Procalcitonin –
Diagnosis of bacterial infection/ sepsis
and monitoring of disease
In the **Egyptian legends** the „u-khed-u“ was mentioned as a disease:
„originating from the intestine spreading via the circulatory system, the disease finally results in death, when seizing the heart“

The word „sepsis“ derives from the **ancient Greeks**. It means a dysequilibrium (foulness and digestion) of body fluids.

**Sepsis** - known since the ancient times of human history
Sepsis definition and diagnostic criteria

ACCP/SCCM Consensus Conference 1992

"Sepsis is the Systemic Inflammatory Response caused by an infection"

„SIRS“ Criteria

Temperature > 38°C or < 36°C
Heart Rate > 90/min
Tachypnoe > 20/min or Hyperventilation (CO₂ < 32 Torr, 4.3kPa)
Leukocytes > 12,000 or < 4,000/mm³ or > 10% immature neutrophiles

Sepsis = SIRS + Infection

Severe Sepsis = Sepsis + Organ Dysfunction

Septic shock = Severe Sepsis + Hypotension inspite of fluid resuscitation
The Challenge: Diagnosis of sepsis in patients with SIRS

The prevalence of SIRS:

- 33% of all in-patients
- 50% of ICU patients
- 80% of surgical ICU patients

Diagnostic uncertainty

C Brun-Buisson, Int. Care Med 2000; 26 Suppl 1: S64-74
What makes the problem so difficult?

- SIRS criteria are very unspecific and present in many patients, independently of sepsis

- Microbiogical proof of infection is often negative or availability is delayed
The Challenge:

Improve diagnosis and therapy

Infection and sepsis

- frequent
- main causes of death
- main cost drivers

in today's intensive care medicine!
Sepsis is a high-frequent disease with further growing incidence

- 660,000 to 751,000 cases of severe sepsis p.a., or 2.4 to 3 % of total population

- 51.1% of these require ICU treatment

- Incidence projected to increase by +1.5% p.a.
  - Increasing number of elderly patients, whose incidence ranges from 5.3 % (>65 years) to 26.2 % (> 85 years)
  - Children < 1 year. Incidence 5.3 %
Sepsis is a disease with continuously high mortality rates

- **Main cause for death on non-cardiological ICUs**
- **Mortality:**
  40 % - 50 % (unchanged since decades)

Sands et al. JAMA 1997; 278: 234
Brun-Buisson et al. JAMA 1995; 274: 968;
Sepsis is a disease causing high costs for the health care systems

USA:
Costs per year: 16.7 billion US$ p.a. (++ adults > 65 years)
Costs per case: 22.100 US$

Germany:
Costs per year: 5.3 billion € p.a., or 19 to 42% of the ICU budgets
Costs per case: 20.000 €
Length of stay in ICU: 18 days (vs 5 days in pts without sepsis)
Costs per day: 1650 €/day (death) / 1160 € (survived)

Angus et al., Crit. Care Med. 2001; Moerer et al., Int. Care Med. 2002; Schmid et al., Wien. Klin. Wochenschr., 2002
Why is *early* diagnosis of sepsis so important?
Mortality rates grow with progression of disease

**Severity of disease**

- SIRS: 7%
- Sepsis: 16%
- Severe Sepsis: 20%
- Septic Shock: 46%

**Number of organ failures:**

- 0 to 1: ~15%
- 2: 33 to 50%
- 3 or more: >70%

Rangel-Frausto et al, JAMA 1995

Angus, Crit.Care Med. 2001
Moerer et al., Int.Care Med. 2002
Mortality rates grow the later sepsis is diagnosed and therapeutic intervention is started

Early ICU admission improves survival:

<table>
<thead>
<tr>
<th>Sepsis acquired before ICU admission</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>47.5%</td>
</tr>
<tr>
<td>Sepsis acquired during ICU admission</td>
<td>37.4%</td>
</tr>
</tbody>
</table>

Early therapeutic intervention increases survival chance

<table>
<thead>
<tr>
<th>&gt; 1h before catecholamine use</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>&lt; 1h before catecholamine use</td>
<td>39%</td>
</tr>
</tbody>
</table>

Moerer et al., Int. Care Med. 2002
Lundberg et al., Crit. Care Med., 1998
Time is organ function !!!

