Sepsis and Sepsis Mimics (Sepsis Update)

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American Certified Tropical Medicine, Fellowship in HIV AIDS Medicine, Adjunct Associate Professor, AHERF, NABH Assessor, Consultant Infectious Diseases, Apollo Hospitals, Chennai.
38 Y, F, T2DM, 7 days fever, Headache, Now SOB 2 days......

• O/e: Confused, Febrile 101F, PR 102/ min, RR 22 / min, BP 90/70
• RS Basal rales,? Terminal neck stiffness
• Inv. TC 12 K, P 85, TB 2.4 ALT 98, Crt: 2.6
• X-ray- Bil infiltrates.
• Completed T. Chloroquine on Ceftriaxone + Levoflox (D 5), IVF

What is your diagnosis?
• 1. SIRS
• 2. Sepsis
• 3. Severe Sepsis
• 4. Septic Shock
• 5. Start antibiotics
38 Y, F, T2DM..... AIDC 2017 Impact!
38 Y, F, T2DM, 7 days fever, Headache, Now SOB 2 days......

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**Now What is your diagnosis?**

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- 2. Sepsis
- 3. Severe Sepsis
- 4. Septic Shock
- 5. Start antibiotics
Objective: How to approach Sepsis in 2017!

Sepsis 3- 2016! Collapsing
Why sepsis at AIDC 2017?
Sepsis is common but neglected entity

Sepsis is one of the most common diseases
Cases per 100,000 population
(US / *Europe)

Sepsis

Million US-Dollars spent for state-funded research 2011
Sepsis research receives the lowest funding

Stroke*

Cancer

Heart

HIV
Why Sepsis today? It is Changing!!

• “Sepsis” is derived from the Greek work “sepo” which literally means “I rot”

• “Inflammation is not itself considered to be a disease but a salutary operation...but when it cannot accomplish that salutary purpose...it dose mischief”
  • John Hunter, MD (1728-1793)

• Sepsis is redefined as: “life-threatening organ dysfunction caused by a dysregulated host response to infection.” Sepsis-3
SIRS Sensitivity

SIRS is an *appropriate* response to infection – or any other stimulus that activates inflammation.

*Conclusions*: Almost half of patients hospitalized on the wards developed SIRS at least once during their ward stay. Our findings suggest that screening ward patients using SIRS criteria for identifying those with sepsis would be impractical.
Sepsis at AIDC 2017 Why?

- JAMA, Feb. 23, 2016: Sepsis-3, New criteria for defining sepsis

Sepsis is redefined as: “life-threatening organ dysfunction caused by a dysregulated host response to infection.”

• **Severe Sepsis: No longer used**

• **Sepsis:**
  – Suspected or documented infection and
  – Acute increase of ≥2 SOFA points (a proxy for organ dysfunction)

• **Septic Shock:**
  – Sepsis and
  – Vasopressor therapy needed to elevate MAP ≥65 mm Hg and
  – Lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation

In Non ICU (ED/ward)

- **qSOFA Score**: A means of rapidly identifying ED and hospital ward (non-ICU) patients with suspected infection at increased risk
  - At least 2 of 3 criteria:
    - RR ≥ 22/min
    - Altered mentation
    - SBP ≤ 100 mmHg

### Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{PaO}<em>2/F</em>\text{O}_2$ (mmHg)</td>
<td>600 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td>Platelets, $\times 10^3$/µL</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Liver</td>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>≤1.2 (20)</td>
<td>1.2-1.9 (20-22)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>MAP ≥ 70 mm Hg</td>
<td>MAP &lt; 70 mm Hg</td>
<td>Dopamine &lt; 5 or dobutamine (any dose)$^b$</td>
<td>Dopamine 5.1-15 or epinephrine ≤ 0.1 or norepinephrine &lt; 0.1$^b$</td>
<td>Dopamine &gt; 15 or epinephrine &gt; 0.1 or norepinephrine &gt; 0.1$^b$</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Glasgow Coma Scale score$^c$</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-0</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal</td>
<td>Creatinine, mg/dL (µmol/L)</td>
<td>≤1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
<td>&gt;5.0 (440)</td>
</tr>
<tr>
<td></td>
<td>Urine output, mL/day</td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**: $\text{FiO}_2$, fraction of inspired oxygen; MAP, mean arterial pressure; $\text{PaO}_2$, partial pressure of oxygen.

