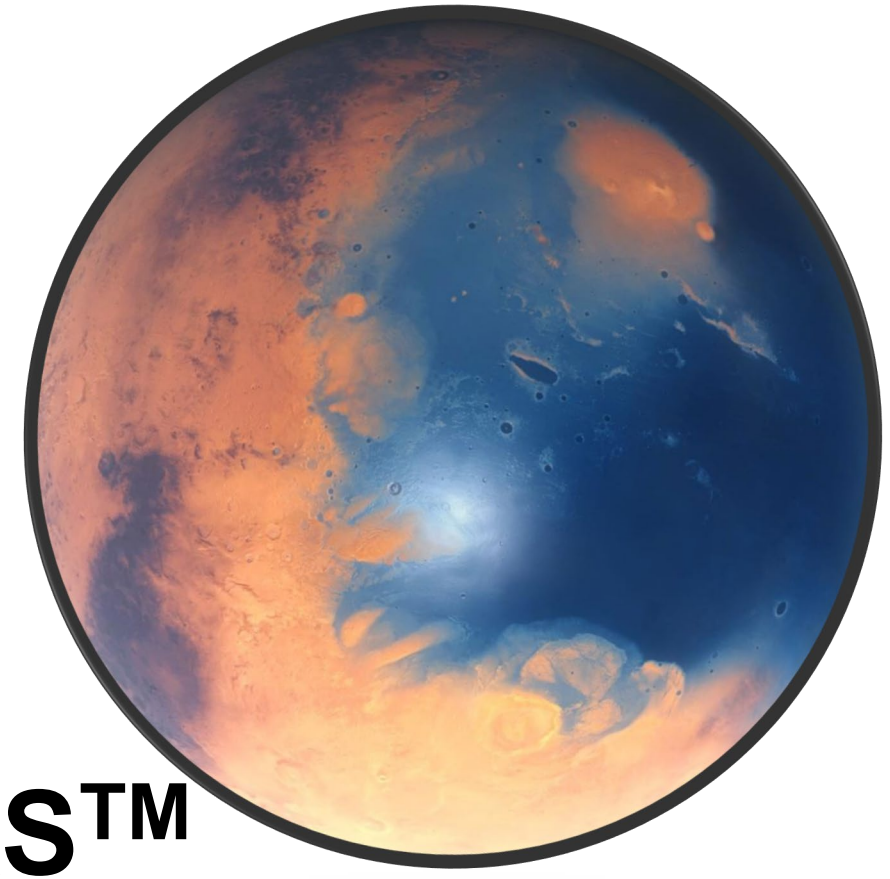
MAYO CLINIC



Pharmacotherapy on MARS™

(Molecular Adsorbent Recirculating System)

Yen Tran, Pharm.D, MBA

Pharmacy Grand Rounds
Sep 01st, 2020

Burden of Liver Failure Disease

>1 million deaths worldwide

1-6 cases per million people/year

Mortality ~50% in acute liver failure

6% of liver-related deaths

7% of orthotopic liver transplant

Richard Moreau et al. Clin Gastroenterol Hepatol. 2015;13(5):836-41
Bower WA et al. Am J Gastroenterol 2007:102(11):2459-63
Brandsaeter B et al. Liver Transpl 2002;8(11):1055-62
Khashab et al. Curr Gastroenterol Rep 2007;9(1):66-73

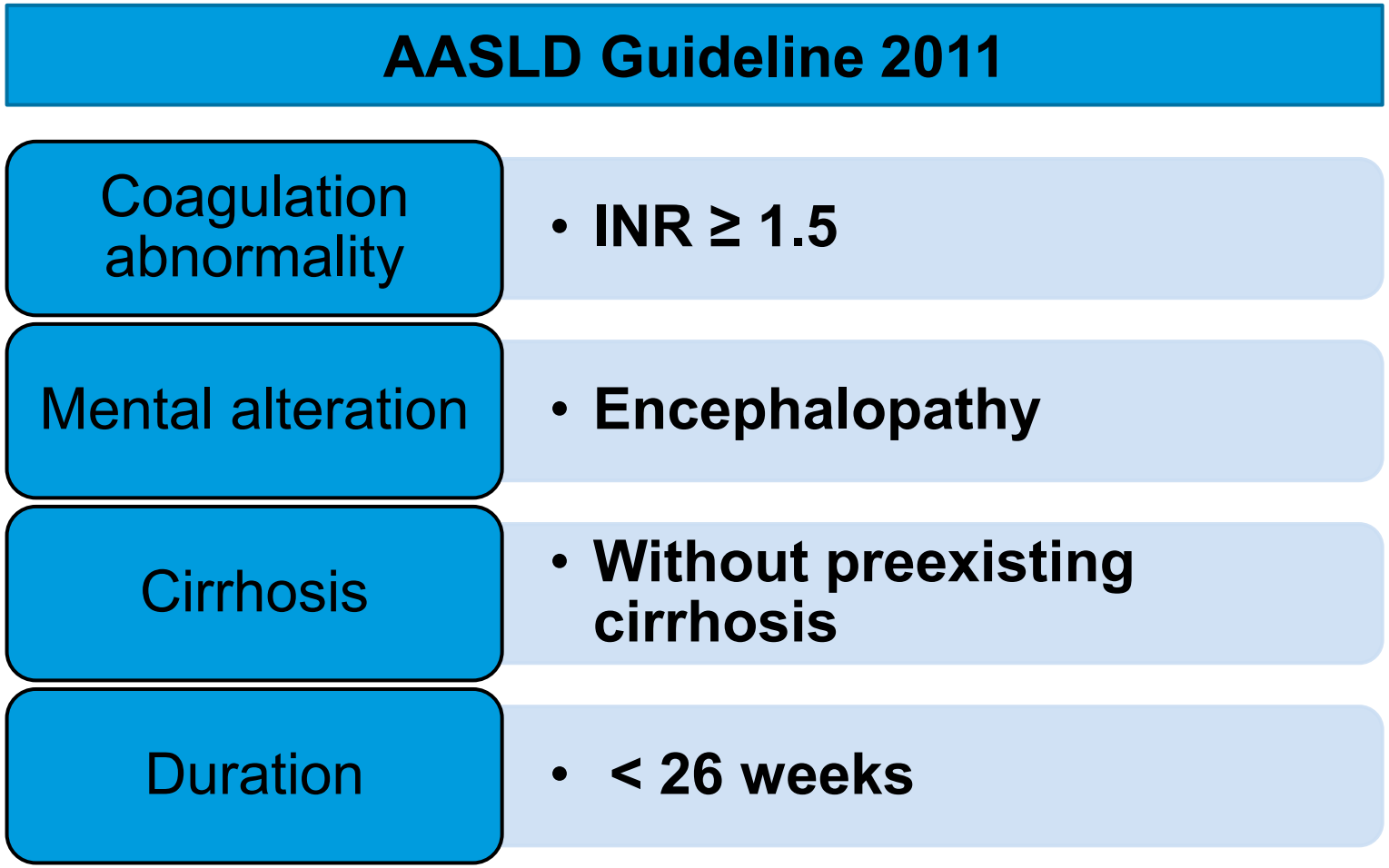
Objective

1. Review the pathophysiology of acute liver failure and the indications for liver dialysis
2. Describe the mechanism of MARS™ (Molecular Adsorbent Recirculating System)
3. Discuss the pharmacokinetic changes of medications affected by MARS™ and the clinically relevant implications

Objective

1. Review the pathophysiology of acute liver failure and the indications for liver dialysis

Definition of Acute Liver Failure



AALSD: American Association for the Study of Liver Disease

Lee W et al. Hepatology September 2011

Acute Liver Failure Subtypes

Classification, clinical features, and prognosis of acute lifer failure

Time from jaundice to encephalopathy (Weeks)

Clinical feature	Hyperacute	Acute	Subacute
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Degree of intracranial hypertension	++	++	+/-
Survival without emergency transplantation	Good	Moderate	Poor
Typical etiology	Acetaminophen Hepatitis A & E	Hepatitis B	Drug induced

+/-: present or absent ;+: mild severity; ++: moderate severity; +++: high severity

O'Grady JG et al. Lancet 1993;342:273-5
EASL CPG ALF. J Hepatol 2017;66:1047–81

Etiologies of Acute Liver Failure

- Drug induced liver injury
- Herbal and supplements
- Viral hepatitis
- Poisoning

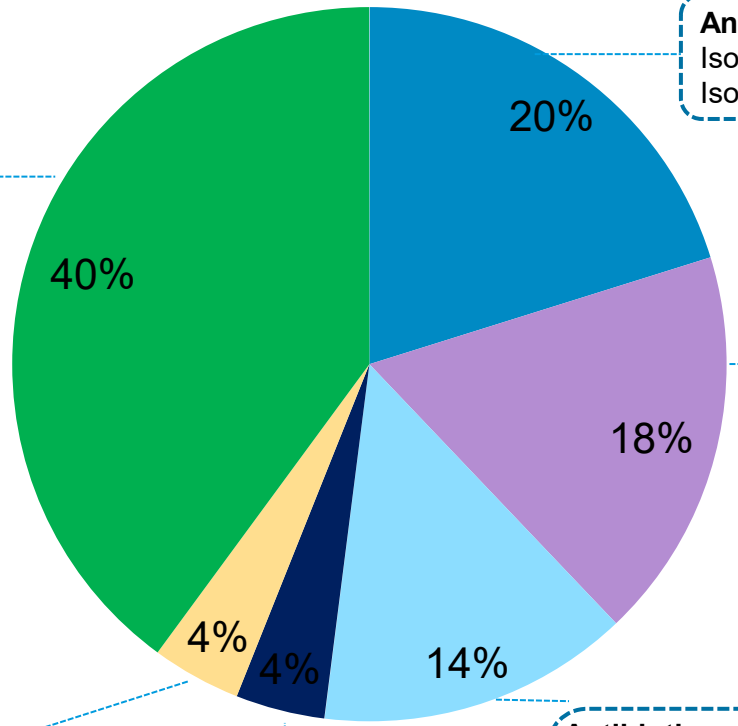
- Genetics:
  - Wilson disease
  - α1-antitrypsin deficiency
  - Galactosemia
  - Hemochromatosis
  - Tyrosinemia

- Others:
  - Pregnancy-related liver disease
  - Ischemic hepatitis
  - Autoimmune hepatitis
  - Malignant infiltration
  - Cryptogenic

Bernal et al. Lancet 2010; 376:190-201
Bernal et al. N Engl J Med 2013:369(26):2525-34
Wand DW et al. World J Gastroenterol 2013:19(41):7069-77
EASL CPG ALF. J Hepatol 2017;66:1047–81
Leise et al. Mayo Clin Proc. 2014;89(1):95-106.

Drugs Associated with Liver Injury and Failure

#1: Acetaminophen



Other drugs:
Propythiouracil (19)
Disulfiram (9)
Halothan (8)
Herbal (6)
Amitriptyline (2)
Nefazodone (2)
Methotrexate (5)
Troglitazone (4)
Methyldopa (5)
Mercaptopurine or Azathioprine (3)
Fialuridine (3)
Single case (33)

Anti-tuberculosis:
Isoniazid (48)
Isoniazid plus another anti-tuberculosis drug (2)

Anti-epileptics:
Phenytoin (20)
Valproate (20)
Carbamazepine (3)
Felbamate (1)

