Inflammation versus Sepsis
Focus on Biomarkers

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Germany
Sepsis since 2016*

„Sepsis“ is defined as life threatening Organ Dysfunction due to uncontrolled response of the organism to infection

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Singer, et al. JAMA 2016: 315;801-810
Definitions of Sepsis (2016)
„Sepsis-3 Definition“

Sepsis = „Infection + Organ Dysfunction“

• increase of SOFA Score +2

or

• $\geq 2$ positive „qSOFA“ points ($\geq 2$)

______respiration rate $>22$/min
change of consciousness
blood pressure $\leq 100$mmHg (systolic)

Singer et al (JAMA 2016; 315:801-10)
# The SOFA-Score
Sequential Organ Failure Assessment-Score
- a basic overview -

<table>
<thead>
<tr>
<th>Organ:</th>
<th>Circulation</th>
<th>Lung</th>
<th>Cogulation</th>
<th>Kidney</th>
<th>Liver</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points 0-4</td>
<td>Vasopressors (µg/kg/min)</td>
<td>PaO2/FiO2 (mmHg)</td>
<td>platelets (tsd/mm3)</td>
<td>creatinine (mg/dl)</td>
<td>bilirubin (mg/dl)</td>
<td>GCS (points)</td>
</tr>
<tr>
<td>0</td>
<td>no vasopressor.</td>
<td>&gt; 400</td>
<td>&gt;= 150</td>
<td>&lt; 1.2</td>
<td>&lt; 1.2</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>MAP &lt; 70</td>
<td>301-400</td>
<td>100-149</td>
<td>1.2-1.9</td>
<td>1.2-1.9</td>
<td>13-14</td>
</tr>
<tr>
<td>2</td>
<td>Dobutamin</td>
<td>201-300</td>
<td>50-99</td>
<td>2.0-3.4</td>
<td>2.0-5.9</td>
<td>10-12</td>
</tr>
<tr>
<td>3</td>
<td>NA &lt;= 0.1</td>
<td>101-200</td>
<td>20-49</td>
<td>3.5-4.9</td>
<td>6.0-11.9</td>
<td>6-9</td>
</tr>
<tr>
<td>4</td>
<td>NA &gt; 0.1</td>
<td>&lt;= 100</td>
<td>&lt; 20</td>
<td>&gt;= 5</td>
<td>&gt;= 12</td>
<td>&lt;= 5</td>
</tr>
</tbody>
</table>
Fig. 1 Schematic representation illustrating a the almost complete overlap of sepsis and infection when the SIRS criteria of the 1992 criteria [3] are used and b the differences between qSOFA and sepsis. qSOFA quick sequential organ failure assessment, SIRS systemic inflammatory response syndrome
Infection

Sepsis

SIRS

Pancreatitis

Trauma

Burn

Bacteriae

Fungi

Parasites

Virus

other Etiology

others

1992 „ACCP/SCCM“-Sepsis Definition (R. Bone et al.)
Diagnosis of Sepsis

Egypt 2000 b.C.:

„ukhed u“ - Dangerous entity, deriving from the gut going to the organism, finally ending deadly

M. Meisner
“Sepsis makes the organism hot from the inside, but cold like ice at the surface”

Hippokrates
460-377 b. C.

Temple of Apollon at Korinth, Greece
“It is SEPSIS,
if there is a FOCUS within the organism,

which spreads BACTERIAE into the BLOODSTREAM
(continuous or dis-continuous),

and this causes SYMPTOMS of DISEASE
(measurable or as reported by the patient („subjective S.)

Schottmüller, 1914
Definitions of Sepsis (1992)

„Sepsis“
• SIRS + Infection

„Severe Sepsis“
• Sepsis + Organ Dysfunction
  • or perfusion abnormalities,
    e.g. oliguria (< 30 ml/h), lactate-acidosis,
    disturbance of consciousness
    art. hypotension, reversible by volume resuscitation

„ Septic Shock “
• Severe Sepsis + Hypotension (or catecholamines)
  • ( persisting after volume resuscitation):
    \[ RR < 90 \text{ mmHg or decline of more than 40 mmHg}, \]
    Perfusion abnormalities in spite of catecholamines
The Trias of Sepsis or:
Sepsis has many Symptoms

Systemic Inflammation?

- Local/invasive/Colonisation
- Culture/Serology

Infection?

- Intervention: Elimination of Focus of
  a) infection
  b) inflammation

Sepsis?

- Intervention: Search and remove focus
- Treat infection
- Treat organ dysfunction

Risk of Organ Dysfunktion!

- Lab Marker, Clinical Signs of Infl.

Severe Sepsis, Sept. Shock

- MODS

- Intervention: Supportive therapy
  (Cytosorb, Pentaglobin, HDF, Ventil)
Infection as one Etiology

Inflammation

as Risk of Organ Dysfunction

Organ Dysfunction

as Risk of Mortality

As „Epiphenomenon“
Definitions of Sepsis (2016)  
„Sepsis-3 Definition“

Sepsis = „Infection + Organ Dysfunction“

- increase of SOFA Score +2
- or positive „qSOFA“ points (>=2)

respiration rate >22/min  
change of consciousness  
blood pressure <= 100mmHg (systolic)

Mortality rate = 13%++ with this Definition

Singer et al (JAMA 2016; 315:801-10)
Data from 2005, Germany, DIVI, 36 ICU´s
45,000 patients, 200,000 days.
Mortality vs Increase of SOFA-Score (dmax-d1)

Data from 2005, Germany, DIVI, 36 ICU’s, 45,000 patients, 200,000 days.
Severity of Sepsis and Procalcitonin (PCT)

PCT

CRP

Lactate

Castelli et al. Critical Care 2004
CRP = C-reactive Protein

Produced in the liver („acute phase protein“), circulating in the blood (stimulated by IL-6, others).

Belongs to the „innate“ immune system. Works as a „pattern recognition molecule“ e.t. CRP binds to phosphocholine at bacteriae and dead cells. Induces complement system. Activates monocytes as well. Is a covalent bound pentamer.

„pentraxin structure“

... binding of C1 to CRP...

The Phe-66 and Glu-81 AA residues together with two Calcium ions produce a „co-crystal“ structure with phosphocholine (from damaged membranes, e.g.)

On the opposite side there is a C1q binding site and a FcGamma putative binding site (link to immunoglobulines).

CRP-receptors are FcgammeRIand II and inhibitory, the ITAM/ITIM.
The Role of PCT for Diagnosis of Sepsis
Correlation with Severity of Disease (Organ Dysfunction)

Harbarth S et al. AJRCC Med. 2001;164:396-402
Onset of Organ Dysfunction

- Septic Shock
- DIC
- Renal Insufficiency
- ARDS
- Liver Dysfunction

Organ Dysfunction (Hours after Admission)
Time Course of Induction of various Markers of the Systemic Inflammatory Response

Plasma Concentration

Time (h)

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Time Course of CRP after Cardiac Surgery
(only patients with increased PCT)

CRP (mg/l)

Postoperative Day

1 2 3 4 5 6 7
Time Course of PCT after Cardiac Surgery
(only patients with increased PCT)

Postoperative Day

PCT (ng/ml)

PCT (ng/ml)

Postoperative Day
Maximum CRP-Levels after different Types of Surgery

1. Minor periph. S.
2. Minor abdom. S.
3. Major abdom. S.
4. Mediast. Retroperit. S.
5. Cardiac.-Thorac. S.

© M. Meisner
Maximum PCT-Levels after different Types of Surgery

1. Minor periph. S.
2. Minor abdom. S.
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4. Mediast. Retroperit. S.
5. Cardiac.-Thorac. S.

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CRP and Sepsis

- indicates inflammation, also less severe

- does not show severity
  - not the high severity (!)
  - poor relation with organ dysfunction
  - may be increased in low severity

- not specific for bacterial response

- kinetic 24-48 hours peak

Low Recommendation for Use for Sepsis Dx
The Logarithmic Scale
(10x10 x 10 x 10 x ...)

... indicates a 3-D duty/job of the molecule

= from local effects
to systemic effects!

1D
- e.g. hormones with high affinity and only few target cells

2D
- local effects e.g. 10x10 mm

3D
- involvement of volume needs exponential growth
Presepsin: another name for the sCD14-ST molecule

N-terminal sequence fragment of CD 14 („soluble CD14 subtype fragment“). CD14 is a protein on membranes of mononuclear cells (55kDalton). CD14 binds lipopolysaccharides (LPS) as a receptor. Soluble parts of the receptor protein are found in serum/plasma during disease like infection, ARDS, AIDS/HIV, SLE... (13kDalton)
Presepsin: +/-SD of Mean or Median?

Optimal cut-off for Sepsis: 407 ng/ml

sCD14-ST (Presepsin): Baseline and Cut-off

Optimal cut-off for Sepsis: 407 ng/ml

Baseline, age-dependence and relation with kidney function were analyzed

Chenevier-Gobeaux C. ... Clin Chim Acta. 2014 Jan 1;427:34-6

Urbonas C ....; Cytokin 62 (2013) 34-7:
sCD14-ST in neutropenic Patients:

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>CI95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUO</td>
<td>356 ng/ml</td>
<td>255-469</td>
<td>0.819</td>
</tr>
<tr>
<td>Bacteremia/Sepsis</td>
<td>401 ng/ml</td>
<td>212-484</td>
<td>= ns</td>
</tr>
</tbody>
</table>
Presepsin and Sepsis

- indicates severity of inflammation

- lower cut-off levels are ambiguous

- needs further investigation
  (relation to organ dysfunction,
  not-bacterial related induction)

- not evaluated to guide Antibiotic Therapy
  (both not for indication and duration)

Recommendation for Research Use only
sTREM-1 does not indicate Severity of Systemic Inflammation

The increase of concentrations is small (less than 10-fold)

sTREM-1 = soluble triggering receptor expressed on myeloid cells-1

sTREM-1 for CAP-Severity & Bacteremia

p = ns

sTREM-1 Gibt (pg/ml)

PSI class

sTREM-1: 0.57 (0.50-0.63)
ProCT: 0.81 (0.76-0.86)
CRP: 0.63 (0.56-0.69)
Lc: 0.68 (0.61-0.74)

sTREM -1 and Sepsis

- does not indicate severity of inflammation

- related with infection

- no correlation with organ dysfunction

- not usable to guide Antibiotic Therapy

Recommendation for Research Use only
In conclusion, in our study we found that serum IL-33 level might be used as a novel biochemical marker in the diagnosis and follow-up of sepsis in preterm infants. We also determined that IL-33 might be useful for predicting sepsis in premature infants. And also, our results demonstrated that IL-33 may not be useful for discrimination of microbiological agents.

Table 2. Comparison of the median serum levels of CRP, IL-6 and IL-33 for the control group and at the 1st, 3rd and the 7th Day of diagnosis for sepsis group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Median (IQR)</th>
<th>Sepsis 1st day Median (IQR)</th>
<th>Sepsis 3rd day Median (IQR)</th>
<th>Sepsis 7th day Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP(mg/L)</td>
<td>2.410(1.91)</td>
<td>54.9(60.9)</td>
<td>23(25.9)</td>
<td>10(16.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-6(pg/ml)</td>
<td>12.10(8.15)</td>
<td>585(1430)</td>
<td>48(99)</td>
<td>16(32.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-33(pg/ml)</td>
<td>0.956(0.413)</td>
<td>2.564(1.13)</td>
<td>1.32(0.83)</td>
<td>0.71(0.41)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
The Aminoacid-Sequence of Procalcitonin (PCT)

1. Ala
2. Ser
3. Ala
4. Leu
5. Glu
6. Ser
7. Ser
8. Pro
9. Ala
10. Asp
11. Pro
12. Ala
13. Thr
14. Leu
15. Ser
16. Glu
17. Asp
18. Ala
19. Leu
20. Leu
21. Ala
22. Ala
23. Leu
24. Ser
25. Ala
26. Lys
27. Arg
28. Cys
29. Gly
30. Asp
31. Ser
32. Gly
33. Thr
34. Cys
35. Met
36. Leu
37. Gly
38. Thr
39. Tyr
40. Thr
41. Gly
42. Asp
43. Phe
44. Asn
45. Lys
46. Phe
47. His
48. Thr
49. Phe
50. Pro
51. Thr
52. Ala
53. Ile
54. Gly
55. Tyr
56. Lys
57. Lys
58. Arg
59. Lys
60. Arg
61. Asp
62. Met

- = N-ProCT
- = Calcitonin
- = Katakalcin

= Cleavage site of Endopeptidases

PAM = Peptidyl-Amidating Monooxygenase
after contact with PCT the migratory response of Monocytes is rapidly deactivated

PCT acts as chemokine and attracts further Monocytes

PCT later also inhibits the migratory response

Vascular smooth muscle cells: Initially PCT inhibits NO production after preincubation with LPS, TNF, IFNg

PCT modulates cytokine response: decreases LPS induced TNF production

PCT stimulates iNOS and hence NO production after preincubation with LPS, TNF, IFNg

Local Response

1st stimulus: infection sepsis, trauma cytokines.

adhesion of monocytes

adherent Monocytes produce PCT for 3-5 hrs.
High PCT levels are related with serious infection, sepsis and systemic inflammation.

Severity of Sepsis and Procalcitonin (PCT)

**PCT**

- No SIRS: 0 ng/ml
- SIRS: 32.9 ng/ml
- Sepsis: 42.2 ng/ml
- Severe Sepsis: 42.2 ng/ml
- Septic Shock: 42.2 ng/ml

**CRP**

- No SIRS: 0 mg/l
- SIRS: 50 mg/l
- Sepsis: 100 mg/l
- Severe Sepsis: 150 mg/l
- Septic Shock: 200 mg/l

**Lactate**

- No SIRS: 2 mmol/l
- SIRS: 4 mmol/l
- Sepsis: 6 mmol/l
- Severe Sepsis: 8 mmol/l
- Septic Shock: 10 mmol/l

Castelli et al. Critical Care 2004
Next Topic:

Inflammation Marker PCT and Guide of Antibiotic Therapy:

- Indication initially (I)
- Success of treatment (II)
- Duration of treatment (III)
**Definition of Infection and Treatment**

**Infection:**
No response of PCT if only local
Presence of microorganism in otherwise sterile tissue

**Colonisation:**
No response of PCT if only colonisation
Growth on surface
- typical: natural and mixed population of germs
- not typical / pathologic:
  - abundant growth
  - not typical germs
  - in vulnerable area (e.g. decubital ulcer)

**Local Infection:**
Sepsis vs local: Cut-off: < 0.3 n/ml
Invasion of tissue. Only local effects (rubor/secretion):
- no systemic involvement/systemic inflammation:
- no organ dysfunction
- no bloodstream contamination

**Systemic Infection:**
Indication for AB/ Surgery ...
Cut-off > 0.5 ng/ml
Is there SEPSIS
or only local infection or
no bacterial infection ?

(Start Antibiotics or Not ?)
PCT: viral, bacterial local and „invasive“ Infection

PCT Measurement

Consequences of low/high PCT

a) PCT is normal or very low (< 0.3 ng/ml):
   - systemic inflammation is not severe
   - risk of organ dysfunction is low

b) PCT is increased (>= 0.5 ng/ml)

Possible consequence, depending on further clinical data:

a) Now: NO acute intervention is required
   Now: NO antibiotic treatment required

b) Aute Antibiotic treatment and focus search are recommended
   - this depends on the individual situation
   - on the individual reaction of the patient´s immune resp
Consequence:

Antibiotic Stewardship Programs (ASP)

„Antibiotic Stewardship“: Where to look at?

