The epidemiology of sepsis
A view towards (and from) the developed world
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Overview

- How is sepsis defined?
- How many cases?
- How much death and disability?
- How does sepsis incidence and care vary?
  - Within or across countries?
Take home messages …

- **Incidence, mortality and morbidity are high**
  - Particularly common in the elderly in the developed world
  - (Higher problem among children in the developing world)

- **Considerable long-term harm – a hidden public health disaster**

- **The gap between ‘developed’ world sepsis and ‘developing’ world sepsis is becoming increasingly arbitrary and unhelpful**
  - Care varies dramatically within the developed world
  - Developed world problems (and opportunities) are coming fast to the developing world

- **For discussion …**
  - A tiered approach to care based on regional resources
Classic paradigm

- **Severe sepsis** = infection PLUS acute organ dysfunction
- ‘Host’ theory

The different faces of sepsis

- ‘Old’ sepsis (phtisis)
- ‘Modern’ sepsis
Another ‘modern’ face of sepsis ...
Typical etiology (in adults)

- **Site**
  - Lung - 53.6%
  - Abdomen - 19.9%
  - Urinary tract - 10.2%
  - Other - 16.3%

- **Blood cultures**
  - Positive - 32.5%

- **Culture and/or Gram stain**
  - Purely gram negative - 23.3%
  - Purely gram positive - 25.1%
  - Mixed - 13.9%
  - Unknown, negative, or not obtained - 37.7%

Bernard et al. NEJM 2001
<table>
<thead>
<tr>
<th>Rank</th>
<th>Disorder</th>
<th>Number of DALYs × 10^6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lower respiratory infections</td>
<td>112.9</td>
</tr>
<tr>
<td>2</td>
<td>Diarrhoeal diseases</td>
<td>99.6</td>
</tr>
<tr>
<td>3</td>
<td>Perinatal disorders</td>
<td>92.3</td>
</tr>
<tr>
<td>4</td>
<td>Unipolar major depression</td>
<td>50.8</td>
</tr>
<tr>
<td>5</td>
<td>Ischaemic heart disease</td>
<td>46.7</td>
</tr>
<tr>
<td>6</td>
<td>Cerebrovascular disease</td>
<td>38.5</td>
</tr>
<tr>
<td>7</td>
<td>Tuberculosis</td>
<td>38.4</td>
</tr>
<tr>
<td>8</td>
<td>Measles</td>
<td>36.5</td>
</tr>
<tr>
<td>9</td>
<td>Road-traffic accidents</td>
<td>34.3</td>
</tr>
<tr>
<td>10</td>
<td>Congenital anomalies</td>
<td>32.9</td>
</tr>
<tr>
<td>11</td>
<td>Malaria</td>
<td>31.7</td>
</tr>
<tr>
<td>12</td>
<td>Chronic obstructive pulmonary disease</td>
<td>29.1</td>
</tr>
<tr>
<td>13</td>
<td>Falls</td>
<td>26.7</td>
</tr>
<tr>
<td>14</td>
<td>Iron-deficiency anaemia</td>
<td>24.6</td>
</tr>
<tr>
<td>15</td>
<td>Protein-energy malnutrition</td>
<td>21.0</td>
</tr>
<tr>
<td>16</td>
<td>War injuries</td>
<td>20.0</td>
</tr>
<tr>
<td>17</td>
<td>Self-inflicted injuries</td>
<td>19.0</td>
</tr>
<tr>
<td>18</td>
<td>Tetanus</td>
<td>17.5</td>
</tr>
<tr>
<td>19</td>
<td>Violence</td>
<td>17.5</td>
</tr>
<tr>
<td>20</td>
<td>Alcohol use*</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Murray et al. GBD study. Lancet 1997
Severe sepsis in the US

- 751,000 cases per year
- ~30% hospital mortality

Reference Diseases

- **Incidence in US (cases per 100,000)**
  - Colon cancer: 50
  - Breast cancer: 110
  - AIDS: 17
  - Congestive heart failure: ~130
  - Severe sepsis: ~300

- **Number of deaths in US each year**
  - Acute myocardial infarction: 211,000
  - Severe sepsis: 215,000
Continued Effect of Sepsis on Survival

Quartin et al. JAMA 1997; 277:1058-1063
Survival at one year after CAP

12 months after admission …
- One in three CAP *survivors* are dead
- Odds of dying are still
  - 2.7x general population
  - 1.4x age, sex, race and co-morbidity-matched hospital controls

*Kaplan et al. Arch Int Med 2003*
# Table 4. Risk of Incident Dementia by Hospitalization Status

<table>
<thead>
<tr>
<th>No Hospitalizations During Study (n = 1601)</th>
<th>One or More Noncritical Illness Hospitalizations (n = 1287)</th>
<th>One or More Critical Illness Hospitalizations (n = 41)</th>
<th>$P$ Value</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of incident dementia, No.</td>
<td>146</td>
<td>228</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Risk of incident dementia, HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.5 (1.3 to 1.9)</td>
<td>&lt;.001</td>
<td>.27</td>
</tr>
<tr>
<td>Adjusted risk of incident dementia, HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.4 (1.1 to 1.7)</td>
<td>.001</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

a Cox proportional hazards regression with age at study visit as the time axis and age at study entry as the beginning of the time period.

b Adjusted for age at study entry, sex, baseline Cognitive Abilities Screening Instrument item response theory score, years of education, and baseline comorbidities of coronary heart disease and cerebrovascular disease, with presence of coronary heart disease at baseline included as a time-varying covariate.
The lingering consequences of sepsis