Delay in diagnosis

Pre-hospital  ED  Ward  ICU

Start of treatment

Burden of organ dysfunction

Prognosis
How to overcome the problem?

Integration of a laboratory parameter into diagnostic process

⇒ Increase accuracy of clinical diagnosis of sepsis

⇒ Win time for earlier therapeutic decision making

Sepsis

Procalcitonin
What is expected from such a marker?

- **Fast increase** -> To be present at the onset or even before the appearance of the clinical signs of infection/sepsis

- To be **highly sensitive and specific for infection/sepsis** (differentiation between infectious and non-infectious causes of inflammation, organ dysfunction and shock)

- **Improve accuracy of clinical diagnosis**

- To **indicate the effectiveness of therapy**
The candidate: PCT (Procalcitonin)

- Propeptide of the hormonal active Calcitonin (116 AA; 12.3 KD)
- Specifically induced by bacterial infections
- Low levels in viral infections or autoimmune disorders
Procalcitonin induction after bacterial challenge

Calcitonin in healthy persons

PCT in bacterially infection

Müller B. et al., JCEM 2001
Fast increase of PCT after bacterial challenge

- Fast increase (after 3-4 hours), high dynamic range
- Plasma concentrations between < 0.05 ng/ml and 1000 ng/ml
- Short half-life time (~ 24 h) independent of renal function
- Easy to measure in serum and plasma - stable in vivo and in vitro
PCT concentrations increase with extension of infection and severity of disease

Continuum of the disease process, from low degree increasing to high values in severe cases (severe sepsis, septic shock)

*There is no "universal" cut-off, but PCT cut-offs depending on the general clinical situation of the patient!*
## Clinical situations for PCT utilisation

<table>
<thead>
<tr>
<th>Where?</th>
<th>What for?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency room</td>
<td>Detection of severe bacterial infection/ sepsis (Differential diagnosis)</td>
</tr>
<tr>
<td>Other hospital wards</td>
<td>Monitoring of disease / therapeutic response</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Haematology</td>
<td></td>
</tr>
<tr>
<td>Medical intensive care unit</td>
<td></td>
</tr>
<tr>
<td>Surgical intensive care unit</td>
<td></td>
</tr>
<tr>
<td>Paediatric emergency</td>
<td>Local vs systemic infection</td>
</tr>
<tr>
<td>Paediatric department</td>
<td>Lower UTI vs Pyelonephritis</td>
</tr>
<tr>
<td>Paediatric ICU</td>
<td>Sepsis diagnosis &amp; monitoring</td>
</tr>
<tr>
<td>Neonatology</td>
<td>Detection of neonatal sepsis</td>
</tr>
</tbody>
</table>
Internal Medicine
Low serum PCT level accurately predicts the absence of bacteraemia in adult patients with acute fever

At admission, a PCT < 0.4 ng/ml enables the exclusion of a positive blood culture with a NPV of 98.8 %

Chirouze et al - CID 2002
PCT to differentiate between inflammatory syndromes and fever in internal medicine department I

173 patients, thereof 60 with documented infection, 113 with inflammatory syndrome)

PCT of 0.5 ng/ml :
sens 65% spec 96% 
PPV 89% and NPV 84%

group II : 5 patients with PCT > 0.5ng/ml, but < 1.2 ng/ml

1.2 ng/ml = recommended threshold for maximum PPV

Delèvaux - Ann Rheum Dis - 2003
PCT to differentiate between inflammatory syndromes and fever in internal medicine department II

173 patients, thereof 60 with documented infection, 113 with inflammatory syndrome)

Final recommendation:
Fever or inflammatory syndrome and PCT > 1.2 ng/ml on admission:

Indication for a bacterial origin of infection -> should motivate a decision to treat immediately using ATB.