$^a$ Adapted from Vincent et al.$^{27}$

$^b$ Catecholamine doses are given as µg/kg/min for at least 1 hour.

$^c$ Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
<table>
<thead>
<tr>
<th></th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEPSIS</strong></td>
<td>SIRS</td>
<td>SUSPECTED/DOCUMENTED INFECTION</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Suspected Infection</td>
<td>2 or 3 on qSOFA (HAT):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension (SBP ≤100 mmHg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMS (GCS ≤13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachypnea (≥22/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rise in SOFA score by 2 or more</td>
</tr>
<tr>
<td><strong>SEVERE SEPSIS</strong></td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBP &lt;90 mmHg or MAP &lt; 65 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lactate &gt; 2.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INR &gt;1.5 or a PTT &gt;60 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilirubin &gt;34 μmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine output &lt;0.5 mL/kg/h for 2 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine &gt;177 μmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets &lt;100 ×109/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SpO2 &lt;90% on room air</td>
<td></td>
</tr>
<tr>
<td><strong>SEPTIC SHOCK</strong></td>
<td>SEPSIS</td>
<td>SEPSIS</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>HYPOTENSION</td>
<td>VASOPRESSORS needed for MAP &gt;65 mmHg</td>
</tr>
<tr>
<td></td>
<td>after adequate fluid resuscitation</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LACTATE &gt;2 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>after adequate fluid resuscitation</td>
</tr>
</tbody>
</table>
Patient with suspected infection

qSOFA ≥2? (see A) → No → Sepsis still suspected? → No → Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

Yes → Assess for evidence of organ dysfunction

SOF A ≥2? (see B) → No → Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

Yes → Sepsis

Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP ≥65 mm Hg AND 2. serum lactate level >2 mmol/L?

No

Yes → Septic shock

A qSOFA Variables
Respiratory rate
Mental status
Systolic blood pressure

B SOFA Variables
PaO\textsubscript{2}/FiO\textsubscript{2} ratio
Glasgow Coma Scale score
Mean arterial pressure
Administration of vasopressors with type and dose rate of infusion
Serum creatinine or urine output
Bilirubin
Platelet count


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Surviving Sepsis Campaign 2016

- EGDT is gone as a specific recommendation
- Guide additional fluid by frequent reassessment of hemodynamic status
- If clinical examination dose not lead to clear diagnosis of volume status, use additional hemodynamic measures
- Use dynamic rather than static variables to predict fluid responsiveness, where available
We recommend the protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

- CVP 8-12 mm Hg
- MAP > 65 mm Hg
- Urine output > 0.5 ml Kg
- ScvO2 > 70%
Supplemental oxygen \( \pm \) endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

- CVP
  - \(<8\) mm Hg
    - Crystalloid
    - Colloid
  - \(8-12\) mm Hg
  - MAP
    - \(<65\) mm Hg
      - Vasoactive agents
    - \(>90\) mm Hg
    - ScvO2
      - \(<70\)%
        - Transfusion of red cells until hematocrit \(>30\)%
      - \(>70\)%
        - Inotropic agents

Goals achieved

- Yes
  - Hospital admission

Early insertion of ScvO2 catheter

Therapy titrated to CVP, MAP and ScvO2

Potential for RBC and Inotropes
Mysterious disappearance of 25 patients who were randomized but never analyzed. Dr. Rivers had major conflicts of interest, including patenting a catheter to monitor svcO2.
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISE Investigators