> 30%  Indication not clear
  - positive urine cultures (asymptomatic)
  - putative respiratory tract infections

Procalcitonin indicates local vs systemic infection!

> 70%  Duration of treatment too long
  - respiratory tract infection
  - urinary tract infections/bacteriuria

Procalcitonin indicates duration of treatment!

n.n.  Postoperative prophylaxis > 24h

< 30%  Wrong antibiotic, wrong dosage, interactions not considered.
Top II
(with support of PCT)

Is initial Therapy (antibiotics or surgery) effective or not?

(Success of Tx)
# 24h-Course of PCT and Lethality in Children 24h after admission to the ICU

<table>
<thead>
<tr>
<th>Children</th>
<th>Decline of PCT*</th>
<th>No Decline of PCT*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethality (n)</td>
<td>9% (n = 2/23) 6 (3-26)</td>
<td>44% (n = 7/16) 11 (4-32)</td>
<td>0.019</td>
</tr>
<tr>
<td>Duration of Tx (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOSF-Score</td>
<td>2 (0-4)</td>
<td>2 (1-4)</td>
<td>0.19</td>
</tr>
<tr>
<td>PRISM-Score</td>
<td>15 (5-49)</td>
<td>18 (2-36)</td>
<td>0.23</td>
</tr>
<tr>
<td>AUC for Predict. of Mortality</td>
<td>PCT = 0.73; IL-10 = 0.67; TNF-a = 0.76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The course of PCT and CRP (day 0-4) in survivors/non-survivors with VAP
Period I: Day 0-3 after onset of AB-Tx

Peak

Rapid decline (average >30% per day indicates successful therapy = continue AB-Tx

- Peak: 3.0 ng/ml
- Day 1: 1.8 ng/ml
- Day 2: 0.8 ng/ml
- Day 3: 0.5 ng/ml
- Day 4: 0.2 ng/ml

Prior ICU or admission

AB-Tx
A) Day 1-3 Rules:

1. Find PCT peak value

2. If PCT declines, infection/inflammation is controlled = continue antibiotics
   (a decline is < 30% of the day before, for 2 or 3 days)

3. If there is no decline?
   Add or change antibiotics or antifungals
   Put question: Is diagnosis correct?
Top III
(with support of PCT)

For how long to treat with Antibiotics?

(Duration of Tx)
Antibiotic Stewardship

The Sepsis-Marker of PCT helps to reduce Duration of Treatment!

- this is an individual approach!
- it requires sequential PCT measurement!
Short Treatment Cycles are not Inferior to „Standard“ (longer) Tx-Courses

Tab. 1 In klinischen Studien ermittelte Nicht-Unterlegenheit einer kürzeren versus längeren Antibiotika-Therapiedauer bei verschiedenen Indikationen.

<table>
<thead>
<tr>
<th>Indikation</th>
<th>Kurzzeit-Therapie</th>
<th>Standard- oder längere Therapie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulant erworbene Pneumonie – mit klinischer Stabilisierung nach wenigen Tagen</td>
<td>3–5</td>
<td>7–10</td>
</tr>
<tr>
<td>Nosokomiale Pneumonie</td>
<td>7–10</td>
<td>11–15</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>5–7</td>
<td>10–14</td>
</tr>
<tr>
<td>Intraabdominelle Infektion – nach chirurgischer Fokussanierung</td>
<td>3–5</td>
<td>7–14</td>
</tr>
<tr>
<td>Cholangitis mit Bakterämie – nach erfolgreicher Gallengangsdrainage</td>
<td>4–7</td>
<td>8–14</td>
</tr>
<tr>
<td>Akute Exazerbation einer COPD</td>
<td>2–5</td>
<td>7–10</td>
</tr>
<tr>
<td>Akute (bakterielle) Rhinosinusitis (mit Indikation für eine Antibiotika-Therapie)</td>
<td>3–5</td>
<td>7–10</td>
</tr>
<tr>
<td>Erysipel</td>
<td>5–7</td>
<td>10–14</td>
</tr>
<tr>
<td>Osteomyelitis (ohne Fremdkörperbeteiligung)</td>
<td>42</td>
<td>84</td>
</tr>
<tr>
<td>Fieber bei Neutropenie – mit klinischer Stabilisierung und ohne Erregersicherung/Fokus (Fieber unklarer Genese)</td>
<td>3–5</td>
<td>7–10</td>
</tr>
</tbody>
</table>
Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients

Are 5-7 days of treatment maybe enough?

Nobre et al, Am J Respir Crit Care Med. 2008;177(5):498-505
Exposure to Antibiotics out of 28 Days

23% less Exposure to Antibiotics

Antibiotic Therapy (%)

Days

Control Group

Procalcitonin

p< 0.001

Bouadma, Lancet 2010; 375(9713):463-474
Period II: Day 3-7 after onset of AB-Tx

Peak

- Decline > 80% of peak or
- PCT back to nl range = Stop AB-treatment

3.0 ng/ml

1.8 ng/ml

0.8 ng/ml

0.5 ng/ml

Peak * 0.2 = < 0.6 ng/ml or normal range

STOP of AB

prior ICU or admission

day 0

AB-Tx

day 1

day 2

day 3

day 4

0.25

0.2 ng/ml

0.5 ng/ml

1.0

3.0
Guidelines for initiating antibiotics according to PCT value
Except any situation requiring immediate antibiotic therapy (septic shock, purulent meningitis, etc.)

- [PCT] < 0.25 μg/l: Antibiotics strongly discouraged
- 0.25 ≤ [PCT] < 0.5 μg/l: Antibiotics discouraged
- 0.5 ≤ [PCT] < 1 μg/l: Antibiotics encouraged
- [PCT] ≥ 1 μg/l: Antibiotics strongly encouraged

Obtain second PCT determination 6–12 hours later if value had been obtained early after the start of the episode

Guidelines for stopping, continuing, or changing antibiotics according to daily measured PCT value

- [PCT] < 0.25 μg/l: Stopping antibiotics strongly encouraged
- 0.25 ≤ [PCT] < 0.5 μg/l or [PCT] ≥ 0.5 μg/l: Stopping antibiotics encouraged
- [PCT] ≤ 80% of [PCT] max and [PCT] ≥ 0.5 μg/l: Continuing antibiotics encouraged
- [PCT] > 80% of [PCT] max and [PCT] previous ≤ 0.5 μg/l: Changing antibiotics strongly encouraged

Bouadma, Lancet 2010; 375(9713):463-474
B) Day 3 – 7 Rules (= How long to treat?)

1. Stop AB (Rule of Day 3-7)
   - if focus has clinically cleared AND
   - PCT-stop criteria apply
     - decline >80% of peak or
     - PCT down to < 0.3-0.5 ng/ml
     = use Bouadma Algorithm (Lancet 2010)

AND

2. Add general stop rule for day 7 (Rule of Day 7)
   = stop Tx latest on day 7
   (unless other reasons are discussed)
Interventions to Stop Antibiotic in the „SAPS“-Study
Evelien de Jong, Jas A van Oers, Albertus Beishuizen, et al.
Lancet Infect Dis 2016; 16: 758-60

Rules:
Decrease of PCT >= 80% of peak value
or
PCT concentration <= 0.5 ng/ml

Patients included: ICU-Patients AND Antibiotics started within 24 hours for tx of proven or assumed infection

Exclusion: Prophylaxis only, prolonged therapy required (endocarditis e.g.), corticosteroides taken, severe immunosuppression, moribund patients, severe infection due to Tbc, virus, parasites)
Efficacy and Safety of Procalcitonin Guidance in reducing the Duration of Antibiotic Treatment in Critically ill Patients: a randomised, controlled, open-label Trial („SAPS“-Study)

Evelien de Jong, Jas A van Oers, Albertus Beishuizen, et al.  
Lancet Infect Dis 2016; 16: 758-60

Results:

Median Duration of Tx (PCT-guided group):  5 (3- 9) days
Median Duration of TX (standard group):  7 (4-11) days

Mortality (28days and 1 year):
PCT group:  20% (149/ 761 pat.) and 35% (265/761)  
Std. group:  25% (196/ 785 pat.) and 41% (321/785)
Efficacy and Safety of Procalcitonin Guidance in reducing the Duration of Antibiotic Treatment in Critically ill Patients: a RCT.

Evelien de Jong, Jas A van Oers, Albertus Beishuizen, et al.
Lancet Infect Dis 2016; 16: 758-60

Antibiotic consumption:

<table>
<thead>
<tr>
<th></th>
<th>PCT-group</th>
<th>Standard-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Tx</td>
<td>5.0 (3.0-9.0)</td>
<td>7.0 (4.0-11.0)</td>
</tr>
<tr>
<td>AB free days</td>
<td>7.0 (0.0-14.5)</td>
<td>5.0 (0.0-13.0)</td>
</tr>
<tr>
<td>Repeated AB-courses</td>
<td>175 (23.0)</td>
<td>173 (22.0)</td>
</tr>
<tr>
<td>Time until re-use of AB</td>
<td>4.0 (2.0-8.0)</td>
<td>4.0 (2.0-8.0)</td>
</tr>
<tr>
<td>Lenth of stay ICU</td>
<td>8.5 (5.0-17.0)</td>
<td>9.0 (4.0-17.0)</td>
</tr>
<tr>
<td>Lenth of stay hospital</td>
<td>22.0 (13.0-39.3)</td>
<td>22.0 (12.0-40.0)</td>
</tr>
</tbody>
</table>
Procalcitonin and Sepsis

- indicates inflammation, both bacterial and others (less vial, less trauma)
- good correlation with severity and organ dysfunction
- reliable lower cut-off (0.5 ng/ml)
- well evidence based and part of guidelines
- used for Antibiotic Stewardship for Indication an Stop of Therapy

PCT: High Recommendation for Use
We need a „Standard“ Algorithm also for „Individual“ Treatment
Infection as one Etiology

Inflammation as Risk of Organ Dysfunction

Organ Dysfunction as Risk of Mortality

As „Epiphenomenon“
Infection as one Etiology

Inflammation as Risk of Organ Dysfunction

Organ Dysfunction as Risk of Mortality

Antibiotics as „Epiphenomenon“
Germany: Resistant Bacteria in Rivers and public Lakes isolated: Experts are worried

Antibiotic-Resistance is particulary dangerous for immune suppressed people, elderly and newborn. Multiple-resistant microbiae are present also here around everywhere. The result of a recent analysis are alarming.

Besonders gefährdet sind durch Krankheit geschwächte Menschen, Ältere und Neugeborene

Especially at risk are weak persons, elderly and newborn

In Creeks, Rivers, Natura Pools
Antibiotic Resistance: Experts are Concerned

Tuesday, 06. February 2018

NTV.De
Recommendations Day 1-3:

„Change or no Change of AB“

If PCT has declined:
   no change of AB-treatment
   continue treatment !

If PCT does not decline:
   change AB-treatment !
   or check diagnosis
B) Recommendations Day 3 - 7
(Follow-up Rules)

Individual STOP-Decision after Day 3 of TX:

Stop AB
- if focus has clinically cleared AND
- PCT-stop criteria apply
  (decline >80%, PCT < 0.3-0.5)

AND

Stop Tx latest on Day 7 (Rule of Day 7)
(unless other reasons are discussed within the team)
New Biomarkers for Severity of Pneumonia
Not in routine...

Selected peptides hormones relevant to Sepsis and Cardiovascular Diseases

Adrenomedullin

Vasopressin

ANP

Endothelin-1

adapted from Struck J.
Summary and Conclusion

Markers for Diagnosis of Sepsis and Antibiotic Stewardship Programs should include Procalcitonin

A PCT-guided approach supports reduction of AB consumption and duration of treatment and reduces resistance pressure and costs

and hence has a positive impact both for Hospitals and Patients
The End

PD Dr. med. habil. Michael Meisner
Klinikum Dresden, Germany
Summary

„Sepsis“ since 2016 is defined as „Infection + Organ Dysfunction"

„Inflammation“ is always connected with diagnosis of „Sepsis“

„Markers of Inflammation“ have different profile regarded
- severity of inflammation
- correlation with organ dysfunction
- sens/spec for lower cut-off value
- use for therapeutic implication  
  (AB therapy, Specificity of Agent)
Diagnosis of Sepsis

Egypt 2000 b.C.:

„ukhed u“ - Dangerous entity, deriving from the gut going to the organism, finally ending deadly

M. Meisner
“Sepsis makes the organism hot from the inside, but cold like ice at the surface”

Hippokrates
460-377 b. C.
1. If PCT is very low, severe infection is unlikely and the need of Antibiotics is questionable (<0.1 ng/ml, <0.25 ng/ml)
   
   - e.g. not treatment of local infection or colonisation
   - e.g. no treatment if there is viral infection
   - e.g. no treatment if infection is not dangerous

In order to maintain/preserve the natural (non-resistant) microbial environment/colonisation of the organism and to avoid negative side effects of Antibiotics (e.g. resistant strains, clostridium difficile, candidiasis)
Main Rules:

1. If PCT is very low, severe infection is unlikely and the need of antibiotics is questionable (<0.1 ng/ml, <0.3 ng/ml)

2. The higher PCT is, the more likely Sepsis is: Antibiotics are urgently recommended!

- Initially even, if this is a false positive
Main Rules:

1. If PCT is very low, severe infection is unlikely and the need of antibiotics is questionable (<0.1 ng/ml, <0.3 ng/ml).

2. The higher PCT is, the more likely Sepsis is: Antibiotics are urgently recommended!

3. „Delta PCT“: If PCT declines, inflammation is controlled, - if not, inflammation continues.
Summary

„Sepsis“ since 2016 is defined as „Infection + Organ

Despite this:

- Sepsis is still a „Syndrome“ related with inflammation and various immunological and clinical symptoms

Crit Care Med 1992; 20:864-874
There are many Signs of Sepsis

Systemic Inflammation?

- Local/invasive/Colonisation
- Culture/Serology

Infection?

- Intervention: Elimination of Focus of:
  - a) infection
  - b) inflammation

Sepsis?

- Lab Marker, Clinical Signs of Infl.

Risk of Organ Dysfunction!

- Intervention:
  - Search and remove focus
  - Treat infection
  - Treat organ dysfunction

Severe Sepsis, Sept. Shock

- Intervention: Supportive therapy
  - (Cytosorb, Pentaglobin, HDF, Ventil)

MODS
Summary

„Sepsis“ now is defined as „Infection + Organ Dysfunction“

„Sepsis“ still needs „Sytemic Inflammation“

Markers of Inflammation are of Diagnostic Importance for Diagnosis of „Sepsis“
(all signs of sytemic inflammation)

Among them, Procalcitonin is most important
- relation to severity and risk of organ dysfunction
- lower cut-off to rule out inflammation
- guide of antibiotic therapy

Crit Care Med 1992; 20:864-874
Selected peptides hormones relevant to Sepsis and Cardiovascular Diseases

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Endothelin-1

adapted from Struck J.
Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients

Interventions:
Antibiotics were stopped,
if PCT decreased more than 90\% than initial value, but not before day 3.

Results:
- 3.5 days shorter Courses of AB (median)
  \( (n= 79, \ p = 0.15) \)
- similar Mortality
Infection with Pathogen isolated at Admission

blue = yes/present
green = no absent
before

"specific pathogens responsible for most ICU infection could be identified at the time of ICU admission"
Antibiotic Treatment

before

- sensitive

- resistant

after
„Antibiotic Stewardship“: Where to look at?

> 30%  Indication not clear  1
  - positive urine cultures (asymptomatic)  2
  - putative respiratory tract infections  3

> 70%  Duration of treatment too long  3, 4
  - respiratory tract infection
  - urinary tract infections/bacteriuria  2

n.n.  Postoperative prophylaxis > 24h  5

< 30%  Wrong antibiotic, wrong dosage, interactions not considered.

