Early antibiotics in septic shock: is it that important?

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A Syndrome produced by Diverse Nocuous Agents

Experiments on rats show that if the organism is severely damaged by acute non-specific nocuous agents such as exposure to cold, surgical injury, production of spinal shock (transcission of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.
Injury: DAMP or PAMP

**DAMP**
Damage Associated Molecular Pattern

**PAMP**
Pathogen Associated Molecular Pattern

DAMP and PAMP are types of molecular patterns that are involved in the body's response to injury and infection.
Interpreting biomarkers in infectious diseases in intensive care unit: the potential role of procalcitonin

Fatihe Hawchar, Zsolt Molnar
This is why SIRS was a wrong concept
Pro-inflammation

Immunosuppression is (one of) the answers for MDRPs
The mantra goes as: „Give antibiotic(s) within the 1st hour!”
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

(Crit Care Med 2006; 34:1589–1596)

Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%.
Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD, for the Surviving Sepsis Campaign Management Guidelines Committee

C. Antibiotic Therapy

1. Intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained.

Grade E

Give AB ASAP!!

D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).
“Each hour’s delay in initiating antibiotics costs lives” is a doctrine that has attained quasireligious status. Like most (quasi) religions, this is founded more on faith and hope than hard fact.”

“The “each hour delay” mantra is, however, being drummed into healthcare providers, hospital administrators, funders, and governmental bodies. Quality-improvement programs are being driven by financial penalty.”
Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study

Peter M. C. Klein Klouwenberg, Olaf L. Cremer, Lonneke A. van Vught, David S. Y. Ong, Jos F. Frencken, Marcus J. Schultz, Marc J. Bonten and Tom van der Poll

Fig. 1 Plausibility of infection stratified by clinical severity upon presentation in patients with presumed sepsis. Comparison between the clinical diagnosis of infection at the time of ICU admission and the actual presence of infection as determined by post-hoc evaluation.

2,579 pts

13%: none

30%: possible
Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study

Frank Bloos, Daniel Thomas-Rüddel, Hendrik Rüddel, Christoph Engel, Daniel Schwarzkopf, John C Marshall, Stephan Harbarth, Philipp Simon, Reiner Riessen, Didier Kehl, Katrin Dey, Manfred Weiß, Susanne Toussaint, Dirk Schäfer, Andreas Weyland, Maximilian Rappeller, Konrad Schwarzkopf, Jürgen Esche, Gerhard Kuhnle, Heike Hoyer, Christine Hartog, Udo Kaisers and Konrad Reinhardt for the VEDUSA Study Group

<table>
<thead>
<tr>
<th>Surgical source control required ((n = 234)^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to antimicrobial therapy &gt;1 hour(^b)</td>
</tr>
<tr>
<td>Initial SOFA score(^c)</td>
</tr>
<tr>
<td>Age(^d)</td>
</tr>
<tr>
<td>Maximum lactate (day 1)(^e)</td>
</tr>
<tr>
<td>Time to source control &gt;6 hours</td>
</tr>
<tr>
<td>Intra-abdominal focus</td>
</tr>
<tr>
<td>Urogenital focus</td>
</tr>
<tr>
<td>Unknown focus(^g)</td>
</tr>
<tr>
<td>Community-acquired infection</td>
</tr>
<tr>
<td>Inadequate empiric antimicrobial therapy</td>
</tr>
<tr>
<td>No de-escalation of antimicrobials within 5 days</td>
</tr>
</tbody>
</table>
Antibiotics are overused/abused worldwide

MDR pathogens – „global crisis”
Rationalizing antimicrobial therapy in the ICU: a narrative review

Jean-François Timsit, Matteo Bassetti, Olaf Cremer, George Daikos, Jan de Waele, Andre Kallili, Eric Kipnis, Marin Kolle, Kevin Laupland, Jose-Artur Paiva, Jesús Rodríguez-Bañó, Étienne Ruppé, Jorge Salluh, Fabio Silvio Taccone, Emmanuel Weiss, and François Barbier

Table 1  Determinants of increased risk of MDRB infection at ICU admission and during the ICU stay

<table>
<thead>
<tr>
<th>Predictors of MDRB infection</th>
<th>At ICU admission</th>
<th>During the ICU stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient features</td>
<td>Co-morbid illness/immunosuppression/recent hospital and/or ICU stay</td>
<td>Higher severity of acute illness/Invasive interventions</td>
</tr>
<tr>
<td>Type of infection</td>
<td>Hospital-acquired &gt; healthcare-associated &gt; community-acquired</td>
<td>ICU-acquired &gt; others</td>
</tr>
<tr>
<td>Antimicrobial selection pressure</td>
<td>Prior antibiotics*/antifungals</td>
<td>Antibiotics*/antifungals in the ICU</td>
</tr>
<tr>
<td>Colonization status</td>
<td>Previously documented colonization with MDRB</td>
<td>In-ICU acquisition of MDRB</td>
</tr>
</tbody>
</table>