Cave!
A PCT level < 0.5 ng/ml is not sufficient to exclude a local bacterial infection (ATB).
Patient should be closely monitored
PCT facilitates early diagnosis of severe infections in patients with active autoimmune disease

53 patients, thereof 18 SLE, 35 AAV; 16 septic episodes involved 11/35 pts

In patients with active phase of autoimmune disease
PCT values > 0.5 ng/ml indicate a concurrent infection with 100% sensitivity and 84% specificity

Unspecific increase of other markers:
CRP, IL-6, Neopterin < 15% specificity!

Eberhard, Arthritis & Rheumatism, 1997
PCT facilitates early diagnosis of severe infections in patients with active autoimmune disease

63 patients with Wegener’s Granulomatosis (WG)

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>PCT level Median (95th %ile)</th>
<th>Patient numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive phase</td>
<td>0.19 (0.42) ng/ml</td>
<td>N=39</td>
</tr>
<tr>
<td>Active phase</td>
<td>0.19 (0.89) ng/ml</td>
<td>N=17</td>
</tr>
<tr>
<td>Active phase with bacterial infection</td>
<td><strong>1.36 (9.78) ng/ml</strong></td>
<td><strong>N= 7; p &lt; 0.01</strong></td>
</tr>
</tbody>
</table>

Conclusion: PCT > 1 ng/ml indicates systemic infection in WG

After initiating AB therapy PCT values declined < 1 ng/ml during the following days

V. Schwenger et al., Infection 1998
Surgical disciplines
Postoperative low or fast decreasing PCT levels indicate uncomplicated course of disease

Comparison CRP, PCT, IL-6

Red/ pink line: postoperative complications

Green/ blue line: normal postoperative course
Detection of post-surgical sepsis and assessment of prognosis

N=312 surgical patients

• Immediately following the surgical invention (D0-D1): Significantly elevated levels of PCT (>2 ng/ml vs 0.8 ng/ml) are an early indication of the onset of sepsis.

• In the later evolution of post-surgical status (D4 and further): maintaining high PCT concentrations (>10 ng/ml) is predictive of a fatal outcome.

Reith, Intensive Care Med, 2000
Early diagnosis: Monitoring of patients at risk for developing sepsis

Case report: Patient with Peritonitis and severe Sepsis, Survivor

PCT decline indicates positive prognosis

Tchaikowsky, K et al. 2002, Crit Care Med 30:1015-1023
Detection of infectious complications in the trauma unit

- **Increased PCT < 2 ng/ml** at D1-D3 also in the absence of complications (peak followed by a regular decrease)

- Patients developing **systemic infection** can be identified by PCT elevations **>> 2 ng/ml** starting with D1

- **High levels of PCT** have an **unfavourable prognosis** (correlated with the incidence and severity of complications)

Wanner, Crit Care Med, 2000
Detection of infectious complications in multiple trauma patients

Serum Procalcitonin, but not C Reactive Protein, Identifies Sepsis in Trauma Patients

« A secondary increase in serum PCT seems to be an adequate indicator of severe and/or bacteriemic infection during the late posttraumatic SIRS, in contrast to the classical acute phase protein, CRP »
Sepsis diagnosis in polytraumatised patients

2 clinical cases:

Monitoring of patients at risk for developing sepsis is helpful for **early diagnosis and targeted intervention**
Paediatrics
Differential diagnosis of bacterial vs viral infection: Meningitis in children

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CSF Cells (µl)</th>
<th>CSF protein levels (g/l)</th>
<th>CRP levels (g/l)</th>
<th>PCT levels (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Meningitis (n=18)</td>
<td>5156±4336 (250 – 17500)</td>
<td>2.3 ± 1.2 (0.4–4.74)</td>
<td>144±69 (28–311)</td>
<td>54.5±35.1 (4.8–110)</td>
</tr>
<tr>
<td>Viral Meningitis (n=41)</td>
<td>391±648 (20 – 3200)</td>
<td>0.62±0.47 (0.12–2.72)</td>
<td>14.8±14.1 (0–48)</td>
<td>0.32±0.35 (0–1.7)</td>
</tr>
</tbody>
</table>

PCT levels < 0.5 ng/ml indicate viral meningitis

Gendrel et al - Clinical Infectious Diseases - 1997
Differential diagnosis of bacterial vs viral meningitis: Children and adults

