“Cytosorb”® a novel Treatment Option in Liver Dysfunction

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Why Cytosorb in liver disfunction?

- Liver plays a major/central role in inflammation
- Liver is the “trigger” of MODS
- Liver failure kills
- Few therapies accepted and demonstrated to be useful in liver failure
- ............??????????
First use of CytoSorb® in a septic shock after LT
Pre-LT assessment and intraoperative management

• 53 yo female, DDLT (33 yo donor, DRI 1,29) for HCV cirrhosis
• At the time of LT....
  – MELD 20, MELD-Na 23 (bilirubin 6.1 mg/dl, INR 1.8, creat 0.91 mg/dL, Na 134 mmol/L)
  – Pancytopenia (WBC 1650/uL, 70% Neut, Hb 6,9g/dL, PLT 25000/uL)
• Surgery (LT):
  – Duration of surgery: 430 min, anhepatic phase 52 min;
  – PRS (+): severe bradycardia (20 bpm)
  – Blood loss: 2000 ml
  – Transfusion: 5 u PRBc, 10 u FFP. 4 std U PLT
  – Maximum vasopressor support 2.2 mg/h (*discontinued at the end of surgery*)
Early postoperative period

- Extubated 10 h after surgery
- Po day 2 severe ARDS – required reintubation
- On po day 4 – **Severe sepsis** (SOFA 13)
- On po day 7 – **Septic shock. MODS** (neurologic, renal, respiratory, hematological, cardiovascular, hepatic dysfunction)
- 3 CVHHDF treatments with CytoSorb® (aprox. 12 h each) were applied po day 8,10,13
- Cytokine levels were measured:
  - Before LT
  - 15 min into the neohepatic phase
  - Postoperative day 1
  - Postoperative day 7 (before the 1st CytoSorb)
  - Postoperative day 8 (after the 1st CytoSorb / before 2nd CytoSorb)
  - Postoperative day 9 (after the 2nd CytoSorb)
  - Postoperative day 13 (after the 3rd CyroSorb)
ARDS / BP (?) and CytoSorb® - severe hypoxemia
PO Day 0 - extubated
Re-Intubated POD1 – ARDS / BP PO Day 3
PO Day 7 – pre- CVVHDF + Cytosorb + prone
PO Day 11 – post CVVHDF + 2 Cytosorb
PO Day 14 – post CVVHDF + 3 Cytosorb
PO Day 20 – CPAP
Blood cultures, SOFA, Inflammation markers

- CytoSorb
- Ig 25g/day
- PCR 15.6
  PCR 168
  PCR 190
  PCR 162
  PCR 101
- PCT 0.2
  PCT 1.28
  PCT 11.1
  PCT 10
  PCT 5.27
- IL-6 45
  IL-6 112
  IL-6 667
  IL-6 100
  IL-6 123
- SOFA 5
  SOFA 9
  SOFA 13
  SOFA 19
  SOFA 22
  SOFA 16
  SOFA 10
- Sterile
  Imipenem/Cilastatin
  Ertapenem
- BAL: Acinetobacter spp
- BAL: Acinetobacter
- Blood culture: Acinetobacter
- Lynezolid
  Levofloxacin
  Colistin
  Anidulafungin
Cytokine levels before and after the use of CytoSorb®

- Values obtained were compared to those from 4 healthy subjects
- Cytokine levels were determined by an Immunology Multiplex Assay (Milliplex MAP Human Cytokine-/Chemokine - Immunoassay Panel, Merck Millipore, Billerica, MA, USA) on a Luminex-200™ System (Luminex, Austin, Texas).

<table>
<thead>
<tr>
<th></th>
<th>GM-CSF</th>
<th>IFNγ</th>
<th>IL-1β</th>
<th>IL-2</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IL-6</th>
<th>IL-7</th>
<th>IL-8</th>
<th>IL-10</th>
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<td>6.52</td>
<td>&lt;2.49</td>
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<td>22.27</td>
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<td>45.00</td>
<td>50.86</td>
<td>29.74</td>
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<td>25.81</td>
<td>52.20</td>
<td>38.70</td>
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<td>26.26</td>
<td>12.66</td>
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<td>12.95</td>
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<td>2009.83</td>
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<td>Normal values</td>
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<td>0.50</td>
<td>2.62</td>
<td>21.81</td>
<td>13.92</td>
<td>12.94</td>
<td>7.25</td>
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<td>20.20</td>
<td>14.23</td>
<td>12.79</td>
<td>18.07</td>
<td>281.61</td>
<td>16.09</td>
</tr>
</tbody>
</table>
Cytokines during CytoSorb ®

