A Research Agenda on Multiple Organ Dysfunction Syndrome (MODS)

Critical Care Canada Forum
November 13, 2019

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Acknowledgement

Thank you to Robert Fowler, Paul Hébert, John Marshall, Deborah Cook and members of the Canadian Critical Care Trials Group (www.ccctg.ca).

Bojan Paunovic (cccs@secretariatcentral.com).
I have nothing to disclose.

Within the last 12 months I have not had any type of financial arrangement or affiliation with commercial interests related to the content of this continuing education activity that requires disclosure.
MODS: PHYSIOPATHOLOGY
MODS: ETIOLOGY

- Severe sepsis (infection)
- Severe trauma
- Cardiopulmonary bypass
- Shock
- Hypoxia
- Cardiac arrest
- Other causes

What is the typical pathophysiology of MODS?

Severity of illness vs. severity of MODS

Well-established MODS
MODS, PATHOPHYSIOLOGY: loss of inflammation retrocontrol

• In healthy patients, pro-inflammatory mediators start to disappear when anti-inflammatory mediators appear.

• In patients with well-established MODS, high blood level of both pro- and anti-inflammatory mediators are observed simultaneously.
  – The anti-inflammatory retroaction is not working adequately.
Mitochondrial dysfunction and cellular energy crisis in well-established MODS

• FINDINGS:
  – Skeletal muscle ATP concentrations: **significantly lower** in
    • 12 critically ill septic non-survivors
    • 16 septic survivors
    • 9 controls (elective hip surgery).
  – Complex I activity: **reduced glutathione (p=0.006)**.

• INTERPRETATION: “These data implicate bioenergetic failure as an important pathophysiological mechanism underlying multiorgan dysfunction.”

MODS, PATHOPHYSIOLOGY: APOPTOSIS

• MODS/severe sepsis are also characterized by disturbed apoptosis.
  – Sepsis increases apoptosis of lymphocytes.
  – TNF$_\alpha$, IL$_1$ and IL$_6$ retard apoptosis of white blood cells and alveolar macrophages.

Spleen from a patient with MODS
Change in heart rate variability (HRV) to predict shock and, may be, MODS

- Hypothesis: change in heart rate variability precedes clinical deterioration.

- Conclusion: heart rate variability might be a good early alarm marker of imminent clinical deterioration in critically ill adults.

MODS pathophysiology: take home messages

- **Molecular level:**
  - High blood concentration of pro- and anti-inflammatory bioreactive agents

- **Cellular level:**
  - Mitochondrial dysfunction
  - Cellular energetic crisis
  - Disturbed apoptosis

- **Organ system level:**
  - Simultaneous dysfunction of many organ systems can be caused by dysfunctional systems interaction:
    - Loss of retroactive controls
    - Loss of normal variability in systems like the inflammatory, respiratory, cardiovascular and endocrinological systems.

The precise mechanisms that start MODS remain to be elucidated.
Research questions: MODS physiopathology

- Is there any difference in the **pathophysiology** of MODS caused by...
  - Infection (sepsis)?
  - Hypoxia?
  - Trauma?
  - Severe insult by surgery?
  - Other etiology?
    - For example, is severe sepsis merely a specific variant of MODS?

- What is the set of biologic mechanisms that trigger MODS?
  - Uncontrolled inflammatory storm?
  - Energy crisis and mitochondrial dysfunction?
  - Loss of chaotic patterns, retrocontrol systems, systems interaction?
Research questions: MODS physiopathology and chaos

• When do the chaotic pattern of systems like the cardiac system (heart rate variability) starts to be disturbed in patients with MODS?
• What causes loss of chaotic pattern like heart rate variability in critically ill patients?
• Would there be any clinical value to monitor heart rate variability or another marker in ICU patients?
  – Goal-directed therapy targeting heart rate variability?
MODS: UNDER RECOGNIZED CLINICAL MANIFESTATIONS
Purpura fulminans

• Etiology: shock with MODS caused by...
  – Neisseria meningitidis.
  – Congenital protein C deficiency.

• Clinical observation:
  – Capillary leak syndrome.
  – Disseminated intravascular coagulation, thrombosis.