Cut-off for children 0.5 ng/ml

Cut-off for adults 0.2 ng/ml

Gendrel et al., Clin Infectious Diseases 1997
Viallon, Clinical Infectious Diseases 1999
Differential diagnosis of bacterial infection in children

360 children (46 invasive bacterial infections - 78 local bacterial infections - 236 viral infections)

**Group 1**: Invasive bacterial infections
   - 23 meningitis + 23 septicaemias

**Group 2**: Local bacterial infections
   - 23 urinary infections, 18 pneumonias, 17 diarrhoeas, 4 otitis…

**Group 3**: Viral infections
   - 64 Enterovirus, 56 syncytial, 43 rotavirus ...

Gendrel, Pediatr Infect Dis J. 1999
Differential diagnosis of bacterial infection in children

Bacterial versus Viral: Group 1+2 Vs Group 3

<table>
<thead>
<tr>
<th>Test and Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Positive Predictive Value 25%</th>
<th>Positive Predictive Value 50%</th>
<th>Negative Predictive Value</th>
<th>Negative Predictive Value 25%</th>
<th>Negative Predictive Value 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT &gt; 1 μg/l</td>
<td>0.83</td>
<td>0.93</td>
<td>0.86</td>
<td>0.80</td>
<td>0.92</td>
<td>0.91</td>
<td>0.94</td>
<td>0.85</td>
</tr>
<tr>
<td>PCT &gt; 2 μg/l</td>
<td>0.65</td>
<td>0.99</td>
<td>0.97</td>
<td>0.96</td>
<td>0.98</td>
<td>0.85</td>
<td>0.89</td>
<td>0.74</td>
</tr>
<tr>
<td>PCT &gt; 3 μg/l</td>
<td>0.57</td>
<td>0.99</td>
<td>0.97</td>
<td>0.95</td>
<td>0.98</td>
<td>0.82</td>
<td>0.87</td>
<td>0.70</td>
</tr>
<tr>
<td>CRP &gt; 10 mg/l</td>
<td>0.96</td>
<td>0.50</td>
<td>0.60</td>
<td>0.40</td>
<td>0.66</td>
<td>0.98</td>
<td>0.99</td>
<td>0.96</td>
</tr>
<tr>
<td>CRP &gt; 20 mg/l</td>
<td>0.83</td>
<td>0.71</td>
<td>0.60</td>
<td>0.49</td>
<td>0.74</td>
<td>0.89</td>
<td>0.93</td>
<td>0.81</td>
</tr>
<tr>
<td>CRP &gt; 40 mg/l</td>
<td>0.73</td>
<td>0.88</td>
<td>0.76</td>
<td>0.67</td>
<td>0.86</td>
<td>0.86</td>
<td>0.91</td>
<td>0.77</td>
</tr>
<tr>
<td>IL-6 &gt; 100 pg/ml</td>
<td>0.51</td>
<td>0.85</td>
<td>0.64</td>
<td>0.53</td>
<td>0.77</td>
<td>0.77</td>
<td>0.84</td>
<td>0.63</td>
</tr>
<tr>
<td>IFN-alpha = 0</td>
<td>0.92</td>
<td>0.79</td>
<td>0.69</td>
<td>0.59</td>
<td>0.81</td>
<td>0.95</td>
<td>0.97</td>
<td>0.91</td>
</tr>
</tbody>
</table>

* Positive and negative predictive values in study sample (prevalence of bacterial infection 34%).
† Positive and negative predictive values when prevalence of bacterial infection in population is 25%.
‡ Positive and negative predictive values when prevalence of bacterial infection in population is 50%.