A Primary mortality outcome of each study

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events, EGDT</th>
<th>Events, control</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers et al. (2001)</td>
<td>0.52 (0.31, 0.86)</td>
<td>38/130</td>
<td>59/133</td>
<td>10.40</td>
</tr>
<tr>
<td>Jones et al. (2010)</td>
<td>1.47 (0.82, 2.60)</td>
<td>34/150</td>
<td>25/150</td>
<td>4.87</td>
</tr>
<tr>
<td>ProCESS Investigators (2014)</td>
<td>1.17 (0.88, 1.55)</td>
<td>92/439</td>
<td>167/902</td>
<td>21.78</td>
</tr>
<tr>
<td>ARISE Investigators (2014)</td>
<td>0.98 (0.76, 1.26)</td>
<td>147/792</td>
<td>150/796</td>
<td>30.71</td>
</tr>
<tr>
<td>ProMISE Investigators (2015)</td>
<td>1.02 (0.80, 1.30)</td>
<td>184/623</td>
<td>181/620</td>
<td>32.23</td>
</tr>
<tr>
<td>Overall (I-squared = 56.7%, p = 0.055)</td>
<td>1.01 (0.88, 1.16)</td>
<td>495/2134</td>
<td>582/2601</td>
<td>100.0</td>
</tr>
</tbody>
</table>

DOI 10.1007/s00134-015-3822-1

**Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock**

The VANISH Randomized Clinical Trial

Anthony C. Gordon, MD; Alexina J. Mason, PhD; Neeraja Thirunavukkarasu, MSc; Gavin D. Perkins, MD; Maurizio Cecconi, MD; Magda Cepkova, MD; David G. Pogson, MB BCh; Hollmann D. Aya, MD; Aisha Anjum, BSc; Gregory J. Frazier, MSc; Shalini Santhakumaran, MSc; Deborah Ashby, PhD; Stephen J. Brett, MD; for the VANISH Investigators

- Factorial 2 x 2 Design, DBRCT

<table>
<thead>
<tr>
<th>Vasopressin + Placebo +/- Norepinephrine PRN</th>
<th>Norepinephrine + Placebo +/- Vasopressin PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin + Hydrocortisone +/- Norepinephrine PRN</td>
<td>Norepinephrine + Hydrocortisone +/- Vasopressin PRN</td>
</tr>
</tbody>
</table>

**Outcome:** No difference in renal failure-free days. No difference in mortality
Sepsis and septic shock are medical emergencies and we recommend that treatment and resuscitation begin immediately.
Surviving Sepsis Campaign 2016

- Optimize antimicrobial dosing based on accepted pharmacokinetic/pharmacodynamics principles and particular drug properties in patients with sepsis/septic shock
  - Increased incidence of renal and hepatic impairment
  - Increased volume of distribution due to rapid expansion of ECV
  - Initiate therapy with full, high-end loading dose to avoid frequent subtherapeutic levels
Effect of timing on survival

Adapted with permission from:
Crit Care Med 2006;34:1589-96

Fraction of total patients

Time from hypotension onset (hours)
Pooled data from the available literature in patients with severe sepsis and septic shock, administration of antibiotics within 3 hours of ED triage or within 1 hour of recognition of severe sepsis/septic shock did not confer mortality benefit.
Antibiotics

• We suggest **empiric combination therapy** (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock.
  • (Weak recommendation; low quality of evidence)

• We suggest that **combination therapy not be routinely used** for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock.
  • (Weak recommendation; low quality of evidence).

• We **recommend against combination therapy** for the routine treatment of neutropenic sepsis/bacteremia.
  • (Strong recommendation; moderate quality of evidence).
Antimicrobial Therapy - Antibiotic Stewardship

- We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.

- We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated with sepsis and septic shock.
  - (Weak recommendation; low quality of evidence)

- We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.

- We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.
  - (Weak recommendation; low quality of evidence)
Old to New?

• Duration of combination therapy has shrunk from 3-5 days (2012 guidelines) to “the first few days” (2016 guidelines).

• The indications for combination therapy have been pared back to only the sickest patients:
Surviving Sepsis Campaign 2016

• 7-10 days of antimicrobial therapy for most serious infections, but shorter duration for some (rapid clinical resolution after intra-abdominal source control, urinary sepsis, uncomplicated pyelonephritis)

• Suggest use of procalcitonin to support shortening duration of antimicrobial therapy
The New Antibiotic Mantra—“Shorter Is Better”