1 Cusini, PLoS one 2010;5:e14011  3 Christ Crain various publ.
2 Spivak, Clin Infect Dis 2017;65:910-7  4 Stolz, Müller, Christ Crain
5 de With, DtschMed Wochenschr 2017; 142:177-82
These bacteria can grow within a host without harming it, until they reach a threshold concentration. Then they become aggressive, developing to the point at which their numbers are sufficient to overcome the host's immune system, and form a biofilm, leading to disease within the host as the biofilm is a protective layer encasing the bacteria population.
Gram-negative single species bacteria Quorum Sensing

Low Density

High Density

Biofilm

A closer look inside the cells

1. Diffuses through cell membranes

2. Attaches to and activates regulatory protein

3. Binds to DNA

4. Creation of new AHL

5. Process repeats

Each bacterial cell produces a specific autoinducer. Gram positive cells release oligopeptides, while gram negative cells release Acyl Homoserine Lactone. Autoinducer production is a way of cell to cell communication to measure population density. Quorum sensing measures population density to assist in the formation of biofilms. S. aureus synthesizes an oligopeptide via the AgrB protein. When the signal molecule reaches a threshold, phosphorylation of the AgrC protein is stimulated. Phosphorylation of AgrC stimulates several signal transduction pathways.
**Definition of Infection and Treatment**

**Infection:**
Presence of microorganism in otherwise sterile tissue

**Colonisation:**
Growth on surface
- typical: natural and mixed population of germs
- not typical / pathologic:
  - abundant growth
  - not typical germs
  - in vulnerable area (e.g. decubital ulcer)

**Local Infection:**
Invasion of tissue. Only local effects (rubor/secretion):
- no systemic involvement/systemic inflammation:
- no organ dysfunction
- no bloodstream contamination

**Systemic Infection:** Indication for AB/ Surgery ...
„Antibiotic Stewardship“: Where to look at?

> 30% Indication not clear
  - positive urine cultures (asymptomatic)
  - putative respiratory tract infections

> 70% Duration of treatment too long
  - respiratory tract infection
  - urinary tract infections/bacteriuria

n.n. Postoperative prophylaxis > 24h

< 30% Wrong antibiotic, wrong dosage, interactions not considered.
Antibiotic Stewardship

We can reduce Duration of Treatment!

- this is an individual approach!
- with support of procalcitonin!
„Antibiotic Stewardship“: Where to look at?

> 30% Indication not clear
  - positive urine cultures (asymptomatic)
  - putative respiratory tract infections

Procalcitonin indicates local vs systemic infection!

> 70% Duration of treatment too long
  - respiratory tract infection
  - urinary tract infections/bacteriuria

Procalcitonin indicates duration of treatment!

n.n. Postoperative prophylaxis > 24h

< 30% Wrong antibiotic, wrong dosage, interactions not considered.
**Short Treatment Cycles are not Inferior to „Standard“ (longer) Tx-Courses**

Tab. 1 In klinischen Studien ermittelte Nicht-Unterlegenheit einer kürzeren versus längeren Antibiotika-Therapiedauer bei verschiedenen Indikationen.

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Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients

Are 5-7 days of treatment maybe enough?

% patients without antibiotics

PCT-guided group (n=31)

Control group (n=37)

HR: 1.9 (1.2-3.1)

p = 0.009

Time to antibiotic discontinuation (days)

Nobre et al, Am J Respir Crit Care Med. 2008;177(5):498-505
The Role of PCT in this Process
Period I: Day 0-3 after onset of AB-Tx

Rapid decline (average >30% per day indicates successful therapy = continue AB-Tx

Peak

3.0 ng/ml

1.8 ng/ml

0.8 ng/ml

0.2 ng/ml

0.5 ng/ml

prior ICU or admission

day 0 AB-Tx
day 1
day 2
day 3
day 4
Top II
(with support of PCT)

For how long to treat with Antibiotics?

(Duration of Tx)
Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients


Interventions:
Antibiotics were stopped, if PCT decreased more than 90% than initial value, but not before day 3.

Results:
- 3.5 days shorter Courses of AB (median) (n= 79, p = 0.15)
- similar Mortality
Period II: Day 3-7 after onset of AB-Tx

Peak

Decline > 80% of peak or PCT back to nl range = Stop AB-treatment

3.0 ng/ml

1.8 ng/ml

0.8 ng/ml

0.5 ng/ml

0.2 ng/ml

Peak * 0.2 = < 0.6ng/ml or normal range

STOP of AB

prior ICU or admission

day 0

AB-Tx
day 1
day 2
day 3
day 4
A) Day 1-3 Rules:

1. Find PCT peak value

2. If PCT declines, infection/inflammation is controlled = continue antibiotics
   
   (a decline is < 30% of the day before, for 2 or 3 days)

3. If there is no decline?
   Add or change antibiotics or antifungals
   Put question: Is diagnosis correct?
**B) Day 3 – 7 Rules** (= How long to treat?)

1. **Stop AB** (Rule of Day 3-7)
   - if focus has clinically cleared AND
   - PCT-stop criteria apply
     - decline >80% of peak or
     - PCT down to < 0.3-0.5 ng/ml
     = use Bouadma Algorithm (Lancet 2010)

AND

2. **Add general stop rule for day 7** (Rule of Day 7)
   = - stop Tx latest on day 7
   (unless other reasons are discussed)
Evidence Base and Consequences:

The course of PCT-concentrations („delta-PCT“) is important

... for follow up of sepsis, focus and antibiotic therapy ...
Approximately 30-50% of our patients do not have antibiotics in our ICU

(mixed ICU, surgical/postsurgical and internal medicine, included neurosurgery, 16 beds with ventilation + 8 as IMCU-equivalent)
We use the Algorithm of Bouadma et al.

(Lancet 2010)
Guidelines for initiating antibiotics according to PCT value

Except any situation requiring immediate antibiotic therapy (septic shock, purulent meningitis, etc.)

- [PCT] < 0.25 µg/l
  - Antibiotics strongly discouraged

- 0.25 ≤ [PCT] < 0.5 µg/l
  - Antibiotics discouraged

- 0.5 ≤ [PCT] < 1 µg/l
  - Antibiotics encouraged

- [PCT] ≥ 1 µg/l
  - Antibiotics strongly encouraged

Obtain second PCT determination 6–12 hours later if value had been obtained early after the start of the episode.

Guidelines for stopping, continuing, or changing antibiotics according to daily measured PCT value

- [PCT] < 0.25 µg/l
  - Stopping antibiotics strongly encouraged

- [PCT] ≤ 80% [PCT] max or
  - 0.25 ≤ [PCT] < 0.5 µg/l
  - Stopping antibiotics encouraged

- [PCT] < 80% [PCT] max and
  - [PCT] ≥ 0.5 µg/l
  - Continuing antibiotics encouraged

- [PCT] ≥ [PCT] previous
  - Changing antibiotics strongly encouraged

Bouadma, Lancet 2010; 375(9713):463-474
Exposure to Antibiotics out of 28 Days

23% less Exposure to Antibiotics

Antibiotic Therapy (%)

Days

Control Group
Procalcitonin

p< 0.001

Bouadma, Lancet 2010; 375(9713):463-474
The PRORATA Trial:

Main Goals:

To demonstrate that

...a Strategy including PCT Cinetic in the Management of the Infection in the ICU ...

- ... leads to an increase of AB free days during the 1st 28 days
- ... without impact on Mortality at Day 28 and Day 60

Bouadma, Lancet 2010; 375(9713):463-474
Interventions to Stop Antibiotic in the „SAPS“-Study
Evelien de Jong, Jas A van Oers, Albertus Beishuizen, et al.
Lancet Infect Dis 2016; 16: 758-60

Rules:
Decrease of PCT $\geq 80\%$ of peak value
or
PCT concentration $\leq 0.5$ ng/ml

Patients included: ICU-Patients AND Antibiotics started within 24 hours for tx of proven or assumed infection

Exclusion: Prophylaxis only, proloegned therapy required (endocarditis e.g.), corticosteroides taken, severe immunosuppression, moribund patients, severe infection due to Tbc, virus, parasites)
Efficacy and Safety of Procalcitonin Guidance in reducing the Duration of Antibiotic Treatment in Critically ill Patients: a randomised, controlled, open-label Trial („SAPS“-Study)

Evelien de Jong, Jas A van Oers, Albertus Beishuizen, et al.
Lancet Infect Dis 2016; 16: 758-60

Results:

Median Duration of Tx (PCT-guided group): 5 (3-9) days
Median Duration of TX (standard group): 7 (4-11) days

Mortality (28days and 1 year):
PCT group: 20% (149/ 761 pat.) and 35% (265/761)
Std. group: 25% (196/ 785 pat.) and 41% (321/785)
Another study by Christ-Crain, indicated that even in patients with severe infection (CAP) a maximum duration of AB-Tx of less than 7-8 days is far enough.
Guidance of Antibiotic Treatment in Patients with Community acquired Pneumonia (CAP) - ProCAP Study -

Primary endpoint: Duration of Antibiotic use

ProCT (ng/ml)

- < 0.1: NO!
- 0.1-0.25: No, follow up in clinical uncertainty
- >0.25: Yes
- > 0.5: YES!

Follow-up days 4 6 8

AB Therapy

STOP or continue Based on same cutoffs as above

AB treatment (according to evidence-based guidelines for 10-14 days)

AB duration according to guidelines

n=151

Standard group

Randomization

n=151

ProCT group

Prospective interventional trial

Christ-Crain M et al. Am J Respir Crit Care Med. 2006; 174: 84-93
The ProCAP Study – Antibiotic Duration

Shorter AB-Courses ⇒ Fewer Resistances!

Christ-Crain M et al, Am J Respir Crit Care Med 2006
PCT-Guidance saved 8 Treatment Days compared to the current Practice

Shorter treatment in less severe cases
(lower PSI, negative blood culture)

Are 5-7 days of treatment maybe enough?

Christ-Crain M et al. Am J Respir Crit Care Med. 2006; 174: 84
Further References
This has been confirmed recently at 1596 Patients by Eveline De Jong (Lancet Infect Dis 2016; 16: 758-60)

At 3 University Medical Centers and 12 Teachings Hospitals in the Netherlands
Efficacy and Safety of Procalcitonin Guidance in reducing the Duration of Antibiotic Treatment in Critically ill Patients: a RCT.


Antibiotic consumption:

<table>
<thead>
<tr>
<th></th>
<th>PCT-group</th>
<th>Standard-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Tx</td>
<td>5.0 (3.0-9.0)</td>
<td>7.0 (4.0-11.0)</td>
</tr>
<tr>
<td>AB free days</td>
<td>7.0 (0.0-14.5)</td>
<td>5.0 (0.0-13.0)</td>
</tr>
<tr>
<td>Repeated AB-courses</td>
<td>175 (23.0)</td>
<td>173 (22.0)</td>
</tr>
<tr>
<td>Time until re-use of AB</td>
<td>4.0 (2.0-8.0)</td>
<td>4.0 (2.0-8.0)</td>
</tr>
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<td>Lenth of stay ICU</td>
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<td>22.0 (13.0-39.3)</td>
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</table>
Basics of „IPAT“

1. Document AB-Tx and all decisions well
   („sepsis“, no infection, PCT,....)

   - Why is the AB prescribed?
     First symptom,
     Suspected source of infection
     Proven source of infection.
     Reason for selection of AB

   - Is infection systemic or local
     Signs of sepsis and of organ dysfunction

   - Course of infection and symptoms
We need a good Documentation for ASP
## Example of Documentation: The five „S“
Document when AB are started, and why („5 „).

<table>
<thead>
<tr>
<th>Date: _____ 22.1.2016</th>
<th>AB prescribed: _____ Zienam _____</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td><strong>Source sus.</strong></td>
</tr>
<tr>
<td>Sputum yellow</td>
<td>Lung/ Pneumonia</td>
</tr>
<tr>
<td><strong>PCT</strong> based</td>
<td><strong>MiBi</strong></td>
</tr>
<tr>
<td>Recommendation</td>
<td>Samples</td>
</tr>
<tr>
<td><strong>2 ng/ml = AB yes</strong></td>
<td>sputum</td>
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</table>
### Example of Documentation: The five „S“

Document when/why AB are stopped.

**Date: **\_28.1.2016\_ AB stopped.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Source sus.</th>
<th>Sign</th>
<th>Sepsis?</th>
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<tr>
<td><strong>PCT based</strong></td>
<td><strong>MiBi Samples</strong></td>
<td><strong>Focus confirmed</strong></td>
<td><strong>Focus elimination</strong></td>
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<tr>
<td>Recommendation</td>
<td><strong>Klebsiella, sensitive</strong></td>
<td>Lung</td>
<td><strong>Yes</strong> AB stopped</td>
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**0.2 ng/ml = AB: no**
We need „Standard“ Algorithm also for „Individual“ Treatment
1. If PCT is very low, severe infection is unlikely and the need of Antibiotics is questionable (<0.1 ng/ml, <0.25 ng/ml)

- e.g. not treatment of local infection or colonisation
- e.g. no treatment if there is viral infection
- e.g. no treatment if infection is not dangerous

In order to maintain/preserve the natural (non-resistant) microbial environment/colonisation of the organism and to avoid negative side effects of Antibiotics (.e.g. resistant strains, clostridium difficile, candidiasis)
Main Rules:

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- initially even, if this is a false positive
Main Rules:

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2. The higher PCT is, the more likely Sepsis is: Antibiotics are urgently recommended!

3. „Delta PCT“: If PCT declines, inflammation is controlled, - if not, inflammation continues.
Recommendations Day 1-3:

„Change or no Change of AB“

If PCT has declined:
no change of AB-treatment
continue treatment!

If PCT does not decline:
change AB-treatment!
or check diagnosis
B) Recommendations Day 3 - 7  
(Follow-up Rules)

Individual STOP-Decision after Day 3 of TX:

Stop AB
- if focus has clinically cleared AND
- PCT-stop criteria apply  
  (decline >80%, PCT < 0.3-0.5)

AND

Stop Tx latest on Day 7 (Rule of Day 7)  
(unless other reasons are discussed within the team)
Conclusion

Procalcitonin (PCT) should be part of any Antibiotic Stewardship Program and Sepsis Diagnosis Pathway

This reduces costs of Antibiotics and Resistance and is helpful both for both Hospitals and Patients
Infection as Etiology

Inflammation as Risk of Organ Dysfunction

Organ Dysfunction as Risk of Mortality

As „Epiphenomenon“
Time is survival: Kumar et al., CCM 2006:

Each hour of delay of Antibiotic Treatment increases Lethality > 7%
Resistance to Carbapenems in Europe (2016, %)
Short Treatment Cycles are not Inferior to „Standard“ (longer) Tx-Courses

Tab. 1  In klinischen Studien ermittelte Nicht-Unterlegenheit einer kürzeren versus längeren Antibiotika-Therapiedauer bei verschiedenen Indikationen.

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**Period II: Day 3-7 after onset of AB-Tx**

- **Peak**
  - 3.0 ng/ml
  - 1.8 ng/ml
  - 0.8 ng/ml
  - 0.5 ng/ml
  - 0.2 ng/ml

**Decline > 80% of peak or PCT back to nl range = Stop AB-treatment**

**STOP of AB**

- Prior ICU or admission
- Day 0
- AB-Tx
- Day 1
- Day 2
- Day 3
- Day 4

Peak * 0.2 =
< 0.6 ng/ml or normal range
Infection ?
(type/invasive ?)