PCT at 1ng/ml: sens 83% spec 93% PPV 86% NPV 91%
CRP at 10mg/l: sens 98% spec 50% PPV 50% NPV 98%

Gendrel, Pediatr Infect Dis J. 1999
Differential diagnosis of bacterial infection in children

Bacterial versus Viral: Group 1+2 Vs Group 3

PCT at 1ng/ml:
sens 83% spec 93%
PPV 86%
NPV 91%

CRP at 10mg/l:
sens 98%
spec 50%
PPV 50%
NPV 98%

Gendrel, Pediatr Infect Dis J. 1999
Differential diagnosis of bacterial infection in children

Bacterial versus Viral: Group 1+2 Vs Group 3

**Fig. 1.** Individual values of procalcitonin, C-reactive protein and interleukin 6 in the three groups of patients.

Gendrel, Pediatr Infect Dis J. 1999
Differential diagnosis of fever with unknown origin in children

124 children - 7 days to 3 years old, Fever > 38°C, No clinical sign of infection
96 benign infections; 28 severe bacterial infections, (4 bacteriaemias, 19 pyelo, 5 pneumonia)

PCT at 0.9ng/ml     sens 93% spec 78%, PPV 97%
CRP at 40 mg/ml     sens 89% spec 75%, PPV 96%
Differentiation invasive vs non-invasive infection in febrile children, also if fever less than 12 hours

**Fever > 12 hours**

Optimal Cut-off PCT: >0.59 ng/mL
- Sensitivity: 91.3 %
- PPV: 90.8 %
- Specificity: 93.5 %
- NPV: 90.1 %

Optimal Cut-off CRP: >27.5 mg/L
- Sensitivity: 78 %
- PPV: 68.5 %
- Specificity: 75 %
- NPV: 80.8 %

**Fever < 12 hours**

Optimal Cut-off PCT: > 0.69 ng/mL
- Sensitivity: 85.7 %
- PPV: 96.9 %
- Specificity: 98.5 %
- NPV: 89.7 %

Optimal cut-off CRP: > 19 mg/L
- Sensitivity: 61.3 %
- PPV: 65.8 %
- Specificity: 80 %
- NPV: 76.5 %

Procalcitonin and lower UTI in children

Values of PCT, CRP and leukocytes differ significantly between LUTI and pyelonephritis

<table>
<thead>
<tr>
<th></th>
<th>LUTI (n=23)</th>
<th>Pyelonephritis (n=37)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>36 ± 9</td>
<td>42 ± 8</td>
<td>.350</td>
</tr>
<tr>
<td>Sex (girls / boys)</td>
<td>14/9</td>
<td>29/8</td>
<td>.140</td>
</tr>
<tr>
<td>Leukocytes/mm3</td>
<td>10939 ± 834</td>
<td>17429 ± 994</td>
<td>.0001</td>
</tr>
<tr>
<td>PCT (ng/ml)</td>
<td>0.38 ± 0.19</td>
<td>5.37 ± 1.9</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>30.3 ± 7.6</td>
<td>120.8 ± 8.9</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Benador, Pediatrics 1998
Procalcitonin and lower UTI in children

**PCT concentration is correlated with the intensity of renal impairment**

At admission, diagnostic performances of PCT and CRP in the prediction of renal impairment are:

- **PCT**: sensitivity 70%, specificity 83%
- **CRP**: Sensitivity 100%, specificity 26%

100% of moderate and severe lesion -> **PCT > 0.6 ng/ml**

Benador, Pediatrics 1998
Procalcitonin and lower UTI in children

54 children 1 week to 15 years
PCT measured with PCT-Q Test

PCT > 0.5 ng/ml indicates 89% probability of pyelonephritis

Gervaix Pediatr Infect Dis J - 2001
# Procalcitonin and lower UTI in children

64 children ages 2 weeks to 3 years old; 42 UTI; 18 pyelonephritis (+ DMSA)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (0.5ng/ml)</td>
<td>94.1</td>
<td>89.7</td>
<td>97.6</td>
<td>85.7</td>
</tr>
<tr>
<td>CRP (20mg/l)</td>
<td>100</td>
<td>18.5</td>
<td>100</td>
<td>30.9</td>
</tr>
</tbody>
</table>

Smolkin, *Pediatr Nephrol* 2002
Suspicion of sepsis in the newborn
Chiesa, *Clinical Infectious Diseases*, 1998

24h after birth, PCT sensitivity is 85.7% versus 46.4% for CRP.