Brad Spellberg, MD

<table>
<thead>
<tr>
<th>Disease</th>
<th>Short</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>3-5</td>
<td>7-10</td>
</tr>
<tr>
<td>Nosocomial pneumonia&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>≤8</td>
<td>10-15</td>
</tr>
<tr>
<td>Pyelonephritis&lt;sup&gt;10&lt;/sup&gt;</td>
<td>5-7</td>
<td>10-14</td>
</tr>
<tr>
<td>Intraabdominal infection&lt;sup&gt;11&lt;/sup&gt;</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Acute exacerbation of chronic bronchitis and COPD&lt;sup&gt;12&lt;/sup&gt;</td>
<td>≤5</td>
<td>≥7</td>
</tr>
<tr>
<td>Acute bacterial sinusitis&lt;sup&gt;13&lt;/sup&gt;</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Cellulitis&lt;sup&gt;14&lt;/sup&gt;</td>
<td>5-6</td>
<td>10</td>
</tr>
<tr>
<td>Chronic osteomyelitis&lt;sup&gt;15&lt;/sup&gt;</td>
<td>42</td>
<td>84</td>
</tr>
</tbody>
</table>

Abbreviation: COPD, chronic obstructive pulmonary disease.

• U.S. professional societies didn’t adopt Sepsis-3 (ACEP, ACCP)

CMS had already released SEP-1 Core Measure criteria based on Sepsis-2 definitions
SSC Guidelines and Sepsis-3 Definitions

• “Sepsis” in place of “Severe Sepsis”

• Sepsis-3 clinical criteria (i.e. qSOFA) were not used in studies that informed the recommendations in this revision
  • Could not comment on use of Sepsis-3 clinical criteria

How do we define “dysregulated” Response

• No current clinical measures
• Best estimate of those most likely to have sepsis
• Interrogation of large data sets iCorrelation with outcomes
qSOFA!!

SOFA and LODS superior in the ICU

qSOFA similar to complex scores outside the ICU

ICU encounters
N = 7,932
AUROC in-hospital mortality

Outside the ICU encounters
N = 66,522
AUROC in-hospital mortality
How Good is qSOFA?

American Journal of Respiratory and Critical Care Medicine

Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit

Matthew M. Churpek, Ashley Snyder, Xuan Han, Sarah Sokol, Natasha Pettit, Michael D. Howell, and Dana P. Edelson

September 20, 2016

- Retrospective review of ED and ward patients with suspected infection
- Compared SIRS, qSOFA, MEWS, and NEWS
- Primary endpoint: in-hospital mortality, and combined endpoint of mortality or ICU admission
How Good is qSOFA?

Conclusions:

• qSOFA has a poor sensitivity
• qSOFA is a late indicator of deterioration
• qSOFA is inferior to the NEWS score (despite the NEWS score being based on data which is equally easy to obtain at the bedside)
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- X-ray- Bil infiltrates.
- Completed T. Chloroquine on Ceftriaxone + Levoflox (D 5), IVF

**Scrub typhus is etiology for septic shock?**

- 1. Yes
- 2. No
- 3. hmmmm
The Global Epidemiology of Sepsis
Does It Matter That We Know So Little?

198/543 cases organism identified

Northern Australia data:
Causes and outcomes of sepsis in southeast Asia: a multinational multicentre cross-sectional study

Southeast Asia Infectious Disease Clinical Research Network

Sepsis in Adults in Asia
Host: How sick is the host?

Causes and outcomes of sepsis in southeast Asia: a multinational multicentre cross-sectional study

Southeast Asia Infectious Disease Clinical Research Network

Summary

Background: Improved understanding of pathogens that cause sepsis would aid management and antimicrobial selection. In this study, we aimed to identify the causative pathogens of sepsis in southeast Asia.

Table 3: Risk factors for 28-day mortality in patients with sepsis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Non-survivors (n=122)</th>
<th>Survivors (n=1413)</th>
<th>Odds ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univariable analysis</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>110 (90%)</td>
<td>630 (45%)</td>
<td>5.1 (2.6–10.0)</td>
</tr>
<tr>
<td>Bacteria identified</td>
<td>45 (37%)</td>
<td>364 (26%)</td>
<td>1.1 (0.7–1.8)</td>
</tr>
<tr>
<td>Viruses identified</td>
<td>13 (11%)</td>
<td>434 (31%)</td>
<td>0.5 (0.3–1.0)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise stated. *Stratified by age groups and study sites.
Sepsis in Asia...