3 times more AB on ICU then on wards

*Especially if agents with broad-spectrum and/or potent activity against intestinal anaerobes

70% of patients receive ABs
ABs are potentially harmful

Organ injury

Mitochondrial dysfunction

Microbiome, Fungal infections

Clostridium difficile infections
### Table 4: Characteristics of patients receiving adequate or inadequate empirical antibiotic treatment (univariate analysis).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n) receiving adequate empirical antibiotic treatment</th>
<th>Patients (n) receiving inadequate empirical antibiotic treatment</th>
<th>p-value</th>
<th>OR (95% CI) for adequate therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>418 (77.6%)</td>
<td>121 (22.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>170 (70.2%)</td>
<td>72 (29.8%)</td>
<td>&lt; 0.001</td>
<td>0.47 (0.31–0.70)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age and range (years)</td>
<td>67 [18–100]</td>
<td>72 [17–97]</td>
<td>0.038*</td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>74 (77.1%)</td>
<td>22 (22.9%)</td>
<td>0.904</td>
<td>0.97 (0.57–1.64)</td>
</tr>
<tr>
<td>41–60 yr.</td>
<td>91 (87.5%)</td>
<td>13 (12.5%)</td>
<td>0.007</td>
<td>2.31 (1.12–4.30)</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>253 (74.6%)</td>
<td>86 (25.4%)</td>
<td>0.034</td>
<td>0.62 (0.40–0.97)</td>
</tr>
<tr>
<td>Ward</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine/Geriatrics</td>
<td>281 (78.3%)</td>
<td>78 (21.7%)</td>
<td>0.399</td>
<td>1.19 (0.80–1.76)</td>
</tr>
<tr>
<td>Surgery</td>
<td>135 (78.9%)</td>
<td>36 (21.1%)</td>
<td>0.733</td>
<td>1.09 (0.70–1.65)</td>
</tr>
<tr>
<td>Medical and surgical intensive care</td>
<td>25 (71.4%)</td>
<td>10 (28.6%)</td>
<td>0.408</td>
<td>0.73 (0.34–1.55)</td>
</tr>
<tr>
<td>Neurology</td>
<td>1 (25.0%)</td>
<td>3 (75.0%)</td>
<td>0.040†</td>
<td>0.10 (0.01–0.94)</td>
</tr>
<tr>
<td>Died in hospital</td>
<td>25 (80.6%)</td>
<td>6 (19.4%)</td>
<td>0.671</td>
<td>1.22 (0.49–3.04)</td>
</tr>
</tbody>
</table>

*28%*
So, what to do?!
International guidelines…

American Thoracic Society Documents

Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America

Is there infection for a start?!
Does the patient have **infection** or not?

**Infection = ABs**

**No infection = No ABs**
Signs of infection

- Clinical signs:
  - Most important

- Fever (>38°C), WBC (>12 000):
  - Low sensitivity (~50%)
  
  Galicier L and Richet H. *Infect Control Hosp.*

- Microbiology:
  - Results: 24 hours or more

Not good enough

Poooor!

Very late!
We need biomarkers!

WARNING!

Using biomarkers is not easy

I♥PCT
Patients with suspected infection = 209

PCT available at $T_1 = 114$

Infection = 85
No-infection = 29

AUC $\Delta$PCT: 0.85
$\Delta$CRP, WBC, T
Interpreting Procalcitonin at the Bedside

J. Fazakas, D. Trásy, and Z. Molnár

Suspected infection

↓

Hemodynamic instability

↓

Yes

↓

AB

No*

↓

PCT ↑

↓

Yes

↓

No AB:
- Observe
- Reassess later

No

↓

AB

Dare not to give AB
Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients: A prospective observational study

Proven infection = 141
Appropriate AB = 108 (77%)
Inappropriate AB = 33 (23%)
No infection/micro = 68

Patients with suspected infection = 209

Pattern of PCT kinetics – could be used early for individualizing treatment: timing, monitoring

AUC PCT₀–₂₄: 0.86

≥ 73%
Medical: ~ 5ng/ml

Surgical: ~20 ng/ml

Preference of kinetics over absolute values!
This concept is not accepted until tested/proven by PRCT(s)...

Interpreting Procalcitonin at the Bedside
J. Fazakas, D. Trásy, and Z. Molnár
Thinking has no alternative!

Auguste Rodin: The Thinker (1880)
Thank you!

500 participants
From 30 countries!
The „new” SepsEast team

Ovidiu Bedrea\nOrganizing Committee

Dorel Sandesc\nChair of Organizing Committee

Jan Benes\nChair SepsEast

Konstanty Szuldrzynski\nSecretary SepsEast

SepsEast 2020: www.sepseast.org
24-26 September, Timisoara, Romania