High(er) Insulin Sensitivity Rules Out Sepsis in Critical Care

Advanced sepsis detection as part of tight glucose control

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Presenter Disclosure Information

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Research Support: None
Speaker’s Bureau: None
Board Member: Intersection LifeSciences Ltd, Christchurch, NZ
Stock/Shareholder: None
Consultant: None
Employee: None
Other: None
Med101 For Engineers: Sepsis is bad!

- Sepsis and septic shock in critical care:
  - Significant incidence rates (2-11% for severe sepsis and higher for all forms)
  - Mortality of 30-80% reported
  - Tight glucose control can reduce mortality in sepsis
  - Annual (est.) cost of $16.7 per year in U.S. [Angus et al, 2001, Crit Care Med]

- Diagnosis is challenging and early treatment is beneficial
  - Gold Standard = positive blood culture should precede treatment but takes 24-48 hours
  - Early goal directed therapy reduced mortality from 46-31% [Rivers et al, NEJM 2001]
  - Therefore other markers are often used:
    - Primarily inflammatory and acute immune response markers with 2-3 hour lag on diagnosis and/or results (TNFα, IL-6, IL-8, CRP and PCT) [Carrigan et al, Clin Chem 2004]

- Insulin sensitivity is significantly affected by sepsis – could it be a marker?
  - Low values indicating sepsis or high values indicating its lack of presence
  - Mechanisms not fully known but assumed related to counter-regulatory and stress response in illness, as well as pro-inflammatory immune response and drug therapy.

- Hypothesis: Could an Insulin Sensitivity marker provide a more accurate diagnostic and reduce the preventative use of (broad coverage) antibiotics?
Methods

- Retrospective Study:
  - 143 patients under tight glucose control using SPRINT at Christchurch Hospital
  - 113 w/o sepsis; 30 diagnosed with sepsis
  - Cohort comprises 26,000+ hours of data

- Each hour was given a:
  - Sepsis score \( (ss) \) on a scale of 0 → 4
  - Clinically validated model-based insulin sensitivity value \( (S_I) \)
  - Simplified insulin sensitivity during periods of constant glucose level based on nutrition and insulin inputs \( (SS_I) \)

- Patients with T1DM or T2DM were excluded

- Ethics approval from South Island Regional Ethics Committee (New Zealand).
Strictly clinical metric

Follows ACCP and SCCM guideline definitions of 1992 and 2003 for sepsis diagnosis

Includes both SIRS and SOFA scores to account for more than a single criteria

Inotrope dosing included due to its common use in treating severe sepsis

**Sepsis Score (ss)**

1. Infection & Inflammatory Response (SIRS ≥ 2)
2. ≥ 1 Organ Failure & Fluid resuscitation
3. Inotrope drugs (low dose)
4. Inotrope drugs (high dose)

### Sepsis Score Table

<table>
<thead>
<tr>
<th>Sepsis score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Sepsis</td>
</tr>
<tr>
<td>2</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>3</td>
<td>Septic shock</td>
</tr>
<tr>
<td>4</td>
<td>Refractory septic shock</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIRS ≥2</th>
<th>Infection during stay</th>
<th>Organ failure ≥1</th>
<th>Fluid resuscitation</th>
<th>Inotrope present</th>
<th>High inotrope dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
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*Adrenaline or noradrenaline ≥0.2 mg min^-1 kg^-1*.
Insulin Sensitivity Metrics

- **Model based insulin sensitivity \( (S_I) \):**
  - Derived from fitting a dynamic model to the data
  - Model clinically validated in several glycaemic control studies and trials in critical care and vs. euglycaemic clamp
  - Readily calculated in real-time by computer

\[ \begin{align*}
\dot{I} &= -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}}{V} \\
\dot{Q} &= kI - kQ \\
\dot{G}_t &= -p_G G_t - S_I G_t \frac{Q}{1 + \alpha_G Q} + \frac{P(t)}{V_G} + P_{end}
\end{align*} \]

