„Antibiotic Resistance, Microbiology and Infection

Do we have to change our approach fundamentally?

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Klinikum Dresden
Germany
Antimicrobial resistance

New antibiotics needed for 12 families of bacteria

27 February 2017 – WHO’s list of antibiotic-resistant “priority pathogens” include bacteria that pose the greatest threat to human health. The list is intended to guide and promote research and development of new antibiotics in an effort to address growing global resistance to antimicrobial medicines.

News release
Global priority list of antibiotic-resistant bacteria

Antimicrobial resistance (AMR) is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it. As a result, standard treatments become ineffective, infections persist and may spread to others.
The Situation in India (and elsewhere...) today
(data: from personal visit and personal communication)

At initial presentation of patient, microbiological pathogens at 
- 80-90% are „3-MRGN“ resistant
  (fluorochinolones, penicillines, cephalosporines)
- 50% are „4-MRGN“ (resistant to carbapenemes)

On the ICU or transferred patients from other hospitals:
- > 90% have „4-MRGN“ resistance
- 30-40% get Colistin resistance

5 years ago: 13-Antibiotics resistance gene reported
2017: 39-Antibiotics resistance gene reported
Candida aureus: Resistant to all - conazoles.
Now coming up: Inhalation of „Overkill-Dosage“

„Prophylactic“ inhalation against Pseudomonas in patients with „VAT“ = ventilator associated tracheitis (inhalation) or Brochiectasis are coming up.

„Collateral Damage“ with spread of resistance within the patient is not regarded (related to long-term mortality)

AND (!): Studies from Germany, Canada, USA - and are NOT comparable with situation in Turkey, UAE, India (final mortality due to resistance not included)
Going on this way means: We are doing something wrong!

New resistance will come up soon
- even against newly developed antibiotics -

But we have the CHANCE NOW to change our habits:
- AB use outside hospitals
- AB use in hospitals
- to change Patients perception / expectations
Origin and Presence of Microbial Resistance

- Agriculture and Animal Farms *(Chicken, Pork, Fish)*

- Waste of AB-Production and Disposal/Sewage

- Overuse in the Population *(Respiratory/Urinary/Diarrhea)*

- Overuse or not correct use in the Hospitals *(this lecture)*
We should avoid at least selection within the patient during (unnecessary) therapy

Where does Resistance come from?

- Imported by transfer of patients to our unit (e.g. from rehabilitation units or other hospitals)

- Hospital transmitted infection from other patient (high risk for clostr. diff, acinetobacter/klebs/pseudom)

- New Resistance coming up during AB-tx (1 new resistance during 1 week of AB-tx reported)

- Selection within the patient during AB Tx (shift well known e.g. for enterococci-species !)
Antibiotic Treatment

before

after

- sensitive
- resistant
The Solution:

1. **Short, individually adapted, AB treatment courses**

2. **No treatment of colonisation and of local infection - if possible**
The antibiotic course has had its day

BJ 2017;358 doi: https://doi.org/10.1136/bmj.j3418 (Published 26 July 2017)

With little evidence that failing to complete a prescribed antibiotic course contributes to antibiotic resistance, it’s time for policymakers, educators, and doctors to drop this message, argue Martin Llewelyn and colleagues.

Antibiotics are vital to modern medicine and antibiotic resistance is a global, urgent threat to human health. The relation between antibiotic exposure and antibiotic resistance is unambiguous both at the population level and in individual patients. Reducing unnecessary antibiotic use is therefore essential to mitigate antibiotic resistance.
Scientists disagree with WHO recommendation of AB-tx

Man muss nicht immer alle nehmen

Forscher widersprechen Antibiotika-Regel

Der verschreibende Arzt ermahnt: Antibiotika-Packungen immer aufbrauchen! Und auch die WHO empfiehlt das. Nun widersprechen Forscher dieser Anordnung aber und äußern Kritik daran. Woher der Sinneswandel?

Forscher haben die Empfehlung infrage gestellt, eine Antibiotika-Packung immer komplett aufzubrauchen. Es gebe keinerlei Beweis dafür, dass eine kürzere Antibiotika-Behandlung die Gefahr resisterter Bakterien vergrößere, schreiben die Wissenschaftler im Fachmagazin "British Medical Journal" (BMJ). Vielmehr sei das Gegenteil der Fall: "Antibiotika länger einzunehmen als notwendig erhöht das Risiko von Resistenzen."
Wordwide critics to WHO-rule
For how long shall we take Antibiotics?

The recommendation, always to finish/use the package of an AB to its end, is increasingly criticized. The risk of resistance hence is increasing.
Kritik an Darstellung auf WHO-Website

Insbesondere kritisieren die Autoren die Darstellung auf der WHO-Website. Dort rät der zuständige Bereichsleiter Marc Sprenger: "Wenn Sie Antibiotika nehmen, schöpfen Sie stets das volle Rezept aus, auch wenn Sie sich besser fühlen, denn ein früher Stopp der Therapie begünstigt das Wachstum resisterter Bakterien." In Großbritannien steht diese Darstellung sogar auf dem Lehrplan von Schulen.


Shorter therapy may be better!

