The Persistent Inflammation, Immunosuppression and Catabolism Syndrome: The Journey From Chronic Critical Illness to ‘Induced Frailty’

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Disclosures/Conflicts of interest

• None
Case

- 64 y/o male
- PMHx: Smoker, COPD
- Hits deer on motorcycle
- Hemorrhagic shock
- “Damage control” laparotomy, splenectomy
- **Day 3:** acute respiratory distress syndrome
- **Day 8:** ventilator associated pneumonia
- **Day 13:** urinary tract infection
- **Day 19:** Discharged to LTAC for ventilator weaning
• 71 y/o male
• PMHx: Diabetes, CAD
• Peritonitis, sepsis
• “Damage control” laparotomy, sigmoidectomy, end colostomy
• Day 2: Stage 3 KDIGO acute kidney injury (i.e. dialysis)
• Day 6: Ventilator associated pneumonia
• Day 10: Post-op wound infection
• Day 18: Discharged to LTAC for wound care and dialysis
Are these clinical victories?
Can we celebrate these outcomes as success?

What does this have to do with Geriatric Medicine?...
My clinical world...Acute Care Surgery

- Trauma
- Operating Room
- Emergency General Surgery
- Surgical Critical Care
Is Critical illness survival, a victory?...

• Inpatient mortality after critical illness and shock has progressively declined.
  • Sepsis: ≈40-50% → 15%
  • Severe Trauma: 22 → 11%

• But does Survival = Success?...
‘Survival’ after critical illness is GREY
The Problem...

Trauma

Then...

Emergency Surgery

Now...
Global populations are aging...

**Population 65 Years and Older by Size and Percent of Total Population: 1900 to 2010**

(For more information on confidentiality protection, nonsampling error, and definitions, see [www.census.gov(prod/cen2010/doc/sf1.pdf](www.census.gov/prod/cen2010/doc/sf1.pdf))

Sources: U.S. Census Bureau, decennial census of population, 1900 to 2000; 2010 Census Summary File 1.
Why should we care...

• Advancing age is a consistent risk factor for poor outcomes after surgery (elective, emergent, trauma, surgical sepsis, etc.)
  • Prolonged hospitalization
  • Prolonged intensive care unit (ICU) length of stay
  • Increased resource utilization (i.e., £££...)
  • Skilled nursing facility placement
  • Increased mortality

• But, surgical inpatient and ICU mortality has significantly DECREASED over the past 30 years...
Patients survive to discharge, but...

- 49% decrease in-hospital mortality
- 47% increase 1-2 year post-discharge mortality

→ Advancing age
→ Discharge to skilled nursing facility
...a subset of patients languish in the ICU

- 51,577 major surgery patients at UF Health 2000-2010
- Nearly 50% of patients that are still in the ICU at 14 days are dead at 2 years
The paradox of surgical intensive care...

- ICU inpatient mortality continues to improve...

- ...but long-term outcomes in critically ill trauma & surgical sepsis patients remain dismal?
How did we get from here to there?...
How did we get from here to there?...

Science, in the very act of solving problems, creates more of them.

— Abraham Flexner —
Chronic Critical Illness (CCI) after Shock

- Advancements in organ support and implementation of evidence-based protocols
  - ↓↓↓ in-hospital mortality
- Clinical burden of sepsis is shifting
  - Early death (Refractory shock/organ failure)
  - Prolonged intensive care
- Chronic critical illness (CCI)
  - ≥14d ICU LOS with persistent, manageable organ dysfunction
  - Recurrent infections/complications
  - Physically debilitated
  - Survive to discharge → LTAC/SNF
  - Long-term outcomes (???)
So, ICU patients with sepsis are really sick...

Who cares?...