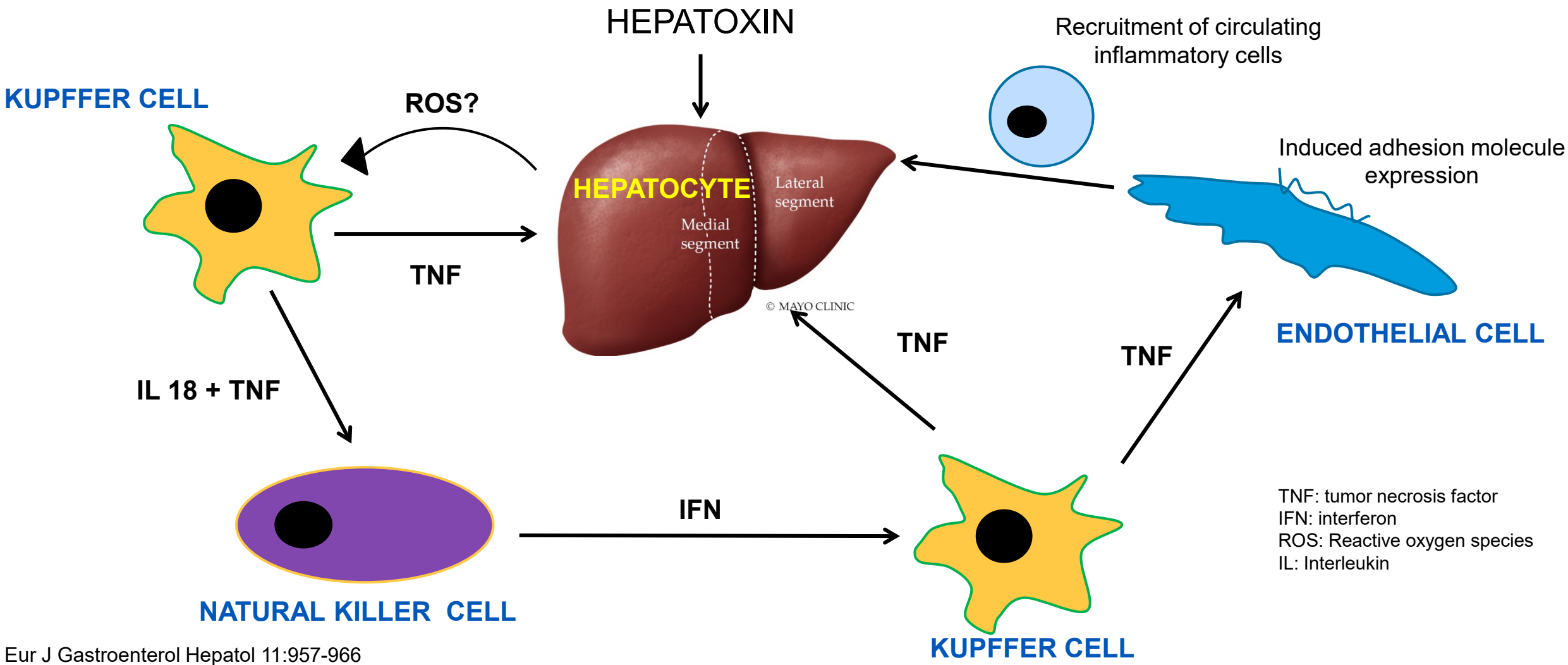
NSAIDs:
Diclofenac (3)
Bromfenac (2)
Ibuprofen (2)
Etodolac (1)
Naproxen (1)
Indometacin (1)

Statins:
Atorvastatin (3)
Cerivastatin (2)
Simvastatin (2)
Pravastatin (1)
Fluvastatin (1)
Ezetimibe (1)

Antibiotics:
Nitrofurantoin (12)
Ketoconazole (8)
Amoxicillin & clavulanate (5)
Trimethoprim-sulfamethoxazole (2)
Minocycline (2)
Terbinafine (1)
Ciprofloxacin (1)
Telithromycin (1)
Levofloxacin (1)
Itraconazole (1)
Moxifloxacin (1)

Bernal W et al. Lancet 2010; 376:190-201

Cytokine Production During Acute Liver Failure



Eur J Gastroenterol Hepatol 11:957-966

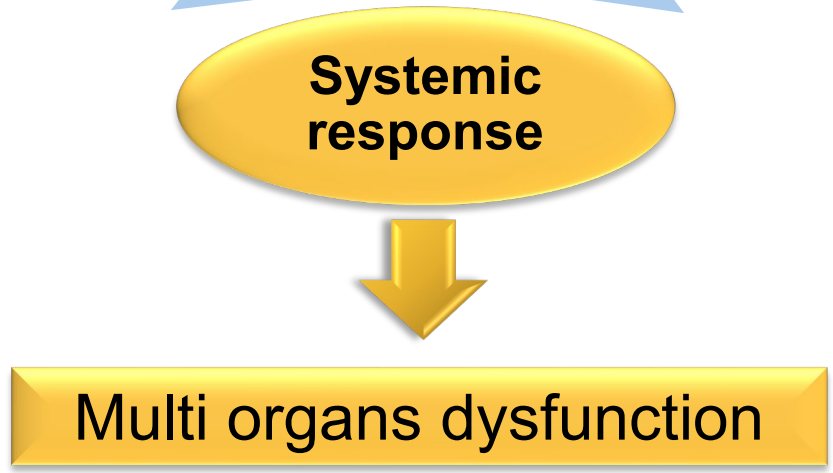
Inflammatory Factors and Toxins

Direct hepatic necrosis

- ⇩ Metabolic function
- ⇩ Gluconeogenesis
- ⇩ Clearance of lactate and ammonia
- ⇩ Synthetic capacity

Release of cytokine and toxin

- ⇧ Tumor necrosis factor (TNF-α)
- ⇧ Interleukin (IL)



Ann Med 2002;34:614-23
Chest 2000;117:1162-72
J Immunol 1985;135:3172-7
J Hepatol 2002:37:536-8

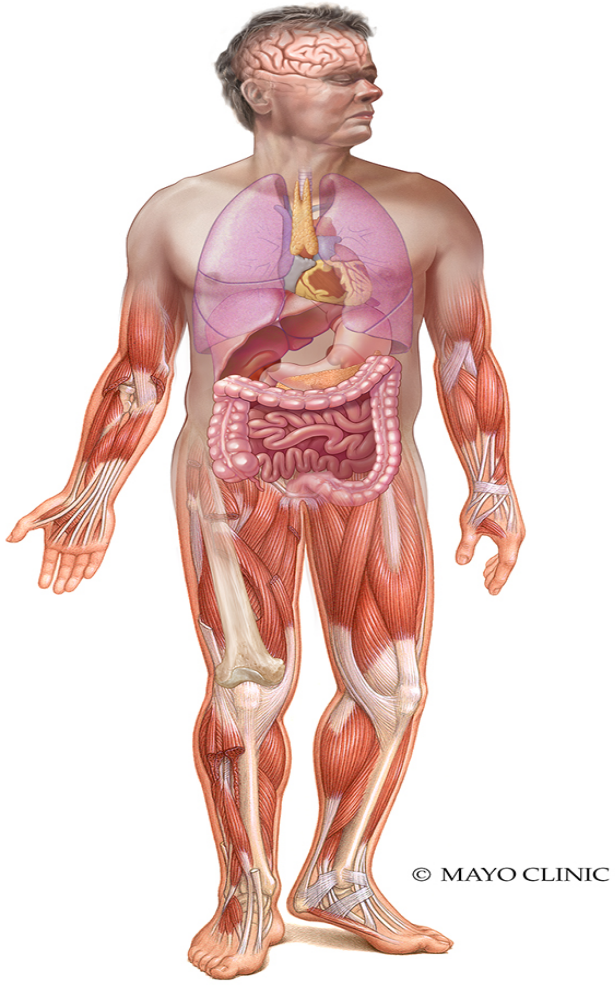
Clinical Features of Acute Liver Failure

Brain
Hepatic encephalopathy
Cerebral edema
Intracranial hypertension
Seizures

Liver
Loss of metabolic function
Hypoglycemia
Hyperammonemia
Coagulopathy
Lactic acidosis

Kidney and adrenals
Hepatorenal syndrome
Hepatoadrenal syndrome
Electrolyte abnormalities

Systemic
Systemic inflammatory response
Immunosuppression
High energy expenditure
Catabolic state



Heart
High output state
Subclinical myocardial injury
Hepatocardiac syndrome

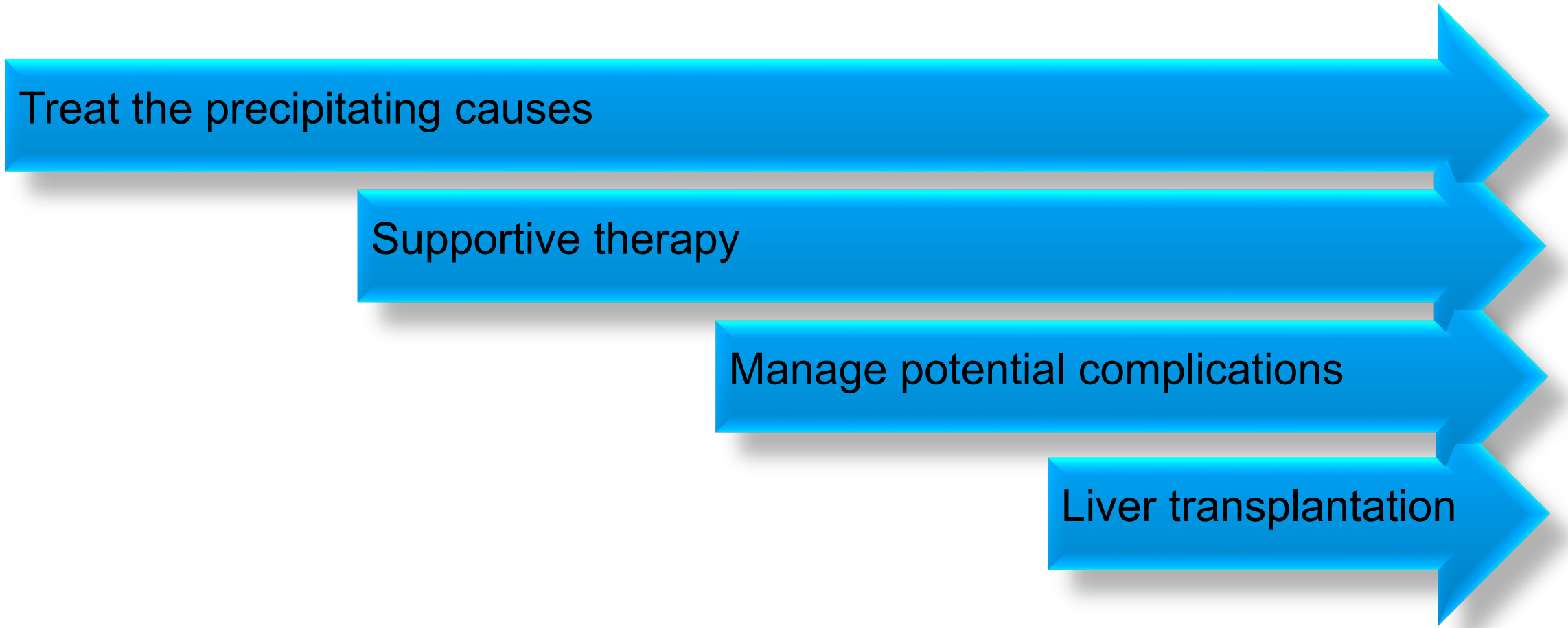
Lung
Acute lung injury
Acute respiratory distress syndrome
Hepatopulmonary syndrome

Pancreas
Pancreatitis

Bone marrow
Frequent suppression
Anemia
Thrombocytopenia

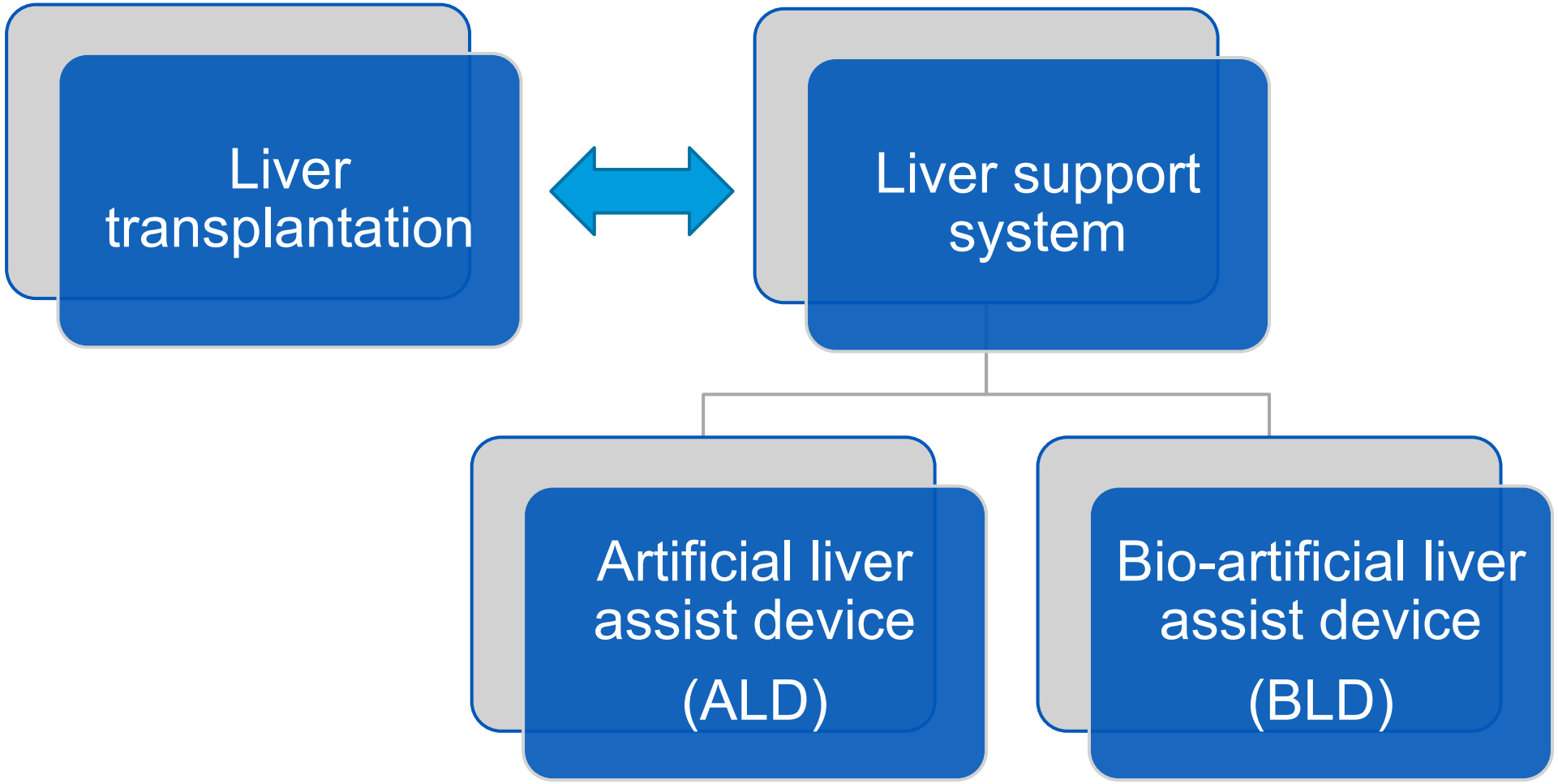
Bernal et al. N Engl J Med 2013:369(26):2525-34
Wand DW et al. World J Gastroenterol 2013:19(41):7069-77

