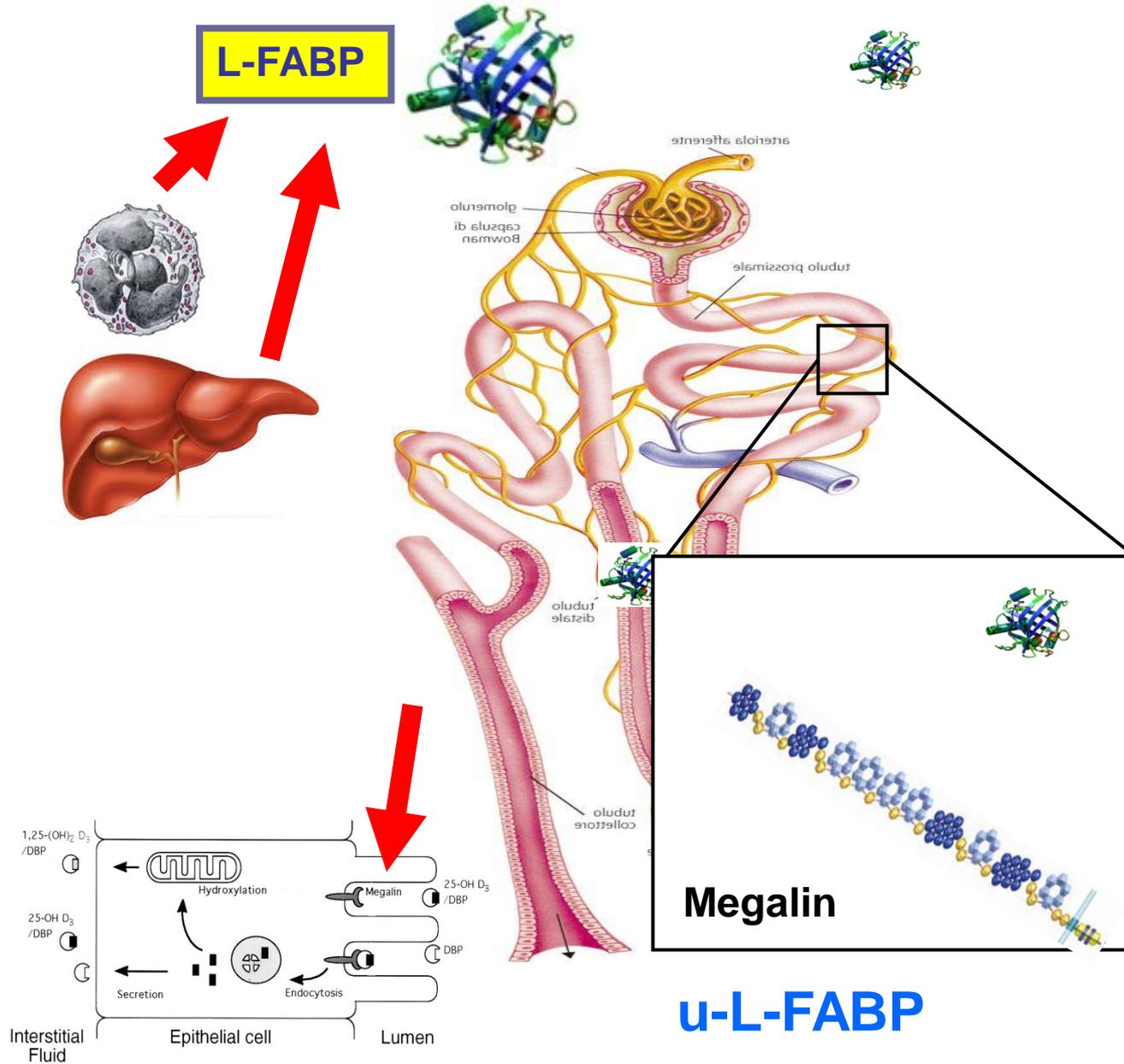
Il coinvolgimento renale è frequente in pazienti con insufficienza epatica.

Non nota l'incidenza di BCN (visti anche i pochi casi descritti), ma indicativamente tutti i pazienti con HRS possono svilupparla.



Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery

D Portilla¹, C Dent², T Sugaya³, KK Nagothu¹, I Kundi¹, P Moore⁴, E Noiri⁵ and P Devarajan⁶



CASE REPORT

RACCORDO ANAMNESTICO ANAMNESI PATOLOGICA REMOTA

- S.C., maschio, anni 72
- Familiarità per **cardiopatía ischemica** e **ipertensione arteriosa**.
- Abile alla leva, fumatore attivo (10/die), non potus.
- Non patologie di rilievo in età giovanile
- Dal 1998: **prostatiti recidivanti e frequenti episodi di IVU** (E. Coli, Proteus M.)
- 2/2003: diagnosi di **RVU di grado medio**, bilaterale.
- 4/2005: **pielonefrite destra** (E coli). Eseguita terapia antibiotica mirata mediante antibiogramma.
- 3/2008: All'ecografia addominale riscontro di **reni severamente ridotti dimensionalmente con insufficienza renale cronica da pielonefrite cronica** (Crs 1.9 mg/dl, BCrC 18 ml/min).
- 8/2010: Crs 2.7 mg/dl, BCrC cca 10 ml/min. **Avvio del trattamento dialitico sostitutivo mediante confezionamento FAV prossimale destra.**

CASE REPORT

RACCORDO ANAMNESTICO ANAMNESI PATOLOGICA REMOTA

6/11/2012

TRAPIANTO RENALE DA DONATORE MARGINALE

IMMUNOSOPPRESSIONE:

TACROLIMUS
MICOFENOLATO MOFETILE
STEROIDE

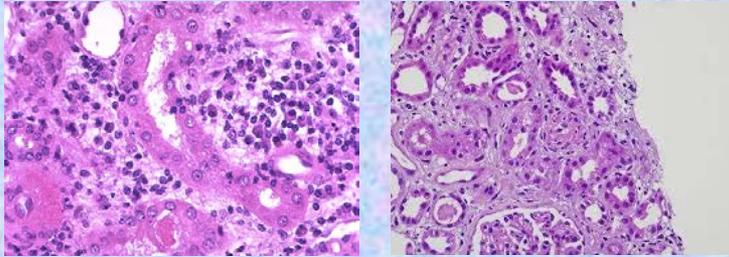
TAC levels 12-15 ng/ml
MMF 500 mg x 2/die
Metilprednisolone 10 e poi 5 mg/die

DELAYED GRAFT FUNCTION

NECESSITA' DI RRT NELL'
IMMEDIATO POST –
TRAPIANTO
(dall' 8 al 24/11)

CASE REPORT

RACCORDO ANAMNESTICO POST TRAPIANTO



4/12/2012
BIOPSIA RENALE

**RIGETTO ACUTO TUBULO-INTERSTIZIALE
E VASCOLARE**

**AVVIATO TRATTAMENTO CON THYMOGLOBULINE
1,5 mg/Kg/die (4 somministrazioni con monitoraggio
emocromo quotidiano)**

Crs 2.6 mg/dl

18/12/2012

**SHOCK SETTICO DA
LEGIONELLA**

**MULTI-ORGAN
FAILURE**

CASE REPORT

RACCORDO ANAMNESTICO POST TRAPIANTO

AKI (Crs 5,2 mg/dl)

- Oligo-anuria
- Sovraccarico centrale

**INDICATA RIPRESA MOMENTANEA DELLA DIALISI
dal 9/1/2013**

FEBBRAIO 2013

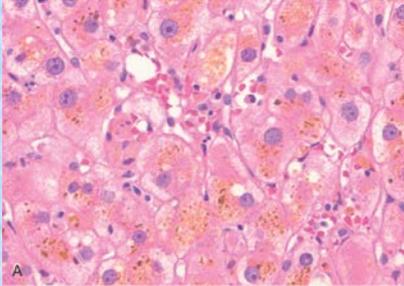
- Bilirubina 42 mg/dl;
- L-FABP 52 ng/ml;
- Sedimento urinario: presenza di cellule tubulari e di intensa positività per la bilirubina;
- u-NGAL 356 ng/ml.

CASE REPORT

RACCORDO ANAMNESTICO POST TRAPIANTO

13/2/2013

BIOPSIA EPATICA



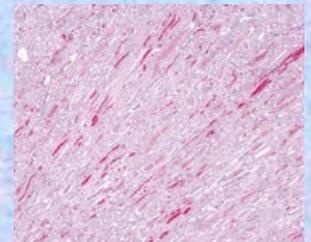
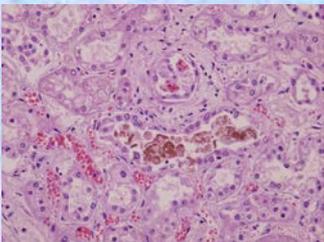
SEGNI DI SEVERA COLESTASI