We get them out of the ICU alive!
“People are often said as dying of ‘natural causes’. The natural cause of death is sepsis...” - Frederick Moore, MD
Medical Sepsis

- Dysfunctional host immune response compounded by age, comorbidities and “inflammaging”
- End stage event for terminal disease processes and severe comorbidity
  - Community acquired pneumonia
  - Influenza
  - Urinary tract infections

“Dying WITH sepsis”

Surgical Sepsis

- ALSO dysfunctional host immune response compounded by age, comorbidities and “inflammaging”
- BUT surgeons automatically apply ‘selection bias’
- De novo surgical emergency or Post injury/surgical complications
  - Intra-abdominal sepsis
  - Necrotizing soft tissue infections
  - Obstructive urosepsis (i.e. stones)
  - Post-op surgical site infection
  - Post-op ventilator associated pneumonia

“Dying OF sepsis”
• Prospective cohort study
• 400 Surgical ICU sepsis patients
• 1-year longitudinal f/u

Prospective cohort study
400 Surgical ICU sepsis patients
1-year longitudinal f/u
3 clinical trajectories after sepsis

Surgical ICU patients admitted with or developed Sepsis (n=301)

- **Early Death** (< 14 days) (n=13) 4%
- **CCI** (ICU LOS ≥14d with persistent organ dysfunction) (n=99) 33%
- **Rapid recovery** (ICU LOS <14d + organ recovery) (n=189) 63%

(Brakenridge et al., Ann Surg submitted)
What determines your clinical trajectory?...

### Table: Clinical Trajectory Determinants

<table>
<thead>
<tr>
<th>Feature</th>
<th>Early Death (n=13; 4%)</th>
<th>CCI (n=99; 33%)</th>
<th>RAP (n=189; 63%)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>8 (61.5)</td>
<td>64 (64.6)</td>
<td>97 (51.3)</td>
<td>0.034</td>
</tr>
<tr>
<td>Age in years, mean ± SD</td>
<td>67.2 (13.1)</td>
<td>61.8 (14.7)</td>
<td>56.9 (15.5)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Charlson comorbidity index, median (25th, 75th)</td>
<td>4 (3, 5)</td>
<td>4 (2, 5)</td>
<td>2 (1, 4)</td>
<td>0.0002</td>
</tr>
<tr>
<td>APACHE II, median (25th, 75th)</td>
<td>29 (21, 38)</td>
<td>22 (16, 26)</td>
<td>14 (10, 19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inter-facility hospital transfer, n (%)</td>
<td>8 (61.5)</td>
<td>53 (53.5)</td>
<td>59 (31.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Septic shock, n (%)</td>
<td>10 (76.9)</td>
<td>39 (39.4)</td>
<td>28 (14.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MOF incidence, n (%)</td>
<td>13 (100)</td>
<td>78 (78.8)</td>
<td>55 (29.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum SOFA score, median (25th, 75th)</td>
<td>15 (12, 21)</td>
<td>10 (8, 12)</td>
<td>5 (3, 8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KDIGO Stage 3 Acute kidney injury, n (%)</td>
<td>9 (69.2)</td>
<td>22 (22.2)</td>
<td>8 (4.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Older patients, in septic shock, with severely deranged physiology and multiple organ dysfunction from infection → CCI

(= Brakenridge et al., Ann Surg submitted)
...and what happens to these “sepsis survivors”?

- They linger in the ICU...
- ...with recurrent nosocomial infections
- Discharged to high resource, long-term care facilities...

<table>
<thead>
<tr>
<th></th>
<th>CCI (n=99)</th>
<th>Rapid Recovery (n=189)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td># Secondary infections per 100 person hospital days, mean (SD)</td>
<td>2.9 (3.1)</td>
<td>1 (2.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU LOS, median (25th, 75th)</td>
<td>21 (15, 29)</td>
<td>4 (2, 9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital LOS, median (25th, 75th)</td>
<td>28 (20, 42)</td>
<td>11 (7, 19)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Discharge disposition, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>“Good” disposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>1 (1)</td>
<td>54 (28.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Home with healthcare services</td>
<td>10 (10.1)</td>
<td>85 (45)</td>
<td></td>
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<tr>
<td>Rehabilitation facility</td>
<td>7 (7.1)</td>
<td>10 (5.3)</td>
<td></td>
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<tr>
<td>“Poor” disposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Term Acute Care facility</td>
<td>41 (41.4)</td>
<td>5 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Skilled Nursing facility</td>
<td>11 (11.1)</td>
<td>35 (18.5)</td>
<td></td>
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<tr>
<td>Another Hospital</td>
<td>10 (10.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hospice</td>
<td>6 (6.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>13 (13.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

(Bräkenridge et al., Ann Surg submitted)
...and succumb to insidious death.