Management of Acute Liver Failure



Lee W et al. Hepatology September 2011
Bernal et al. N Engl J Med 2013:369(26):2525-34

Liver Transplantation vs Liver Support System



Mandal AK et al. Liver Pathology
http://dx.doi.org/10.5772/intechopen.91287

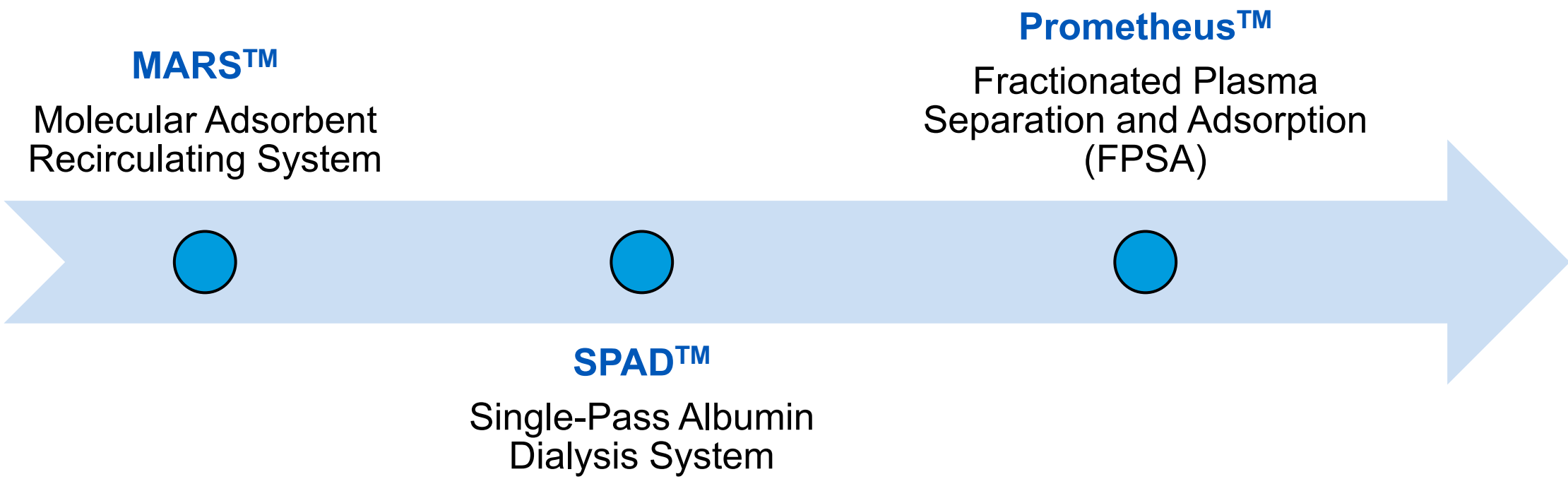
Question 1

- Which medication is the number one cause of drug-induced liver injury?
  - A. Isoniazid
  - B. Acetaminophen
  - C. Statin
  - D. Phenytoin

Objective

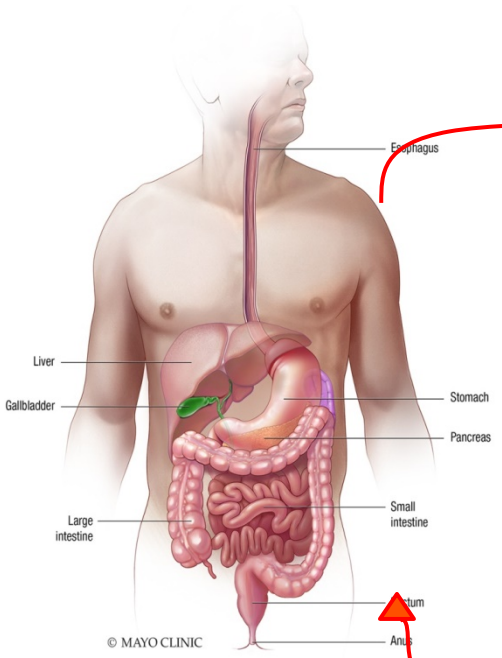
2. **Describe the mechanism of MARS™ (Molecular Adsorbent Recirculating System)**

Albumin Dialysis Concept-Based Systems



Mandal AK et al. Liver Pathology
http://dx.doi.org/10.5772/intechopen.91287

Mechanism of MARS™



MARS membrane

100 g of albumin
150-250 ml/min
Albumin dialysate

Dialysis membrane

Blood from patient

Blood to patient

Anion exchange resin

Activated charcoal

Haemofiltration/
Haemodialysis
Circuit
150-250 ml/min

Blood plasma

Albumin with toxin bound

Binding sites on MARS membrane

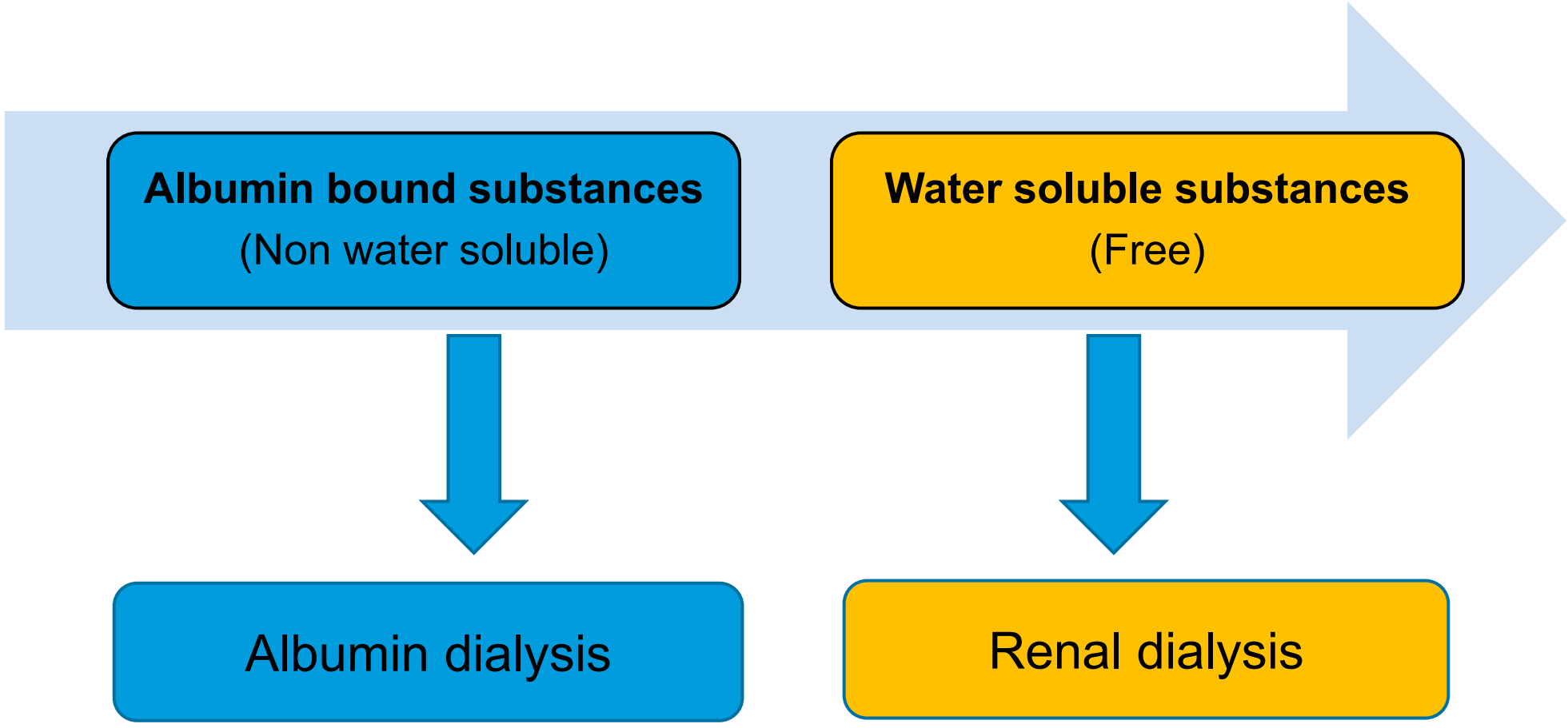
Albumin

Toxin

Albumin dialysate

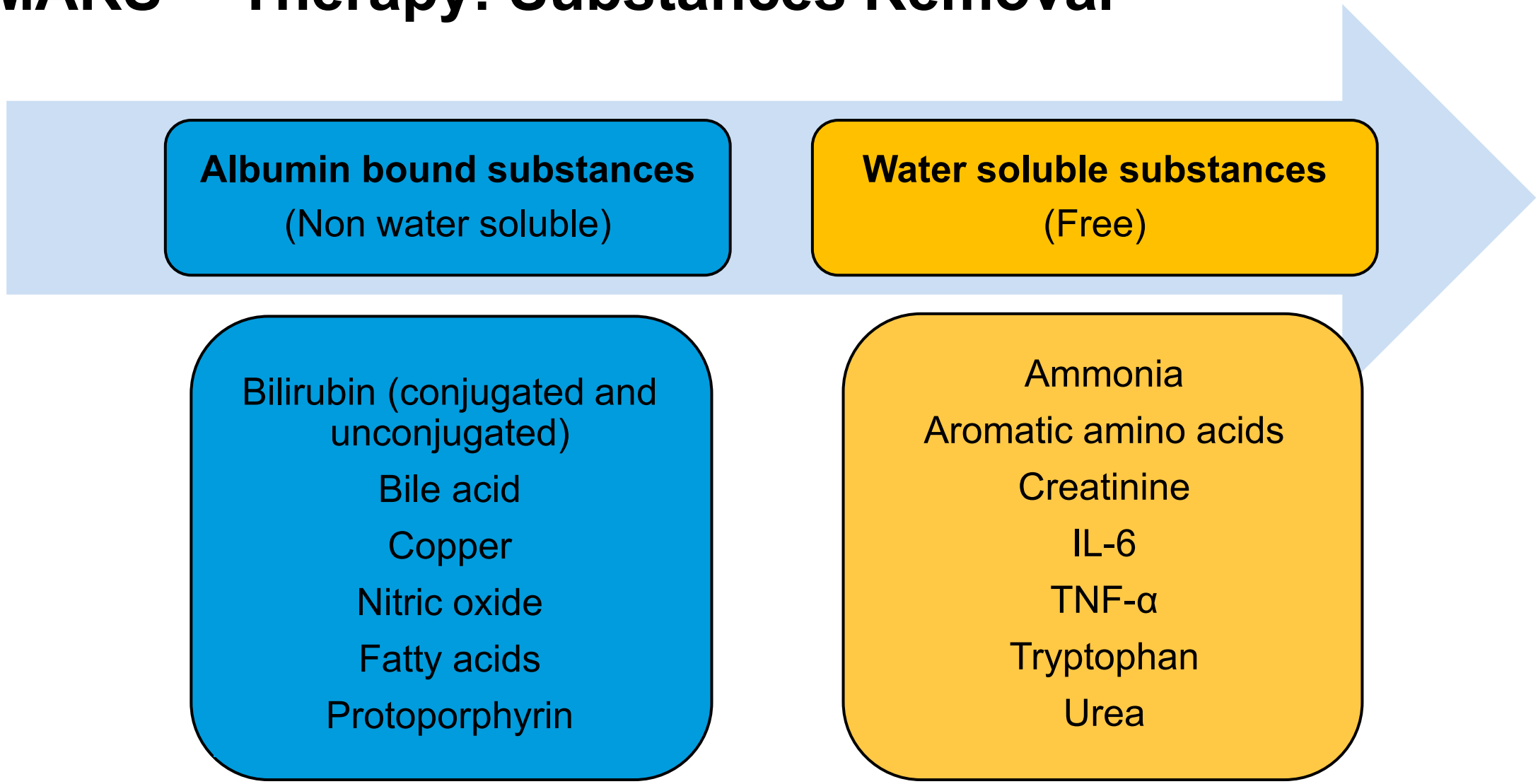
Inter J of Biochemistry & Cell Biology 35 (2003) 1306-1311
GAMBRO Renal products, Traditional 510 (k) for MARS ® - 2012