Inflammation
(systemic ?)

Patient
(individual reaction)

Organ Dysfunction
(mortality !)
Infection ?
(type/location/invasive ?)

Inflammation
(systemic ?)

Patient
(individual reaction)

Organ Dysfunction
(mortality !)
Infection ?
(type/location/invasive ?)

Patient
(individual reaction)

Organ Dysfunction
(mortality !)

Inflammation
(systemic ?)
Infection?
(type/location/invasive?)

Inflammation
(systemic?)

Patient
(individual reaction)

Organ Dysfunction
(mortality!)
Mortality rate increases with increasing severity.

Mortality was:

- **7%** in patients with **SIRS**
- **16%** in patients with **Sepsis**
- **20%** in patients with **Severe Sepsis**
- **46%** in patients with **Septic Shock**

*Rangel-Frausto et al. (JAMA 1995)*
Diagnosis of Sepsis

Positive Cultures ....

*Positive* bacterial cultures were found in:

- 76% of patients with sepsis
- 86% of patients with severe sepsis
- 98% of patients with septic shock

35% were treated with antibiotics

© M. Meisner

Rangel-Frausto et al. (JAMA 1995)
Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study

Marianna Parlato¹, François Philippart²,³, Alexandra Rouquette⁴,⁵, Virginie Moucadel⁶, Virginie Puchois¹, Sophie Blein⁶, Jean-Pierre Bedos⁷, Jean-Luc Diehl⁸,⁹, Olfa Hamzaoui¹⁰, Djillali Annane¹¹,¹², Didier Journiós¹⁵,¹³, Myriam Ben Boutieb⁴, Laurent Estève⁶, Catherine Fitting¹, Jean-Marc Treluyer⁵,¹⁴, Alexandre Pachot⁶, Minou Adib-Conquy¹, Jean-Marc Cavaillon¹, Benoît Misset²,¹⁵,¹⁶* and The Captain Study Group

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Patients screened (SIRS), n=363

Patients not included, n = 84
- absence of consent: n = 7
- inclusion criterion missing: n = 50
  - absence of hypo- or hyperthermia: n= 34
  - other: n = 16
- non-inclusion criterion present:
  - immunosuppression: n= 8
  - legal protection: n = 8
  - already on antibiotics: n = 8
  - already included in the same study: n = 3

Patients included, n= 279

Sepsis, n = 188
- With cell surface biomarkers n = 77
- Without cell surface biomarkers n = 111

Non-septic SIRS, n = 91
- With cell surface biomarkers n = 33
- Without cell surface biomarkers n = 58
Fig. 2 Univariate performance of the 28 quantitative markers, according to different imputation methods. X-axis, name of each biomarker; Y-axis, ROC-AUC values of each biomarker ranked between 0 and 1. Each bar corresponds to the 95% confidence interval of the ROC-AUC. For each biomarker, three bars are provided, corresponding to each of the first, second, and third imputation method for values below LLoQ, over ULoQ, and for missing values (ESM Table 6). *RNA

PSP = pancreatic stone protein, MMP8 = metalloprotinase 8, ...
Time Course of CRP after Cardiac Surgery
(only patients with increased PCT)

![Graph showing the time course of CRP after cardiac surgery for postoperative days 1 to 7. The y-axis represents CRP (mg/l) with values ranging from 0 to 280. The x-axis represents postoperative days from 1 to 7. Each data point shows the mean CRP level with confidence intervals.](image-url)
Time Course of PCT after Cardiac Surgery

(only patients with increased PCT)
Markers and Increase of Concentrations

The Logarithmic Scale
(10x10 x 10 x 10 x ...)

.... indicates a 3-D duty/job of the molecule

= from local effects

to systemic effects!

1D
e.g. hormones wiith high affinity and only few target cells

3D
involvement of volume needs exponential growth

2D
local effects e.g. 10x10 mm

Control  No Infection  Infection
sTREM-1 does not indicate severity of Systemic Inflammation

The increase of concentrations is small (less than 10-fold)

*sTREM-1 = soluble triggering receptor expressed on myeloid cells-1*

sTREM-1 for CAP-Severity & Bacteremia

$p = ns$

<table>
<thead>
<tr>
<th>PSI class</th>
<th>sTREM-1 Giot (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.50</td>
</tr>
<tr>
<td>II</td>
<td>0.53</td>
</tr>
<tr>
<td>III</td>
<td>0.56</td>
</tr>
<tr>
<td>IV</td>
<td>0.59</td>
</tr>
<tr>
<td>V</td>
<td>0.63</td>
</tr>
</tbody>
</table>

- sTREM: 0.57 (0.50-0.63)
- ProCT: 0.81 (0.76-0.86)
- CRP: 0.63 (0.56-0.69)
- Lc: 0.68 (0.61-0.74)

In conclusion, in our study we found that serum IL-33 level might be used as a novel biochemical marker in the diagnosis and follow-up of sepsis in preterm infants. We also determined that IL-33 might be useful for predicting sepsis in premature infants. And also, our results demonstrated that IL-33 may not be useful for discrimination of microbiological agents.

Table 2. Comparison of the median serum levels of CRP, IL-6 and IL-33 for the control group and at the 1st, 3rd and the 7th Day of diagnosis for sepsis group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Median (IQR)</th>
<th>Sepsis 1st day Median (IQR)</th>
<th>Sepsis 3rd day Median (IQR)</th>
<th>Sepsis 7th day Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>2.410 (1.91)</td>
<td>54.9 (60.9)</td>
<td>23 (25.9)</td>
<td>10 (16.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>12.10 (8.15)</td>
<td>585 (1430)</td>
<td>48 (99)</td>
<td>16 (32.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-33 (pg/ml)</td>
<td>0.956 (0.413)</td>
<td>2.564 (1.13)</td>
<td>1.32 (0.83)</td>
<td>0.71 (0.41)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
The Aminoacid-Sequence of Procalcitonin (PCT)

1. **ProCalci**

- **N-Pro CT**
- **Calcitonin**
- **Katacalc**
- **Cleavage site of Endopeptidases**

**PAM** = Peptidyl-Amidating Monooxygenase
The absolute and relative PCT values are important

**PCT levels increase with increasing systemic consequences of infection and severity of disease and organ dysfunction**

- **High Range of Concentrations**

- **Parallels to Severity of Inflammation**
  - 0.5 ng/ml: no Sepsis
  - 0.5-2ng/ml: Sepsis likely
  - > 2 ng/ml: High Risk of Patient: Sepsis/Sev.Sep/SS!

- **Stable in Blood Samples**
  - Store at Room Temperature
Presepsin: another name for the sCD14-ST molecule

N-terminal sequence fragment of CD 14 („soluble CD14 subtype fragment“). CD14 is a protein on membranes of mononuclear cells (55kDalton). CD14 binds lipopolysaccharides (LPS) as a receptor. Soluble parts of the receptor protein are found in serum/plasma during disease like infection, ARDS, AIDS/HIV, SLE... (13kDalton)
**Presepsin: +/- SD of Mean or Median?**

**Optimal cut-off for Sepsis:** 407 ng/ml

---

sCD14-ST (Presepsin): Baseline and Cut-off

*Chenevier-Gobeaux C. et al.*
*Clin Chim Acta.*
2014 Jan 1;427:34-6

Baseline, age-dependence and relation with kidney function were analyzed.

**Urbonas C., et al.: Cytokin 62 (2013) 34-7:**
sCD14-ST in neutropenic Patients:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median</th>
<th>CI95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUO</td>
<td>356 ng/ml</td>
<td>255-469</td>
<td>0.819</td>
</tr>
<tr>
<td>Bacteremia/Sepsis</td>
<td>401 ng/ml</td>
<td>212-484</td>
<td>= ns</td>
</tr>
</tbody>
</table>

Optimal cut-off for Sepsis: 407 ng/ml
Mean and Median?
SEPSIS? or (Sepsis/Severe Sepsis/Septic Shock)?

Table 2
Comparison of clinical data in different groups with the severity of sepsis

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>APACHEII score</th>
<th>Presepsin (pg/ml)</th>
<th>PCT (μg/L)</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Median(min,max)</td>
<td>Median(min,max)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>33</td>
<td>13.73 ± 4.118</td>
<td>719.97 ± 215.890</td>
<td>0.80(0.05,13.67)</td>
<td>1.00(0.2,5.1)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>24</td>
<td>22.17 ± 6.329*</td>
<td>1421.21 ± 643.182*</td>
<td>2.94*(0.19,76.57)</td>
<td>2.0*(0.5,6.9)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>15</td>
<td>26.47 ± 8.026*</td>
<td>2564.13 ± 1557.556*</td>
<td>3.46(0.33,150.41)</td>
<td>2.6(0.8,10.5)</td>
</tr>
<tr>
<td>Statistics</td>
<td>29.046*</td>
<td>27.098*</td>
<td>12.685</td>
<td>18.891</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.002</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Statistics * mean F value, other statistics mean χ² value; compared with sepsis group, *P < 0.05; compared with severe sepsis, **P < 0.05.


3.2. Comparison of sepsis and non-sepsis (including normal and SIRS group) patients

The median level of presepsin was 965 pg/ml (range: 656.3–1665.5) in sepsis group (n = 72), 231 pg/ml (range: 234–393) in normal group (n = 20), 298 pg/ml (range: 234–393) in SIRS group (n = 23). The presepsin level of sepsis group was higher than the normal group and SIRS group (U = 105, P < 0.01 and U = 76, P < 0.01, respectively).

Table 1
Characteristics of subjects in this study

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>SIRS</th>
<th>sepsis</th>
<th>Severe sepsis</th>
<th>Septic shock</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case amount</td>
<td>20</td>
<td>23</td>
<td>33</td>
<td>24</td>
<td>15</td>
<td>115</td>
</tr>
<tr>
<td>Male</td>
<td>10(50%)</td>
<td>13(57%)</td>
<td>22(67%)</td>
<td>10(42%)</td>
<td>10(67%)</td>
<td>65(57%)</td>
</tr>
<tr>
<td>Female</td>
<td>10(50%)</td>
<td>10(43%)</td>
<td>11(33%)</td>
<td>14(58%)</td>
<td>5(33%)</td>
<td>50(43%)</td>
</tr>
<tr>
<td>Average age (range)</td>
<td>60.6</td>
<td>59.7</td>
<td>54.1</td>
<td>70.5</td>
<td>69.2</td>
<td>62.1</td>
</tr>
<tr>
<td></td>
<td>(18–85)</td>
<td>(18–92)</td>
<td>(18–100)</td>
<td>(18–92)</td>
<td>(24–95)</td>
<td>(18–100)</td>
</tr>
</tbody>
</table>
Sepsis (Sepsis, Severe Sepsis, Septic Shock) vs SIRS

PCT

CRP

Lactate

Presepsin
Survivors vs Non-Survivors

Procalcitonin on D1-3 in non-survivors vs. survivors

CRP on D1-3 in non-survivors vs. survivors

Presepsin on D1-3 in non-survivors vs. survivors

Lactate on D1-3 in non-survivors vs. survivors
Selected peptides hormones relevant to Sepsis and Cardiovascular Diseases

- Adrenomedullin
- Vasopressin
- ANP
- Endothelin-1

(adapted from Struck J.)
Selected Prohormones relevant to Sepsis and Cardiovascular Diseases?

N-20 terminal peptide (PAMP) 1-21 45 92 95 146 185

Endothelin-1 1-17 53 74 93 212

Vasopressin (ADH) 1-19 29

Adrenomedullin 124-151

Neurophysin-2 126-164

Copeptin

adapted from Struck J.
Standard markers in Pneumonia

CRP

Leukocytes

Temperature

Helpful only as general indicators of inflammation, low specificity ....
New Biomarkers for Severity of Pneumonia
Not in routine...

Infection as Etiology

Inflammation as Risk of Organ Dysfunction

Organ Dysfunction as Risk of Mortality

As „Epiphenomenon“
Infection as Etiology

Inflammation as Risk of Organ Dysfunction

Organ Dysfunction as Risk of Mortality

As „Epiphenomenon“
Asthma

measure IgE

IgE (high)  IgE (low)

1) Allergic Pathway

Try Anti-IgE if allergic („Omalizumab“)

if Corticosteroids and other substances did not work sufficiently

2) Non-Allergic Pathway

Measure Eosinophiles (>300/µl)

If high, try AntiIL-5-Antibody („Mepolizumab“ or „Reslizumab“)

Measure Neutrophiles:
If high, try LTB4-inhibitor
If low, try Corticosteroids
## Bacterial and viral Meningitis

### PCT (ng/ml)

<table>
<thead>
<tr>
<th></th>
<th><strong>bacterial</strong></th>
<th><strong>viral</strong></th>
<th><strong>false negative</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gendrel</strong></td>
<td><strong>54 ± 35</strong></td>
<td><strong>0.32 ± 0.35</strong></td>
<td>0/18</td>
</tr>
<tr>
<td><em>Clin Inf Dis</em></td>
<td>4.8 - 110</td>
<td>0 - 1.7</td>
<td></td>
</tr>
<tr>
<td><em>1997</em></td>
<td><em>n = 18</em></td>
<td><em>n = 41</em></td>
<td></td>
</tr>
<tr>
<td><strong>Schwarz</strong></td>
<td><strong>1.75</strong></td>
<td><strong>0.24</strong></td>
<td>3(5)/16</td>
</tr>
<tr>
<td><em>Crit Care Med</em></td>
<td>0.16 - 60</td>
<td>0.12 - 0.29</td>
<td></td>
</tr>
<tr>
<td><em>2000</em></td>
<td><em>n = 16</em></td>
<td><em>n = 14</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>p &lt; 0.001</em></td>
<td><em>p &lt; 0.001</em></td>
<td></td>
</tr>
</tbody>
</table>

© M. Meisner
PCT: viral, bacterial local and „invasive“ Infection
Resistance to Carbapenems in Europe (2016, %)
„Antibiotic Stewardship“:
Where to look at?

> 30%  Indication not clear  
  - positive urine cultures (asymptomatic)
  - putative respiratory tract infections

> 70%  Duration of treatment too long
  - respiratory tract infection
  - urinary tract infections/bacteriuria

< 30%  Wrong antibiotic, wrong dosage, interactions not considered.

1 Cusini, PLoS one 2010;5:e14011
2 Spivak, Clin Infect Dis 2017;65:910-7
3 Christ Crain various publ.
4 Stolz, Müller, Christ Crain
5 de With, DtschMed Wochenschr 2017; 142:177-82
Definition of Infection and Treatment

**Infection:**
Presence of microorganism in otherwise sterile tissue

**Colonisation:**
Growth on surface
- typical: natural and mixed population of germs
- not typical / pathologic:
  - abundant growth
  - not typical germs
  - in vulnerable area (e.g. decubital ulcer)

**Local Infection:**
Invasion of tissue. Only local effects (rubor/secretion):
- no systemic involvement/systemic inflammation:
- no organ dysfunction
- no bloodstream contamination

**Systemic Infection:** Indication for AB/ Surgery ...
Infection with Pathogen isolated at Admission

blue = yes/present
green = no absent
before

“specific pathogens responsible for most ICU infection could be identified at the time of ICU admission”
„Antibiotic Stewardship“: Where to look at?

> 30%  Indication not clear
- positive urine cultures (asymptomatic)
- putative respiratory tract infections

> 70%  Duration of treatment too long
- respiratory tract infection
- urinary tract infections/bacteriuria

n.n.  Postoperative prophylaxis > 24h

< 30%  Wrong antibiotic, wrong dosage, interactions not considered.
„Antibiotic Stewardship“: Where to look at ?