- Anuria
- Crs 4,3 mg/dl
- Tendenza al sovraccarico centrale

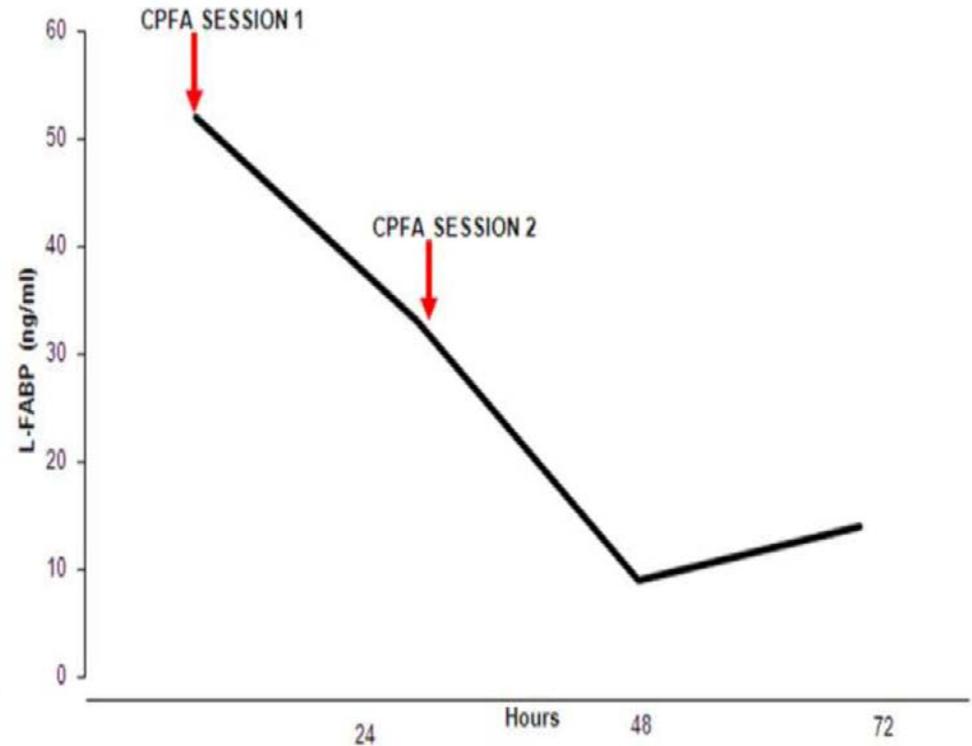
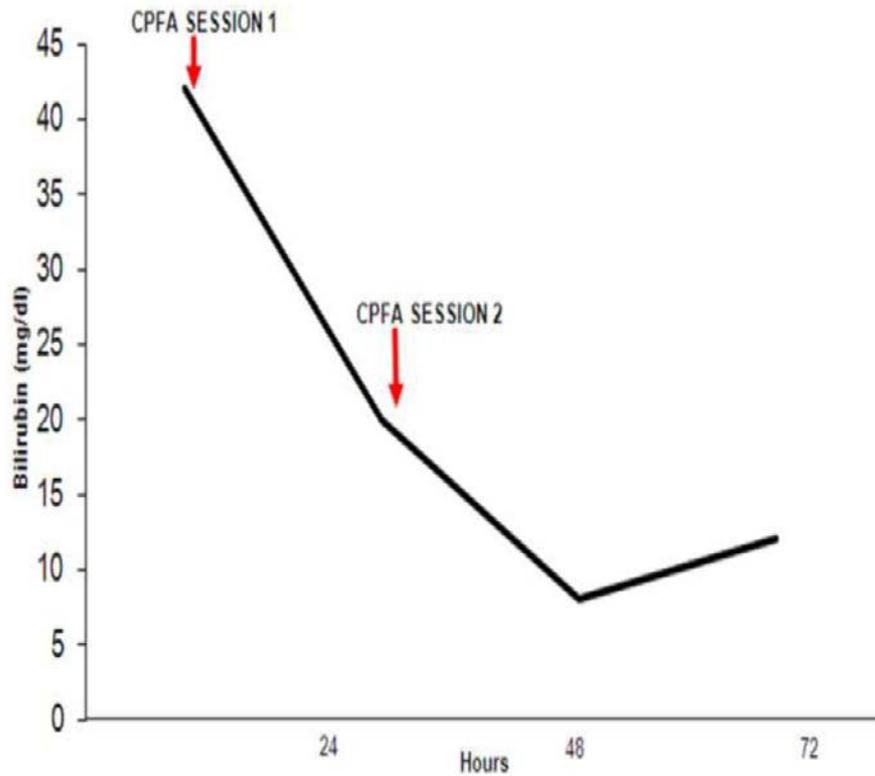
21/2/2013: II^ BIOPSIA RENALE