MARS™ Therapy: Substances Removal



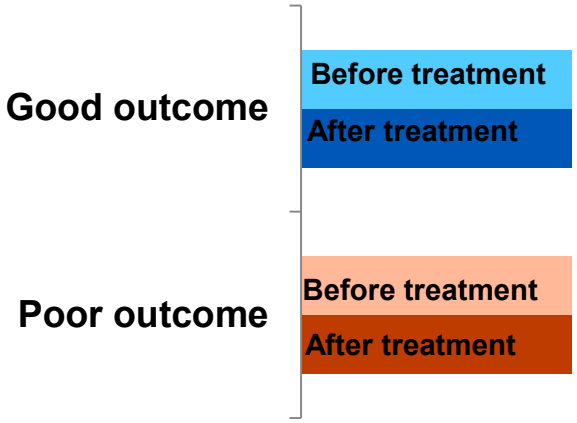
Steffen R. Mitzner et al. ASAIO Journal 2009;55:498-502
Inter J of Biochemistry & Cell Biology 35 (2003) 1306-1311
GAMBRO Renal products, Traditional 510 (k) for MARS ® - 2012

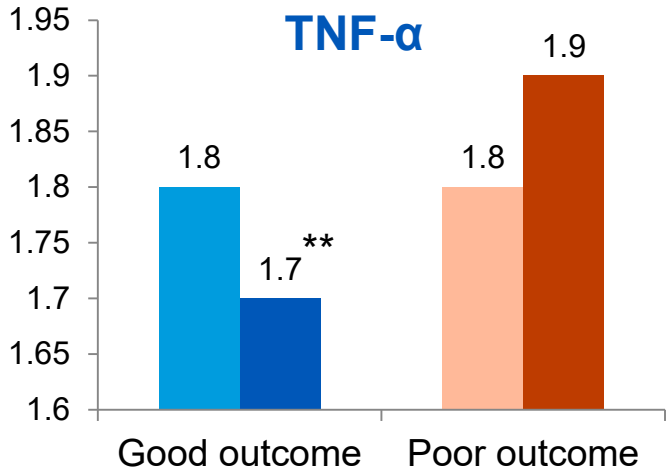
MARS™ Therapy: Substances Removal

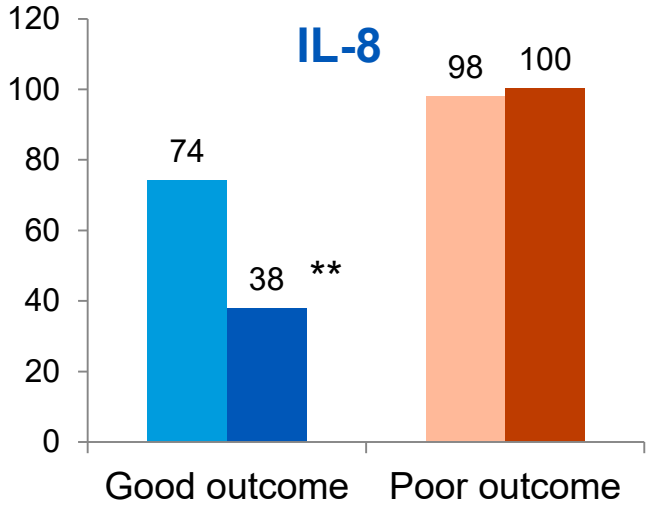


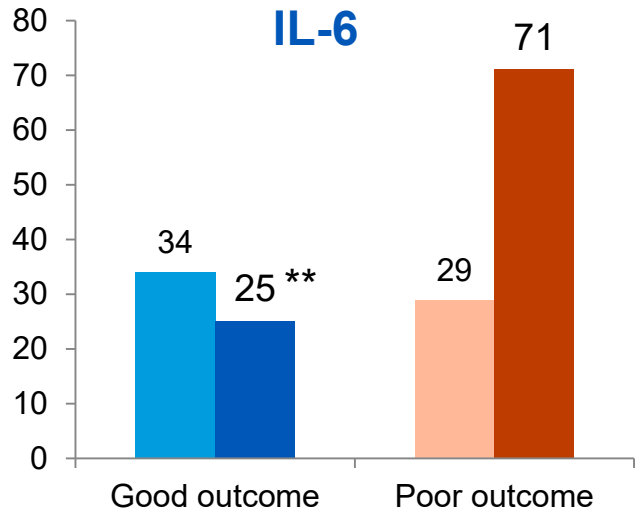
Steffen R. Mitzner et al. ASAIO Journal 2009;55:498-502
Inter J of Biochemistry & Cell Biology 35 (2003) 1306-1311
GAMBRO Renal products, Traditional 510 (k) for MARS ® - 2012

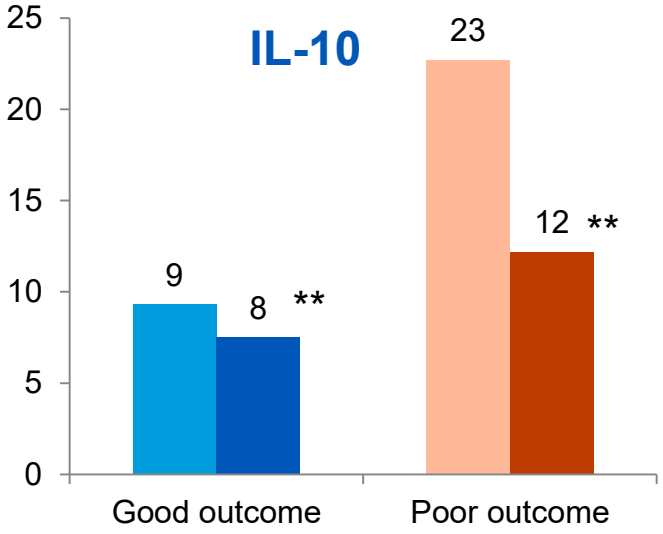
Cytokines Reduction Associated with Good Outcome

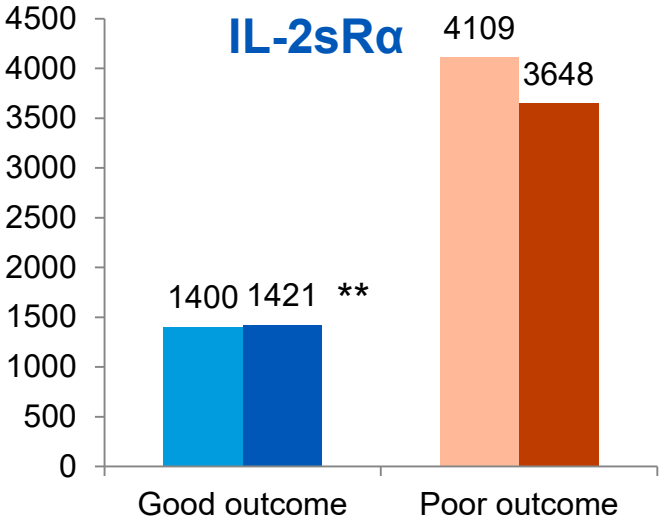












Ilonen I et al. Artificial Organs 32(1):52-60

MARS™ Indications

- **Drug overdose and poisonings**
  - Dialyzable (in unbound form) and bound by charcoal and/or ion exchange resins
- **Hepatic encephalopathy due to decompensation of a chronic liver disease**

Steffen R. Mitzner et al. ASAIO Journal 2009;55:498-502
Inter J of Biochemistry & Cell Biology 35 (2003) 1306-1311
GAMBRO Renal products, Traditional 510 (k) for MARS ® - 2012

Suggested Indications of MARS™

- Acute decompensation on chronic liver disease
  - Complicated by progression jaundice, hepatic encephalopathy, renal dysfunction
- Intractable pruritus in cholestasis
- Liver failure secondary to graft dysfunction
- Post-transplant or post-surgical liver failure
- Bridge to liver transplantation

Saliba et al. Critical Care 2006: 10(10):186-9

Early Experience with MARS™

- Improvement in hemodynamic parameters
- Usefulness in the treatment of hepatic encephalopathy
- Successful case studies in the treatment for poison-induced liver injury
- Benefits in drug-induced liver injury cases

Heemann U et al. Hepatology 2002;36:949-958
Sen S et al. Liver Transplantation. 2004;10(9):1109-1119
Hanish SI et al. 2017;266(4):677-684
Eapen J et al. Oxford case reports. 2018;2018(1):omx077
Ostapowicz G et al. Annals of Internal Medicine. 2002;137(12):947-954
Leise et al. *Mayo Clin Proc*. 2014;89(2):241-253.

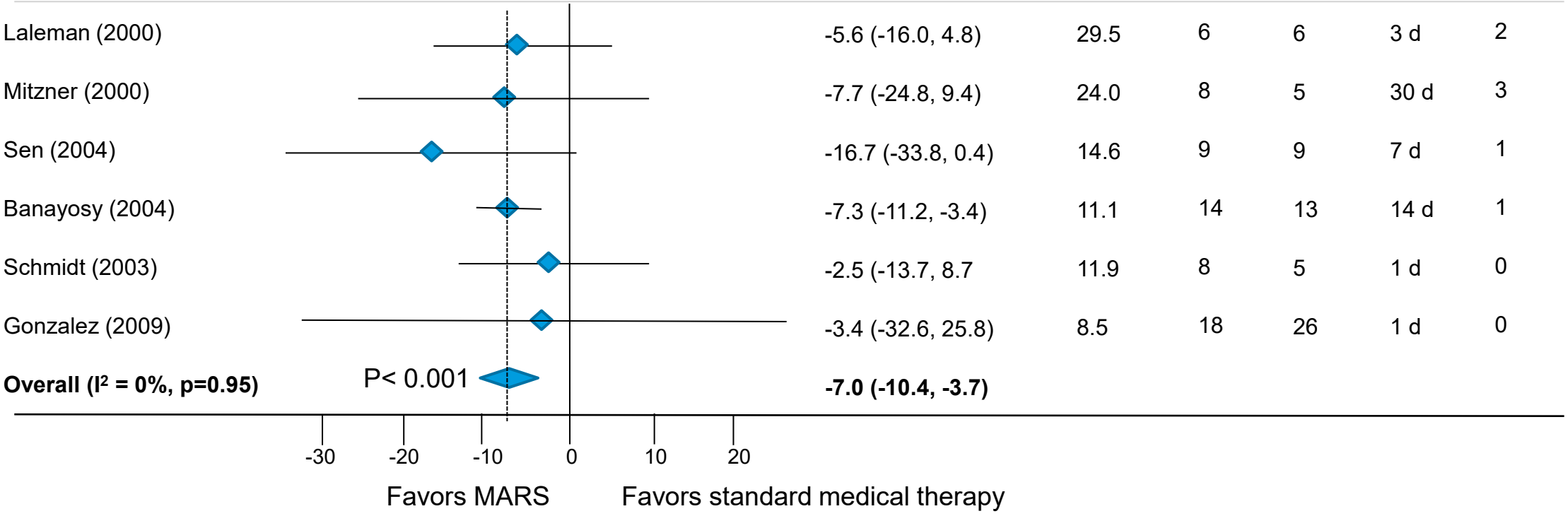
MARS™ Therapy for Liver Failure
Meta-Analysis

