Staging Sepsis: How Far Have We Come?

John C. Marshall MD

ISF Colloquium/Critical Care Canada Forum
Toronto Canada

October 26, 2015

St. Michael’s Hospital

University of Toronto
Simple Diseases

- Single biologic/anatomic abnormality
- Distinctive clinical phenotype
- Limited therapeutic options
- Predictable response to therapy
Complex Disease

- Biologic heterogeneity
- Clinical heterogeneity
- Multimodal therapy
- Variable response to therapy
The recognition that even simple diseases have elements of complexity is the foundation of precision medicine...

... the recognition that a disease is complex underlines the importance of therapeutic staging.
Therapeutic Options in Breast Cancer

- Surgery – lumpectomy, mastectomy
- Radiotherapy
- Chemotherapy
- Hormonal therapy
- Trastuzumab
- Signal transduction inhibitors
5-Year Relative Survival Rate for Breast Cancer

A History of Cancer Staging

International Union Against Cancer

Pierre Denoix
Primary Tumor (T)
TX: Primary tumor cannot be evaluated
T0: No evidence of primary tumor
Tis: Carcinoma in situ (CIS; abnormal cells are present but have not spread to neighboring tissue; although not cancer, CIS may become cancer and is sometimes called preinvasive cancer)
T1, T2, T3, T4: Size and/or extent of the primary tumor

Regional Lymph Nodes (N)
NX: Regional lymph nodes cannot be evaluated
N0: No regional lymph node involvement
N1, N2, N3: Degree of regional lymph node involvement (number and location of lymph nodes)

Distant Metastasis (M)
MX: Distant metastasis cannot be evaluated
M0: No distant metastasis
M1: Distant metastasis is present
The TNM System
(Tumor, Nodes Metastasis)

A biologic model of disease

Staging of and Prognosis for Colorectal Cancer
Trastuzumab Improves Disease-Free Survival in HER2 Positive Breast Cancer


<table>
<thead>
<tr>
<th></th>
<th>No. at Risk</th>
<th>Months after Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus trastuzumab</td>
<td>235 152 63 15</td>
<td></td>
</tr>
<tr>
<td>alone</td>
<td>234 103 25  6</td>
<td></td>
</tr>
</tbody>
</table>

Graph showing progression-free survival rates for chemotherapy alone and chemotherapy plus trastuzumab with a statistical significance of P<0.001.
HER2 Positivity and Response to Paclitaxel

Staging

- Prognosis
- Response to therapy
  (modifiable prognosis)
Sepsis

- Tachycardia
- Tachypnea
- Hypo- or hyperthermia
- Leukocytosis of leukopenia

± Organ dysfunction, shock
### Cytokine Levels in Human Sepsis

<table>
<thead>
<tr>
<th></th>
<th>Median (pg/ml)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>83</td>
<td>7 – 57,151</td>
</tr>
<tr>
<td>IL-6</td>
<td>965</td>
<td>8 – 1,553,435</td>
</tr>
<tr>
<td>IL-8</td>
<td>2130</td>
<td>16 – 651,338</td>
</tr>
</tbody>
</table>

- MONARCS, Unpublished
Can we stage sepsis to guide therapy?
Insult (Infection) | Response | Organ Dysfunction
---|---|---
Microbiology | Clinical | Aggregate
Biochemical | Specific
Staging

- Prognosis
- Response to therapy
  (modifiable prognosis)
Influence of Infectious Challenge on Response to Neutralization of TNFα

Absolute Risk Reduction (%)

Salmonella

Candida

Listeria

M. tuberculosis

## Impact of TLR4 Inhibition on 28 Day Survival

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Eritoran</td>
<td>p.</td>
<td></td>
</tr>
<tr>
<td>Gram positive</td>
<td>24.7%</td>
<td>33.8%</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>(N=182)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram negative</td>
<td>22.3%</td>
<td>21.9%</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>(N=215)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Impact of Source Control in Patients with Low IL-6 Levels

<table>
<thead>
<tr>
<th>Source Control</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate (N=545)</td>
<td>126 (23.1%)</td>
</tr>
<tr>
<td>Inadequate (N=121)</td>
<td>48 (39.7%)*</td>
</tr>
</tbody>
</table>

* p<0.001
### Impact of Source Control in Patients with High IL-6 Levels

<table>
<thead>
<tr>
<th>Source Control</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate (N=419)</td>
<td>177 (42.3%)</td>
</tr>
<tr>
<td>Inadequate (N=85)</td>
<td>40 (47.1%)*</td>
</tr>
</tbody>
</table>

* p=0.49
IL-6 and Response to Anti-TNF

Baseline IL-6 (ng/ml)

28 Day Mortality (%)

Baseline IL-6 (ng/ml)

Anti-TNF MAb

Placebo
# Impact of Organ Dysfunction on Response to Antibiotics

<table>
<thead>
<tr>
<th>LOD</th>
<th>ICU Mortality</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>4</td>
<td>21/36 (59%)</td>
<td>20/36 (56%)</td>
</tr>
<tr>
<td>≤ 4</td>
<td>2/27 (7%)</td>
<td>16/43 (37%)</td>
</tr>
</tbody>
</table>

Anti-TNF is Most Efficacious in Patients without Organ Dysfunction

*p = 0.003;
OR 0.51 (0.32-0.80)
The PIRO Concept

- Predisposition
- Insult
- Response
- Organ dysfunction

- Crit Care Med 31:1250, 2003
What Do We Need?

- Secondary analysis of trials to detect differential treatment responsiveness
- Creation of UICC equivalent structure to guide development of staging system
- Registries and large databases to define natural history and probe potential sources of variability