**Specificity of PCT: 97.5%**

*Calculations performed on the basis of 97.5 centile*
Reference ranges and interpretation of results
PCT concentrations increase with extension of infection and severity of disease. There is no "universal" cut-off, but PCT cut-offs depending on the general clinical situation of the patient! Continuum of the disease process, from low degree increasing to high values in severe cases (severe sepsis, septic shock).
Reference values
(except newborns < 48h)

- < 0.05 ng/ml healthy individuals
- < 0.5 ng/ml $\implies$ probability of sepsis is low, local infections possible
- between 0.5 and 2 ng/ml $\implies$ grey zone, needs to be remeasured 6 to 12 hrs later
- > 2 ng/ml $\implies$ probability of sepsis is high

Interpretation of PCT values only in the clinical context of the patient!!!
Interpretation of PCT values only in the clinical context of the patient!!!

**Increased PCT levels without systemic bacterial infection:**

- **Primary inflammation syndrome following trauma**: multiple trauma, extensive burns, post major surgery (cardiac, transplant, abdominal)
- **Treatment that acts upon the proinflammatory CK cascade** (OKT3, injection therapy TNFα, IL-2, anti-lymphocyte globulins)
- **Certain cancers** (medullary CT-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma)
- **During prolonged circulatory failure** (prolonged cardiogenic shock, haemorrhagic shock, thermal shock)
- **Newborn < 48hr** -> increased PCT-values (physiological peak)
Superior Procalcitonin Performance
Specific increase of PCT after bacterial challenge

Differentiation of bacterial infection vs non-infectious inflammation

Meta-analysis: 10 Studies, 905 patients

PCT: 88% Sensitivity / 81% Specificity
CRP: 75% Sensitivity / 67% Specificity

PCT: highest sensitivity and specificity for sepsis diagnosis!
PCT does significantly improve the accuracy of clinical diagnosis

In contrast: IL-6, IL-8 or CRP did not have any impact on the accuracy of clinical diagnosis!
PCT utilisation for therapeutic decision making

Can PCT play a role in reducing costs?
PCT and therapeutic decision? / Influence on costs?

Early identification/exclusion of bacterial infection

- Early start of therapy in patients with bacterial infection/sepsis
- Withhold AB therapy from patients where bacterial infection is unlikely

Monitoring of AB therapy

- Identification of non-responders -> change of therapy
- Shortening of AB therapy in responders

ER
ICU admission

ICU
PCT in management of antibiotic use during an epidemic of enteroviral meningitis

**Goal ⇒ exclude bacterial infection early and stop unnecessary AB treatment**
(PCT measurement: 3x per week/ PCT-Q)

<table>
<thead>
<tr>
<th>AB monitoring</th>
<th>Children</th>
<th>treated</th>
<th>Mean duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>with PCT (May-June 00)</td>
<td>58</td>
<td>17</td>
<td>2.06 days / patient</td>
</tr>
<tr>
<td>without PCT (1995-96)</td>
<td>41</td>
<td>19</td>
<td>4.47 days / patient</td>
</tr>
</tbody>
</table>

The decision to stop antibiotic treatment at a **PCT of < 0.5 ng/ml**, without clinical counter-argument (modified purulent meningitis excluded), resulted in **savings ⇒ 2.4 days of antibiotics per patient**  (29.000 € in 2 months)

Marc et al., Arch Pédiatr 2002
PCT for early exclusion of bacteraemia in adult patients with acute fever

At admission, \( \text{PCT} < 0.4 \text{ ng/ml} \) enables the exclusion of a positive blood culture with a NPV of 98.8 %

\( \rightarrow \) Limit empirical use of AB

Chirouze et al - CID 2002
Procalcitonin and monitoring of antibiotic therapy

(ICA patients, n=105, medians)

F. Stüber, University Bonn, Lecture at ISICEM, Brussels 2001
## Cost reduction for antibiotics by therapeutic monitoring in the ICU