BILE-CAST NEPHROPATHY E SEVERO DANNO TUBULARE

START CPFA
dal 23/2



EFFETTO CPFA SU BILIRUBINA E L-FABP PLASMATICI

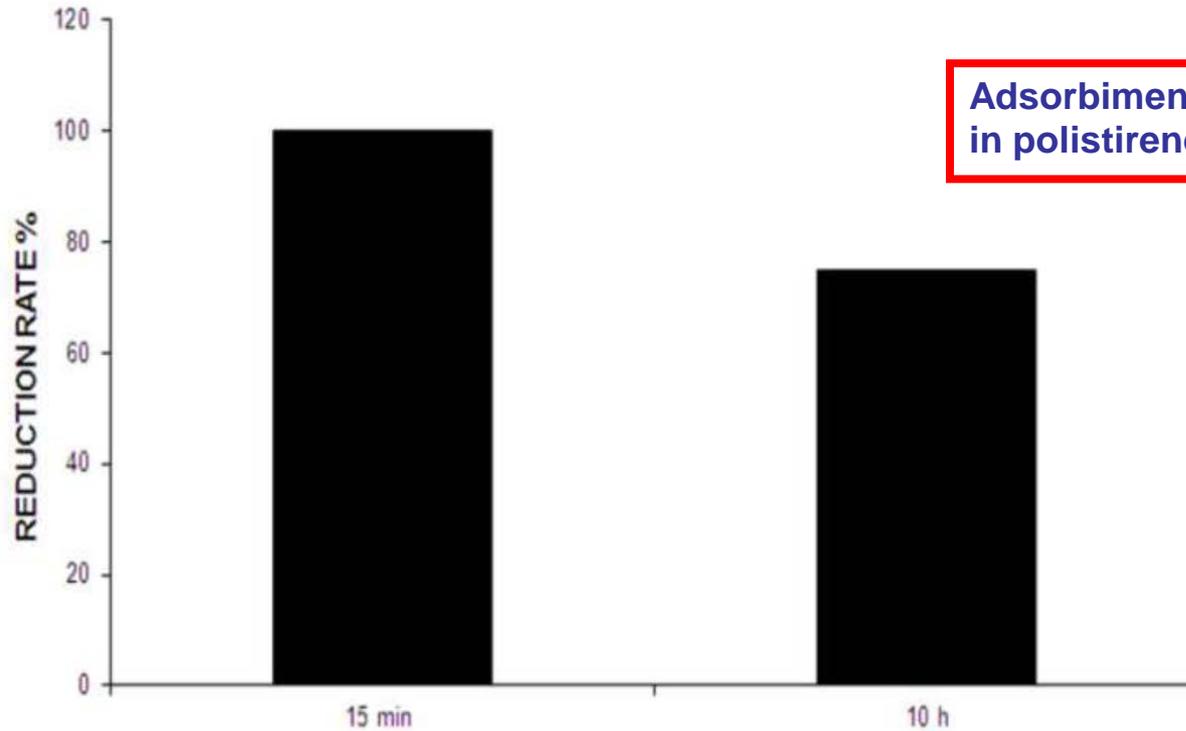


Andamento temporale dopo avvio CPFA dei livelli plasmatici di bilirubina e di L-FABP.

Efficienti risultati di CPFA in termini di riduzione dei livelli di bilirubina (< 15 mg/dl) ed L-FABP (9 ng/ml) plasmatici, associato ad incremento dell'output urinario.