Author	Year	Study period	Etiology of liver failure	No of Patients	Age (years)
Mitzner	2000	30 days	Alcoholic/viral hepatitis	13	47
Heemann	2002	30 days	Alcoholic	24	52
Schmidt	2003	1 day	Predominant acetaminophen toxicity	13	42
Sen	2004	7 days	Alcoholic/viral hepatitis	18	45
Banayosy	2004	14 days	Cardiogenic shock	27	63
Laleman	2006	3 days	Alcoholic liver disease	12	56
Hassanein	2007	5 days	Alcoholic/viral hepatitis	70	51
Gonzalez	2009	1 day	NR	45	48
Hessel	2010	3 years	Predominant alcoholic liver disease	149	49
Banarest	2010	28 days	NR	189 (pp-156)	NA

Vaid A et al. ASAIO Journal 2012;58:51-59

MARS™ Therapy for Liver Failure
Meta-Analysis

Net change in total bilirubin levels

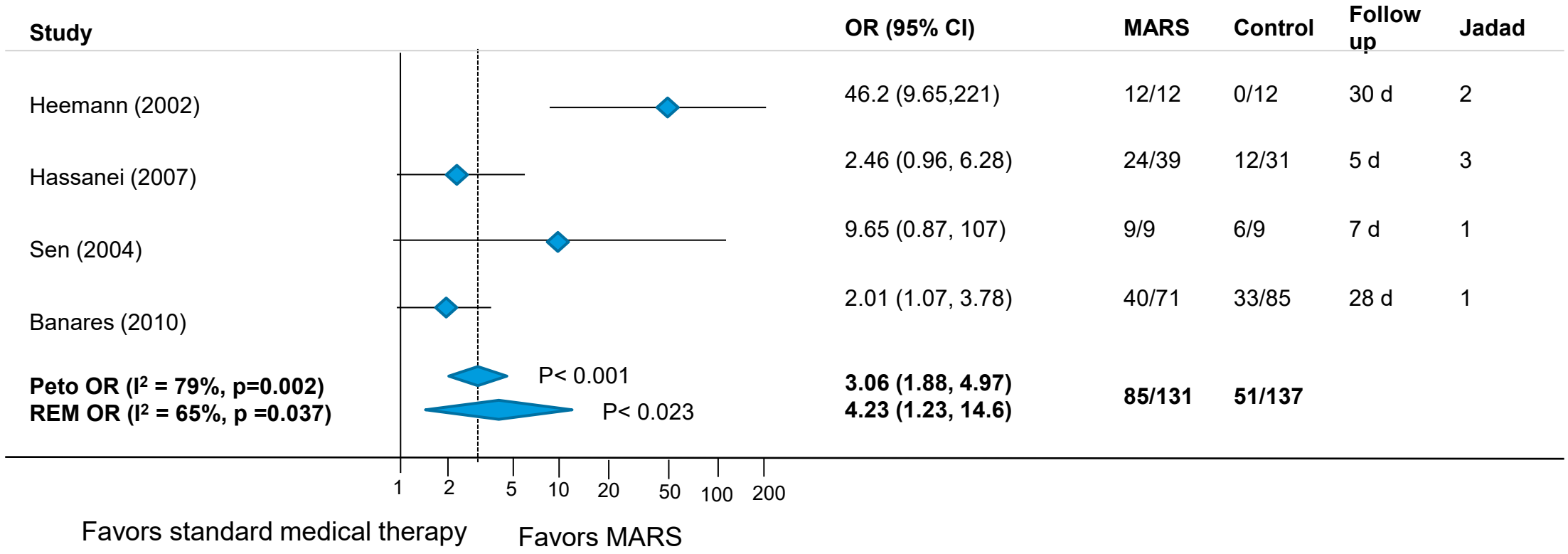


Study	Net change (95% CI)	Total bilirubin	N MARS	N Control	Follow up	Jadad
Laleman (2000)	-5.6 (-16.0, 4.8)	29.5	6	6	3 d	2
Mitzner (2000)	-7.7 (-24.8, 9.4)	24.0	8	5	30 d	3
Sen (2004)	-16.7 (-33.8, 0.4)	14.6	9	9	7 d	1
Banayosy (2004)	-7.3 (-11.2, -3.4)	11.1	14	13	14 d	1
Schmidt (2003)	-2.5 (-13.7, 8.7	11.9	8	5	1 d	0
Gonzalez (2009)	-3.4 (-32.6, 25.8)	8.5	18	26	1 d	0
Overall (I^2 = 0%, p=0.95)	**-7.0 (-10.4, -3.7)**					

Vaid A et al. ASAIO Journal 2012;58:51-59

MARS™ Therapy for Liver Failure
Meta-Analysis

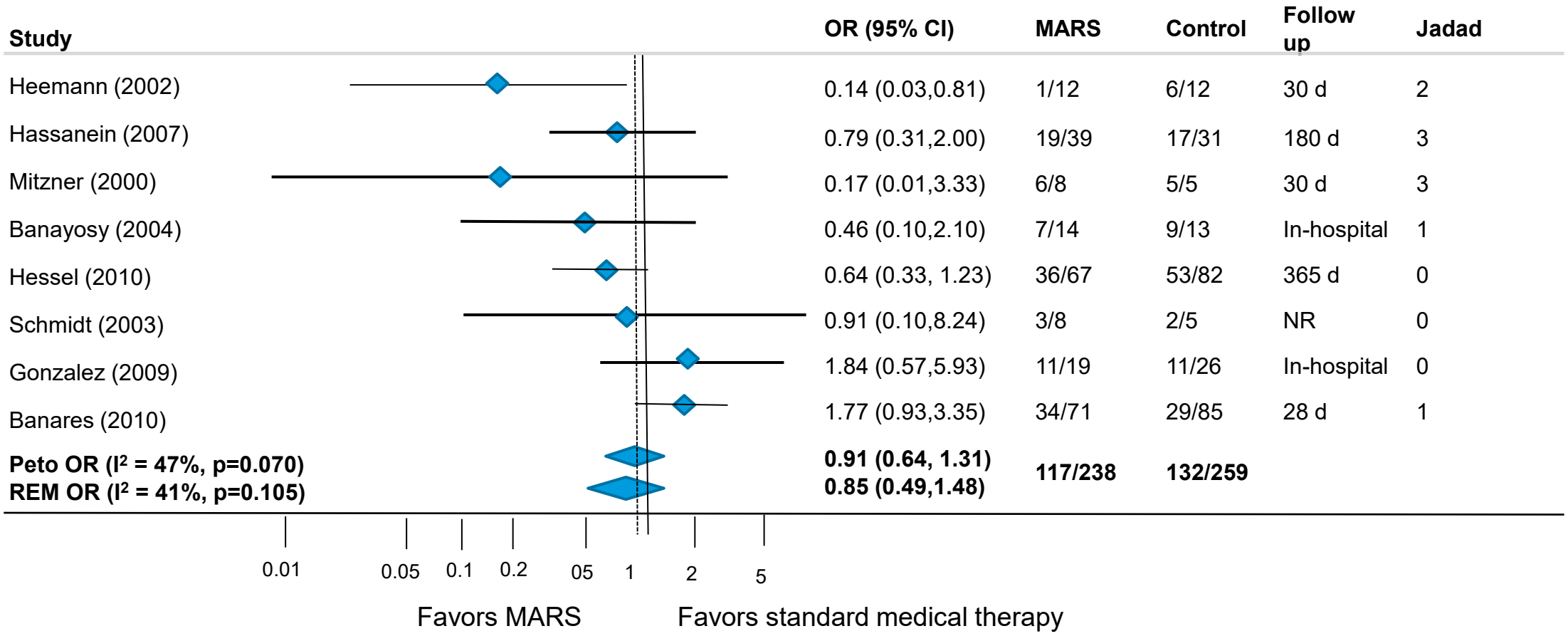
Improvement in hepatic encephalopathy



Vaid A et al. ASAIO Journal 2012;58:51-59

MARS™ Therapy for Liver Failure
Meta-Analysis

Reduction in mortality



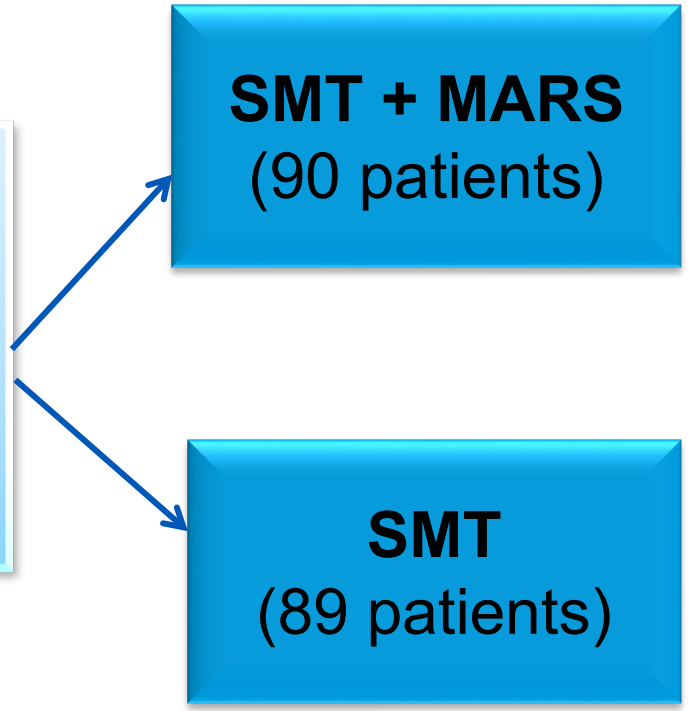
Vaid A et al. ASAIO Journal 2012;58:51-59

RELIEF Trial
MARS™ in Acute-on-Chronic Liver Failure

Prospective randomized controlled trials

19 hospitals in Europe

- Acutely decompensated cirrhosis
- Serum bilirubin > 5 mg/dL
- And at least one:
  - Hepatorenal syndrome
  - Hepatic encephalopathy ≥ grade II
  - Rapidly progressive hyperbilirubinemia



MARS therapy

- First 4 days: 1 session/day followed by 3 sessions/week until sustained improvement
- Maximum: 10 sessions/21 days

SMT: Standard medical therapy

Rafael B et al. Hepatology 2013:57:1153-1162

RELIEF Trial

MARS™ Improved Laboratory Parameters….

Percentage of change from baseline value in intention-to-treat population

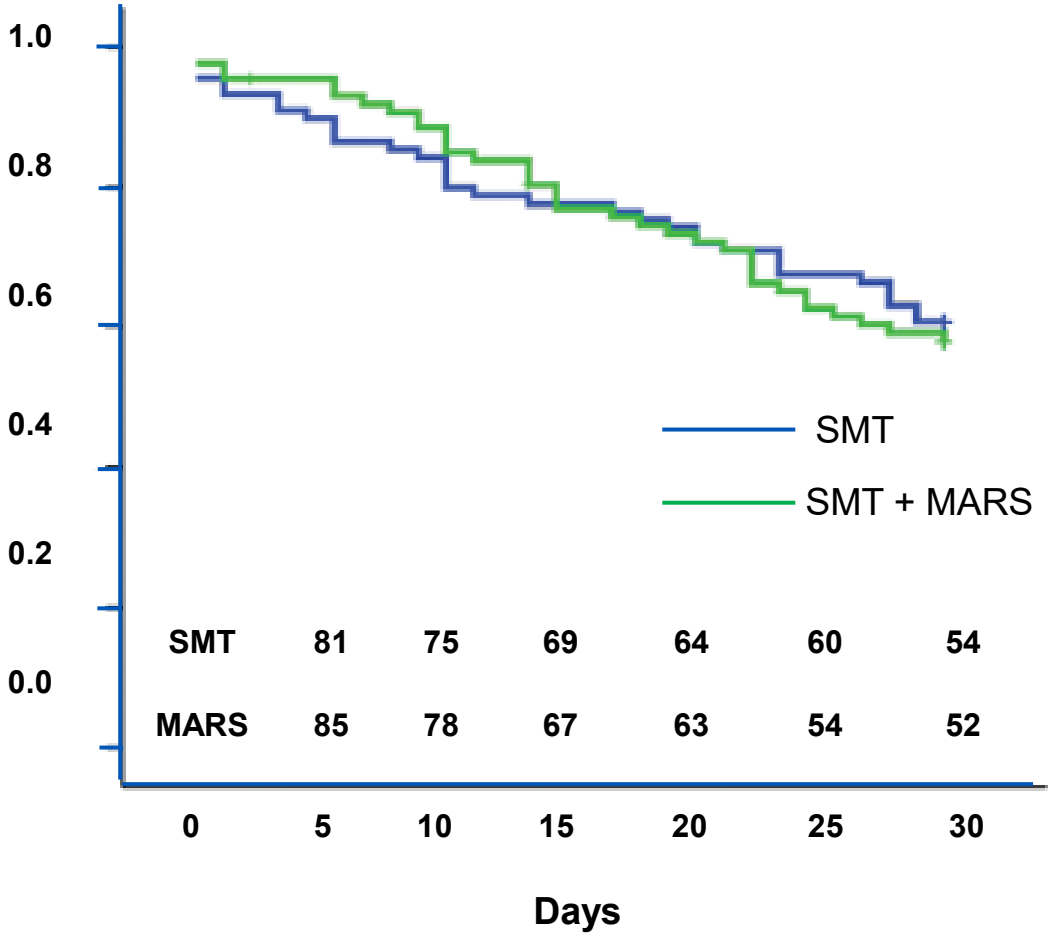
Laboratory Parameters	MARS + SMT	SMT	P value
Bilirubin (mg/dL)	-26.4	-8.92	<0.001
Creatinine (mg/dL)	-20.04	-6.43	0.022
Serum sodium (mEq/L)	2.94	1.44	0.081
Albumin (g/L)	7.83	5.67	0.587
INR	0.00	6.38	0.098
Hemoglobin (g/dL)	-7.16	0.15	0.009
Platelet (*10^3/mm^3)	-29.06	-1.80	<0.001