Decrease IL 6, TNFa
Hemodynamic parameters, vasopressor and lactate during CytoSorb ®

- Decrease in lactate levels (from 3 mmol/l to 0.9 mmol/l)
- Decrease in vasopressor support (from a maximum of 4.2 mg/h, discontinued after the 3rd CytoSorb)
- CI, SVRI returned to normal values
Liver function during CytoSorb®

- Decrease in ALT and AST levels
- Decrease in total bilirubin
During the use of CytoSorb ® we observed

- Improvement in haemodynamics (CI, SVRI) and decrease in vasopressor support
- Improvement in PaO2/FiO2 from 89 to > 300
- Decrease in serum transaminases and bilirubin levels
Conclusions

• the use of CytoSorb® shifted the immunological cascade from a SIRS state to a compensatory anti-inflammatory response syndrome and a mixed antagonist response syndrome, so it helped to regain control and acted as immunotherapy.

✔ To be continued.....
Use of Hemoadsorption Columns in Severe Rhabdomyolysis Following Acute Liver Failure after Mushroom Poisoning
Wild mushrooms are a problem?

- Gathering and cooking of wild mushrooms is a frequent habit among villagers that reside in the vicinity of a forest.
- Most patients present in small local hospitals that are not equipped to deal with mushroom poisoning.
- Many cases are first misdiagnosed as acute gastroenteritis.
- Mushroom poisoning is dangerous/deadly, affects "les conaisseurs".
Current situation...

- Fundeni Clinical Institute - the only center in Romania that can provide effective treatment for ALF due to mushroom poisoning in terms of...
  - Hepatic dialysis: PROMETHEUS, MARS
  - Liver transplantation
Case report

- 36 yo man (O+) hand-picked mushrooms in a nearby forest in Sibiu County...

- Cooked them and then.....
A friend replied that the mushrooms were poisonous

He presented to Sibiu emergency hospital, received supportive treatment and was transferred to Fundeni Clinical Institute 5 days later
Admission to Fundeni Clinical Institute

- coma (Glasgow 6 pt) – CT scan: diffuse cerebral edema, frontal hemorrhagic suffusion 7/4mm.

- Febrile, 38°C, mild ARDS (PaO2/FiO2 220) – *intubated* and MV for airtransport in BiPAP FiO2 0.5

- cardiovascular: minimal vasopressor support (noradrenalin 0.6 mg/h), CI 3.8 l/min/m², SVRI 1800 dyne*s*cm⁻⁵*m² , SVV 8%

- 12 hours after admission – atrial fibrillation (220 beats/min) with increase in vasopressor support → electrical cardio version 200J → sinus rhythm
Head CT at admission
Laboratory data at admission

- **Inflammatory response:**
  - WBC 20310/uL
  - NEUT 93%
  - PCR 132 mg/L
  - PCT 11.21 Ng/ml

- **Liver function:**
  - Cytolysis: ALT 513 U/L, AST 153 U/L
  - Cholestasis: total bilirubin 14.2 mg/dl, direct bilirubin 12.8 mg/dl, ALP 105 U/L
  - Synthesis: albumin 2 g/dl, chol 28 mg/dl, fibrinogen 262 mg/dl

- **Hemostasis:** aPTT 39.1sec, PT 38.4sec, INR 2.68, PLT 32000/ul
- **Rhabdomyolysis:** CK 2300 U/L
- **Renal:** diuresis 100ml/h, creatinine 1.64 mg/dl, BUN 69 mg/dl
- **Acid-base:** pH 7.42, PaCO2 33 mmHg, PaO2 110 mmHg, BE -2.8 mmol/l, HCO3 21.6 mmol/l, Na 153 mmol/l, K 3.21 mmol/l, Cl 118 mmol/l, lactate 5.02 mmol/l
Coagulation assessment

- Standard coagulation tests (24h after admission)
  - aPTT 37 sec
  - Fib 320 mg/dl
  - INR 1.78
  - PLT 12000/uL
- F II 23%
- F V 36%
- F VII 33%
- F VIII 62%
- F IX 68%
- F X 69%
- AT III 60%
- Pc 60%
- Ps 55%
### Criteria for LTx in ALF