EFFETTO CPFA SU ADSORBIMENTO L-FABP

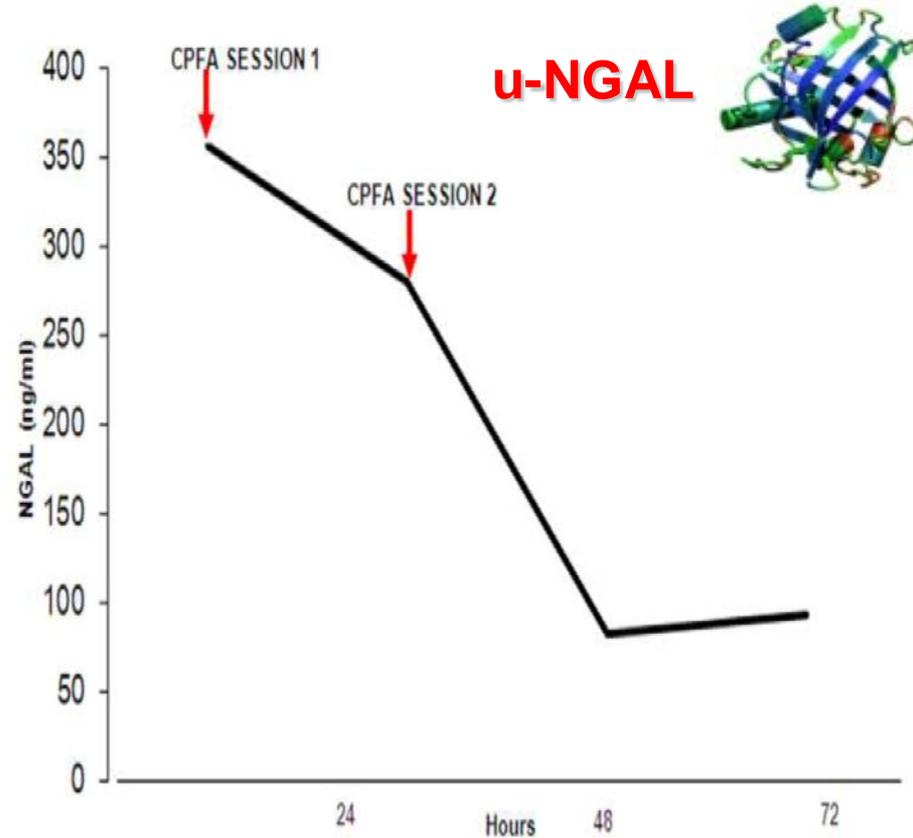
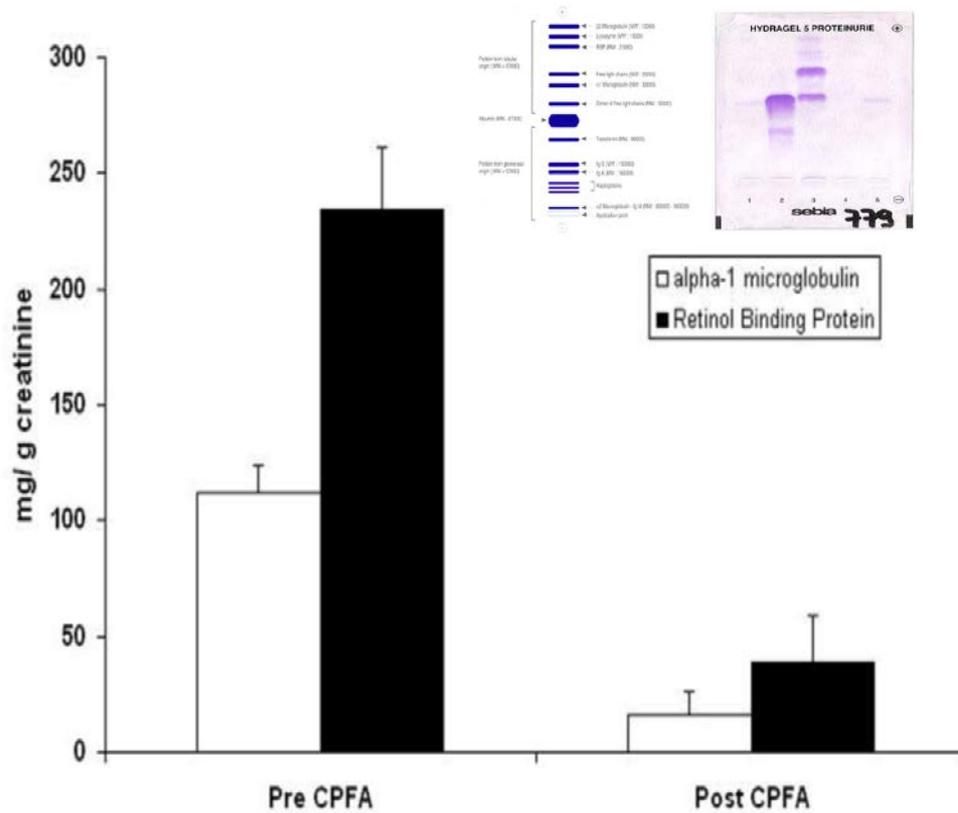
L-FABP ADSORPTION



Adsorbimento statico *in vitro* di L-FABP alla resina in polistirene dopo 15 minuti e dopo 10 ore

