25 Hydroxyvitamin D concentrations in critically ill children: deficiency rates and relationship with illness severity

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Background

- There are 10,000 PICU admissions in Canada each year (accounting for ~40,000 ICU days)

- Pediatric critical illness leads to
  - Mortality
  - Morbidity (acute and chronic)
  - Family stress and loss of income
  - Significant health resource utilization

- Therapies that target disease prevention or hasten resolution of critical illness are required
Vitamin D is a pleiotropic hormone important for the proper functioning of multiple organs.

Adult critical care studies
- Lucidarme et al. 2010. ICM. 36: 1609
- McKinney et al. 2011 JAMDA. 12:208

Associations between vitamin D & greater illness severity and mortality
There are no pediatric studies reporting prevalence or investigating the potential role of vitamin D in critical illness

- Well almost none
Vitamin D Deficiency in Young Children With Severe Acute Lower Respiratory Infection

J. Dayre McNally, MD, PhD, Karen Leis, MD, Loren A. Matheson, PhD, Chandima Karuananyake, PhD, Koravangattu Sankaran, MD, and Alan M. Rosenberg, MD*

Study objectives

- PRIMARY
  - Determine the prevalence of vitamin D deficiency in critically ill children

- SECONDARY
  - Investigate associations between vitamin D levels and illness severity and morbidity
Methods

Secondary analysis of a multicentre prospective study determining prevalence of adrenal insufficiency in critically ill children *

- Multi-center study (7 PICUs, 2005 - 2008)
- Eligibility Criteria
  - Between newborn and 17 years
  - Central venous or arterial line in place
  - Consent obtained within 24 hours of admission
  - No HPA dysfunction, etomidate use, steroid exposure

Menon K et al. 2010. Am J Respir Crit Care Med. 182(2):246
Methods

☑ Obtain permission from investigators and REB
  - 6 of 7 REBs provided permission (337/389)

☑ Funding obtained - CHEORI grant (2010)

☑ Ontario Screening Laboratory at CHEORI develops 25(OH)D assay
  - Validated assay using DEQAS and HSC samples
  - Serum available for 326 of 337 participants

☑ Statistical Analysis and Manuscript preparation
### Results: Demographic Data

<table>
<thead>
<tr>
<th>Patient Characteristic (n=326)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Medical – No (%)</td>
<td>97 (30)</td>
</tr>
<tr>
<td>Surgical, cardiac – No (%)</td>
<td>122 (37)</td>
</tr>
<tr>
<td>Surgical, noncardiac – No (%)</td>
<td>107 (33)</td>
</tr>
<tr>
<td>PRISM score – median (IQR)</td>
<td>6 (3, 10)</td>
</tr>
<tr>
<td>Mechanical Ventilation – No (%)</td>
<td>235 (72)</td>
</tr>
<tr>
<td>PICU length of stay – median (IQR)</td>
<td>4 (3, 7)</td>
</tr>
<tr>
<td>Received catecholamines – No (%)</td>
<td>88 (27)</td>
</tr>
</tbody>
</table>

- Representative PICU population
Results: How common is deficiency?

Deficiency (69%)
Severe (14%)
Sufficiency (8%)
Vitamin D Levels: Literature review

25 (OH)D (nmol/L)

ADULT ICU

ICU PEDS

CANADIAN PEDIATRIC, CONTROL POPULATIONS

Lee, 2009
McKinney, 2011
Lucidarme, 2010
THIS STUDY
Roth, 2007
McNally, 2009
Stoian, 2011
Langlois, 2010
Langlois, 2010

Lee, 2009
McKinney, 2011
Lucidarme, 2010
THIS STUDY
Roth, 2007
McNally, 2009
Stoian, 2011
Langlois, 2010
Langlois, 2010
Results: 25(OH)D vs. organ

CATECHOLAMINES

- None
- Required

FLUID BOLUS

- < 40 cc/kg
- > 40 cc/kg

MECHANICAL VENTILATION

- None
- Required

HYPOCALCEMIA

- No
- Yes
Results: Clinically Important Outcome

- MORTALITY
  - Common in adult critical illness, rate of 15–30%
  - Uncommon in pediatric critical illness, rate of 3%

<table>
<thead>
<tr>
<th>PICU survival status by Vitamin D subgroup</th>
<th>Alive</th>
<th>Dead</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D &lt; 50 nmol/L</td>
<td>220</td>
<td>5</td>
<td>0.15</td>
</tr>
<tr>
<td>Vitamin D &gt; 50 nmol/L</td>
<td>101</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Results: Clinically Important Outcome