<table>
<thead>
<tr>
<th>King’s College</th>
<th>Clichy criteria</th>
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<tbody>
<tr>
<td>INR &gt; 6.5</td>
<td>HE grade 3 or 4</td>
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<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td>1. Age &lt;10 or &gt; 40 y</td>
<td>And</td>
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<tr>
<td>2. Etiology: undetermined or drug-induced</td>
<td>Factor V &lt; 30% if over 30 yo</td>
</tr>
<tr>
<td>3. Time interval icterus to encefalopathy &lt; 7 days</td>
<td>Factor V &lt; 20% if under 30 yo</td>
</tr>
<tr>
<td>4. INR &gt; 3.5</td>
<td></td>
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<tr>
<td>5. Bilirubin 17.5 mg/dl</td>
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<tr>
<td><strong>2/5 criteria</strong></td>
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</table>
Specific therapy

- Emergency listing for liver transplantation (LRLT) – brother (34 yo, B+)

- 3 consecutive sessions of MARS were applied as bridging therapy

- Supportive measures
  - Hypothermia 35°C
  - Sedation
  - MV
  - Broad Spectrum AB-therapy

- Monitoring
  - Advanced haemodynamic
    - radial art, CVC
  - No ICP monitoring
Dynamics of lab results

![Graph showing lab results over time with different markers for MARS, MV - BiPAP / CPAP, NIV - CPAP, and grades of HE.]}
The use of MARS was associated with...

- Decrease in hepatocitolysis
- Decrease in cholestasis
- Decrease in lactate levels
- Increase in fibrinogen
The use of MARS was associated with...

- Regression of pulmonary infiltrates
- Improvement of hepatic encephalopathy  \( \text{IV} \rightarrow \text{II} \)
- Possibility to be weaned from mechanical ventilation

At admission

After extubation
Rhabdomyolysis

- CK levels begin to rise and reached maximum levels in day 7  CK **47961 U/L**

- No other organ dysfunctions were noted

- A novel therapy (a hemoadsorption column) – CytoSorb® was applied in conjunction with standard veno-venous hemofiltration (CVVHF) in three consecutive sessions (24h each).

- CK levels were measured before and after each session
The CytoSorb treatment was performed in combination with standard CVVHF:
- blood flow 150 ml/h
- ultrafiltrate 3500 ml/h
- removal 100 ml/h
- regional anticoagulation: heparin

The CytoSorb cartridge was placed before the hemofilter for CVVHF.
Tricholoma equestre.

Brief Report

WILD-MUSHROOM INTOXICATION AS A CAUSE OF RHABDOMYOLYSIS

REGIS BROSSY, M.D.,
ISABELLE BAUDRIMONT, PHARM.D., PH.D.,
GERARD DEFFIEUX, PHARM.D., PH.D.,
EDMOND E. CREPPY, PHARM.D., PH.D.,
JEAN P. MORES, M.D., PH.D., JEAN M. RAGAUD, M.D.,
MICHEL DURON, M.D., DIDIER NEAL, M.D.,
CLAUDINE GRENIER, M.D., STEPH DE VITTE, M.D.,
JEAN C. CHAPALAIN, M.D., AND PIERRE GODAUX, M.D.

The growing popularity of eating wild mushrooms has led to an increase in the incidence of mushroom poisoning. Most fatalities are due to amatoxin-containing species, which cause fulminant hepatic necrosis, and to cortinarius species, which lead to acute renal damage. A 1996 report described a patient with hepatic failure, encephalopathy, and anemia related to the ingestion of Amanita phalloides. Since 1992, 12 cases of delayed rhabdomyolysis have occurred in France after meals that included large quantities of the edible wild mushroom Tricholoma equestre. The circumstances of these 12 cases clearly implicates T. equestre as the cause. The mushroom was positively identified, and no other cause, such as bacterial, viral, fungal, or immune disease or exposure to a toxin, was found. Three of the 12 patients died.

Figure 1. Tricholoma equestre.
The cap of this species measures 6 to 8 cm, and the stem is 7 to 10 cm long and 1.5 cm in diameter.

CASE REPORTS

Seven women (age range, 22 to 60 years) and five men (age range, 24 to 61 years) were hospitalized between 1992 and 2000 with severe rhabdomyolysis approximately one week after eating wild

The New England Journal of Medicine
Why CytoSorb®?