- Longitudinal analysis of the Health and Retirement Study
- 3-fold increase in moderate/severe cognitive impairment
- 3-fold increase in physical function impairment

Iwashyna et al JAMA (in press)
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Author</th>
<th>Cases / 100 ICU admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Italy</td>
<td>Salvo</td>
<td>~11</td>
</tr>
<tr>
<td>1995</td>
<td>France</td>
<td>Brun-Buisson</td>
<td>9.1</td>
</tr>
<tr>
<td>1995</td>
<td>US</td>
<td>Rangel-Frausto</td>
<td>~12</td>
</tr>
<tr>
<td>1997</td>
<td>US</td>
<td>Sands</td>
<td>10.4</td>
</tr>
<tr>
<td>2001</td>
<td>US</td>
<td>Angus</td>
<td>11.2</td>
</tr>
<tr>
<td>2003</td>
<td>UK</td>
<td>Padkin</td>
<td>27.1</td>
</tr>
<tr>
<td>2003</td>
<td>US</td>
<td>Teres</td>
<td>11.3</td>
</tr>
<tr>
<td>2003</td>
<td>Europe</td>
<td>Alberti</td>
<td>11.3</td>
</tr>
<tr>
<td>2004</td>
<td>France</td>
<td>EPISEPSIS</td>
<td>14.6</td>
</tr>
<tr>
<td>2004</td>
<td>Australia</td>
<td>ANZICS</td>
<td>11.8</td>
</tr>
<tr>
<td>2004</td>
<td>Netherlands</td>
<td>van Gestel</td>
<td>11.0</td>
</tr>
<tr>
<td>2004</td>
<td>Brazil</td>
<td>Silva</td>
<td>17.4</td>
</tr>
</tbody>
</table>

But log-fold variation in population incidence

Linde-Zwirble Crit Care 2004
So what’s going on here?

- **Since 2004**
  - **Finland**
    - 10.4% of ICU admissions
  - **Spain**
    - 12.4% of ICU admissions
Resources Available Per Capita

- 7x variation in ICU beds/pop
- 3.5 ICU beds for every 100 hosp beds

Wunsch H, et al. CCM 2008
Across-country variation

- Variation in incidence proportional to ICU bed availability
- What is happening to sepsis cases in countries with fewer ICUs?
  - Do not exist?
  - Ex. Fewer elderly patients?
  - Exist but denied ICU care?
  - Marginal benefit or harm?
Severe sepsis rates and mortality in the ICU

ICU bed availability (probably) drives sepsis casemix and outcome

Race

Martin et al. NEJM 2003;348:1546-1554
Racial variation in sepsis by age

Barnato et al. AJRCCM 2008
Susceptibility to sepsis

Race (compared to White)
- Black
- Hispanic

Gender (compared to female)
- Male

% poverty (compared to 0-10)
- 10-20
- 20-30
- 30-40
- >40

Urbanization (compared to suburban)
- Rural
- Urban

Higher incidence of severe sepsis than reference category

Barnato et al. AJRCCM 2008
75% of African-Americans who incur invasive pneumococcal disease do so before they are eligible for vaccination.
**TLR4** polymorphisms, infectious diseases, and evolutionary pressure during migration of modern humans

- Variance not explained by genetic drift alone
- **Asp299Gly/399WT** haplotype
  - Negative effects in sepsis
  - Positive effects in malaria
Resuscitation in sub-Saharan Africa

FEAST

- RCT in 6 hospitals in East Africa
- 3,600 children presenting with fever and hypotension
- Normal saline vs. no fluids

No fluids is current standard of care

- WHO guidelines
- No IV fluids in absence of CVP monitoring because of risk of exacerbating cerebral malaria
Mortality after Fluid Bolus in African Children with Severe Infection


Maitland et al. NEJM 2011
Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study


Scott et al. Lancet 2011
Some thoughts on global sepsis …

- Traditionally divided into ‘developed’ and ‘developing’

- Developed …
  - Modern, well-financed urban populations in the developed world

- Developing …
  - Poor rural populations in sub-Saharan Africa and Asia

- Two worlds of sepsis
  - Elderly pneumonia patient in the ICU on life support
  - 3 year old malnourished village child with no access to clean water or food, let alone healthcare

- Strong ethos to avoid ‘hand-me downs’
  - Don’t just hand down ‘developed’ world solutions

- However, the two worlds are colliding …
Global urbanization

- 1900 - 3% of the world lived in an urban environment
- 2008 - 50%
  - 74% in developed world
  - 44% in developing world
- 2050 - >70% of entire population will live in cities
Where is the developing world?

50% of the world’s population within 2000 miles
The developing world is urbanizing …

Largest Urban Agglomerations, 1975, 2000, 2025

Size of Urban Population
- ○ 10 million and over since 1975
- ● 10 million and over since 2000
- ⬤ 10 million and over in 2025 (projected)


Ex: 231 of 800 million Sub-Saharan Africans live in cities
- ♦ 166 in urban slums
- ★ UN Habitat 2003
Multi-level targets …

- Well-financed urban settings
- Poorly-financed urban settings
  - Slums with cell phone towers and Britney Spears on the radio
- Remote, poor, rural settings
Conclusions

- Incidence, mortality and morbidity are high
  - Particularly common in the elderly in the developed world
  - Higher problem among children in the developing world

- Considerable long-term harm – a hidden public health disaster

- Across developed countries, treated incidence is extremely variable
  - Consistent relationship to the availability of ICU resources
  - Unknown fate for those not admitted

- Within countries, incidence also highly variable
  - Potential opportunities to improve care

- ‘Developed’ world sepsis is coming fast to the developing world
  - Time to think about inexpensive ‘modern’ resuscitation