> 30%  Indication not clear
  - positive urine cultures (asymptomatic)
  - putative respiratory tract infections

**Procalcitonin indicates local vs systemic infection !**

> 70%  Duration of treatment too long
  - respiratory tract infection
  - urinary tract infections/bacteriuria

**Procalcitonin indicates duration of treatment !**

n.n.  Postoperative prophylaxis > 24h

< 30%  Wrong antibiotic, wrong dosage, interactions not considered.
PCT Measurement

Consequences of Low PCT

PCT is normal or very low:
- systemic inflammation is not severe
- risk of organ dysfunction is low

Depending on further clinical signs/data:
NOW maybe NO acute intervention required
Antibiotic treatment may NOT be reuquired

however,
depends on individual situation
depends on individual reaction of
the patient’s immune system
Period I: Day 0-3 after onset of AB-Tx

Peak

Rapid decline (average >30% per day indicates successful therapy = continue AB-Tx)

3.0 ng/ml

1.8 ng/ml

0.8 ng/ml

0.5 ng/ml

0.2 ng/ml

prior ICU or admission

day 0 AB-Tx
day 1 day 2 day 3 day 4
A) Day 1-3 Rules:

1. Find PCT peak value

2. If PCT declines, infection/inflammation is controlled = continue antibiotics
   
   *(a decline is < 30% of the day before, for 2 or 3 days)*

3. If there is no decline?
   
   Add or change antibiotics or antifungals
   
   Put question: Is diagnosis correct?
B) Day 3 – 7 Rules (= How long to treat?)

1. Stop AB (Rule of Day 3-7)
   - if focus has clinically cleared AND
   - PCT-stop criteria apply
     - decline >80% of peak or
     - PCT down to < 0.3-0.5 ng/ml
     = use Bouadma Algorithm (Lancet 2010)

AND

2. Add general stop rule for day 7 (Rule of Day 7)
   = - stop Tx latest on day 7
     (unless other reasons are discussed)
Period II: Day 3-7 after onset of AB-Tx

- Peak * 0.2 = < 0.6 ng/ml or normal range
- Decline > 80% of peak or PCT back to nl range = Stop AB-treatment

Prior ICU or admission
AB-Tx

Day 0
Day 1
Day 2
Day 3
Day 4
High PCT levels are RELATED WITH serious infection, sepsis and systemic inflammation.
PCT in Patients with and without Sepsis


© M. Meisner
Conclusion I/III

„Sepsis“ is caused by „infection“

„Sepsis“ has different symptoms:
  - clinical symptoms
  - systemic inflammation
  - organ dysfunction

Early Treatment is important

Early signs of sepsis often seen by „Systemic Inflammation“, 

However:
Host response may be individual (maybe 10% of patients)
Conclusion II/III

Regarded Sepsis many Topics must be looked at:

- Diagnosis of Infection (Cultures, CT, „NGS“ in future)

- Early detection of Systemic Inflammation is important
  (unspecific + specific markers)

- Prevention of Organ Dysfunction is important
  („Sepsis-3“)

Goal of Diagnosis (= the role of markers of inflammation):
- early treatment, to prevent organ dysfunction (mortality)
- to avoid antibiotic treatment, if not required
Conclusion III/III

„Markers of Inflammation“ of Sepsis“:

- Play a significant role for diagnosis
- Have different characteristics:
  - relation to severity of inflammation
    (e.g. PCT, IL-6, Presepsin)
  - good discrimination of „no“ = „0“ and „yes = positive“
    (e.g. PCT)
  - one only indicator of „infection“ is not sufficient
    (TREM-1, Endotoxin, ...)
  - can be used to guide antibiotic therapy (PCT)
    confirmation or exclusion of sepsis, duration of tx
Not always the bad one's
Time Course of Induction of various Markers of the Systemic Inflammatory Response

Plasma Concentration

Time (h)

© M. Meisner

CRP = C-reactive Protein

Produced in the liver („acute phase protein“), circulating in the blood (stimated by IL-6, others).

Belongs to the „innate“ immune system. Works as a „pattern recognition molecule“ e.t. CRP binds to phosphocholine at bacteriae and dead cells. Induces complement system. Activates monocytes as well. Is a covalent bound pentamer.

The Phe-66 and Glu-81 AA residues together with two Calcium ions produce a „co-crystal“ structue with phosphocholine (from damaged membranes, e.g.)

On the opposite side there is a C1q binding site and a FcGamma putative binding site (link to immunoglobulines).

CRP-receptors are FcgammeRIand II and inhibitory, the ITAM/ITIM.
The Role of PCT for Diagnosis of Sepsis
Correlation with Severity of Disease (Organ Dysfunction)

PCT (ng/mL)

<table>
<thead>
<tr>
<th>Categories</th>
<th>n=32</th>
<th>n=161</th>
<th>n=106</th>
<th>n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-6</td>
<td>7-12</td>
<td>13-18</td>
<td>19-24</td>
</tr>
<tr>
<td></td>
<td>p&lt; 0.001</td>
<td>p&lt; 0.001</td>
<td>p&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

CRP (mg/mL)

<table>
<thead>
<tr>
<th>Categories</th>
<th>n=32</th>
<th>n=161</th>
<th>n=106</th>
<th>n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>13-18</td>
<td>19-24</td>
</tr>
<tr>
<td></td>
<td>p&lt; 0.001</td>
<td>p&lt; 0.001</td>
<td>p&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Categories in the SOFA Score

Harbarth S et al. AJRCC Med. 2001;164:396-402
Sepsis-Markers and Score-Systems of Organ Dysfunction / Risk


APACHE II

PCT

< 9 10-19 20-29 > 30

0.1 1 10

n=2 n=54 n=193 n=67

CRP

10 100

n=2 n=161 n=106 n=7

SOFA-Score

PCT

ng/ml 1-6 7-12 13-18 19-24

10 100

CRP

mg/l 1-6 7-12 13-18 19-24

10 100
Definition of Infection:
Antibiotics questionable

Infection:
Presence of microorganism in otherwise sterile tissue

Colonisation:
a) natural = typical
b) growth on surface
   - abundant
   - not typical
   - in vulnerable area (e.g. decubital ulcer)

Local Infection:
Only local effects (rubor/secretion), no systemic involvement:
   like no organ dysfunction, no inflammation, no bloodstream contamination
The Questions remain:

(to be answered NOT by laboratory, but by physician)

- is this contamination ?
- is this a part of the natural microbiological surface ?
- is this colonisation ?
- is this **local infection, invasive infection** or **systemic infection** ?

Must these condition really be treated by antibiotics ?

The answer should be:
„Treated should be only systemic inflammation and destructive local infection“
Definition of Infection: Antibiotics urgently required

„Systemically active“ infection:
+ Clinical Symptoms of Sepsis

+ Positive markers of sepsis observed
  - specific and unspecific markers can be used
    (Procalcitonin, others)

+ Latest: if acute organ dysfunction is seen

Diagnosis is positive, if a minimum of 1 of these criteria is seen

Stop of Antibiotics possible, of criteriae are negative
(Inflammation measured by Procalcitonin)
"Procalcitonin in Pediatric Emergency Department for the Early Diagnosis of Invasive Bacterial Infections in Febrile Infants"


**PCT especially indicates the severe types of infection**

Viral vs. Bacterial (none-invasive)

- **AUC (PCT)** 0.82
- **AUC (CRP)** 0.78

None-invasive vs. invasive bact. Infection

- **AUC (PCT)** 0.95
- **AUC (CRP)** 0.81
Maximum PCT-Levels after different Types of Surgery

1. Minor periph. S.
2. Minor abdom. S.
3. Major abdom. S.
4. Mediast. Retroperi t. S.
5. Cardiac. Thorac. S.

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Maximum CRP-Levels after different Types of Surgery

<table>
<thead>
<tr>
<th>Type of Surgery (1-5)</th>
<th>CRP (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Minor periph.S.</td>
<td>100 - 300</td>
</tr>
<tr>
<td>2. Minor abdom.S.</td>
<td>100 - 300</td>
</tr>
<tr>
<td>3. Major abdom. S.</td>
<td>100 - 300</td>
</tr>
<tr>
<td>4. Mediast. Retroperit.S.</td>
<td>100 - 300</td>
</tr>
<tr>
<td>5. Cardiac.- Thorac. S.</td>
<td>100 - 300</td>
</tr>
</tbody>
</table>

© M. Meisner
Time Course of CRP after Cardiac Surgery
(only patients with increased PCT)
Time Course of PCT after Cardiac Surgery
(only patients with increased PCT)
Postoperativ niedrige oder schnell rückläufige PCT-Werte zeigen einen komplikationslosen Verlauf an.

Vergleich von CRP, PCT, IL-6

Rote, rosa Linie: Postoperative Komplikationen

Grüne, blaue Linie: Normaler postoperativer Verlauf

Reith, Intensive Care Med, 2000
Postoperatively low or rapidly declining PCT levels indicate normal postoperative course

Three markers: CRP, PCT, IL-6

Red, pink line: Postoperative complications

Green, blue line: Regular postoperative course

Reith, Intensive Care Med, 2000
PCT: highest sensitivity and specificity for sepsis diagnosis

no SIRS
no Infection

no SIRS
no Infection

SIRS, Sepsis
Sepsis, Severe Sepsis

Sepsis Shock

IL-6 and Diagnosis of Sepsis

Are PCT and Presepsin Competitors?
Soluble CD14-Subtype is called “Presepsin”

- higher grey zone and lower discrimination for diagnosis of sepsis (cut-off 400-500 ng/ml cut-off)
  - age, renal function, SIRS-sepsis, FUO -

- not evaluated for antibiotic stewardship

- not able to discriminate FUO and bact/sepsis in oncology (both for Presepsin and sHLA-G, Urbonas C, et al. Cytokine 62 (2013)34-7)

- used on an experimental level,

- not an evidence based or guideline recommended marker

<table>
<thead>
<tr>
<th>Pubmed citations (Feb 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procalcitonin (+ sepsis)</td>
</tr>
<tr>
<td>Presepsin/sCD14-ST</td>
</tr>
</tbody>
</table>
Sepsis is caused by „infection“

Sepsis is different symptoms:

- clinical
- inflammation
- organ dysfunction

Early Treatment is important

**Sepsis and Systemic Inflammation:**

*Early signs of sepsis often seen by „Systemic Inflammation“*

*However:*

*Host response may be individual (maybe 10% of patients)*
"Markers of Inflammation" of Sepsis

need different characteristics:
  - relation to severity of inflammation
    (PCT, IL-6, Presepsin)
  - good discrimination of "no" / "zero" and "positive"
    (PCT)
  - only an indicator of "infection" is not enough
    (TREM, Endotoxin, ...)
  - can be used to guide antibiotic therapy (PCT)
Conclusion III

All is important:

- Diagnosis of Infection (mibi, culture, later „NGS“)

- Early detection of Systemic Inflammation is important (unspecific + specific markers)

- Diagnosis of Organ Dysfunction is important („Sepsis-3 Definition)

To reach the Goal (the role of inflammation markers):
- early treatment, to prevent organ dysfunction (mortality)
- to avoid antibiotic treatment, if not required
What do we expect from a Marker of Sepsis / Systemic Inflammation?

- A Difference between „0“ and „positive“
- A Relation to different kinds of Infection/Inflammation
- A Relation to Severity of Inflammation
Is the Marker clinical useful?

- Kinetic of Induction / Elimination
- Relation to Organ Dysfunction
- Antibiotic Stewardship and Guide of Antibiotic Therapy
Which Marker we have?

Kinetic of Induction / Elimination

Relation to Organ Dysfunction

Antibiotic Stewardship and Guide of Antibiotic Therapy
<table>
<thead>
<tr>
<th>Markers and Phenomena</th>
<th>Details</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker of Pathogens</td>
<td>DNA, Endotoxins, Antibodies</td>
<td>Focus elimination + Colonisation vs Infection?</td>
</tr>
<tr>
<td>Epiphenomena of Inflammation</td>
<td>Fever, Leukocytosis, Activation of Coagulation, Serum Markers (Albumin, PO4-, Lactate)</td>
<td>General „watch-up“! + Not Specific for Sepsis</td>
</tr>
<tr>
<td>Marker of Systemic Inflammation</td>
<td>Cytokines (IL-1-IL33), Cell-Surface Markers (CRP, PCT, Presepsin)</td>
<td>Sepsis is present + High Risk of Organ Dysfunction!</td>
</tr>
</tbody>
</table>

"Which Marker do we have?"
Definitions of SIRS and Sepsis

„SIRS“

- Temperature > 38°C oder < 36°C
- Heart Rate > 90/min
- Tachypnoe > 20/min oder Hyperventilation ($CO_2$ < 32mmHg)
- Leukocytes > 12 000 oder < 4000 oder >10% immature cells

>>>>>> at least 2 of the above conditions <<<<<<
Definition der Sepsis

„Sepsis“
- SIRS mit infektiöser Ursache

„Schwere Sepsis“
- Organfunktionsstörungen oder Minderperfusion
  z.B. Oligurie (< 30 ml/h), Laktat-Azidose, Bewußtseinsstörungen.
  Hypotonie, behebbar durch Volumengabe

„Septischer Schock“
- Hypotonie trotz adäquater Volumentherapie:
  - RR < 90 mmHg oder Ausgangswert minus 40 mmHg
  - Perfusionsstörungen trotz Katecholamintherapie
  - Organfunktionsstörungen
Fig. 1 Schematic representation illustrating a the almost complete overlap of sepsis and infection when the SIRS criteria of the 1992 criteria [3] are used and b the differences between qSOFA and sepsis. qSOFA quick sequential organ failure assessment, SIRS systemic inflammatory response syndrome.
qSOFA does not replace SIRS in the definition of sepsis

Jean-Louis Vincent¹*, Greg S. Martin² and Mitchell M. Levy³

The recently published consensus definitions for sepsis [1] have raised a lot of discussion and controversy. We all agree on the fundamental importance of identifying sepsis early and of applying effective and complete
Definitions of Sepsis

„Sepsis“
• SIRS of infectious etiology

„Severe Sepsis“
• Organ dysfunction or perfusion abnormalities
e.g. oliguria (< 30 ml/h), lactate-acidosis,
disturbance of consciousness
art. hypotension, reversible by volume resuscitation

„Septic Shock“
• Hypotension in spite of volume resuscitation:
  - RR < 90 mmHg or decline of more than 40 mmHg
  - Perfusion abnormalities in spite of catecholamines
  - Organ Dysfunction like severe sepsis

Crit Care Med 1992; 20:864-874
What do we expect from a Marker of Sepsis / Systemic Inflammation?

