TO MARS AND BEYOND: WHAT'S ALL THIS ABOUT “LIVER DIALYSIS?”

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September 30, 2017

OBJECTIVES

• Define MARS therapy as well as other options available for “Liver Dialysis.”
• Define appropriate indication and use of MARS therapy and other forms of “Liver Dialysis.”
• Review current literature regarding MARS therapy as well as possible other future opportunities.

ACUTE LIVER FAILURE

- Definition: Liver failure - severe acute liver injury with encephalopathy and impaired synthetic liver function (INR of ≥1.5)
  - Patient without cirrhosis or pre-existing liver disease
  - Acute Liver Failure: <26 weeks - hyperammonia, acute, or subacute
  - Chronic Liver Failure: > 10 weeks
- Presents as: fatigue/malaise, lethargy, anorexia, nausea and/or vomiting, right upper quadrant pain, pruritus, jaundice, abdominal distension from ascites, various lab abnormalities

LIVER FAILURE

- Leads to production of toxins and decreased drug clearance
  - Different bile acids, bilirubin, prostacyclins, nitric oxide, fatty acids, thiol, glutathione depletion, and free radical damage
  - Toxins production and accumulation leads to further necrosis and apoptosis thus propagating this damaging cycle
- The above processes have significant impact on the bodies ability to function and heal

Manifestations of hepatic encephalopathy include which of the following:

A. State of Consciousness
B. Intellectual Function
C. Personality-Behavior
D. Neuromuscular Abnormalities
E. All of the above
MANIFESTATIONS OF HEPATIC ENCEPHALOPATHY

ETIOLOGY OF ACUTE LIVER INJURY

- Acetaminophen (paracetamol)
- Idiosyncratic drug reactions
- Viral hepatitis
- Alcoholic hepatitis (in which case it is considered to be acute-on-chronic liver failure)
- Autoimmune hepatitis
- Wilson disease
- Inherited hyperphenylalaninemia
- Budd-Chiari syndrome
- Veno-occlusive disease
- Acute fatty liver of pregnancy/HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome
- Liver abscesses (most often from cholecystitis, non-cholesterol, or mycotic)
- Portal hypertension
- Vasculitis
- Drug-induced (including medications causing hepatic failure or hepatic impairment)
- Sepsis
- Heat stroke
- Hemophagocytic lymphohistiocytosis (primarily a disorder of children)

DRUGS ASSOCIATED WITH ACUTE LIVER INJURY

- Abacavir
- Acetaminophen (paracetamol)
- Alcohol
- Allopurinol
- Amiodarone
- Amoxicillin
- Aspirin
- Carbamazepine
- Carbon tetrachloride
- Ciprofloxacin
- Cocaine
- Comfrey
- Dapsone
- Didanosine
- Dideoxyinosine
- Disulfiram
- Doxycycline
- Efavirenz
- Gemtuzumab
- Gold
- Greater celandine
- Halothane
- He Shon Wu
- Herbalife®
- Hydroxycut®
- Isoflurane
- Isoniazid
- Itraconazole
- Kava Kava
- Ketoconazole
- Labetalol
- LipoKinetix®
- Ma Huang
- MDMA (Ecstasy)
- Methamphetamine
- Monoamine oxidase inhibitors
- Methyldopa
- Nicotinic acid
- Nitrofurantoin
- Nonsteroidal anti-inflammatory drugs
- Phenprocoumon
- Phenytoin
- Poison mushrooms (Amanita phalloides)
- Propylthiouracil
- Pyrazinamide
- Rifampin
- Senecio
- Statins
- Sulfonamides
- Terbinafine
- Tetracycline
- Tolcapone
- Tricyclic antidepressants
- Valproic acid

LIVER FAILURE MNEMONIC

“Liver Dialysis” includes all of the following except:

A. Single Pass Albumin Dialysis
B. ELAD System
C. Molecular Adsorbent Recirculating System
D. Fresenius System
E. None of the above
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SINGLE PASS ALBUMIN DIALYSIS

PROMETHIUS SYSTEM

MARS
MARS therapy removes which of the following substances?