1-year mortality – 21%

30-day mortality - 10%

Survival Probability

Days

Overall sepsis cohort

(n=301)

(Brakenridge et al., Ann Surg submitted)
Especially if you are older adult...

1-year mortality

12%
14%
33%
...and linger in the ICU with organ dysfunction

1-year Mortality – 5%

1-year Mortality – 41%

In-hospital mortality - 13%

Rapid recovery

(Brakenridge et al., Ann Surg submitted)
What is the underlying mechanism of poor outcomes in those that ‘survive sepsis’ but develop CCI?...
Trauma and sepsis are diseases of host immune dysfunction

- Acute “Inflammatory hit”
- Activation innate immune system
  - DAMPs/PAMPs
- Acute Inflammatory “Storm”
  - Innate immune transcriptome
  - Cytokines
  - Dysfunctional robust response
- Persistent immune dysfunction
  - Low-grade inflammation
  - Prolonged organ dysfunction
  - Chronic immunosuppression
  - Recurrent Infections
Persistent Inflammation, Immunosuppression & Catabolism Syndrome (PICS)

- Early death
- MOF
- Anti-inflammatory
- Pro-inflammatory
- Rapid recovery
- Sepsis/Trauma
- "Genomic Storm"

Persistent Inflammation, Immunosuppression & Catabolism Syndrome (PICS)

- Discharge to LTAC
- Recurrent infections
- Insidious death

Persistent inflammation, immunosuppression, catabolism syndrome

- Progressive immunosuppression
- Catabolic state → Muscle Wasting

CHRONIC CRITICAL ILLNESS (CCI)

Time:
- 14d
- 6 mo.
- 12 mo.
Persistent inflammation in CCI patients

(n=145)

IL-6

CCI
Rapid Recovery

P < 0.05

IL-8

CCI
Rapid Recovery

P < 0.05

(Stortz et al., JTACS 2018)
Persistent immunosuppression in CCI patients

**Absolute Lymphocyte Count**

![Graph showing lymphocyte count over days post sepsis event for CCI and Rapid Recovery groups. The graph indicates a significant difference (P < 0.05) between the groups.](image)

**sPDL-1**

![Graph showing sPDL-1 levels over days post sepsis event for CCI and Rapid Recovery groups. The graph indicates a significant difference (P < 0.05) between the groups.](image)

*(Stortz et al., JTACS 2018)*
Non-resolving catabolism in CCI patients

Urine 3-Methylhistidine : Cr

IGFBP-3

(n=145)

(Stortz et al., JTACS 2018)
The ‘Vicious Cycle’ of PICS in the older adult
‘Muscle failure’, the forgotten organ dysfunction...

Muscle ‘fails’ (i.e., muscle mass loss) with persistent MOF

(-) muscle Synthesis/Breakdown balance

(Puthucheary et al., JAMA 2013)
Acute muscular inflammation is associated with acute muscle mass loss in critically ill patients

(Puthucheary et al., JAMA 2013)
Acute muscle loss after sepsis persists at 3 months
Activity deficits persist after sepsis/CCI
CCI patients linger with severe disability...

(n=301)
With high risk of death...and age matters

CCI Survival Probability

Time from sepsis onset (days)

- Age <45 years
- Age 45-64 years
- Age >65 years
What is the clinical & functional phenotype of “sepsis survivors” that develop CCI (+PICS) and ultimately succumb with dismal long-term outcomes?

‘Induced Frailty’
‘Induced Frailty’: A novel phenotype

- **Frailty Syndrome**
  - State of high vulnerability for adverse health outcomes
    - Disability
    - ADL dependency
    - Weakness/falls
    - Long-term care needs
    - High risk of 1-5 year mortality

- **CHRONIC dysfunctional inflammation**

- **CHRONIC, progressive change in health status**

- Associated and progresses with advanced age
‘Induced Frailty’: A novel phenotype

- ‘Induced Frailty’
  - State of high vulnerability to adverse health outcomes
  - NEW health state
  - Develops after ACUTE inflammatory insult/chronic critical illness
    - Sepsis/Trauma/Burn
  - ACUTE, progressive detrimental change in health status
  - Advanced age predisposes high risk for new morbid status
"Frailty"
Physiologic & functional deficits

"Pre-Frail"
"Robust"

Early Death
CCI

"Induced Frailty"
Frailty
Comorbidity
Disability

Late Death

Recovery

Baseline
Acute insult (Sepsis/Trauma)
3 mo.
6 mo.
1 yr.
“Frailty”
Physiologic & functional deficits

“Pre-Frail”

Baseline
Acute insult (Sepsis/Trauma)

Pre-event assessment
Inpatient Course
Outpatient assessment

3 mo.
6 mo.
1 yr.