Courtesy by M.L. Caiazzo
Bellco Scientific Affairs

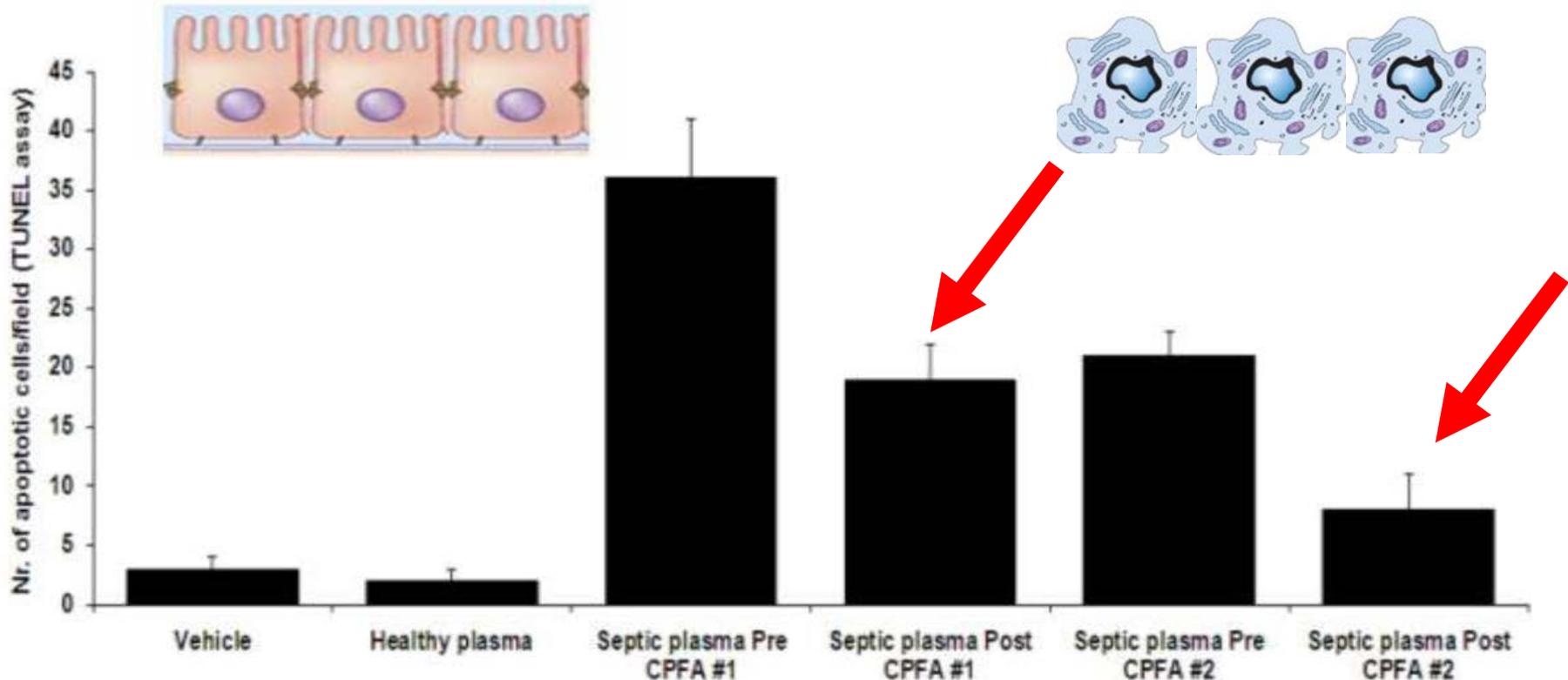
EFFETTO CPFA SU PROTEINURIA A BASSO PESO MOLECOLARE E NGAL URINARIO



Andamento temporale dopo avvio CPFA dei livelli urinari di NGAL e delle proteine di basso peso molecolare.

Efficienti risultati di CPFA in termini di riduzione dei livelli di NGAL urinario (82 ng/ml) e di proteine di basso peso molecolare, associato ad incremento dell'output urinario.