A. Benzodiazepines  
B. Ammonia  
C. Immunoglobulins  
D. Albumin  
E. All of the above  
F. A and B  
G. C and D

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**WHAT MARS DOES NOT REMOVE**

- Clotting Factors
- Immunoglobulins
- Hormone proteins
- Albumin

**INDICATIONS**

- Circulatory failure and organ malperfusion in liver failure
- Hepatic encephalopathy and cerebral edema*
- Kidney dysfunction/Hepatorenal syndrome
- Liver synthetic dysfunction
- Bridging of ALF-patients to liver transplantation
- Quality of life issues in chronic liver disease (pruritus, fatigue)
- Drug overdose/Intoxication*

* FDA Approved Indications

**WHICH OF THE FOLLOWING ARE NOT FDA APPROVED INDICATIONS OF MARS:**

A. Drug overdose  
B. Intoxication  
C. Hepatic encephalopathy  
D. Cerebral Edema  
E. Liver synthetic dysfunction

**WHICH OF THE FOLLOWING ARE NOT FDA APPROVED INDICATIONS OF MARS:**

A. Drug overdose  
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C. Hepatic encephalopathy  
D. Cerebral Edema  
E. Liver synthetic dysfunction

**Molecular adsorbent recirculating system and single-pass albumin dialysis in liver failure – a prospective, randomised crossover study**

**RESULTS**

- MARS and SPAD both systems significantly reduced plasma bilirubin levels
  - MARS: median $-68\mu\text{mol/L}$, interquartile range $[-107.5$ to $-33.5$, $p = 0.001$]
  - SPAD: $-59\mu\text{mol/L}$, $-84.5$ to $+36.5$, $p = 0.001$]
- Bile acids, creatinine and urea reduced only by MARS
- Albumin-binding capacity was increased only in MARS
- Cytokine levels of interleukin (IL)-6 and IL-8 and hepatic encephalopathy were altered by neither MARS nor SPAD.

**AUTHOR’S CONCLUSIONS**

- Both procedures were safe for temporary extracorporeal liver support.
- Plasma bilirubin levels were reduced by both systems.
- Only MARS affected other paraclinical parameters.
- Caution should be taken with regard to metabolic derangements and electrolyte disturbances, particularly in SPAD using regional citrate anti-coagulation.
Molecular Adsorbent Recirculating System Can Reduce Short-Term Mortality Among Patients With Acute-on-Chronic Liver Failure: A Retrospective Analysis. Critical Care Medicine (2017).

MARS Treatment improved short term survival in acute-on-chronic liver failure and multiple organ failure

MARS may provide a viable option as a bridge to liver recovery or transplant

Mortality Prediction by Recursive Partitioning Analysis

• Both randomized clinical trials (RCTs) and observational studies
• Evaluated differences in mortality
• Acute-on-Chronic Liver Failure (ACLF)
• Artificial liver support system (ALSS) or Standard Medical Therapy
RESULTS

• Ten studies, 7 RCTs, and 3 controlled cohorts were enrolled.
• Total of 1682 ACLF patients (7 RCT’s, 3 controlled cohorts).
• 842 were treated with ALSS.
• ALSS reduced the risk of short-term (1-month and 3-month) mortality by nearly 30%.
• Good internal and external validity respectively with consistent findings.
• Meta-analysis suggests treatment and survival data trends towards medium-term (6-month and 1-year) and long-term (3-year) mortality risk by up to 30% and 50% respectively.

AUTHOR’S CONCLUSIONS

• ALSS therapy could reduce short-term mortality in patients with ACLF.
• Meanwhile, its impacts on medium- and long-term survival seem to be promising but remained inconclusive. Clinical utility of this system for survival benefit may be implied.