• 2 years, 1578 patients (763 children and 815 adults).
• Severe sepsis was identified on enrolment in 194 (28%) of 731 children and 546 (68%) of 804 adults, and was associated with increased mortality
  • Dengue viruses (n=122 [8%]),
  • Leptospira spp (n=95 [6%]),
  • Rickettsial pathogens (n=96 [6%])
  • Escherichia coli (n=76 [5%]), and
  • Influenza viruses (n=65 [4%]) were commonly identified in both age groups;

• Plasmodium spp (n=12 [1%]) and Salmonella enterica serovar Typhi (n=3 [0 • 2%]) were rarely observed.

• Emerging pathogens identified included
  • Hantaviruses (n=28 [2%]),
  • Non-typhoidal Salmonella spp (n=21 [1%])
  • Streptococcus suis (n=18 [1%])
  • Acinetobacter spp (n=12 [1%]), and
  • Burkholderia pseudomallei (n=5 [<1%]).
<table>
<thead>
<tr>
<th>Study Location</th>
<th>Study Dates</th>
<th>Total no. of patients in study</th>
<th>Hospital type</th>
<th>Age (population type)</th>
<th>Diagnostic tests conducted</th>
<th>N (%) of diseases searched in review investigated in study</th>
<th>Patients with confirmed infection</th>
<th>Patients infected with HIV (proportion of patients tested)</th>
<th>Most common pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal, Kathmandu; July</td>
<td>2002—June 2004</td>
<td>103</td>
<td>Urban, referral community general hospital</td>
<td>&gt; 17 years</td>
<td>Blood culture. Serology for scrub typhus, murine typhus, leptospirosis, dengue. Included only for blood culture and paired acute and convalescent sera.</td>
<td>3 (12.0%) blood culture, 14 (13.5%) confirmed serology</td>
<td>29 (28.1%) positive blood culture</td>
<td></td>
<td>Salmonella enterica serotype Typhi, Salmonella enterica Paratyphi A, R. typhii</td>
</tr>
<tr>
<td>South India; January</td>
<td>2007—January 2008</td>
<td>388</td>
<td>Tertiary care referral hospital</td>
<td>&gt; 16 years</td>
<td>Blood culture, thick and thin blood smears, serological testing for scrub typhus, Dengue virus, Leptospora spp, SFG rekettsiiosis did not meet serological case definitions</td>
<td>1 (4.0%) positive blood culture, 88 malaria slide positive</td>
<td></td>
<td></td>
<td>Salmonella enterica serotype Typhi, Salmonella enterica Paratyphi A, Plasmodium spp</td>
</tr>
<tr>
<td>Bangladesh; December</td>
<td>2008—November 2009</td>
<td>482</td>
<td>Six tertiary level, teaching, referral hospital</td>
<td>Unspecified, Primary adults</td>
<td>Malaria rapid diagnostic test. Serological testing for dengue virus. Did not meet dengue case definition</td>
<td>1 (4.0%) positive for malaria rapid diagnostic test</td>
<td></td>
<td></td>
<td>Plasmodium spp</td>
</tr>
<tr>
<td>India; June 2008—</td>
<td>December 2008</td>
<td>1,680</td>
<td>Urban tertiary hospital</td>
<td>1 month-12 years</td>
<td>Thick and thin blood films for malaria parasites</td>
<td>1 (4.0%) malaria slide positive</td>
<td></td>
<td></td>
<td>Plasmodium spp</td>
</tr>
<tr>
<td>Nepal, Kathmandu; Jan</td>
<td>2001—March 2001 and</td>
<td>876</td>
<td>Urban, general hospital</td>
<td>&gt;14 years old</td>
<td>Blood culture. Urinary antigen testing, serological testing for IgM antibodies Dengue virus, Leptospirosis, Scrub typhus and R. typhi. Did not meet serological case definition</td>
<td>1 (4.0%) positive blood culture</td>
<td></td>
<td></td>
<td>Salmonella enterica serotype Typhi, Salmonella enterica Paratyphi A</td>
</tr>
<tr>
<td>India; 2008-2009</td>
<td>August 2001</td>
<td>67</td>
<td>Teaching hospital</td>
<td>&gt;15 years</td>
<td>Blood culture. NAAT</td>
<td>1 (4.0%) No positive results</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** This table summarizes data on etiology of severe febrile illness in low- and middle-income countries from various studies.
• The new definitions are based on the assessment of a large cohort of patients in (private) hospitals in California and Pittsburgh, USA.
• The majority of sources of infection were hospital patients in referral centres with respiratory and postoperative infections.
• These definitions are of help for research purposes, they may not be representative of the whole world.
• In LMIC the incidence of community-acquired infections would be higher, with a greater prevalence of gastroenteritis, tropical infections, septic abortion, and skin and soft tissue infections as causes of septic shock.
• We are not certain that parasitic, viral, and fungal conditions, very common in LMIC, should be combined with bacterial infections in the definition of sepsis.
• Clinical practice shows that hypoxemia can be very severe both in viral and bacterial pneumonia.
• Unfortunately, the new position paper again ignores the crucial role of the organisms, sites of infection, and early diagnostic techniques.
Way Forward: Sepsis care needs improvement….