- **Simplified insulin sensitivity metric \( (SS_I) \):**
  - Matches the ISI of euglycaemic clamp (ISI/G normalisation)
  - Valid during periods of relatively constant glucose levels
  - Can be calculated by hand in real-time

\[ SS_I = P(t) \frac{60}{I(t)G_t} \]
Patients

- Retrospective data study
- T1DM and T2DM excluded if diagnosed
- Sepsis patients were all diagnosed by blood culture

### Summary of Patient hours in each subset of the ICU cohort

<table>
<thead>
<tr>
<th></th>
<th>Sepsis</th>
<th>Non-Sepsis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>30</td>
<td>113</td>
<td>143</td>
</tr>
<tr>
<td><strong>Total Hours</strong></td>
<td>6,744</td>
<td>19,709</td>
<td>26,453</td>
</tr>
<tr>
<td><strong>Total Hours where dG/dt ~ 0 for SS</strong></td>
<td>2,036</td>
<td>5,493</td>
<td>7,529</td>
</tr>
</tbody>
</table>
ROC Results (for $ss \geq 3$)

- **Model based ($S_f$):**
  - Sensitivity = 78%
  - Specificity = 82%
  - Positive Prediction = 2.8%
  - Negative Prediction = 99.8%
  - $S_f$ Cutoff = 8.5e-5
  - % Measurements < cutoff = 15%

- **Simple ($SS_f$):**
  - Sensitivity = 69%
  - Specificity = 82%
  - Positive Prediction = 2.5%
  - Negative Prediction = 99.7%
  - Lower numbers of hours
Is $SS_i$ an effective metric?

- Good correlation at low cutoff values
- Spread at higher values above cutoff values
- Spread thus does not affect usefulness of simple metric ($SS_i$) as a negative predictor of sepsis in place of the model based metric ($S_i$)

$NB: I \geq 2U/hr$

$r = 0.82$
Why not positive prediction?

- Any number of clinical causes of low insulin sensitivity
- Drug therapies can lower insulin sensitivity in survivors
- Mortality and lower insulin sensitivity may also go together (level of acuity)
- These results are from a study of steroids and insulin sensitivity in 53 Subarachnoid Haemorrhage patients
- Positive prediction will require a way to filter out other causes of low insulin sensitivity
Conclusions and Positive Prediction

- Both metrics provide **negative prediction** for/over a significant amount of the patient hours.
  - May thus reduce unnecessary preventative antibiotic use

- Both insulin sensitivity metrics can be readily available at bedside
  - $S_I$ requires a model and computation (e.g. PDA)
  - $SS_I$ requires a consistent and an effective glycaemic control protocol

- **Positive prediction** is $\sim 0$ because very low insulin sensitivity may be indicative of sepsis or a variety of other conditions and/or drug therapies

- Future necessities:
  - Improve cutoff values and validate prospectively (tighter metric)
  - Better sepsis score?
  - Improve positive prediction via additional heuristics or symptoms in addition to insulin sensitivity to discriminate between sepsis and other conditions?
Acknowledgements … or how I did this all myself!

Dunedin
- Dr. Kirsten McAuley
- Prof Jim Mann

The Danes
- Prof Steen Andreassen
- Dr. Chris Hahn

Maths + Stats
- Dr. Dom Lee

Some guys named Geoff
- Geoff Shaw and Geoff Chase

Don't let this happen to you!

Other individuals:
- Jess Lin
- Thomas Lott
- Aaron LeCompte
- Jason Wong et al.
- Hans Geschwindner
- Lusann Yang
- Amy Blakemore & Piers Lawrence
- Carmen Doran
- Kate Moorhead
- Sheng-Hui Wang
- Uli Goltenbott
- Simone Scheurle
- Norma Razak
- Chris Pretty
- Jackie Parente
Questions?