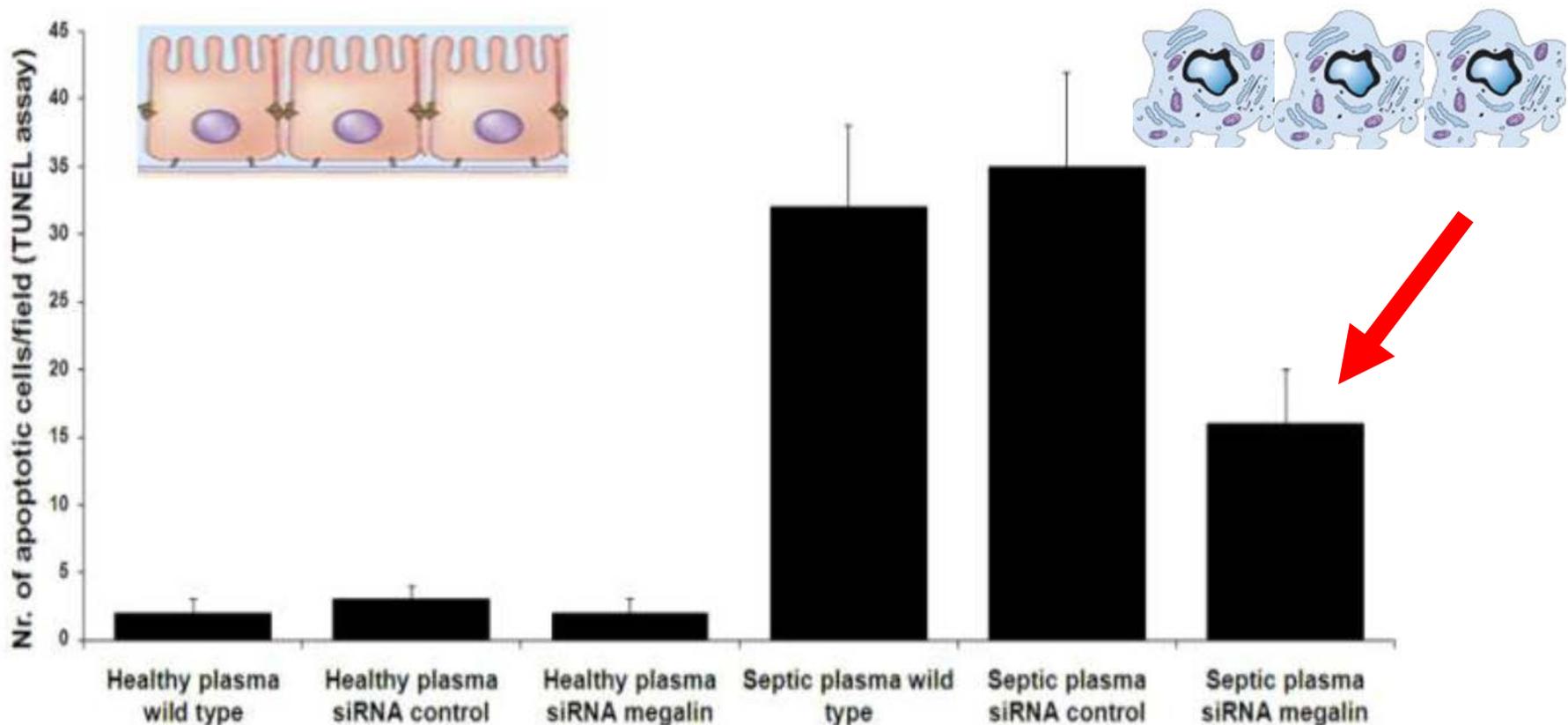
EFFETTO CPFA SU APOPTOSI TEC



Valutazione dell'apoptosi *in vitro* (TUNEL assay detecting DNA fragmentation) esercitata dal plasma settico stoccato dal paziente trapiantato del case report su TEC uname coltivate.

CPFA riduce significativamente l'apoptosi indotta dal plasma su TEC ($p < 0,05$).

RUOLO DELLA MEGALINA NELL'APOPTOSI TUBULARE



Valutazione dell'apoptosi *in vitro* (TUNEL assay) esercitata dal plasma settico stoccato dal paziente trapiantato di rene del case report descritto su TEC wild type o su TEC transfettate con un control siRNA o con un siRNA volto al knock-down della megalina, il recettore L-FABP.

L'effetto pro-apoptotico del plasma settico su TEC modulate tramite siRNA megalina era significativamente ridotto ($p < 0,05$). Tale effetto non era osservato in wild type TEC ed in TEC transfettate con siRNA di controllo.

SINDROME EPATORENALE

Elena Mancini



Artificial liver support devices as treatment option for liver failure

Nevens F et al.



OLT



BRIDGE



ARTIFICIAL SUPPORT

Cirrotici che sviluppano HRS: critici.

AKI + insufficienza epatica comporta una sindrome da insufficienza multi-organica.