- UK National Confidential enquiry into patient outcomes and death report
- 543 cases of sepsis analyzed
- Delay in diagnosing (avg 9 hours) Sepsis 36% Severe Sepsis 51% Septic shock 33%
- Essential Investigations not done in 39% and delayed in 39%
• **Sepsis is a heterogeneous disorder**, which can be associated with many different types of infection and several other characteristics.

• Sepsis is clearly more than just an infection that can be identified by the affected organ (eg, pneumonia, urinary tract infection, meningitis) and the type of microorganism (eg, pneumococcal, meningococcal, *Candida*, herpes virus).

• Whenever possible, clinicians should be source-specific sepsis, sepsis secondary to pneumonia, and so on.

• **Why can’t we simply refer to the disorder as severe infection?**
# Sepsis: older and newer concepts

*Jean-Louis Vincent, Jean-Paul Mira, Massimo Antonelli*

## Table 2: The predisposing factors, infection, response, organ dysfunction (PIRO) classification model

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Laboratory or treatment-related</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predisposing factors</strong></td>
<td>Age, immunosuppression, comorbidities, alcoholism, drugs, etc</td>
</tr>
<tr>
<td>Infection</td>
<td>Signs of pneumonia, meningitis, peritonitis, purpura, etc</td>
</tr>
<tr>
<td>Response</td>
<td>Fever, tachycardia, tachypnoea, etc</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Shock, oliguria, respiratory failure, coagulopathy, etc</td>
</tr>
</tbody>
</table>

Screening For Sepsis (Severe infection) Need of hour

We recommend that hospitals and hospital systems have a performance improvement program for sepsis including sepsis screening for acutely ill, high-risk patients.
EPIDEMIOLOGY OF INTENSIVE CARE UNIT INFECTIONS AND IMPACT OF INFECTIOUS DISEASE CONSULTANTS IN MANAGING RESISTANT INFECTIONS

1Ravi, K.P., 2Suresh Durairajan, 1Sankalp Parivar,
1Ramesh Venkataraman, 2V. Ramasubramanian and 1N. Ramakrishnan

<table>
<thead>
<tr>
<th>Organism</th>
<th>Resistance pattern</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli</td>
<td>Carabapenem Resistance</td>
<td>5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Multidrug Resistance</td>
<td>35</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>Multidrug Resistance</td>
<td>92</td>
</tr>
</tbody>
</table>

401 patients admitted to ICU during the study period (1 year) 25% had positive cultures. 60% of the cultures grew Gram negative organisms with *E. coli*, *Pseudomonas* and *Acinetobacter* species being the commonest isolated pathogens. Mortality among culture positive patients in the Intensive Care Unit (ICU) was 31%.
Development of a mortality prediction formula due to sepsis/severe sepsis in a medical intensive care unit

Anant Mohan, Prajwal Shrestha, Randeep Guleria, Ravindra Mohan Pandey, Naveet Wig

Department of Pulmonary Medicine and Sleep Disorders, Medicine, and Biostatistics, All India Institute of Medical Sciences, New Delhi, India