SMT: Standard Medical Therapy

Rafael B et al. Hepatology 2013:57:1153-1162

RELIEF Trial

…But Did Not Improve 28-day Survival



Survival analysis according to predetermined subgroups

ITT Population Subgroup	MARS + SMT (n, %)	SMT (n, %)	P value
Hepatorenal syndrome	25/48 (52%)	25/47 (53%)	0.914
HE ≥ grade II	16/32 (50%)	19/39 (49%)	0.896
Progressive hyperbilirubinemia	21/57 (37%)	19/62 (31%)	0.475
MELD > 20	30/71 (42%)	29/62 (47%)	0.601

ITT: intention-to-treat
HE: Hepatic encephalopathy
MELD: Model for End-Stage Liver Disease
SMT: Standard Medical Therapy

Rafael B et al. Hepatology 2013:57:1153-1162

MARS™ Therapy – Adverse Events and Monitoring

- Hypotension
- Renal dysfunction
- Electrolyte imbalances
- Decrease platelets
- Bleeding
- Inadequate removal of toxin

Steffen R. Mitzner et al. ASAIO Journal 2009;55:498-502
Inter J of Biochemistry & Cell Biology 35 (2003) 1306-1311
GAMBRO Renal products, Traditional 510 (k) for MARS ® - 2012

Question

In RELIEF trial, for patients with acute on chronic liver failure, MARS™ therapy was proven to improve:

A. Significantly reduced serum bilirubin

B. Significantly reduced serum creatinine

C. Improve 28-days survival among patients with encephalopathy

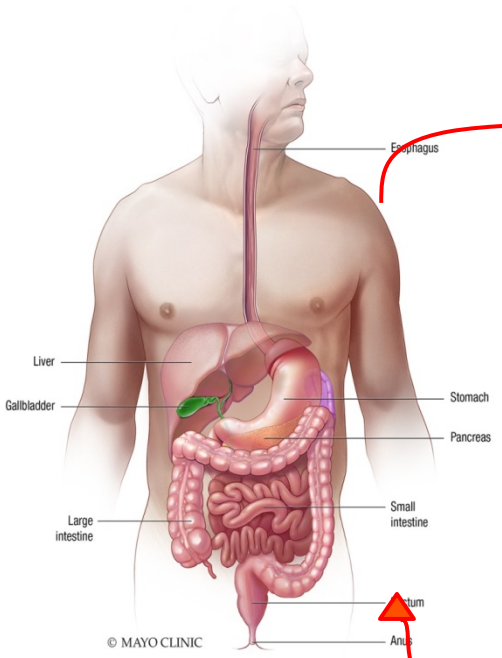
D. A&B

E. All of the above

Objective

3. Discuss the pharmacokinetic changes of medications affected by MARS^{TM} and the clinically relevant implications

Mechanism of MARS™



MARS membrane

100 g of albumin
150-250 ml/min
Albumin dialysate

Dialysis membrane

Blood from patient

Blood to patient

Anion exchange resin

Activated charcoal

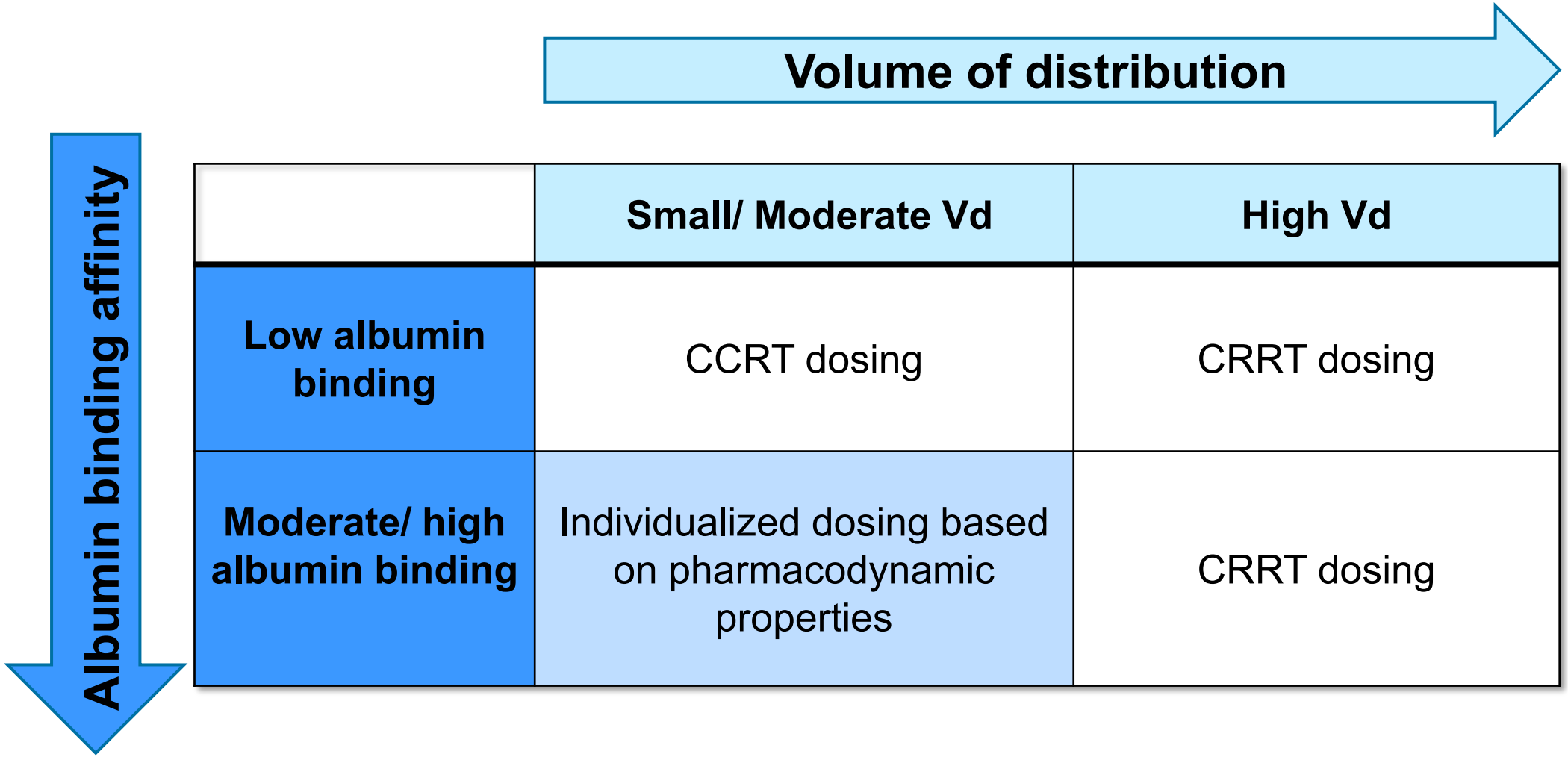
Haemofiltration/
Haemodialysis
Circuit
150-250 ml/min

Albumin binding affinity

Volume of distribution

Inter J of Biochemistry & Cell Biology 35 (2003) 1306-1311
GAMBRO Renal products, Traditional 510 (k) for MARS ® - 2012

Medication Dosing Strategy in MARS™



	Small/ Moderate Vd	High Vd
Low albumin binding	CCRT dosing	CRRT dosing
Moderate/ high albumin binding	Individualized dosing based on pharmacodynamic properties	CRRT dosing

Maicher-Peszynska J, et al. *Z Gastroenterol.* 2001;39 (Suppl 2):33-35.

Medication Dosing Strategy in MARS™ Consideration for Antimicrobials

	Small/ Moderate Vd	High Vd
Low albumin binding	CCRT dosing	CRRT dosing
Moderate/ high albumin binding	Individualized dosing based on pharmacodynamic properties	CRRT dosing

Antimicrobial Pharmacodynamic Property	Dosing Considerations
T > MIC	Re-dose during albumin dialysis Continuous infusions/extended infusion Increase frequency Bolus dose prior to MARS
AUC/MIC	Increase dose and frequency
Cmax/MIC	Increase dose

Drug Dosing in Albumin Dialysis with MARS™ Selected Antimicrobials

Protein binding		
High (> 70%)	Moderate (31-69%)	Low (≤ 30%)
Ceftriaxone Daptomycin Micafungin **Anidulafungin** Rifampin Gentamicin	Aztreonam **Levofloxacin** Vancomycin Trimethoprim/ Sulfamethoxazole	Cefepime Fluconazole Ganciclovir Linezolid **Meropenem** **Piperacillin/Tazobactam**

Prescribing information
Micromedex

Drug Dosing in Albumin Dialysis with MARS® Ceftriaxone

Protein binding	Vd	CRRT dosing	Consideration for MARS dosing
HIGH 85 -95%	LOW 0.3 L/kg	No change	Bolus dose prior to MARS

Ceftriaxone concentration change during 6 hours	
Conventional CVVHD	MARS dialysis
⇩ (20%) from 117.3 to 94.4 mg/L	⇩ (71%) from 119.2 to 34.9 mg/L

Maicher-Peszynska J, et al. Z Gastroenterol. 2001;39 (Suppl 2):33-35
Micromedex.
Mayo Clinic CCRT Dosing Guideline

Drug Dosing in Albumin Dialysis with MARS® Levofloxacin

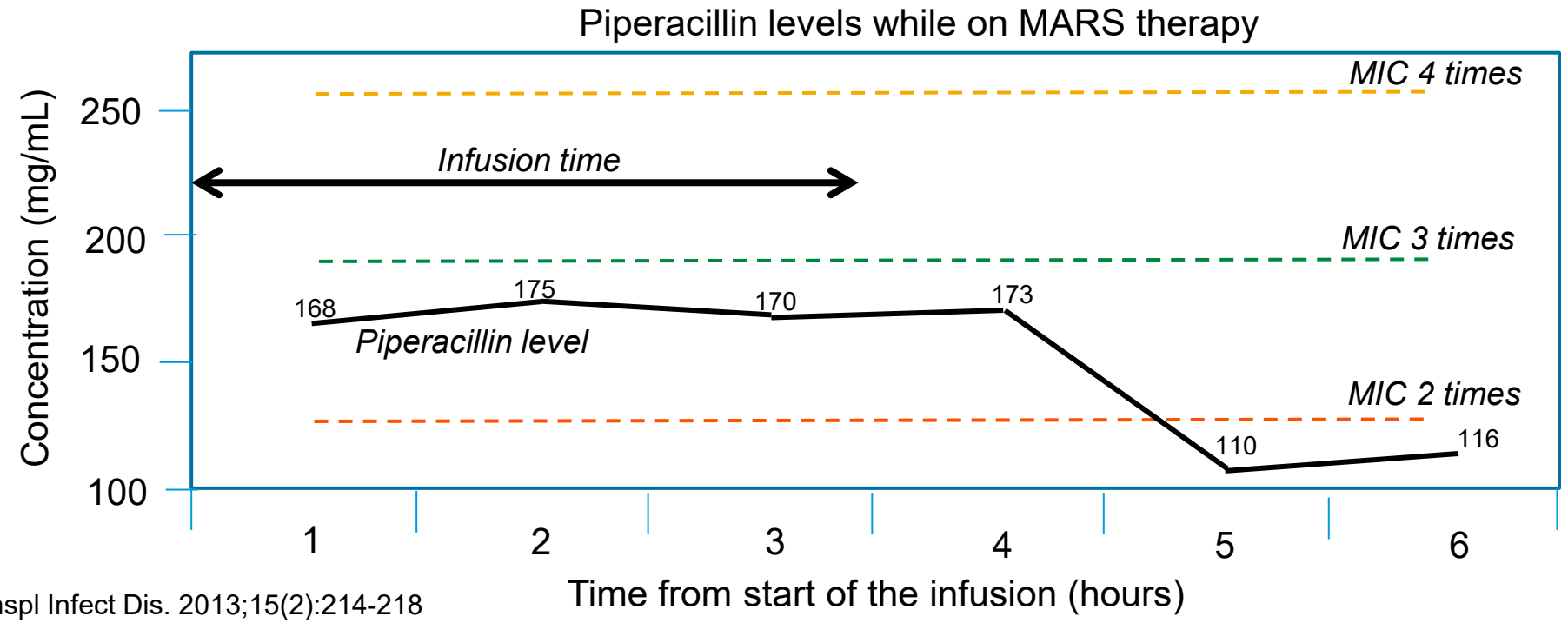
Protein binding	Vd	CRRT dosing	Consideration for MARS dosing
LOW/MODERATE 24-38%	MODERATE 0.8 L/kg	250-750 mg Q24h	Cmax/MIC Bolus dose prior to MARS Re-dose after MARS