- A difference between „0“ and „positive“
- A relation to different kinds of infection/inflammation
- A relation to Severity of Inflammation
sTREM-1

sCD14 („Presepsin“)

IL-33
The triggering receptor expressed on myeloid cells (TREM)-1 is a recently identified molecule involved in the inflammatory response. It belongs to the immunoglobulin superfamily and is expressed on the surface of neutrophils, mature monocytes, and macrophages. The engagement of TREM-1 synergizes with the Toll-like receptors signaling pathway in amplifying the inflammatory response mediated by several microbial components. The expression of the membrane-bound TREM-1 is strongly upregulated on monocytes during sepsis. Besides its membranous form, a soluble counterpart of TREM-1 exists that is specifically released during several infectious processes. The measurement of that soluble form in biological fluids may be useful as a diagnostic tool, especially during severe sepsis and pneumonia. Moreover, the evolutionary pattern of TREM-1 may be interesting during the follow-up of septic patients.
Table 2. Diagnostic Performance of Different Predictors of Infection Defined according to the Criteria Proposed by the American College of Chest Physicians/Society of Critical Care Medicine*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Soluble TREM-1</th>
<th>Procalcitonin</th>
<th>C-Reactive Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff value†</td>
<td>60 ng/mL</td>
<td>0.6 ng/mL</td>
<td>70 mg/L</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>96 (92–100)</td>
<td>84 (72–93)</td>
<td>76 (63–86)</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>89 (82–95)</td>
<td>70 (50–83)</td>
<td>67 (47–80)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>8.6 (3.8–21.5)</td>
<td>2.8 (1.4–5.5)</td>
<td>2.2 (1.2–4.3)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.04 (0.01–0.2)</td>
<td>0.23 (0.1–0.6)</td>
<td>0.36 (0.2–0.8)</td>
</tr>
<tr>
<td>Area under the receiver-operating characteristic curve</td>
<td>0.97 (0.94–1.00)</td>
<td>0.85 (0.81–0.89)</td>
<td>0.77 (0.69–0.85)</td>
</tr>
</tbody>
</table>

* Infected patients (n = 47) were those with a diagnosis of sepsis, severe sepsis, or septic shock. Noninfected patients (n = 30) were those with a diagnosis of a systemic...
In addition to being a reliable marker of bacterial infection, plasma sTREM-1 appears to be valuable during the follow-up of the septic process. A progressive, declining sTREM-1 concentration might witness treatment accuracy. Conversely, persistently elevated sTREM-1 level should lead to a reevaluation of the therapy. Finally, plasma sTREM-1 concentration at admission may be relevant in predicting outcome of septic patients.

Gibot S.,
Crit Care Med 2005; 33:792-796
sTREM-1 does not indicate Severity of Systemic Inflammation

The increase of concentrations is small (less than 10-fold)

sTREM-1 for CAP-Severity & Bacteremia

$p = \text{ns}$

<table>
<thead>
<tr>
<th>PSI class</th>
<th>sTREM-1 Gibot (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0-400</td>
</tr>
<tr>
<td>II</td>
<td>400-800</td>
</tr>
<tr>
<td>III</td>
<td>800-1200</td>
</tr>
<tr>
<td>IV</td>
<td>1200-1600</td>
</tr>
<tr>
<td>V</td>
<td>1600-2000</td>
</tr>
</tbody>
</table>

- **sTREM**: 0.57 (0.50-0.63)
- **ProCT**: 0.81 (0.76-0.86)
- **CRP**: 0.63 (0.56-0.69)
- **Lc**: 0.68 (0.61-0.74)

Markers and Increase of Concentrations

The Logarithmic Scale
(10 x 10 x 10 x 10 x ...)

.... indicates a 3-D duty/job of the molecule

= from local effects

to systemic effects!

1D

e.g. hormones with high affinity and only few target cells

2D

local effects e.g. 10x10 mm

3D

involvement of volume needs exponential growth
SIRS versus Sepsis/severe Sepsis/Septic Shock

The utility of presepsin in diagnosis and risk stratification for the emergency patients with sepsis

Bin Lu a,1, Yan Zhang a,1, Chen Li a, Chenyan Liu a, Ying Yao a, Minghuan Su b, Songtao Shou a,1

a Department of Emergency Medicine, Tianjin Medical University General Hospital, Tianjin 300052, PR China
b Department of Emergency Medicine, Institute of Hematology and Blood Diseases Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Tianjin 300052, PR China

n(SIRS) = 23
n(S,SS) = 72
sCD14-ST (Presepsin): Baseline and Cut-off

Chenevier-Gobeaux C. ... Clin Chim Acta. 2014 Jan 1;427:34-6

Baseline, age-dependence and relation with kidney function were analyzed

**sCD14-ST in neutropenic Patients:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median</th>
<th>CI95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUO</td>
<td>356 ng/ml</td>
<td>255-469</td>
<td>0.819</td>
</tr>
<tr>
<td>Bacteremia/Sepsis</td>
<td>401 ng/ml</td>
<td>212-484</td>
<td>= ns</td>
</tr>
</tbody>
</table>
Mean and Median?
SEPSIS? or (Sepsis/Severe Sepsis/Septic Shock)?

Table 2
Comparison of clinical data in different groups with the severity of sepsis

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>APACHE II score Mean ± SD</th>
<th>Presepsin (pg/ml) Mean ± SD</th>
<th>PCT (µg/L) Median(min, max)</th>
<th>Lactate (mmol/L) Median(min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>33</td>
<td>13.73 ± 4.118</td>
<td>719.97 ± 215.890</td>
<td>0.80 (0.05, 13.67)</td>
<td>1.00 (0.2, 5.1)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>24</td>
<td>22.17 ± 6.329*</td>
<td>1421.21 ± 643.182*</td>
<td>2.94* (0.19, 76.57)</td>
<td>2.0* (0.5, 6.9)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>15</td>
<td>26.47 ± 8.026*</td>
<td>2564.13 ± 1557.556*</td>
<td>3.46 (0.33, 150.41)</td>
<td>2.6 (0.8, 10.5)</td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.685</td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
</tbody>
</table>

Statistics * mean F value, other statistics mean χ² value; compared with sepsis group, *P < 0.05; compared with severe sepsis, *P < 0.05.


3.2. Comparison of sepsis and non-sepsis (including normal and SIRS group) patients

The median level of presepsin was 965 pg/ml (range: 656.3–1665.5) in sepsis group (n = 72), 231 pg/ml (range: 234–393) in normal group (n = 20), 298 pg/ml (range: 234–393) in SIRS group (n = 23). The presepsin level of sepsis group was higher than the normal group and SIRS group (U = 105, P < 0.01 and U = 76, P < 0.01, respectively).

Table 1
Characteristics of subjects in this study

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>SIRS</th>
<th>sepsis</th>
<th>Severe sepsis</th>
<th>Septic shock</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case amount</td>
<td>20</td>
<td>23</td>
<td>33</td>
<td>24</td>
<td>15</td>
<td>115</td>
</tr>
<tr>
<td>Male</td>
<td>10(50%)</td>
<td>13(57%)</td>
<td>22(67%)</td>
<td>10(42%)</td>
<td>10(67%)</td>
<td>65(57%)</td>
</tr>
<tr>
<td>Female</td>
<td>10(50%)</td>
<td>10(43%)</td>
<td>11(33%)</td>
<td>14(58%)</td>
<td>5(33%)</td>
<td>50(43%)</td>
</tr>
<tr>
<td>Average age (range)</td>
<td>60.6</td>
<td>59.7</td>
<td>54.1</td>
<td>70.5</td>
<td>69.2</td>
<td>62.1</td>
</tr>
<tr>
<td></td>
<td>(18–85)</td>
<td>(18–92)</td>
<td>(18–100)</td>
<td>(18–92)</td>
<td>(24–95)</td>
<td>(18–100)</td>
</tr>
</tbody>
</table>
Sepsis (Sepsis, Severe Sepsis, Septic Shock) vs SIRS

**PCT**

**CRP**

**Lactate**

**Presepsin**
Presepsin: +/-SD of Mean or Median?

Optimal cut-off for Sepsis: 407 ng/ml

Data from 2005, Germany, DIVI, 36 ICU's 45,000 patients, 200,000 days.
Mortality vs Increase of SOFA-Score (dmax-d1)

Data from 2005, Germany, DIVI, 36 ICU’s, 45,000 patients, 200,000 days.
Survivors vs Non-Survivors

Procalcitonin on D1-3 in non-survivors vs. survivors

CRP on D1-3 in non-survivors vs. survivors

Presepsin on D1-3 in non-survivors vs. survivors

Lactate on D1-3 in non-survivors vs. survivors
Table 3: Area under the ROC curve analysis of association between biomarkers and mortality on D1.

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>PCT</th>
<th>PRE</th>
<th>LAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under the ROC curve</td>
<td>0.701</td>
<td>0.844</td>
<td>0.734</td>
<td>0.778</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.0711</td>
<td>0.0496</td>
<td>0.0677</td>
<td>0.0629</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>0.569;0.812</td>
<td>0.727;0.925</td>
<td>0.604;0.840</td>
<td>0.652;0.875</td>
</tr>
<tr>
<td>Significance level P</td>
<td>0.0048</td>
<td>&lt;0.0001</td>
<td>0.0006</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 4: Biomarkers in survivors vs. non-survivors on D1-3.

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>PCT</th>
<th>PRE</th>
<th>LAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis + SIRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>33 (3, 146)</td>
<td>0.3 (0.1, 3.6)</td>
<td>1017 (535, 1781)</td>
<td>1.6 (1.2, 3.0)</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>156 (77, 358)</td>
<td>10.8 (4.9, 62.2)</td>
<td>2228 (1299, 2808)</td>
<td>3.2 (2.4, 4.4)</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.012</td>
<td>0.000</td>
<td>0.003</td>
<td>0.000</td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>133 (86, 199)</td>
<td>1.6 (0.6, 7.8)</td>
<td>1031 (552, 1937)</td>
<td>1.3 (0.9, 2.4)</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>161 (104, 228)</td>
<td>21.6 (3.7, 41.5)</td>
<td>2380 (1348, 3960)</td>
<td>2.1 (1.7, 8.6)</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.200</td>
<td>0.002</td>
<td>0.004</td>
<td>0.003</td>
</tr>
<tr>
<td>D3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>142 (92, 293)</td>
<td>1.4 (0.8, 8.6)</td>
<td>1103 (583, 1841)</td>
<td>1.0 (0.9, 1.4)</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>199 (139, 238)</td>
<td>7.6 (1.9, 16.8)</td>
<td>1843 (1110, 2940)</td>
<td>1.7 (1.2, 3.0)</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.489</td>
<td>0.027</td>
<td>0.047</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Figure 1. ROC curve, representing AUC (area under the curve) for sepsis.
Serum interleukin-33 as a biomarker in predicting neonatal sepsis in very low birth weight infants.

Halit Halil, Cuneyt Tayman, Mehmet Buyuktiryaki, Nilufer Okur, Ufuk Cakir (1) and Utku Serkant (2)
(1) Division of Neonatology, Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey
(2) Department of Biochemistry, Golbasi Public Health Hospital, Ankara, Turkey.

Table 2. Comparison of the median serum levels of CRP, IL-6 and IL-33 for the control group and at the 1st, 3rd and the 7th Day of diagnosis for sepsis group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Median (IQR)</th>
<th>Sepsis 1st day Median (IQR)</th>
<th>Sepsis 3rd day Median (IQR)</th>
<th>Sepsis 7th day Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP(mg/L)</td>
<td>2.410(1.91)</td>
<td>54.9(60.9)</td>
<td>23(25.9)</td>
<td>10(16.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-6(pg/ml)</td>
<td>12.10(8.15)</td>
<td>585(1430)</td>
<td>48(99)</td>
<td>16(32.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-33(pg/ml)</td>
<td>0.956(0.413)</td>
<td>2.564(1.13)</td>
<td>1.32(0.83)</td>
<td>0.71(0.41)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

„In conclusion, in our study we found that serum IL-33 level might be used as a novel biochemical marker in the diagnosis and follow-up of sepsis in preterm infants. We also determined that IL-33 might be useful for predicting sepsis in premature infants. And also, our results demonstrated that IL-33 may not be useful for discrimination of microbiological agents.“
PCT
IL-6
CRP
Lactate
PCT in the Ultrasensitive Range (pg/ml)

## Markers of Sepsis and Inflammation: Basic Properties

<table>
<thead>
<tr>
<th>Marker</th>
<th>0 vs plus Systemic Inflammation / Scale / Severity of Inflamm.</th>
<th>Bakt Infection vs Others /viral</th>
<th>Induction and Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTREM-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presepsin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>+/+</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mibi</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Biomarker der Sepsis

Inflammation und Sepsis

Spezifität
Sensitivität

1

PCT
CRP
IL-6
Laktat

**Markers of Sepsis and Inflammation:**
**Basic Properties**

<table>
<thead>
<tr>
<th>Marker</th>
<th>0 vs plus</th>
<th>Systemic Inflammation / Scale</th>
<th>Bakt Infection vs Others /viral</th>
<th>Induction and Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTREM-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presepsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mibi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hormone-like Markers (Precursors of Hormons):

Copeptin (Prohormone-of Vaspressin)
Adrenomedulxin (MR-ProADM)
Endothelin
Pro ANP and ProBNP
Results of Orhan Cinars Study from Istanbul/Ankara
## Markers of Sepsis and Inflammation: Basic Properties

<table>
<thead>
<tr>
<th>Marker</th>
<th>0 vs plus / Scale</th>
<th>Systemic Inflammation / Severity of Inflamm.</th>
<th>Bakt Infection vs Others /viral</th>
<th>Induction and Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTREM-1</td>
<td>-/-</td>
<td>-/-</td>
<td>+/-</td>
<td>+/*</td>
</tr>
<tr>
<td>Presepsin</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/+</td>
</tr>
<tr>
<td>Lactate</td>
<td>-</td>
<td>-/+</td>
<td>-/-</td>
<td>-/-</td>
</tr>
<tr>
<td>CRP</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>PCT</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
</tr>
<tr>
<td>Cytokines</td>
<td>+/+</td>
<td>+/+</td>
<td>-/-</td>
<td>+/-</td>
</tr>
<tr>
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<td>-/-</td>
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<td>+/-</td>
</tr>
<tr>
<td>Mibi</td>
<td>+/+</td>
<td>./-/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Zeichen und Symptome der Sepsis

- Thrombozytopenie
- Leukozytose
- Leukopenie
- Katecholamine
- Hypothermie
- Tachykardie
- Fieber
- Rubor
- Dolor
- Verwirrtheit, zentralnervöse Symptome
- Zentralisation der Zirkulation
- Oligurie
- Laktatämie
- Störung der Gerinnung
- Infektion
- Calor
- Infektion
- Verschlechterte Oxygenierung
- PCT-Anstieg
- IL-6
- a-Protein C
- CRP
- AT-III
- Elastase
Körpertemperatur und Leukozytenzahl
bei früher Sepsis (n=61)

Inzidenz:

- Schüttelfrost 22%
- Temperatur-Veränderungen (>1.5°C) 59%
- Temperatur (37.5 - 38.5 °C) 18%
- Normothermie 5%
- Hypothermie 9%
- Leukopenie (< 4g/l) 29%
- Leukozytose (> 12g/l) 57%
- Normal (4-12 g/l) 14%

Biomarker des Sepsis

„Calcitonin Precursors are reliable markers of Sepsis in a medical intensive care unit“

Sensitivität/Spezifität (%) am Cut-off:

<table>
<thead>
<tr>
<th></th>
<th>Sensitivität</th>
<th>Spezifität</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>(1 ng/ml)</td>
<td>89</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>IL-6</td>
<td>(50 pg/ml)</td>
<td>65</td>
<td>79</td>
<td>71</td>
</tr>
<tr>
<td>CRP</td>
<td>(100 mg/l)</td>
<td>71</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>Laktat</td>
<td>(2 mmol/l)</td>
<td>40</td>
<td>77</td>
<td>58</td>
</tr>
</tbody>
</table>
Diagnose and treat Sepsis early!