Extracorporeal Therapy for the Removal of Myoglobin Using the CytoSorb in Patients With Rhabdomyolysis

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2014 by CytoSorbents, Inc

Sponsor:
CytoSorbents, Inc

Collaborator:
San Antonio Military Medical Center (SAMMC), US Army Institute of Surgical Research-Burn Center

Information provided by (Responsible Party):
CytoSorbents, Inc

ClinicalTrials.gov Identifier:
NCT02111018

First received: March 19, 2014
Last updated: July 21, 2014
Last verified: April 2014
History of Changes

Purpose
Prospective, randomized non-blinded, controlled study to assess the feasibility of the CytoSorb as an adjunct to the standard of care in patients with rhabdomyolysis requiring renal replacement therapy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Rhabdomyolysis</td>
<td>Device: CytoSorb Device</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Procedure: CVVH</td>
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</tbody>
</table>

Study Type: Interventional
Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Dynamics of lab results
Dynamics of lab results
Dynamics of CK and LDH levels
CytoSorb® and SIRS

![Graph showing WBC levels over time with MARS and CytoSorb interventions, along with PCT and PCR values and antibiotic recommendations for different bacterial species.](image-url)
The use of CytoSorb® was associated with...

- Decrease in CK levels to normal values
- Decrease in inflammatory markers (PCR, PCT, WBC)
- Clinical improvement
Outcome

• D 14: ARDS (PaO2/FiO2 = 190)
  - INTUBATION

• D 15: severe sepsis (BAL: Acinetobacter spp)

• D 16: septic shock (increased doses of vasopressor)

• D 17: cardiopulmonary arrest (unresponsive to CPR manoeuvres)
Questions to be answered.....was it better to transplant?
ALF WILSON’S Disease
ICU admission

- 17 yo patient, admitted in the ICU for
  - hepatic encephalopathy (grade II-III) Ammonia= 137 micromol/
  - Respiratory distress
- Known history of Wilson’s disease (for 4 years), neglected treatment
- MELD 45
- Laboratory results: Tbil 65 mg/dl, Dbil 54 mg/dl, INR 2.5, PT 33sec, Fibrinogen 204 mg/dL PLT 125000, Hb 6.1g/dl WBC 9130
- ARDS: Chest X-Ray bilateral infiltrates, SpO2=75% while breathing room-air, required intermitent NIV (CPAP)
- PCT 2.49 ! PCR 36,2
- Listed for emergency LT
Management

• Rapid deterioration

• 1 therapeutic plasmaexchange treatment was applied ICUday 1 for severe cholestasis (Tbil 60 mg/dl) and pruritus after ICU admission (plasma volume 2600 ml)

• after plasmaexchange - supraventricular tachicardia (HR 220 bpm) that converted to sinus rythm after 300 mg Amiodarone

• **Before LT** a CVVH treatment using a CytoSorb column was applied (blood flow 150 ml/min, ultrafiltrate 1500ml/h, removal 150 ml/h) and **continued** during surgery (for a total time of 12h)
  
  – ARDS
  – PCT 2.49
  – High Bilirubin
  – Peripheral oedema

• Rapid investigation of a potential living donor

• **Emergency LTx < 48 h from admission**
Liver transplantation (1)

- Duration of surgery: 380 min
- Anhepatic phase 30 min
- Blood loss: 3.5 l requiring transfusion of 4 u PRBc
- No PRS
- **BUT** intraoperative atrial fibrillation (HR 140-170 bpm) followed by sinus bradycardia (HR 45-50 bpm) and haemodynamic instability
LRLT Right lobe

Intraoperative

CytoSorb
Postoperative period & outcome

• No ARDS – extubated within 12 h
• Grade II hepatic encephalopathy

• Delayed graft function (within the first 3 po days):
  – Increased hepatic citolysis (up to ALT 3850 U/L and AST 2144 U/L)
  – Increased bilirubin levels (from 18 to 30 mg/dl)
  – Low synthesis (required administration of Fibrinogen 1g/day)
  – Lactate levels remained high (2-4 mmol/l)

• Repeated episodes of supraventricular tachicardia

• Good liver function – discharged from PACU PO 11
Happy end....

• Another Cytosorb® might have been useful?
• Is Cytosorb® a possible “bridging” therapy to LT?
• A challenging case
  – Emergency LT
  – LRLT for ALF
• Now... graduated high school