Levofloxacin concentration change during 6 hours	
Conventional CVVHD	MARS dialysis
⇩ **(99.3%)** from 7.7 to 0.05 mg/L	⇩ **(99.3%)** from 7.02 to 0.05 mg/L
Level 0.05 mg/L by **180-240 min**	Level 0.05 mg/L by **30 min**

Maicher-Peszynska J, et al. Z Gastroenterol. 2001;39 (Suppl 2):33-35
Bellmann R. Artif Organs. 2003;26(4):358-259
Micromedex
Mayo Clinic CCRT Dosing Guideline

Drug Dosing in Albumin Dialysis with MARS® Piperacillin-Tazobactam

Protein binding	Vd	CRRT dosing	Consideration for MARS dosing
LOW 30%	SMALL 10-16L	3.375 g Q6h or 4.5 g Q8h	Increase frequency?

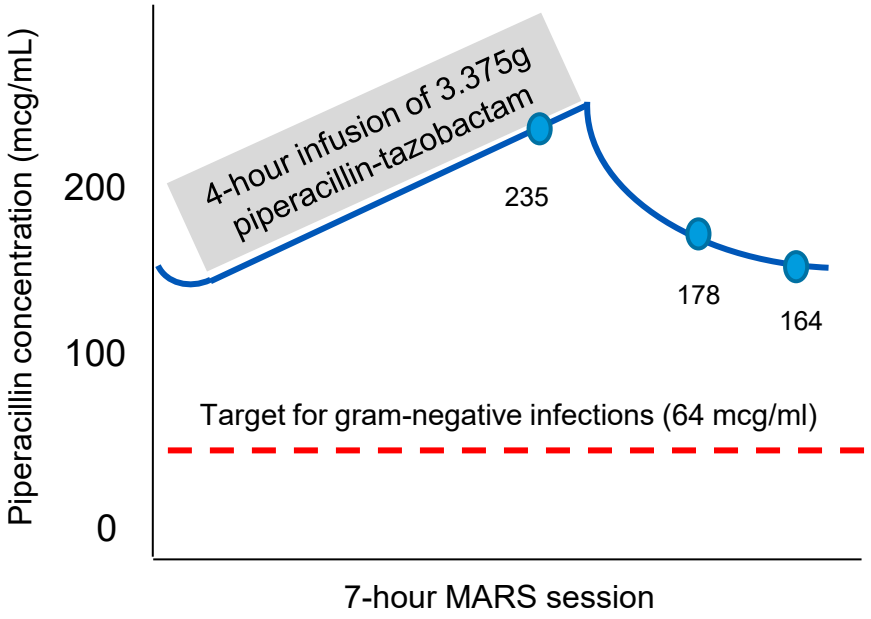


Ruggero, et al. Transpl Infect Dis. 2013;15(2):214-218
Micromedex
Mayo Clinic CCRT Dosing Guideline

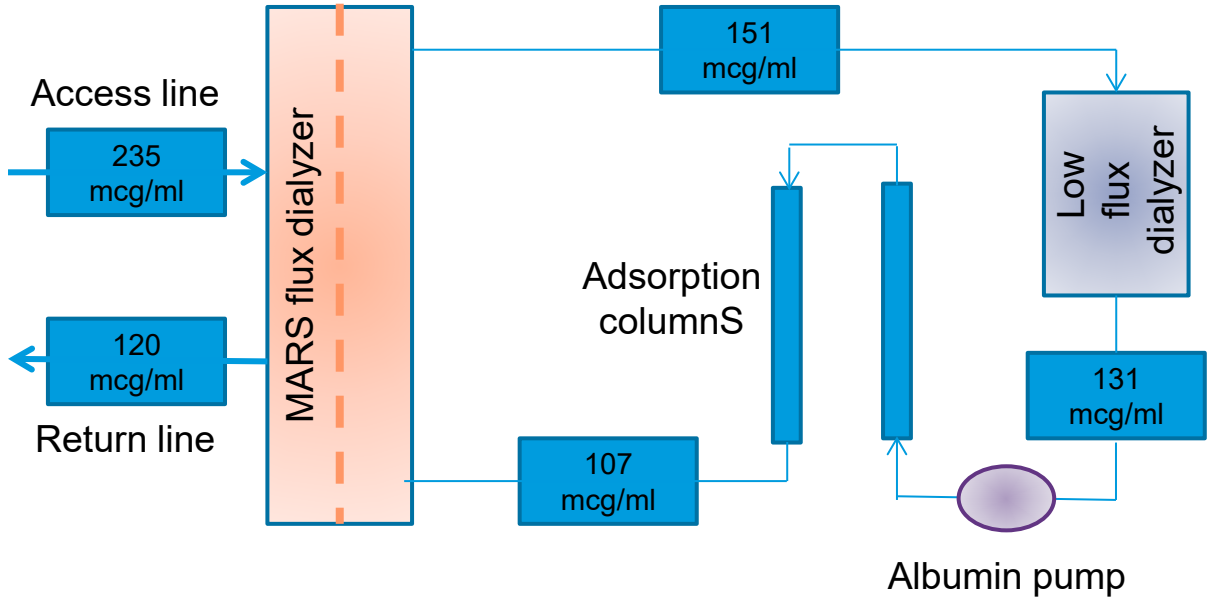
Drug Dosing in Albumin Dialysis with MARS® Piperacillin-Tazobactam

Protein binding	Vd	CRRT dosing	Consideration for MARS dosing
LOW 30%	SMALL 10-16L	3.375 g Q6h or 4.5 g Q8h	Extended infusion Frequency Q6-Q8h

Patient 1



Patient 2



Personett H et al. Pharmacotherapy 2015;35(8):e136-e139
Micromedex
Mayo Clinic CCRT Dosing Guideline

Drug Dosing in Albumin Dialysis with MARS® Meropenem

Protein binding	Vd	CRRT dosing	Consideration for MARS dosing
LOW 2%	SMALL 12-20 L	1g Q8-Q12h	Increase dose Extended infusion?

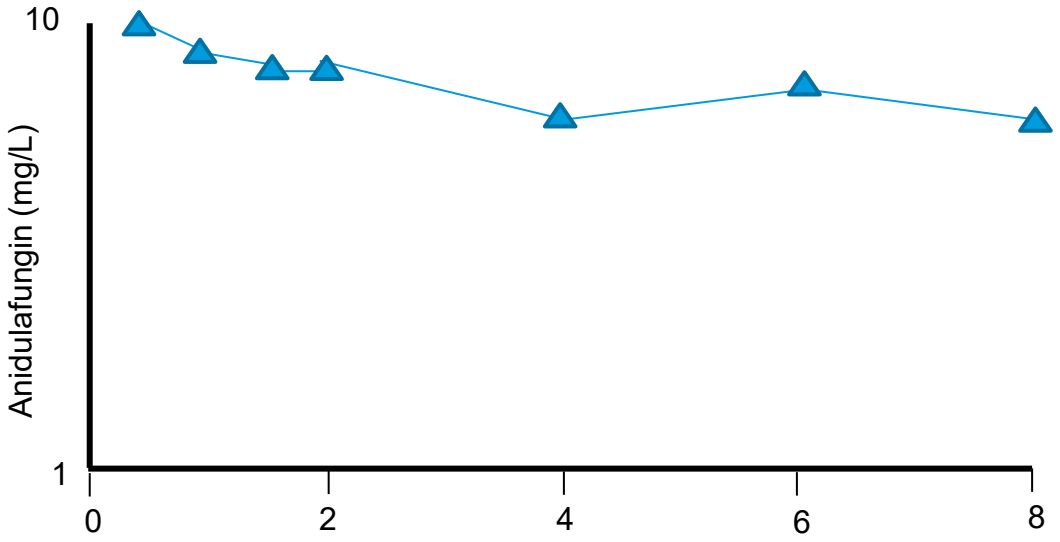
- Model: Meropenem LD 1g, followed by 2g IV over 8hr Q8h
- Meropenem concentration in the return line after MARS constantly lower than in the access line
- Charcoal removed the majority of meropenem

Removal of meropenem in the mock MARS circuit after initiation	
MARS flux dialyzer	50.43%
Low-flux dialyzer	20.49%
Activated charcoal	23.81%
Anion exchanger	3.89%
Total removal	98.62%

Roth GA, et al. *Acta Anaesthesiol* Scand. 2013;57(4):461-7
Micromedex
Mayo Clinic CRRT Dosing Guideline

Drug Dosing in Albumin Dialysis with MARS® Anidulafungin

Protein binding	Vd	CRRT dosing	Consideration for MARS dosing
HIGH >99%	SMALL 30-50L	No change	Cmax/MIC Dose after MARS session



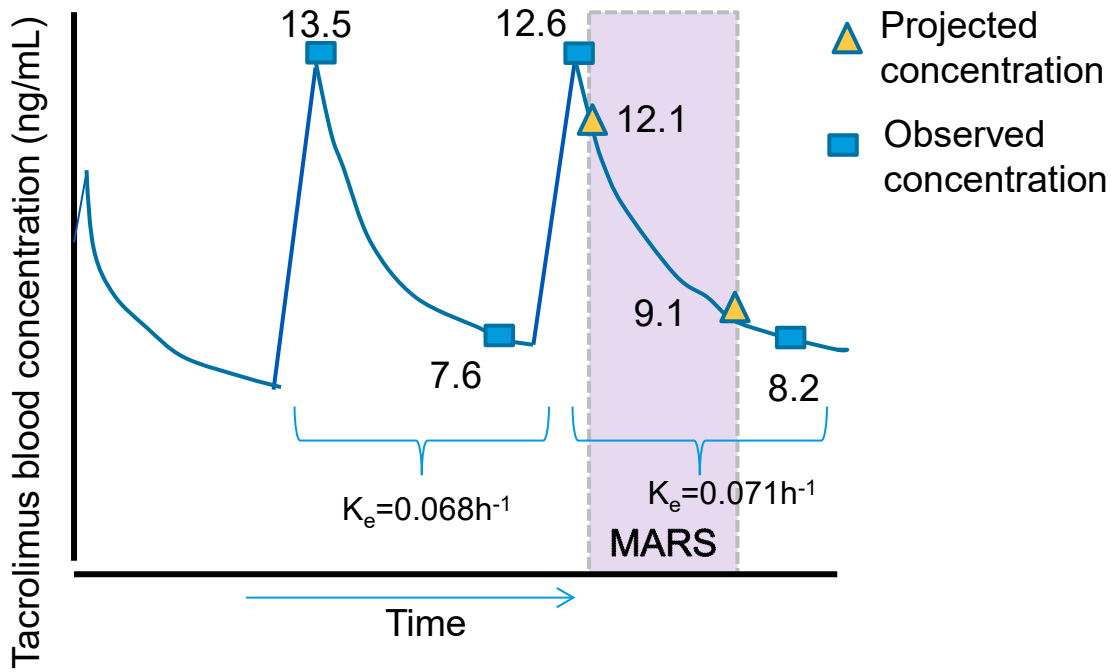
Peak plasma concentration with 100 mg dose on day 4	9.45 mg/L
AUC from 0-8 hours	53.7 hours*mg/L
T1/2	17.81 hr

Roth GA, et al. *Acta Anaesthesiol* Scand. 2013;57(4):461-7
Micromedex

Drug Dosing in Albumin Dialysis with MARS® Tacrolimus

Protein binding	Vd	CRRT dosing	Consideration for MARS dosing
HIGH 99%	LOW-MODERATE 0.85 -1.41 L/kg	Level monitoring	Dose adjustment based on drug level

Tacrolimus trough level			
Days from MARS	Morning dose (mg)	Evening dose (mg)	Whole blood trough (ng/mL)
0	3	3	7.2
1	4.5	3	8.6
2	3	3	7.6
3	3	3	8.0
5	3	3	7.9
7	3	3	7.0
8	3	3	7.7
9	3	3	8.6
10	3	3	7.4



Personett H. et al. Transplantation Proceedings,46,2440-2442 (2014)
Micromedex

Individualized Medication Dosing Strategy in MARS™

Mechanism	Problems	Suggested Approach
High protein bound medications removed by MARS	No recommended dosing strategy	• Alternative with low protein binding, providing same therapeutic efficacy
MARS runs 6-8 hours per session for 3-5 days, with the transition to CRRT in the between sessions	Intermittent dosing strategy between MARS and CRRT	When MARS is off: • Dose adjustment follows CRRT • Administer non-critical medication
High ultrafiltration rates and/or dialysis flow rate	Extra drug removal by MARS/ dialysis	• Dose adjustment • Monitor clinical response
Longer MARS run	Extra drug removal by MARS	
Patient with residual renal function	Extra drug removal by kidney	

Question

What factors would you consider when adjust medication dosing during MARS™ therapy?