Cerebral insult

Myocardial infarction

The Golden Hours

Sepsis
Severe Sepsis
Septic Shock

Multiple trauma
Time is survival: Kumar et al., CCM 2006:

Each hour of delay of Antibiotic Treatment increases Lethality > 7%
Mortality rate increases with increasing severity

Mortality was:

- 7% in patients with SIRS
- 16% in patients with Sepsis
- 20% in patients with Severe Sepsis
- 46% in patients with Septic Shock

Rangel-Frausto et al. (JAMA 1995)
The GOLDEN Bullet is a Triplet

Treatment of Sepsis has SUCCESS if early recognized .... by

(1) Identification and Diagnosis of Systemic Inflammation
    (clinical signs, laboratory signs + specific markers)

AND

(2) Diagnosis and Tx of the FOCUS of Inflammation
    (X-ray, CT-Scan, patient history, physical examination)

AND

(3) Identification of the Pathogen involved (if there is one)
    (Microscopic, Cultures, plus Resistance, PCR, DNA-Analysis)
Unspecific (antibiotic) Treatment

of

- colonisation or local infection only

or of

- systemic inflammation without a focus

(if search for a focus is negative, unless initially or specific conditions)

should be avoided

- in order to reduce development of multi-resistant bacteriae within the patient treated
Remember,

- Most of our antibiotic treatments treat colonisation or local infection or systemic inflammation without infection only (do not do this, if possible)

- Severe systemic inflammation is highly correlated with positive bacterial findings and endotoxins (as an epiphenomenon of the impaired specific immunologic functions during in such conditions)

- It needs the Doctor/Physician at the BEDSIDE to differentiate these conditions (not the LABORATORY or PATHOLOGY or PHARMACY)

_Treatment of acute sepsis and of systemic inflammation may also involve elimination of mediators of inflammation (Cytokine (Cytosorb) and Endotoxin (Ateco) Adsorption Methods)
Other Markers

There is a variety of different markers of inflammation and sepsis:

CD 64, CD 14 and sCD14 („presepsin“),
suPAR, (soluble -urokinase-type-plasminogen-activator-receptor,
sSTREM1, (soluble triggering receptor expressed on myeloid cells)
Cytokines (IL-6, IL-1...)
Markers of the Coagulation System
Endothelin, ....

But these markers are

- not superior to Procalcitonin (PCT)
- not evidence based as clinical Routine tests

Thus, for experimental use or study use
Conclusions: Presepsin did not outperform traditional sepsis biomarkers in diagnosing sepsis from SIRS and in prognostication of mortality in critically ill patients. Presepsin may have a limited adjunct value for both diagnosis and an early risk stratification, performing independently of clinical illness severity.
In conclusion, presepsin could discriminate between SIRS and sepsis in D1-3 contrasting CRP and PCT that could do so only on D1-2. However, diagnostic accuracy of CRP and PCT was superior to presepsin. Lactate levels were similar in SIRS and sepsis. Presepsin did not correlate with illness severity on D1 whereas other biomarkers did. Higher presepsin levels were associated with 28-day
PCT and other Markers

Novel biomarkers for sepsis: A narrative review
Frederik Fruergaard Larsen a, J. Asger Petersen b,*

a Department of Internal medicine, Amager Hospital, Italiensvej 1, 2300 Copenhagen, Denmark
b Department of Day Surgery, Hvidovre Hospital, Keternagards Alle 30, 2650 Hvidovre, Denmark

CD 64
CD 14 and soluble form of CD14 („presepsin“)
suPAR (soluble -urokinase-type-plasminogen-activator-receptor)
sTREM1 (soluble triggering receptor expressed on myeloid cells)

Presepsin: So, while the physiologic role in the inflammatory cascade make presepsin an attractive diagnostic target in sepsis, its clinical utility needs to be established further, before it can be recommended for routine use in clinical care [26].
The Role of PCT for Diagnosis of Sepsis:
Correlation with Disease Severity (Organ Dysfunction)

PCT (ng/mL)

<table>
<thead>
<tr>
<th>Categories in the SOFA Score</th>
<th>n=32</th>
<th>n=161</th>
<th>n=106</th>
<th>n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>7-12</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>13-18</td>
<td>100</td>
<td>1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>19-24</td>
<td>100</td>
<td>1</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

$\text{PCT} \quad p<0.001$

CRP (mg/mL)

<table>
<thead>
<tr>
<th>Categories in the SOFA Score</th>
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<th>n=161</th>
<th>n=106</th>
<th>n=7</th>
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<tr>
<td>19-24</td>
<td>100</td>
<td>1</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

$\text{CRP} \quad p<0.001$

Harbarth S et al. AJRCC Med. 2001;164:396-402
PCT: highest sensitivity and specificity for sepsis diagnosis

Presepsin: + / - SD of Mean or Median?

Optimal cut-off for Sepsis: 407 ng/ml

Figure 1. Levels of Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM-1) in Bronchoalveolar-Lavage Fluid from 64 Patients without Pneumonia, 38 Patients with Community-Acquired Pneumonia, and 46 Patients with Ventilator-Associated Pneumonia.
Are PCT and Presepsin Competitors?
Soluble CD14-Subtype is called “Presepsin”

- higher grey zone and lower discrimination for diagnosis of sepsis *(cut-off 400-500 ng/ml cut-off)*
  - age, renal function, SIRS-sepsis, FUO -

- not evaluated for antibiotic stewardship

- not able to discriminate FUO and bact/sepsis in oncology
  (both for Presepsin and sHLA-G, Urbonas C, et al. Cytokine 62 (2013)34-7)

- used on an experimental level.

<table>
<thead>
<tr>
<th>Pubmed citations (Feb 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procalcitonin (+ sepsis)</td>
</tr>
<tr>
<td>Presepsin/sCD14-ST</td>
</tr>
</tbody>
</table>

- not an evidence based or guideline recommended marker
Early Therapy of Sepsis

*Early therapy is important to improve the outcome!*

<table>
<thead>
<tr>
<th>Time interval until onset of therapy</th>
<th>%</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 hour until Catecholamines given</td>
<td>89%</td>
<td>70%</td>
</tr>
<tr>
<td>&lt; 1 hour until Catecholamines given</td>
<td>43%</td>
<td>39%</td>
</tr>
</tbody>
</table>

J.S. Lundberg et al.

*Crit Care Med 1998*
Time is survival: Kumar et al., CCM 2006:

Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. Black bars represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The gray bars represent the cumulative fraction of patients having received effective antimicrobials at any given time point.
Kumar et al., Crit Care Med. 2006:

- Retrospective Cohort Study 1998-2004
- 2,731 adult patients analyzed (septic shock)
- 14 ICUs (Canada, USA, Medical, Surgical)
- Outcome-measure: Survival from hospital
- Time of onset of Hypotension from infection
- Time of first effective antimicrobial treatment (EAT)

**Median time to effective Antibiotic Therapy was 6 hrs!**
The absolute and relative PCT values are important. PCT levels increase with increasing systemic consequences of infection and severity of disease and organ dysfunction.

- **High Range of Concentrations**

- **Parallels to Severity of Inflammation**
  - 0.5 ng/ml: no Sepsis
  - 0.5-2 ng/ml: Sepsis likely
  - > 2 ng/ml: High Risk of Patient: Sepsis/Sev.Sep/SS!

- **Stable in Blood Samples**
  - Store at Room Temperature
PCT in the Ultrasensitive Range (pg/ml)

Control  No Infection  Infection
High PCT levels are the Connection between Infection, Sepsis and Systemic Inflammation

PCT (ng/ml)

Control  No Infection  Infection


Sepsis

Local infection
Time Course of Induction of various Parameters of the Systemic Inflammatory Response

Plasma Concentration

Time (h)

IL-6

PCT

CRP

TNF

IL-10

The Role of PCT for Diagnosis of Sepsis:
Correlation with Disease Severity (Organ Dysfunction)

Harbarth S et al. AJRCC Med. 2001;164:396-402
Severity of Sepsis and Procalcitonin (PCT)

- Procalcitonin (PCT)
- C-reactive protein (CRP)
- Lactate

Castelli et al. Critical Care 2004
Onset of Organ Dysfunction

- Septic Shock
- DIC
- Renal Insufficiency
- ARDS
- Liver Dysfunction

Organ Dysfunction (Hours after Admission)
Data from 2005, Germany, DIVI, 36 ICU's, 45,000 patients, 200,000 days.
Mortality vs Increase of SOFA-Score (dmax-d1)

Data from 2005, Germany, DIVI, 36 ICU's, 45,000 patients, 200,000 days.
Table 2
Comparison of clinical data in different groups with the severity of sepsis

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>APACHEII score</th>
<th>Presepsin(pg/ml)</th>
<th>PCT (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Median(min,max)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>33</td>
<td>13.73 ± 4.118</td>
<td>719.97 ± 215.890</td>
<td>0.80(0.05,13.67)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>24</td>
<td>22.17 ± 6.329*</td>
<td>1421.21 ± 643.182*</td>
<td>2.94(0.19,76.57)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>15</td>
<td>26.47 ± 8.026*</td>
<td>2564.13 ± 1557.556*</td>
<td>3.46(0.33,150.41)</td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td>29.046*</td>
<td>27.098*</td>
<td>12.685</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
<td>0.002</td>
</tr>
</tbody>
</table>
What about „New Markers“?

Severity of Disease:

„Old“: PCT, IL-6, IL-8.
„New“: Pro-ANP, Copeptin, ProAdrenomodulin.

„Infection-Markers“:

„Old“: PCT, LBP, CRP
„New“: sTREM-1, MBL, ...

(soluble/surface triggering receptor expressed on myeloind cells -1)
(mannan-binding-lectin)
Requirements for a good marker:

- indicate severity of inflammation (3)
  \((PCT, IL-6, IL-8)\)

- indicate possible bacterial cause (2)
  \((PCT, LBP, CRP, sTREM, MIF...)\)

- to be specific (-)
  \((none? Or PCT, LBP, sTREM ?)\)

- to have a suitable half-live (1)
  \((PCT, IL-6.....?)\)

- to have a broad data base (4)
  \(\text{("Evidence base")}\)
### Bacterial and viral Meningitis: PCT (ng/ml)

<table>
<thead>
<tr>
<th></th>
<th>bacterial</th>
<th>viral</th>
<th>false negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gendrel</td>
<td>54 ± 35</td>
<td>0.32 ± 0.35</td>
<td>0/18</td>
</tr>
<tr>
<td>Clin Inf Dis 1997</td>
<td>4.8 - 110</td>
<td>0 - 1.7</td>
<td></td>
</tr>
<tr>
<td>n = 59</td>
<td>n = 18</td>
<td>n = 41</td>
<td></td>
</tr>
<tr>
<td>Schwarz</td>
<td>1.75</td>
<td>0.24</td>
<td>3(5)/16</td>
</tr>
<tr>
<td>Crit Care Med 2000</td>
<td>0.16 - 60</td>
<td>0.12 - 0.29</td>
<td></td>
</tr>
<tr>
<td>n = 30</td>
<td>n = 16</td>
<td>n = 14</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

© M. Meisner
Antibody-associated Vasculitis

Infection (+) / No Infection (-)

- PCT (ng/ml)
  - $p < 0.01$

- Neopterin (nmol/l)
  - $p = 0.18$

- IL-6 (pg/ml)
  - $p = 0.15$

- CRP (mg/l)
  - $p = 0.01$

Eberhard et al., Arthritis Rheum 1997; 40:1255-6

Antibody-associated Vasculitis

Inflammation and Sepsis
Correlation of PCT and SOFA-Score in Patients with and without Infection
Correlation of CRP and SOFA-Score in Patients with and without Infection
1. Stop AB (Rule of Day 3-7)
   - if focus has clinically cleared AND
   - PCT-stop criteria apply
     - decline >80% of peak or
     - PCT down to < 0.3-0.5 ng/ml
       = use Bouadma Algorithm (Lancet 2010)

AND

2. Add general stop rule for day 7 (Rule of Day 7)
**Period II: Day 3-7 after onset of AB-Tx**

Peak

3.0 ng/ml

Stop sign =
Peak minus 80% = 0.6 ng/ml
or
PCT back to nl. range

Peak * 0.2 = 0.6 ng/ml
or PCT < 0.5 ng/ml (back to normal range)

STOP of AB recommended

Prior ICU or admission

AB-Tx

day 0

day 1

day 2

day 3

day 4
A) Day 1-3 Rules:

1. Find PCT peak value

2. If PCT declines, infection/inflammation is controlled
   = continue antibiotics
   
   (a decline is < 30% of the day before, for 2 or 3 days)

3. If there is no decline?
   Add or change antibiotics or antifungals
Period I: Day 0-3 after onset of AB-Tx

Peak
3.0 ng/ml

Rapid decline (>30% per day) indicates successful therapy = continue AB-Tx

0.25
0.2 ng/ml

1.0
1.8 ng/ml

3.0
3.0 ng/ml

prior ICU or admission
AB-Tx
day 0
day 1
day 2
day 3
day 4
The absolute and relative PCT values are important. PCT levels increase with increasing systemic consequences of infection and severity of disease and organ dysfunction.

- **High Range of Concentrations**

- **Parallels to Severity of Inflammation**
  - 0.5 ng/ml: no Sepsis
  - 0.5-2 ng/ml: Sepsis likely
  - > 2 ng/ml: High Risk of Patient: Sepsis/Sev.Sep/SS!

- **Stable in Blood Samples**
  - Store at Room Temperature
The Aminoacid-Sequence of Procalcitonin (PCT)
Procalcitonin

Thyroid
White Blood Cells
Perit. Macrophages
Spleen
Lung
Liver
Kidney
Adrenal
Brain
Spine
Pancreas
Stomach
Small Bowel
Colon
Heart
Muscle
Skin
Fat Tissue
Testis

Control  Sepsis

Infection

ProCT

after contact with PCT the migratory response of Monocytes is rapidly deactivated.

PCT modulates cytokine response: decreases LPS induced TNF production.

1st stimulus: infection, sepsis, trauma, cytokines.

PCT acts as chemokine and attracts further Monocytes.

PCT later also inhibits the migratory response.

Adipocytes and other cells start to produce PCT and CGRP after contact with activated monocytes.

Vascular smooth muscle cells:
- PCT stimulates iNOS and hence NO production after preincubation with LPS, TNF, IFNγ.
- PCT inhibits iNOS production.

Systemic Response:
- Adherent Monocytes produce PCT for 3-5 hrs.