<table>
<thead>
<tr>
<th>Category</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin level (g/dL)</td>
<td>≥12.0</td>
<td>&lt;12.0</td>
</tr>
<tr>
<td>SAPS II score</td>
<td>&lt;35</td>
<td>&gt;35</td>
</tr>
<tr>
<td>SOFA score</td>
<td>&lt;6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>SAPS III score</td>
<td>&lt;47</td>
<td>&gt;47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>84.9</td>
<td>42.5</td>
</tr>
<tr>
<td>SAPS II</td>
<td>81.1</td>
<td>59.5</td>
</tr>
<tr>
<td>SAPS III</td>
<td>81.1</td>
<td>51.1</td>
</tr>
<tr>
<td>SOFA</td>
<td>69.8</td>
<td>72.3</td>
</tr>
</tbody>
</table>

SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

of mortality in sepsis. A sepsis mortality prediction formula (AIIMS Sepsis Score) based on SAPS II, SAPS III, and SOFA scores and hemoglobin has greater predictive power than these scoring methods individually. Routine use of critical illness scoring systems and a composite mortality prediction formula may provide useful early prognostic information.
More to Diagnosis!!

- We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if doing so results in no substantial delay in the start of antimicrobials.
  - Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).
Source Control

• We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.
Surviving sepsis in low-income and middle-income countries: new directions for care and research

Create New Sepsis Bundle

Laboratory testing
- Blood count (including haematocrit, leucocytes)
- Blood chemistry (lactate, urinalysis)
- Cultures (blood, urine, and other body fluids)
- HIV rapid test
- Malaria thick and thin blood smear
- Other (depending on local relevance)

Source identification and control
- Eg. abscess drainage

Antimicrobials
- Early administration of appropriate antimicrobials
- Antimalarial(s)
- Antibiotic(s)
- Other (depending on local relevance)

Fluid resuscitation
- Intravenous or oral

Assessment of endpoints (treatment response)
- Lactate clearance
- Blood pressure
- Heart rate

Teach

1. Educate providers and clinicians throughout LMICs about the clinical signs, symptoms, and pathophysiology of sepsis.
2. Develop and validate sepsis management algorithms for LMICs either independently or extrapolated from established data.
3. Develop and validate cost-effective, easily used, and clinically appropriate diagnostic tests to identify ill patients and guide endpoints of resuscitation.
4. Develop clinical laboratory capacity including microbiological testing.
5. Develop regional recommendations regarding initial broad-spectrum antimicrobial coverage for patients with sepsis based on local ecology and resistance patterns.
6. Improve and augment LMIC critical-care systems and resources including referral systems and tertiary-care centres.
7. Develop systems to assure high quality, cost-effective, and affordable sepsis care.
### Simple Protocols

<table>
<thead>
<tr>
<th>Give 3</th>
<th>Take 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. OXYGEN:</strong> Titrate $O_2$ to saturations of 94-98% or 88-92% in chronic lung disease.</td>
<td><strong>1. CULTURES:</strong> Take blood cultures <em>before</em> giving antimicrobials (if no significant delay i.e. &gt;45 minutes) and consider source control.</td>
</tr>
<tr>
<td><strong>2. FLUIDS:</strong> Start IV fluid resuscitation if evidence of hypovolaemia. 500ml bolus of isotonic crystalloid over 15mins &amp; give up to 30ml/kg, reassessing for signs of hypovolaemia, euvolaemia, or fluid overload.</td>
<td><strong>2. BLOODS:</strong> Check point of care lactate &amp; full blood count. Other tests and investigations as per history and examination.</td>
</tr>
<tr>
<td><strong>3. ANTIMICROBIALS:</strong> Give IV antimicrobials according to local antimicrobial guidelines.</td>
<td><strong>3. URINE OUTPUT:</strong> Assess urine output and consider urinary catheterisation for accurate measurement in patients with severe sepsis/septic shock.</td>
</tr>
</tbody>
</table>
Sepsis Screening Form

Healthcare Professional who contacted the doctor to complete this section:

Date:  
Time Started:  
Healthcare Professional’s Name:  
Healthcare Professional’s Signature:  
MCRN/NMSI PIN: 

Doctor to review within 30 mins (use ISBAR). DOCTOR TO COMPLETE REMAINDER OF THIS DOCUMENT AS APPROPRIATE

Clinical Suspicion of Infection

AND 2 or more Systemic Inflammatory Response Syndrome (SIRS) criteria

Respiratory rate > 20 bpm
Heart rate > 90 bpm
Change in mental status
Blood glucose < 60 mg/dL

OR
“Unwell and at risk of Septicemia”
*Note: The risk is even greater for septicemia patients over the age of 65, in those with uncontrolled diabetes, in the presence of a fever greater than 38.5°C, and in those with a history of recent surgery.

