Extracorporeal Albumin Dialysis with Molecular Adsorbent Recirculating System (MARS®) and the Effect on Antimicrobial Removal

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Background
• MARS® is a liver support system used for the removal of hydrophilic compounds and highly protein bound lipophilic substances that accumulate during liver failure ¹

• Very limited literature to guide antimicrobial dosing in MARS® patients

• Clearance of albumin-bound toxins poses risk for removal of highly-bound antimicrobials

• Select drug dosing recommendations based on protein binding and drug V_d were developed at ASLMC in 2014 to prepare for MARS® use ²

Objective
• Evaluate MARS® antimicrobial dosing recommendations developed at ASLMC

Methods
• Observational study with IRB approval

• Inclusion criteria: consent obtained, ASLMC SICU patient, ≥ 18 years old, current MARS®, receiving at least 1 antimicrobial

• Three blood samples per patient collected during a single MARS® run (pre, mid, and post)

• Drug concentrations measured via high performance liquid chromatography (HPLC)

• ASLMC SICU organism data reviewed and compared measured drug concentrations

Results

HPLC Analysis

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Pre-MARS</th>
<th>MID-MARS</th>
<th>Post-MARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>42.9 ± 0.0</td>
<td>42.7 ± 0.0</td>
<td>43.0 ± 0.0</td>
</tr>
<tr>
<td>Cefepime</td>
<td>17.3 ± 0.0</td>
<td>17.4 ± 0.0</td>
<td>17.5 ± 0.0</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>56.2 ± 0.0</td>
<td>56.3 ± 0.0</td>
<td>56.4 ± 0.0</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>74.7 ± 0.0</td>
<td>74.8 ± 0.0</td>
<td>74.9 ± 0.0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>33.2 ± 0.0</td>
<td>33.3 ± 0.0</td>
<td>33.4 ± 0.0</td>
</tr>
</tbody>
</table>

Note: Patient 1 had serum vancomycin level of 117.7 mcg/mL from routine monitoring sent to ACL Laboratories that corresponded to the timing of the MARS level. Through analyzing this discrepancy, it was identified that vancomycin co-elutes with a naturally occurring molecule in the blood to increase its HPLC analytical peak. Further investigation is ongoing to correct via analytical means.

Patient Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Race</th>
<th>MELD Score</th>
<th>Reason for Hepatic Failure</th>
<th>MARS Run Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>White</td>
<td>36</td>
<td>NAFLD, HCV- Allograft Rejection</td>
<td>7.98</td>
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<tr>
<td>2</td>
<td>F</td>
<td>White</td>
<td>35</td>
<td>Fulminant Hepatitis Failure, HCV, APAI</td>
<td>4.33</td>
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<tr>
<td>3</td>
<td>F</td>
<td>White</td>
<td>35</td>
<td>ETOH Abuse</td>
<td>11.8</td>
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<tr>
<td>4</td>
<td>F</td>
<td>White</td>
<td>22</td>
<td>Sclerosing Cholangitis</td>
<td>6.66</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>White</td>
<td>43</td>
<td>Cirrhosis – Autoimmune Hepatitis and ETOH</td>
<td>23.5</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>White</td>
<td>15</td>
<td>OLT – ETOH and Hep C Cirrhosis</td>
<td>17.3</td>
</tr>
</tbody>
</table>

NAPLD: non-alcoholic fatty liver disease; HCV: hepatitis C virus; APAI: autoimmune hepatitis; ETOH: alcoholic liver disease; OLT: orthotopic liver transplant

ASLMC SICU Historical Organism MIC Evaluation

• Minimum inhibitory concentration (MIC) report for organisms grown out of cultures from ASLMC SICU patients 2010/2014 – 2015 was obtained from ACL Laboratories

• Data from culture sites classified as blood, respiratory, urine, wound/tissue, or fluid/other were evaluated

• MIC data compared to HPLC concentrations for antimicrobials measured in the study showed patient levels for beta-lactam antibiotics remained at therapeutic levels at all three data points except for one patient on piperacillin/tazobactam (P/T) (see Results Summary)

Results Summary

• MARS® duration varied from 6.7 to 23.5 hours

• All drugs analyzed are classified as having LOW protein binding with the exception of daptomycin which has HIGH protein binding

• Lowest observed concentration (mcg/mL, rounded) of each antimicrobial: Cefepime (236.2), Daptomycin (2) Flucloxacilin (3.6), Metronidazole (11.4), Piperacillin (1.8), Vancomycin (11.7)

• These concentrations remain at appropriate clinical levels based on SICU MIC data except for Piperacillin

• Two patients on P/T were retrospectively identified as being under-dosed pre-MARS® and had low measured P/T concentrations

• One of the two patients had P/T dose increased during the MARS® run to be compliant with our dose recommendations guideline, which then yielded a clinically appropriate post-run P/T level

Conclusions

• The internal recommendations for empiric antimicrobial dosing in MARS® patients in the ASLMC SICU achieved adequate concentrations for the drugs sampled in our small patient population

• Due to the observational study design, the potential impact on antimicrobial pharmacokinetics could not be accurately evaluated

• Most drugs analyzed were classified as having low protein binding, which may limit application to highly bound drugs

• Increasing the length of MARS run times may yield results inconsistent with our observations, and thus must be considered when using the dosing recommendations in our reference tool

References

1. MARS® System, Gambro, www.gambro.com