A. Protein binding affinity

B. Volume of distribution

C. Individualized strategy

D. Clinical response

E. All of the above

Conclusions

- Challenge in management for patients with liver failure
- Liver support system as one of treatment modality
- MARS™ with proven benefits for symptomatic improvement
- Individualized strategy approach for medication dosing for patients treated with MARS™

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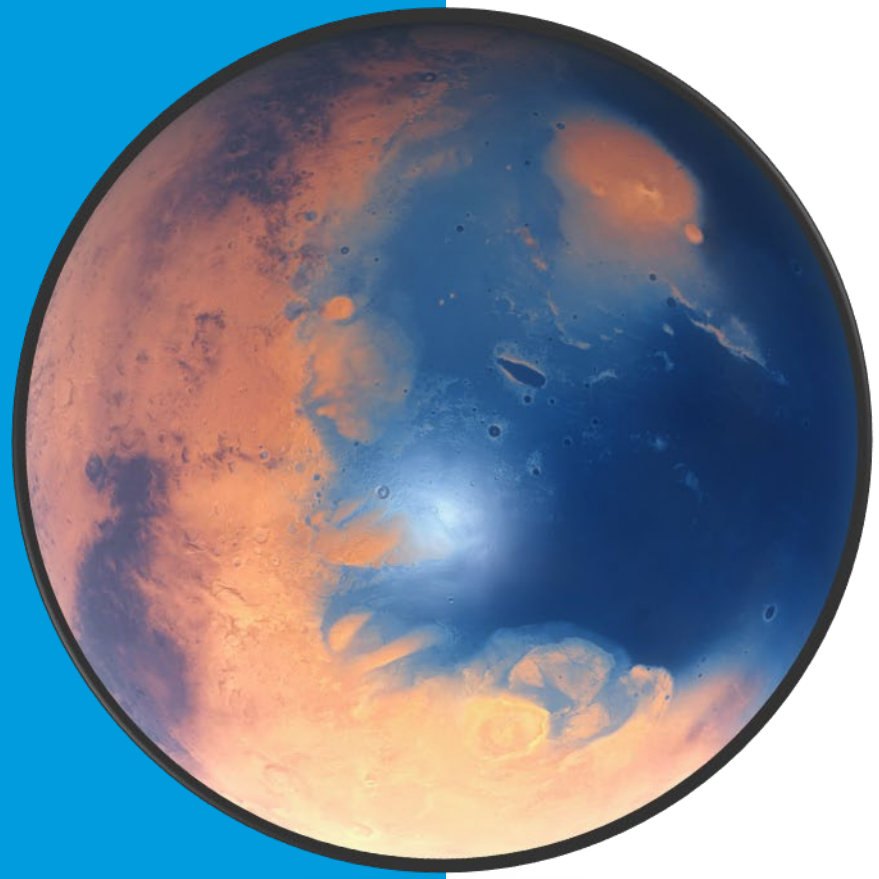
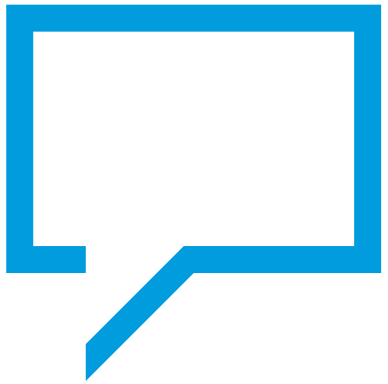
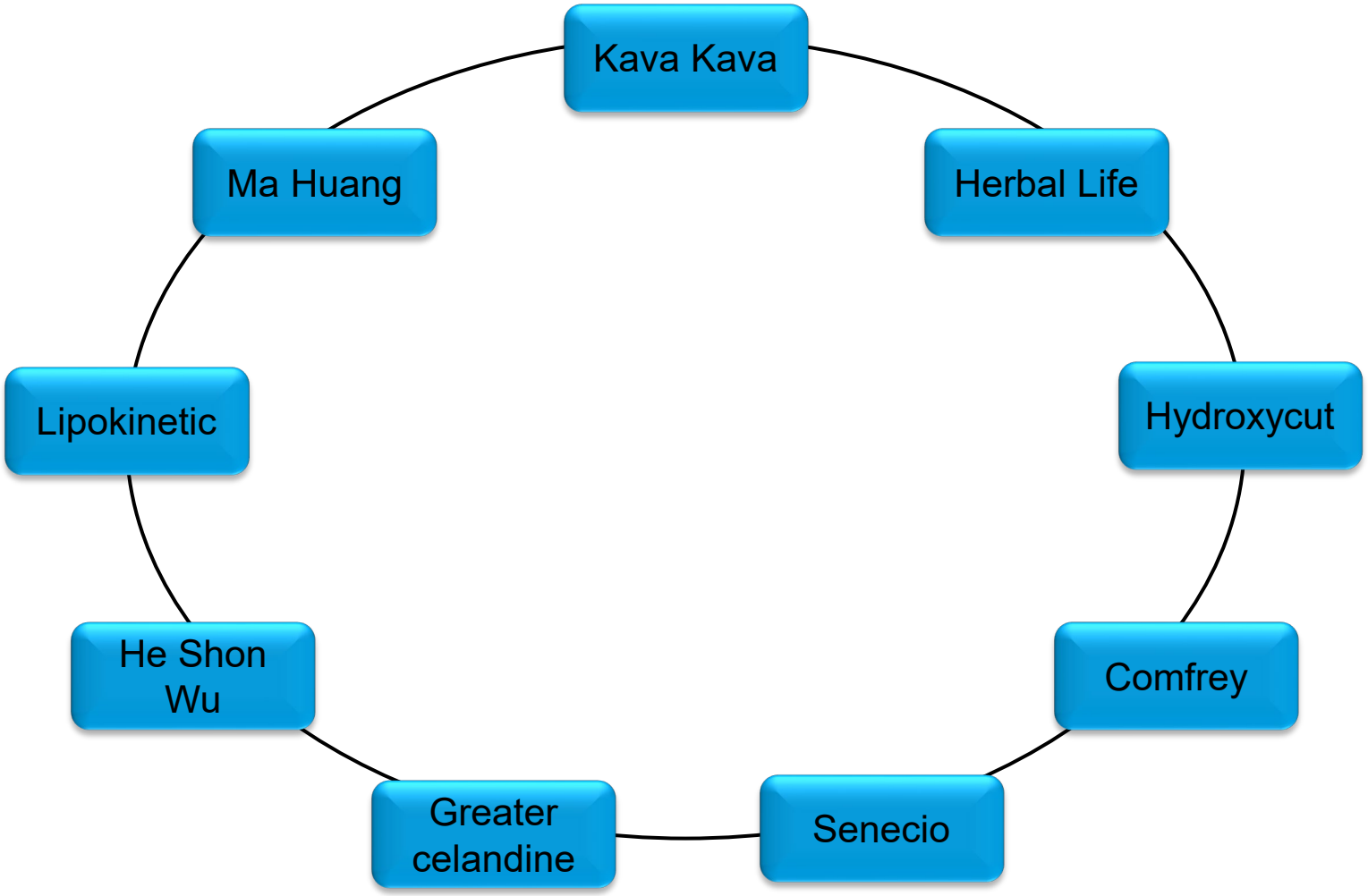
THANK YOU



QUESTIONS & ANSWERS



Herbal Products and Dietary Supplements Associated with Hepatotoxicity



Hepatology September 2011
Lancet 2010; 376:190-201

Cytokines and Inflammatory Factors in ALF

Pro-inflammatory cytokines	Anti-inflammatory cytokines	Other
• TNF-α • IL-8	• IL-10 • IL-6	• IL-2sRα

Hypotension
Cerebral edema
Organ dysfunction

Ann Med 2002;34:614-23
Chest 2000;117:1162-72
J Immunol 1985;135:3172-7
J Hepatol 2002:37:536-8

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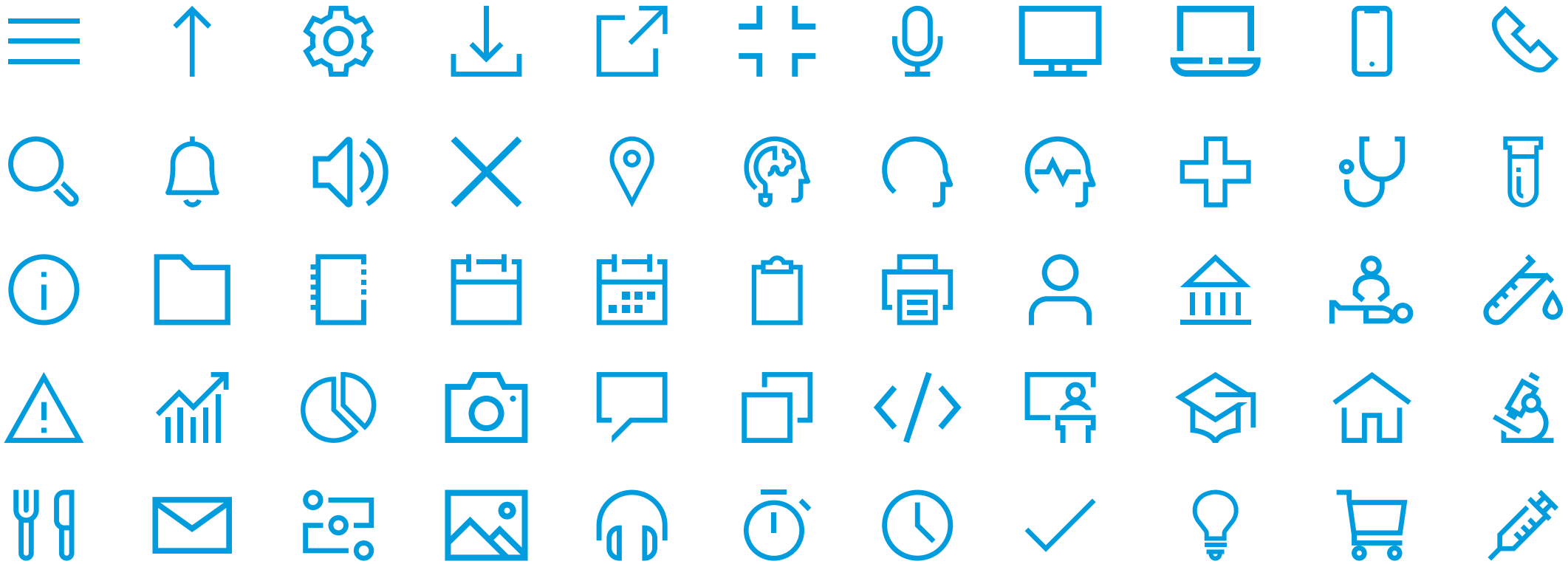

BRAND ICONOGRAPHY