Site

WCC < 4 x 10^9/L
Temperature > 38°C or < 36°C
Bile duct aspirate > 0.5 x 10^9/L

YES. THIS IS SEPSIS

Disclosure:  

Time Zero:  
Sepsis Six Regimen to be completed within 1 hour

TAKE 3

BLOOD CULTURES: Take blood cultures before giving antibiotics.
BLOOD: Check point-of-care lactate & 4 blood count. Other tests and investigations are at the discretion of the healthcare professional.
URINE OUTPUT: Assess urine output and consider urinary catheterization for accurate measurement of urine output.

GIVE 3

OXYGEN:  
FLUID: Start IV fluid resuscitation (if in hypovolemic shock) and give saline bolus of 20 mL/kg. If shock persists, consider 3rd generation cephalosporin.
ANTIMICROBIAL: Give 1st or 2nd generation cephalosporin and 1-2 doses of 3rd generation cephalosporin.

Laboratory tests should be requested as EMERGENCY aiming to have results available and reviewed within 1 hour.

Look for signs of new organ dysfunction:

- Systolic BP ≤ 90 or Mean Arterial Pressure (MAP) ≤ 65
- Systolic BP more than 40 below patient’s normal
- Need for oxygen to achieve saturation ≥ 90%
- Lactate ≥ 2 mmol/L
- Urine output < 0.5 mL/kg in 2 hours
- Acute altered mental status
- Glucose > 7.7 mmol/L
- Creatinine > 1.7 mmol/L
- Bilirubin > 10 μmol/L
- INR > 1.5 or PT/PTT > 40s
- Platelets < 100 x 10^9/L

Any new organ dysfunction due to infection: IMMEDIATELY INFORM REGISTERED OR CONSULT IMMEDIATELY. REASSURE PATIENT.

Consult other investigations not mentioned in above (if patient is intubated). Consider review of fluid status, electrolyte and acid-base balance, consider review of renal function, consider review of liver function, consider review of coagulation.

Pathway Modification

All pathway modifications need to be agreed by the hospital’s Sepsis Steering Committee and be in line with the National Clinical Guideline.
Consider other Sepsis mimics
Target other paths in the Pathogenesis of sepsis

- Pathogen
- Infection
- Host responses
  - Activation of coagulation
  - Inhibition of fibrinolysis
  - Endothelial dysfunction
  - Tissue factor expression
  - Microvascular flow redistribution
    - Leucocyte activation
      - Anti-inflammatory mediators
        - e.g. IL-10, IL-1ra receptor antagonists
      - Pro-inflammatory mediators
        - e.g. Tumour necrosis factor, IL-1, IL-6, IL-8, nitric oxide
    - Mitochondrial dysfunction
      - Organ dysfunction
      - Tissue injury
    - Inhibition of fibrinolysis
    - Activation of coagulation
      - Death
      - Microvascular coagulation/thrombosis
Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

Jason A Roberts, Mohd H Abdul-Aziz, Jeffrey Lipman, Johan W Mouton, Alexandre A Vickers, Timothy W Felton, William W Hope, Andreas Farkas, Michael N Neely, Jerome Schentag, George Drusano, Otto R Frey, Ursula Theuretzbacher, Joseph L Exls; on behalf of The International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases

**Figure:** The range of altered pathophysiology in patients with critical illness, and its effects on drug concentrations.

RRT = renal replacement therapy. ECMO = extracorporeal membrane oxygenation.
Post-Antibiotic Era Mortality: What the Future Holds?

Infectious Disease Mortality in the United States, 1900 to 1996

Mortality Rate per 100,000

Year

CDC
Just Think..

• “We shall now discuss in a little more detail the struggle for existence.”

  C Darwin 1859
Thank you

I am only responsible for what I say, not for what you understand.
www.healthythoughts.in