• Risk of amputation.
Complication of MODS: reactive hemophagocytic syndrome (RHS)

• Clinical markers: fever with...
  – histiocytic proliferation
  – hemophagocytosis that causes low platelet count, leucopenia and anemia
  – hepatosplenomegaly
  – generalized lymphadenopathy
  – hypertriglyceridemia
  – hypofibrinogenemia

• Diagnosis: bone marrow aspiration.

• Consequences:
  – More transfusions.
  – Immunosuppression, infections.
  – Disseminated intravascular coagulation, bleeding.

• RHS is not a cancer. It is not rare in critically ill children and adults.

Histiocyte (H) phagocyting an erythroblast (E) and a meta-myelocyte (M)
Other complications of MODS

- ICU weakness (polyneuropathy/myopathy).
- Immune suppression, nosocomial infections.
- Gastro-intestinal bleeding, stress gastritis.
- Endocrinological system (loss of circadian rhythm):
  - Insulin resistance.
  - Sick euthyroid syndrome. †
  - Increased serum cortisol. †
  - Attenuated pulsatility of growth hormone. †*


- Chronic anemia.
- Hyperresorptive bone failure.


- Other?
Research questions: under recognized manifestations of MODS

• Is there any other under recognized clinical problems that can be attributable to MODS?
  • What is their epidemiology?
• Should we include the under recognized clinical problems in the list of diagnostic criteria of MODS?
• Can we prevent these complications in ICU?
• What is the post-ICU trajectory of survivors who presented these complications?
SHOULD WE IMPROVE THE DIAGNOSTIC CRITERIA OF MODS?
MODS: diagnosis

- MODS is a syndrome.
- A syndrome can become a disease if a specific etiology is found.
  - Example: homocysteinemia vs. Marfan syndrome.
  - Test: homocysteinemia is now diagnosed if the blood level of homocysteine is above 15 µmol/L.

- MODS:
  - We do not have a test or a bundle of tests that can be used as a reference standard (gold standard) to diagnose MODS.
  - MODS remains presently a clinical diagnosis defined by the simultaneous dysfunction of at least 2 organ systems.
MODS: DIAGNOSIS

• Three lists of diagnostic criteria of pediatric MODS have been published.
  – Seven organs and systems were considered by Proulx, six by Goldstein et al.
    • Respiratory
    • Cardiovascular
    • Neurological
    • Hematological
    • Renal
    • Hepatic
    • ± Gastrointestinal.

MODS: pediatric diagnostic criteria of respiratory dysfunction (Goldstein, PCCM 2005)

- \( \text{PaO}_2/\text{FiO}_2 < 300 \) in absence of cyanotic heart disease or preexisting lung disease or
- \( \text{PaCO}_2 > 65 \) torr or 20 mm Hg over baseline \( \text{PaCO}_2 \) or
- Proven need\(^\dagger\) for > 50% \( \text{FiO}_2 \) to maintain saturation \( \geq 92\% \) or
- Need for non-elective invasive or non-invasive mechanical ventilation \(^\Psi\)

\(^\dagger\) Proven need assumes \( \text{O}_2 \) requirement was tested by decreasing flow with subsequent increase in flow if required.

\(^\Psi\) In postoperative patients, this requirement can be met if the patient has developed an acute inflammatory of infections process in the lungs that prevents him or her from being extubated.
The lists of diagnostic criteria of pediatric MODS are old:

- Proulx et al: 1996
- Goldstein et al: 2005

The diagnostic criteria of pediatric MODS should be revisited and the new list of criteria should be validated.

- The NIH allocated a grant to PODIUM to improve the diagnosis and monitoring of MODS.
  - PODIUM is led by Jerry Zimmerman and Melania Bembea.
  - The ‘diagnostic committee’ of PODIUM is led by Scot Weiss.
Research questions: Diagnostic criteria of MODS

- What clinical criteria and/or test(s) can tell us that a MODS is starting (black arrow)?
  - 1\textsuperscript{st} candidate: heart rate variability...?
- What clinical criteria and/or test(s) can be used as a gold standard to diagnose well-established MODS (white arrow)?
- Should we add “under recognized manifestations of MODS” in the list of diagnostic criteria of MODS?
- How many organ dysfunctions do we need to diagnose MODS: 2, 3, 4, more than 4?
MODS-RELATED OUTCOMES POST-ICU DISCHARGE
There is a link between MODS and post-intensive care syndrome

• “Post intensive care syndrome (PCIS): new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute hospitalization”.