<table>
<thead>
<tr>
<th>Year</th>
<th>AB therapy (d)</th>
<th>Monitoring</th>
<th>Therapeutic measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996/97</td>
<td>8.5 ± 1.2</td>
<td>Without IL-6, PCT</td>
<td>Antibiotic therapy</td>
</tr>
<tr>
<td>1998</td>
<td>7.0 ± 0.8</td>
<td>IL-6, PCT</td>
<td>No written recommendations/orders for consequences</td>
</tr>
<tr>
<td>1999/00</td>
<td>6.5 ± 0.9</td>
<td>IL-6, PCT</td>
<td>SOP: if PCT during AB therapy over 3 days decreases by 50% =&gt; stop of AB (clinical condition should not deteriorate and other markers of infection should decline)</td>
</tr>
</tbody>
</table>

There was no negative influence of the shortening of the antibiotic treatment on the outcome!

Costs of diagnostics: 80 TDM minus reduced costs for AB: -120 TDM = Annual savings of 40 000 DM per year

F. Stüber, University Bonn, Lecture at ISICEM, Brussels 2001
PCT as prognostic marker of therapeutic failure in VAP patients

Kinetics of serum procalcitonin in patients who died (●), had pulmonary and/or extrapulmonary infection recurrence (●) or had favorable outcome (●) from day 1 to day 7.

*p < 0.05
**p < 0.001

Increased PCT values on day 7 > 0.5 ng/ml predict treatment failure (AUC 0.9; sensitivity 90%, specificity 88%; odds ratio 64.2)

Luyt et al., AJRCCM 2004
Shortening AB therapy in patients with VAP

<table>
<thead>
<tr>
<th>Type of protocol</th>
<th>Mortality rate</th>
<th>Recurrent pulmonary infection</th>
<th>Multi-resistant strains (p=0.04)</th>
<th>Days without ATB (p &lt; 0.0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Protocol (n=197)</td>
<td>18.8 %</td>
<td>28.9 %</td>
<td>42.1 % *</td>
<td>13.1 ± 7.4 *</td>
</tr>
<tr>
<td>Long Protocol (n=204)</td>
<td>17.2%</td>
<td>26 %</td>
<td>62.3 %</td>
<td>8.7 ± 5.2</td>
</tr>
</tbody>
</table>

Besides a significant decrease in emerging multi-resistant strains, standardising the antibiotic protocol to 8 days would generate significant savings in managing patients with respiratory resuscitation, without causing excess mortality or morbidity.

PCT for therapeutic monitoring
-> Shortening AB therapy in patients with CAP

Preliminary results:
Reduction of treatment days by >50%

Christ-Crain et al., ICAAC Oct 2004
Division of costs related to Severe Sepsis

- Little more investment into diagnosis may save significant amount of therapeutic costs

1 Moerer et al., Int. Care Med. 2002
PCT - Confidence for diagnostic and therapeutic decision

Integrating the PCT value of the patient into the diagnostic process increase safety of decision making:

- Diagnosis of clinically relevant infection/ sepsis
- Therapeutic decisions (AB, surgery)
- Ressource allocations
PCT (Procalcitonin): Relevant marker for bacterial infection and sepsis

- Best-performing early marker for the differential diagnosis of bacterial infection with generalized inflammation
- Marker with kinetics that closely correlate to infection control
- No “universal” threshold: varies according to the use in question
- Simplicity of sampling and assay
- Choice of various standardised techniques
Procalcitonin

Measurement
PCT Assay Technologies

- BRAHMS PCT LIA
- BRAHMS PCT –Q
- BRAHMS PCT KRYPTOR
Immunoluminometric quantitative assay

Sample: 20 µL serum/plasma
Incubation: 1 hour
Analytical sens.: 0.1 ng/ml
Functional sens.: 0.3 ng/ml

Marker (acrydinium ester)
Monoclonal anti-Calcitonin Ab
Monoclonal anti-Katacalcin Ab
Procalcitonin
Calcitonin
Katacalcin
Semi-quantitative assay for rapid PCT determination

200 µl Serum or plasma
Result in 30 minutes
Automated quantitative PCT assay

Test sample: 50 µL serum/ plasma
Incubation: 19 min
Analytical sens.: 0.02 ng/ml
Functional sens.: 0.06 ng/ml

Result in 19 min - whenever requested