“Induced Frailty”

Recovery
"Induced frailty" – Frailty status worsens after sepsis

Rockwood Clinical Frailty Scale

Mean (Sd Err)

- Very fit
- Managing Well
- Mildly Frail
- Severely Frail
- Moribund

Overall sepsis cohort

(*p<0.01)
"Induced frailty" – Frailty status worsens and persists after sepsis & CCI
“Induced frailty” - New deficits persist after sepsis & CCI
Comorbidity burden worsens & persists after CCI
Does the phenotype of “Induced Frailty” represent accelerated biologic aging?
Short of the obvious...

Can we do ANYTHING treat CCI/PICS?...
So just treat the inflammation, right?...

- Pre-clinical models show great promise for immunomodulation, but...

- Attempts to modulate the immune system in acute pro-inflammatory disease states (i.e. sepsis, trauma) have universally failed...
  - Steroids
  - TNF antagonists
  - Activated Protein C
Where can we intervene?

- **MODULATE EARLY INFLAMMATION & DYSFUNCTION**
- **RESTORE IMMUNE COMPETENCE**
- **BREAK LATE INFLAMMATORY “VICIOUS CYCLE” (MDSC)**

**INSIDIOUS DEATH**
Restoring immune competence after sepsis

• **α-PDL-1**
  – “immune checkpoint inhibitor”
  – Restores T-cell competence
  – FDA “fast-track” agent for multiple cancers (i.e. Nivolumab)

• **Interleukin-7**
  – Anti-apoptotic common γ-chain cytokine
  – Stimulates T/B-cell proliferation and functional recovery

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**Immune Checkpoint Inhibition in Sepsis: A Phase 1b Randomized, Placebo-Controlled, Single Ascending Dose Study of Antiprogrammed Cell Death-Ligand 1 (BMS-936559)**

(Hotchkiss, Moldawer, Brakenridge et al, Crit Care Med 2019)

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**Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial**

(Francois, Morre, Hotchkiss et al, JCI Insight 2017)
"Frailty"  
Cognitive  
Physiologic  
Functional  
Baseline  
Acute insult  
(Sepsis/Trauma)  
"Induced Frailty"  
Frailty  
Comorbidity  
Disability  
Recovery  
"Pre-Frail"  
"Robust"  
"Frail"  
Screening/intervention  
"Window"  
Early Death  
Late Death  
CCI  
PICS  
"Pre-Frail"  
3 mo.  
6 mo.  
1 yr.  
Recovery  
"Robust"
Frailty

Cognitive

Physiologic

Functional

Baseline

Acute insult
(Sepsis/Trauma)

Early Death

Late Death

3 mo.

6 mo.

1 yr.

Recovery

"Frail"

"Pre-Frail"

"Robust"

Recovery

BGS Spring Meeting 2019
What can YOU (the Geriatrician) do about all this?...

- Optimize the health status (and resilience) of your aging patients
- Establish “Goals of care” with patients (and families...) in the outpatient setting
- Geriatric “hospitalist” engagement/integration with surgical services is invaluable
- Engage with those doing research to advance the field
CCI/PICS – Takeaway points

- Survival to ICU discharge is **NOT** the end of the game...
  - Especially older adults!...

- Advancing age & severity of initial physiologic insult → CCI

- CCI patients exhibit persistent inflammation, immunosuppression and catabolism (*PICS*) driven by low-grade, multi-organ inflammation

- New physical/functional defects persist after CCI (*Induced Frailty*)

- Understanding the biology of inflammation AND aging is key to developing strategies and therapies to improve outcomes
Acknowledgements

• P50 GM111152
• R01 GM104481
• R01 GM113945
• T32 GM008721
• R03 AG056444
• P30 AG050499