• “PCIS-F (PCIS-family): can be applied to a family member experiencing anxiety, depression, post-traumatic stress disorder (PTSD), etc.”

• “PCIS-P (pediatric): post intensive care syndrome in children”.

Davidson JE Crit Care Med 2012
Manning JC et al. Ped Crit Care Med 2018
Post-ICU outcomes in critically ill adults and their family

One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Angela M. Cheung, M.D., Ph.D., Catherine M. Tansey, M.Sc., Andrea Matte-Martyn, B.Sc., Natalia Diaz-Granados, B.Sc., Fatma Al-Saidi, M.D., Andrew B. Cooper, M.D., Cameron B. Guest, M.D., C. David Maze, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Aliaa Barri, Ph.D., Deborah Cook, M.D., and Arthur S. Slutsky, M.D., for the Canadian Critical Care Trials Group

One-Year Outcomes in Caregivers of Critically Ill Patients


Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matte, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Maze, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group

- We do not have similar data in critically ill children.
Post-PICU follow-up clinic at CHU Sainte-Justine

• Patient’s outcomes after PICU discharge are a growing concern of pediatric intensivists.
• In 2018, we launched a post-PICU outpatient clinic.
• Patients are seen about 3 months post ICU discharge.

Geneviève Du Pont-Thibodeau
Laurence Ducharme-Crevier
Post-PICU mid-term (months) and long-term (years) morbidity

- **Respiratory problems.**
  - Abnormal voice.
  - Persistent dyspnea.

- **Neuromuscular problems.**
  - Neurodevelopmental delay, lower IQ, memory deficit, etc.
  - ICU-acquired weakness: critical illness polyneuropathy and/or myopathy.
  - Sleep disorder, night terrors.

- **Digestive problems.**
  - Disturbed growth.
  - Swallowing problem.
  - Eating disorder.

- **Chronic kidney injury.**

- **Psychosocial disorders.**
  - Disturbed emotional, social & school functioning.
  - Behavioral disorder, hyperactivity.
  - Post-traumatic stress disorder (PTSD).
  - Depression, anxiety.

- **Other:**
  - Bad quality of life.
  - Severe pain (bone, muscle, etc.).
  - Metabolic syndrome.
  - Chronic inflammation.
  - Persistent anemia.
  - Post-thrombotic syndrome.
  - Amputation.

- **Post intensive care syndrome family**
• What is the epidemiology of post-PICU adverse outcomes?
  • The exact prevalence of post-intensive care syndrome (PICS) is unknown.
  • The risk factors of PICS are not well characterized.

• Is there an association between severity of MODS and post-ICU outcomes?

• Is there a cause-effect relationship between severity of MODS and post-ICU outcomes?

• Does decreasing severity of MODS improve post-ICU outcomes?
MODS AS AN OUTCOME MEASURE IN CLINICAL TRIALS
Should we mind using MODS as an outcome measure in clinical trials?
New and progressive MODS: definition

• **New MODS:**
  – For patients with no organ dysfunction at time zero (PICU entry or randomization), the development of two or more concurrent organ dysfunctions at any time during the study period.
  – For patients with one organ dysfunction at time zero, the development of at least one other concurrent organ dysfunction after the time of randomization.

• **Progressive MODS:**
  – Patients with MODS at time zero (PICU entry, randomization) can contract progressive MODS, which is defined as the development of at least one additional concurrent organ dysfunction or death at any time during the study period.
New/progressive MODS: why?

- NP/MODS is a composite outcome (MODS + death).
  - Adding progressive to new MODS almost doubled the number of MODS that appears after day 1 in PICU (from 15.3% to 27.8%).
  - The incidence rate of NP/MODS (27.8%) was 7.5 times the incidence rate of PICU mortality (3.7%) in Ste-Justine PICU.
  - Using NP/MODS as the primary outcome measure of a randomized controlled trial should decrease significantly the required sample size.