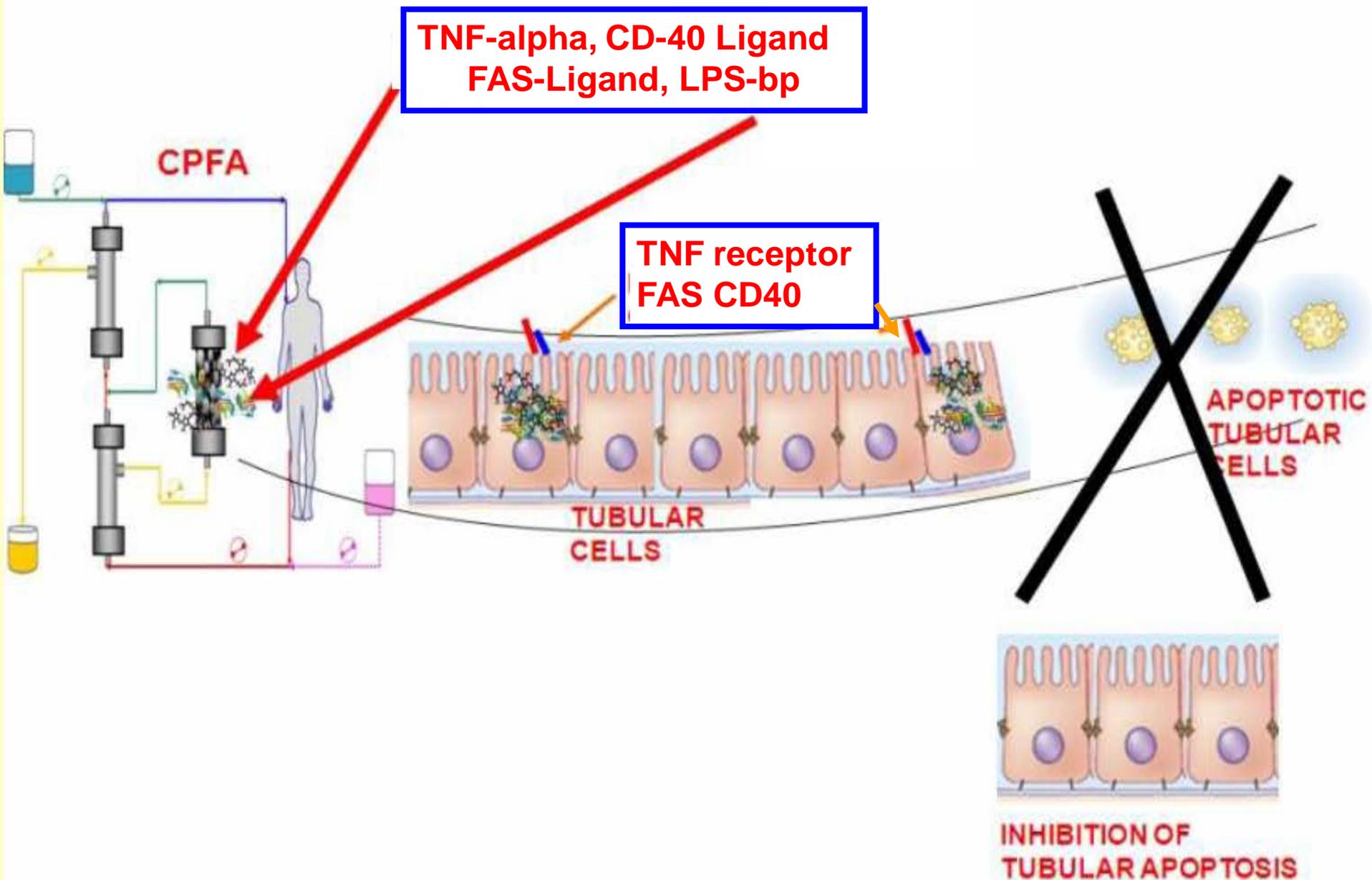
Fino a pochi anni fa il trapianto ortotopico di fegato era l'unica via di salvezza.

L'introduzione di nuovi schemi terapeutici ha cambiato l'evoluzione della HRS, offrendo buone possibilità di uscita da questa complicanza.

L'associazione di sistemi di depurazione extracorporea alle terapie note è ancora supportata da pochi studi tipo trial randomizzato, ma le prime esperienze cliniche hanno dimostrato un buon risultato sul controllo di sintomi (es. encefalopatia) e migliore sopravvivenza rispetto a chi riceve sola terapia medica standard.

Questi risultati supportano l'affermazione che i sistemi di liver support possano essere utilmente impiegati nei soggetti con HRS come bridge al trapianto di fegato o in attesa di valutare la risposta alla terapia farmacologica.

EFFETTO PROTETTIVO DI CPFA SUL DANNO TUBULARE IN CORSO DI SEPSI





Grazie per l'attenzione



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