Molecular adsorbent recirculating system (MARS) in acute liver injury and graft dysfunction: Results from a case-control study

Hans U. Gerth[1,2], Michael Potthoff[2], Gerald Thiede[1], Hermann Poonen[2], Vincent Brand[1], Christian Brune[1], Anna Houing-Rabar[1], Dennis Gerstl[1], Yadv Rabar[1], Harriet H. J. Schmal[2]

• How would MARS impact outcomes in acute liver injury in normal and post-transplant patients?
• Studied the effects of MARS therapy compared to standard medical treatment (SMT) in two patient cohorts.
• 6.5-year period with 73 patients treated with SMT or with SMT and MARS (MARS group).
• 53 patients suffered from acute liver injury in native liver (SMT: n = 31, MARS: n = 22).
• 20 patients - severe graft dysfunction after transplant (SMT: n = 10, MARS: n = 10).
Table 3. Short-term response of laboratory parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>MARS</th>
<th>SMT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>14.3 (6.0)</td>
<td>8.0 (6.0)</td>
<td>6.0 (4.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>14.6 (1.4)</td>
<td>12.5 (1.4)</td>
<td>12.5 (1.4)</td>
<td>0.077</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.3 (6.0)</td>
<td>38.0 (6.0)</td>
<td>37.0 (6.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet count (x10^9/L)</td>
<td>270 (210-300)</td>
<td>240 (210-300)</td>
<td>200 (150-300)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

**COMMENTS/RESULTS**

- Hemodynamically and respiratory stable patients
- Low hepatic encephalopathy grade
- Model of end-stage liver disease (MELD) score of 20.57 (MARS) or 22.51 (SMT, p = 0.555).
- MARS improved the patients’ bilirubin values in the short term compared to SMT alone.
- In acute liver injury, this response was sustained even after the end of MARS therapy.
- Majority of patients with GD and an initial response to MARS therapy experienced worsened hyperbilirubinemia.
- No differences in 28-day mortality were observed with respect to acute liver injury
  - MARS 5.3% (95% CI: 0 – 15.3), SMT 3.3% (95% CI: 0 – 9.8), p = 0.754
  - GD (MARS 20.0% (95% CI: 0 – 44.7), SMT 11.1% (95% CI: 0 – 31.7), p = 0.478).

**AUTHOR’S CONCLUSIONS**

Conclusions

Although it did not improve 28-day mortality, MARS therapy improved the short-term response in patients with acute liver injury as well as in those with GD. In cases of acute hepatic injury, the use of MARS therapy resulted in the sustained stabilization of liver function and improved liver regeneration. A short-term response to MARS may predict the future course of the disease.
FUTURE STUDIES FOR MARS SHOULD TARGET WHICH OF THE FOLLOWING?

A. Other Toxic Ingestions  
B. Trauma  
C. Sepsis  
D. ECMO  
E. Optimal Timing of Mars initiation  
F. Long-Term Impact of MARS vs SPAD  
G. All of the Above  
H. None of the Above

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FUTURE DIRECTIONS

• MARS in Specific Disease States  
• Other Toxic Ingestions  
• Trauma  
• Sepsis  
• ECMO  
• Optimal Timing of Mars initiation  
• Long-Term Impact of MARS vs SPAD

SUMMARY

• “Liver Dialysis” has been shown to be beneficial in liver failure associated with many different etiologies  
• MARS and SPAD have been shown to have similar impact bilirubin level reduction  
• Only MARS has demonstrated impact on bile acids, creatinine and urea  
• Albumin-binding capacity was increased only in MARS  
• Cytokine levels of interleukin (IL)-6 and IL-8 and hepatic encephalopathy were altered by neither MARS nor SPAD  
• Short-term survival benefits well-documented with MARS therapy  
• Medium and Long-Term Survival impacts still unknown at this time.  
• Impact of use in other disease states currently unknown

QUESTIONS

REFERENCES

• Joseph NA, Kumar LK. Liver support devices: Bridge to transplant or recovery? Indian J Respir Care 2017;6:807-12.  
• Joseph NA, Kumar LK. Liver support devices: Bridge to transplant or recovery? Indian J Respir Care 2017;6:807-12.  
• Gerth HU, Pohlen M, Thölking G, et al. Molecular Adsorbent Recirculating System Can Reduce Short-Term Mortality Among Patients With Acute and Chronic Liver Failure: Results From a Prospective, Randomized Controlled Trial. Critical Care Medicine 2017.  