NP/MODS in 799 consecutive PICU patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>New MODS (N/MODS)</td>
<td>15.3%</td>
</tr>
<tr>
<td>Progressive MODS (P/MODS) †</td>
<td>12.5%</td>
</tr>
<tr>
<td>Total (NP/MODS)</td>
<td>27.8%</td>
</tr>
</tbody>
</table>

† Includes PICU mortality (3.7%)

MOD score (Crit Care Med 1995;23:1638-52)

- The score includes descriptors from 6 systems:
  - **Respiratory** system (PO$_2$/FiO$_2$ ratio);
  - **Renal** system (serum creatinine concentration);
  - **Hepatic** system (serum bilirubin concentration);
  - **Hematologic** system (platelet count);
  - **Central nervous system** (Glasgow Coma Scale).
  - **Cardiovascular** system (pressure-adjusted heart rate, which is calculated as the product of the heart rate and the ratio of central venous pressure to mean arterial pressure):

- Maximal score: 24.
- Discrimination (prediction of mortality): area under the ROC curve was 0.936 in the development set, 0.928 in the validation set.
- The difference between maximal scores and scores obtained on 1$^{st}$ day [i.e., delta Multiple Organ Dysfunction Score or $\Delta$ MODS)] also demonstrated a strong correlation with ICU mortality rate.
PELOD-2

- 3671 consecutive PICU patients
- Median age: 15.5 months (IQR: 2.2–70.7)
- Mortality: 6.0%
- PELOD-2 score:
  - 10 variables
  - 5 organ dysfunctions.
- Discrimination: 0.934.
- Calibration: p=0.317.

• Some MODS scores are old. They must be...
  – ...updated,
  – ...validated
  – ...and compared to prevalent scores.
• Another issue with scores is whether to treat them as continuous or categorical.
• MODS can be a useful outcome measure in trials targeting subpopulations of critically ill patients with a low risk of mortality.
  – For example, adults undergoing complex cardiac surgery.
MODS: useful outcome in trials conducted in adults?

- Participants: > 12 years of age undergoing complex cardiac surgery.
- Hypothesis: transfusion of red cell units stored ≤ 10 days is better than transfusion of units stored ≥ 21 days?
- Primary outcome: change in MODS score.
- 7-day / 28 day mortality:
  - Short-term group: 2.8%/4.4%.
  - Longer-term group: 2.0%/5.3%.

Research questions: MODS as an outcome measure

- What is the best MODS-related metrics that can be used as an outcome measure in critically ill children?
  - New/progressive MODS?
  - Scores (PELOD, pediatric SOFA)?
  - Organ dysfunction-free days?
Monitoring MODS: take home messages

• There is room for enhanced and more precise monitoring of MODS. Several markers are candidate to serve in this role:
  – Daily MODS scores.
  – Continuous monitoring of heart rate variability.
  – Repeated measurements of biomarkers (redox balance, etc.).

• The reliability and the added value of markers monitoring the severity of MODS over time must be studied and compared.
Research questions: Monitoring progression of MODS

• What is the best metrics to monitor progression of severity of MODS?
  – MODS scores and/or variation in MODS score (for example $\Delta$ MOD score, $\Delta$ daily PELOD-2, etc.)?
  – Tests: heart rate variability, redox balance...?

• Is it useful to monitor MODS progression?
  – MODS metrics: are they meaningful and reliable outcomes in cohort studies and randomized controlled trials?
  – Can change (trends) over time of MODS score ($\Delta$ MODS score) be used to adjust treatment of single ICU patients?
TAKE-HOME MESSAGES AND CONCLUSION
Take-home messages

• Severe sepsis is probably a specific variant of MODS.
• We must improve the list of MODS diagnostic criteria.
• We must find a reference standard to diagnose MODS.
• We must learn if MODS can be used as a surrogate outcome measure in ICU-related trials.
• We must improve the treatment of MODS.
Research agenda on MODS: a new hope

• “Life is like riding a bicycle. To keep your balance, you must keep moving” (Albert Einstein).

• I hope that we keep moving and address the questions on MODS raised in this talk and in the medical literature.

• MODS must become a research priority.
  – Granting agencies should allocate more funds to research on MODS.
THANK YOU!