- PICU LENGTH OF STAY
  - Linear Regression Analysis
    - Controlling for other predictors (diagnosis, PRISM score or illness severity, PICU site) vitamin D level < 50 nmol/L was associated with longer length of stay
      - Effect size, 1.92 days (CI: +0.17, 3.96)
      - Statistical level, p=0.03
Conclusions

- Demonstrated that critically ill children commonly have inadequate vitamin D levels at time of PICU admission

- Demonstrated an association between vitamin D deficiency, organ dysfunction & length of stay
  - Agree with recently completed adult ICU studies
  - Not powered to evaluate mortality
Future Direction

- Determine the impact of critical illness and ICU related therapies on vitamin D
- Evaluate functioning of the vitamin D parathyroid axis
- Determine whether rapid repletion improves recovery time in pediatric critical illness and/or prevents subsequent illness
Acknowledgements

- Dr. Dermot Doherty (PICU/Anesthesia)
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- Mylene Theriault (Newborn screening lab)
- Kathryn Williams (statistics)
- Nathalie Earl (research assistant)

Funding source:
- CHEO Research Institute (Resident/Fellows grant)
CHD: Perioperative 25(OH)D levels

40–50 % decline in 25(OH)D
CHD: Perioperative 25(OH)D levels

40–50 % decline in 25(OH)D

Vitamin D levels in CHD patients (n=58)

<table>
<thead>
<tr>
<th>Severe deficiency (&lt; 25 nmol/L)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency, (&lt; 50 nmol/L)</td>
<td>15 (27%, 17-40%)</td>
</tr>
<tr>
<td></td>
<td>48 (86%, 74-93%)</td>
</tr>
</tbody>
</table>
CHD: Perioperative 25(OH)D levels

No increase in post-operative, 125(OH)2D levels over first 2 days
**Results: Catecholamine use & 25(OH)D**

No significant difference pre-operatively ($p = 0.32$)

Highly statistically significant post-op difference in 25(OH)D levels between groups ($p < 0.0001$)
Low ionized $Ca^{2+}$

Parathyroid gland

PTH secretion

Kidneys

Vitamin D activation

25(OH)D

1,25(OH)$_2$D

End Organs

Restoration of $Ca^{2+}$

Congenital Dysgenesis
- 22q11 deletion
- Latent Hypoparathyroidism

$2^\circ$ Parathyroid dysfunction
- Ischemia
- Inflammation

$2^\circ$ Kidney Damage
- Ischemia
- Inflammation

$1^\circ$ Deficiency
- Dietary inadequacies
- Reduced sun exposure

$2^\circ$ Deficiency
- Cardiopulmonary bypass
- Ultrafiltration
- Capillary Leak
- Hemodilution

End Organ Resistance
- Ischemia
- Inflammation
Results: Clinically Important Outcome

LENGTH OF PICU STAY

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>95% CI</th>
<th>p - value</th>
</tr>
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<tbody>
<tr>
<td>Intercept</td>
<td>0.98</td>
<td>(-1.24, 3.21)</td>
<td>0.384</td>
</tr>
<tr>
<td>Central Ontario</td>
<td>3.84</td>
<td>(1.78, 5.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Southern Ontario</td>
<td>0.77</td>
<td>(-1.87, 3.40)</td>
<td>0.568</td>
</tr>
<tr>
<td>Central Prairies</td>
<td>1.28</td>
<td>(-2.43, 5.00)</td>
<td>0.497</td>
</tr>
<tr>
<td>Western Prairies</td>
<td>0.86</td>
<td>(-1.80, 3.53)</td>
<td>0.524</td>
</tr>
<tr>
<td>West Coast</td>
<td>1.66</td>
<td>(-3.97, 7.29)</td>
<td>0.562</td>
</tr>
<tr>
<td>Vitamin D &lt; 50 nmol/L</td>
<td>1.92</td>
<td>(0.17, 3.68)</td>
<td>0.032</td>
</tr>
<tr>
<td>Medical</td>
<td>3.45</td>
<td>(1.31, 5.59)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical, cardiac</td>
<td>1.16</td>
<td>(-0.96, 3.28)</td>
<td>0.283</td>
</tr>
<tr>
<td>PRISM score</td>
<td>0.15</td>
<td>(-0.008, 0.31)</td>
<td>0.09</td>
</tr>
</tbody>
</table>