Local Response:
- Adhesion of monocytes.
The ProRata Trial

1315 Patients Assessed for Eligibility

- 685 Ineligible
  - 158 had expected ICU stay < 3 days
  - 138 had SAPS II > 65
  - 104 had received AB for > 24 hours
  - 99 required prolonged therapy
  - 63 not enrolled for logistic reasons
  - 46 had do-not-resuscitate orders
  - 31 were neutropenic
  - 15 had no medical insurance
  - 12 had been enrolled in other studies
  - 10 refused consent
  - 9 excluded for other reasons

- 158 had expected ICU stay < 3 days
- 138 had SAPS II > 65
- 104 had received AB for > 24 hours
- 99 required prolonged therapy
- 63 not enrolled for logistic reasons
- 46 had do-not-resuscitate orders
- 31 were neutropenic
- 15 had no medical insurance
- 12 had been enrolled in other studies
- 10 refused consent
- 9 excluded for other reasons

630 Randomized

- 311 Assigned to the PCT Group
  - 4 withdrew consent
  - 307 Included in Analysis (I lost to follow-up on day 15)

- 319 Assigned to the Control Group
  - 1 randomized twice
  - 4 withdrew consent
  - 314 Included in Analysis (1 lost to follow-up on day 22)

Bouadma, Lancet 2010; 375(9713):463-474
INFEKTION als Ursache von SIRS

SIRS als Folge/Symptom der Inflammation

„SIRS“

„Sepsis“

Schwere Sepsis

Septischer Schock

INFEKTION als Ursache von SIRS

INFECTION als Krankheit

Organdysfunction / Inflammation

Sepsis
INFEKTION als Ursache von SIRS

SIRS als Folge/Symptom der Inflammation

„SIRS“

Schwere Sepsis

„Sepsis“

INFEKTION als Ursache von SIRS

INFEKTION als Folge/Symptom der Inflammation

Septischer Schock

SIRS

Sepsis

Organdysfunction / Inflammation
Correlation of PCT and SOFA-Score in Patienten with and without Infection
Correlation of CRP and SOFA-Score in Patienten with and without Infection
Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study

Marianna Parlato, François Philippart, Alexandra Rouquette, Virginie Moucadel, Virginie Puchois, Sophie Blein, Jean-Pierre Bedos, Jean-Luc Diehl, Olfa Hamzaoui, Djillali Annane, Didier Journoux, Myriam Ben Boutieb, Laurent Estève, Catherine Fitting, Jean-Marc Treluyer, Alexandre Pachot, Minou Adib-Conquy, Jean-Marc Cavaillon, Benoît Misset and The Captain Study Group

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Patients screened (SIRS), n=363

- Patients not included, n = 84
  - absence of consent: n = 7
  - inclusion criterion missing: n = 50
    - absence of hypo- or hyperthermia: n = 34
    - other: n = 16
  - non-inclusion criterion present:
    - immunosuppression: n = 8
    - legal protection: n = 8
    - already on antibiotics: n = 8
    - already included in the same study: n = 3

Patients included, n=279

- Sepsis, n = 188
  - With cell surface biomarkers, n = 77
  - Without cell surface biomarkers, n = 111

- Non-septic SIRS, n = 91
  - With cell surface biomarkers, n = 33
  - Without cell surface biomarkers, n = 58
**Fig. 2** Univariate performance of the 28 quantitative markers, according to different imputation methods. X-axis, name of each biomarker; Y-axis, ROC-AUC values of each biomarker ranked between 0 and 1. Each bar corresponds to the 95% confidence interval of the ROC-AUC. For each biomarker, three bars are provided, corresponding to each of the first, second, and third imputation method for values below LLoQ, over ULoQ, and for missing values (ESM Table 6). *RNA  

PSP = pancreatic stone protein, MMP8 = metalloprotinase 8, ...
**Infobox 1** Kriterien des „systemic inflammatory response syndrome“

- Tachykardie > 90/min
- Tachypnoe > 20/min oder $p_a\text{CO}_2 < 32$ mm Hg
- Hyperthermie > 38 °C oder Hypothermie < 36 °C
- Leukozytenzahl < 4/μl oder > 12/μl

**Infobox 2** „Quick-Sequential-Organ-Failure-Assessment“ (qSOFA)-Kriterien

- Atemfrequenz ≥ 22/min
- Veränderung der Bewusstseinslage
- Systolischer Blutdruck ≤ 100 mm Hg

- Respiration frequency ≥ 22/MIN
- Change of consciousness
- Systolic Blood pressure < 100 mmHg

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Die „Neue“ SEPSIS-3-Definition

Singer et al. schlagen deshalb folgende neue Begrifflichkeiten und Definitionen vor:

- Sepsis ist definiert als eine lebensbedrohliche Organdysfunktion, verursacht durch eine fehlgeleitete Wirtsantwort auf eine Infektion.
- Organdysfunktion kann als eine akute Verschlechterung des Sequential Organ Failure Assessment (SOFA) Score (Tab.1) ≥2 Punkte infolge der Infektion definiert werden.
- Als Ausgangswert für den SOFA Score kann bei Patienten, bei denen keine vorbestehenden Organdysfunktionen bekannt sind, der SOFA Score mit „0“ angenommen werden.
- Die unspezifischen SIRS-Kriterien (z. B. Fieber, Neutrophilie) sollen weiterhin zur allgemeinen Diagnose der Infektion herangezogen werden.
- Um aus der Gruppe der Patienten, bei denen der Verdacht auf eine Infektion besteht, diejenigen herauszufiltern, bei denen ein hohes Letalitätsrisiko und eine hohe Wahrscheinlichkeit auf einen langen Intensivstationsaufenthalt durch ein Organversagen bestehen, soll der Quick SOFA (qSOFA; Infobox 2) angewendet werden. Der qSOFA soll speziell zum Screening im Rettungs- und Notarztdienst, in der Notaufnahme und auf der Normalstation eingesetzt werden, da die Erhebung des eigentli-
Abb. 1 ▲ Vorgeschlagener Algorithmus zur Diagnose der Sepsis gemäß SEPSIS-3. Bei unkritischer
Organ Dysfunction is triggered by Systemic Inflammation following Infection

Systemic inflammation is the host response to infection

Organ Dysfunction is a (sequential) host response to infection
Organ Dysfunction is related with increased Mortality By Sepsis

Hence, Sepsis should be treated and diagnosed early

„The golden Bullet“ of Diagnosis
Die Mortalitätsrate steigt mit steigendem Schweregrad.

Die Mortalität war:

- 7% bei Patienten mit SIRS
- 16% bei Patienten mit Sepsis
- 20% bei Patienten mit schwerer Sepsis
- 46% bei Patienten mit septischem Schock

Rangel-Frausto et al. (JAMA 1995)
Diagnose der Sepsis

Keine Infektion

Negative bakterielle Kulturen wurden gefunden bei:

→ 24% der Patienten mit Sepsis

→ 14% der Patienten mit schwerer Sepsis

→ 2% der Patienten mit sept. Schock

35% wurden empirisch mit Antibiotika behandelt
Diagnose der Sepsis

Keine Infektion

Positive bakterielle Kulturen wurden gefunden bei:

- 76% der Patienten mit Sepsis
- 86% der Patienten mit schwerer Sepsis
- 98% der Patienten mit sept. Shock

35% wurden empirisch mit Antibiotika behandelt

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Checking for Organ Dysfunction

is descriptional only

(weak improvement of lethality!)

Required for

- Organ Supportive Therapy
- Diagnosis of live threatening condition
- Scoring (SOFA/Sepsis)
- For Follow-up
Checking for Systemic Inflammation
may indicate early condition
before Organ Dysfunction is present:

Required for
- early Diagnosis
- Severity assessment and risk of Organ Dysfunction.
- early Treatment

- For Follow-up
- Indication or Stop of Antibiotics (PCT)
Diagnosis of Infection/Sepsis

**Specific Methods**

Antibodies: too slow!

Mibi/Cultures: gold standard

Coming up:
DNA-recovery/NGS
- Biofire (Biomerieux)
- Septifast (Roche)
- xxx (Diamed)
- Amplifcat+Pyrosequencing
- "NGS" = next gen. Sequenzen
  (e.g. Nanopore, Thermofisher)

**„indirect“ = Inflammation**

Routine/Cheap/Unspecific
- Leukos
- Acute Phase Proteins
- Accidental:
  - Coagulation
  - Thrombocytes
  - Albumin

**„Special Lab“:**
- Cytokines
- Procalcitonin
- Other Tests
  - TREM-1
  - Endothelin
  - MR-proADM
  - Presepsin
The 2 (TWO) Main Questions:

A) Is it really INFECTION ?

B) How „severe“ is INFECTION
   - with regard to inflammation ?
     = if high: = sign of ALERT / ALARM !

   - with regard to organ dysfunction ?
     if present = bad, late
Definition of Infection and Treatment

Infection:
Presence of microorganism in otherwise sterile tissue

Colonisation:
Growth on surface
- typical: natural and mixed population of germs
- not typical / pathologic:
  - abundant growth
  - not typical germs
  - in vulnerable area (e.g. decubital ulcer)

Local Infection:
Invasion of tissue. Only local effects (rubor/secretion):
- no systemic involvement/systemic inflammation:
- no organ dysfunction
- no bloodstream contamination

Systemically active infection: Indication for AB/ Surgery ...
"Eine SEPSIS liegt dann vor, wenn sich innerhalb des Körpers ein HERD gebildet hat, von dem aus kontinuierlich oder intermittierend BAKTERIEN in die BLUTBAHN gelangen, und zwar in der Art, daß durch diese Invasion subjektive und objektive KRANKHEITSERScheinungen ausgelöst werden".

Schottmüller, 1914
„Antibiotic Stewardship“: Where to look at?

> 30%  **Indication not clear**  
- positive urine cultures (asymptomatic) 
- putative respiratory tract infections

> 70%  **Duration of treatment too long**  
- respiratory tract infection 
- urinary tract infections/bacteriuria

n.n.  **Postoperative prophylaxis > 24h**

< 30%  **Wrong antibiotic, wrong dosage, interactions not considered.**

1 Cusini, PLoS one 2010;5:e14011  
2 Spivak, Clin Infect Dis 2017;65:910-7  
3 Christ Crain various publ.  
4 Stolz, Müller, Christ Crain  
5 de With, DtschMed Wochenschr 2017; 142:177-82
„Antibiotic Stewardship“: Where to look at?

> 30%  Indication not clear
  - positive urine cultures (asymptomatic)
  - putative respiratory tract infections
**Procalcitonin indicates local vs systemic infection!**

> 70%  Duration of treatment too long
  - respiratory tract infection
  - urinary tract infections/bacteriuria
**Procalcitonin indicates duration of treatment!**

n.n.  Postoperative prophylaxis > 24h

< 30%  Wrong antibiotic, wrong dosage, interactions not considered.
History of „Sepsis“:

Greece  400 b.C.:

Dual System of „Sepsis“ and „Pepsis“

„Sepsis makes the organism hot like fire from the inside, but cold as ice from at the surface”

Hippokrates 460-377 v. Chr.
History of „Sepsis“:

Rom 0 v. Chr.:

„Myasma“ – „Air and Soil make sick“:

→ Bad air coming from the Swamps leading to Malaria

Francois Magendie 1823
History of „Sepsis“:

- A. van Leuvenhoeck (1632-1723) Microscope
- Louis Pasteur (1822-1885) Microbiology
- Robert Koch (1843-1910) Microbiology
- Ignatz Semmelweis 1847 Desinfect. by „Chlorkalk“
- Joseph Lister 1867 Carbolic Acid Desinfect.
- W. S. Halsted Rubber Gloves
- W. Bergmann und 1892 Aseptic treatment of wounds
- C. Schimmelbusch
- G. Domagk, F. Mietsch 1935 Sulfonamides
- A. Fleming 1939 Penicilline
- S. A. Waksman 1944 Streptomycin
- and many others....
Diagnosis of Sepsis

M. Meisner

Dept. of Anaesthesiology and Intensive Care Therapy, Friedrich-Schiller-University, Jena, Germany
History of „Sepsis“:

Egypt 2000 b.C.:

„ukhed u“ - Dangerous entity, deriving from the gut going to the organism, finally ending deadly
1992: R. Bone:

**Sepsis-1 Definition:**

- Sepsis = SIRS + Infection
- Severe Sepsis/ Septic Shock = + Organ Dysfunction

2003: Levy/Fink/Marshall:

**Sepsis-2 Definition = Modification**

- More inflammation markers included
  - + PIRO-Concept

2016: Singer et al (JAMA 2016; 315:801-10)

**Sepsis-3 Definition:**

- Sepsis = Infection + Organ Dysfunction
  - (qSOFA and/or >=2 SOFA points)
1992: R. Bone:

**Sepsis-1 Definition:**

- Sepsis = SIRS + Infection
- Severe Sepsis/ Septic Shock = + Organ Dysfunction

2003: Levy/Fink/Marshall:

**Sepsis-2 Definition = Modification**

- More inflammation markers included
- + PIRO-Concept

2016: Singer et al (JAMA 2016; 315:801-10)

**Sepsis-3 Definition:**

- Sepsis = Infection + Organ Dysfunction
- (qSOFA and/or >=2 SOFA points)
Sepsis-Markers and Score-Systems of Organ Dysfunction / Risk

**APACHE II**

- **PCT**
  - < 9
  - 10-19
  - 20-29
  - > 30

- **CRP**
  - < 9
  - 10-19
  - 20-29
  - > 30
  - n=2
  - n=54
  - n=193
  - n=67

**SOFA-Score**

- **PCT**
  - 1-6
  - 7-12
  - 13-18
  - 19-24

- **CRP**
  - 1-6
  - 7-12
  - 13-18
  - 19-24
  - n=2
  - n=161
  - n=106
  - n=7

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Definitions of SIRS and Sepsis (1992)

„SIRS“

• Temperature > 38° C or < 36° C
• Heart Rate > 90/min
• Tachypnoea > 20/min or Hyperventilation (CO₂ < 32mmHg)
• Leukocytes > 12 000 or < 4000 or >10% immature cells

>>>>>> at least 2 of the above conditions <<<<<<

Crit Care Med 1992; 20:864-874
Definitions of Sepsis (2003)

„Any Type of Inflammation“

- Inflammation + Infection

  e.g. Procalcitonin, C-reactive Protein, IL-6...
  ... if elevated above standard value

+ „PIRO“ concept for research classification

- PIRO = not a definition
  Predisposition
  Infection
  Response (host/immune)
  Organ Dysfunction

Levy Fink, Marshall
Infection
Sepsis
SIRS
Pancreatitis
Trauma
Burn
other Etiology
Bacteriae
Fungi
Parasites
Virus
others
1992 „ACCP/SCCM“-Sepsis Definition (R. Bone et al.)
The Role of PCT for Diagnosis of Sepsis
Correlation with Severity of Disease (Organ Dysfunction)

PCT

CRP

Categories in the SOFA Score

Harbarth S et al. AJRCC Med. 2001;164:396-402
Onset of Organ Dysfunction

- Septic Shock
- Renal Insufficiency
- DIC
- ARDS
- Liver Dysfunction

Organ Dysfunction (Hours after Admission)

Patients (n)
Early Therapy of Sepsis is essential

The Golden Hours

Cerebral insult

Myocardial-infarction

Sepsis
Severe Sepsis
Septic Shock

Multiple-trauma
Time is survival: Kumar et al., CCM 2006:

Each hour of delay of Antibiotic Treatment increases Lethality > 7 %
Time Course of Induction of various Markers of the Systemic Inflammatory Response

High PCT levels are related with serious infection, sepsis and systemic inflammation.

The Role of PCT for Diagnosis of Sepsis
Correlation with Severity of Disease (Organ Dysfunction)

Categories in the SOFA Score

Harbarth S et al. AJRCC Med. 2001;164:396-402
Markers and Increase of Concentrations

The Logarithmic Scale
\((10 \times 10 \times 10 \times 10 \times \ldots)\)

... indicates a 3-D duty/job of the molecule

\[= \text{from local effects} \]

\[\text{to systemic effects!} \]

Control  No Infection  Infection


\[1D \quad \text{e.g. hormones with high affinity and only few target cells} \]

\[2D \quad \text{local effects e.g. 10x10 mm} \]

\[3D \quad \text{involvement of volume needs exponential growth} \]
Definitions of Sepsis (2016) "Sepsis-3 Definition"

Sepsis = "Infection + Organ Dysfunction"

- increase of SOFA Score +2
- >= 2 positive "qSOFA" points (>=2)
  - respiration rate >22/min
  - change of consciousness
  - blood pressure <= 100mmHg (systolic)

Singer et al JAMA 2016; 315:801-10
Infection

Sepsis

SIRS

Pancreatitis

Trauma

Burn

other Etiology

Bacteriae

Fungi

Parasites

Virus

others

1992 „ACCP/SCCM“-Sepsis Definition (R. Bone et al.)
Definitions of Sepsis (2016)
„Sepsis-3 Definition“

Sepsis = „Infection + Organ Dysfunction“

- increase of SOFA Score +2
- or positive „qSOFA“ points (>=2)

--------- respiration rate >22/min
--------- change of consciousness
--------- blood pressure <= 100mmHg (systolic)

Mortality rate = 13%++ with this Definition

Singer et al (JAMA 2016; 315:801-10)