Kürzere Therapie kann vorteilhaft sein


Das seien zwingende Resultate, schrieb Brad Spellberg von der University of Southern California in Los Angeles damals in einem "JAMA"-Kommentar: "Es gibt keinen Hinweis dafür, dass die Einnahme von Antibiotika über den Punkt hinaus, an dem die Symptome.
But what is „short“?
What are we doing in our ICU today?
Just imagine, to be in a Microbiological Laboratory ...

Antibiotic xyz

add it now...

20 different bacterial Germs/Strains

50 Liter of Growth Medium
Just imagine, to be in a Microbiological Laboratory ... 

Antibiotic xyz

20 different bacterial Germs/Strains

50 Liter of Growth Medium

After which time bacteriae are dead or growth-inhibited?
Just imagine, to be in a Microbiological Laboratory ...

Antibiotic xyz

20 different bacterial Germs/Strains

50 Liter of Growth Medium

After which time bacteriae are dead or growth-inhibited?

6-12h
Just imagine, to be in a Microbiological Laboratory ...

Antibiotic xyz

What is happening after 7 days of Incubation at 37°C?

20 different bacterial Germs/Strains

50 Liter of Growth Medium

7 Days
Just imagine, to be in a Microbiological Laboratory ... 

Antibiotic xyz 

Either:  
(1) They are all dead  
(2) There is something growing... („resistent“)

20 different bacterial Germs/Strains 

7 Days 

50 Liter of Growth Medium
Just imagine, to be in a Microbiological Laboratory ... 

Antibiotic xyz

Mibi- and Clinical Experience teaches us:

SOLUTION 2 is more likely

50 Liter of Growth Medium
Antibiotic Treatment

- sensitive
- resistant
Our Goal: Less Antibiotic Exposure!
The Golden Rules of „IPAT“
IPAT = Individual, Patient-adapted Antibiotic Therapy

1. **Treat only invasive infection**
   Avoid to treat local infection or colonisation.
   *We often need Procalcitonin for this decision.*

2. **Avoid to treat „suspected“ infection only**
   unless sepsis/ severe sepsis is suspected
   *We often need Procalcitonin for this decision.*
„IPAT“ means:

3. Do only treat as long as individually required!
   This are usually not more than 3-7 days (this is an individual decision!)
   
   We need PCT for this monitoring!

4. Communicate your decisions with all doctors and Document your decisions well
   
   E.g. The „four S“ and knowledge of „IPAT“/PCT algorithm)
But what is „short“?
Case Report, admitted November 1, 2017 to Hospital/ICU: 58 year old female patient admitted after seizure to our ICU with suspected aspiration.

November 2
Fever 38.5 C, purulent yellow sputum, cough
But also has history of chronic bronchitis with sputum
CXR- normal; Piperacillin/Tazobactam started. CRP 1.5mg/l

Start with PCT Monitoring: PCT < 0.02 ng/ml

November 3 to 4: New Med. Doctor of Internal Medicine on Duty.
Reports me at visit on 5th of November:
CRP is high (increasing to 43 and 81 mg/l)
Patient is on Antibiotics. Patient is doing well.

What whould you do (according to IPAT) ?
What would you do (according to IPAT?)

Situation:
Fever is down/ resolved
Patient wants ongoing antibiotics
CRP reported „increasing“ (from 1.5 to 81mg/l, then 49mg/l)

Procedure according to IPAT:
Order Procalcitonin (PCT) and Chest X-Rax (CXR):

Results:
PCT is 0.06 ng/ml (negative) = suggests „STOP“ according to PCT-algorithm
CXR is normal

Consequence:
AB stopped, central venous line next day removed and patient could be early sent to normal ward.
Staedd. KH Dresden-Neustadt
Herold, Christine
04.04.1959 / 014076901
Thorax

05.11.2017, 10:04:57 F
### Anzeige aller Werte einer Leistung

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<th>Stätisches Klinikum Dresden</th>
<th>Report RN2KUMLEIST</th>
<th>Benutzer MEISNER</th>
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### Anzeige aller Werte einer Leistung

Der Bericht von RN2KUMLEIST wurde am 07.11.2017 14:12:19 erstellt.

**Patient:** Herold, Christine  
**Geburtsdatum:** 04.04.1959  
**Patientennummer:** 50437994  
**Fallnummer:** 21760144  
**Pflegerische OE:** N1

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<th>Datum (Lei)</th>
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What would you do (according to IPAT?)

**Situation:**
Fever is down/ resolved
Patient wants ongoing antibiotics
CRP reported „increasing“ (from 1.5 to 81mg/l, then 49mg/l)

**Procedure according to IPAT:**
Order Procalcitonin (PCT) and Chest X-Rax (CXR):

**Results:**
PCT is 0.06 ng/ml (negative)
CXR is normal

**Consequence:**
AB stopped, central venous line next day removed and patient could be early sent to normal ward.
Using PCT.... We have 2 periods
- measure PCT 1x per day -

a) Day 1-3 of Treatment:
Estimate Success of Therapy

b) Day 3-..... Day ...7
Find End of Therapy
Specific PCT algorithm used
The Basics: Why Procalcitonin (PCT)?

- Increase and decrease of PCT indicates activity of systemic inflammation.

- Higher diagnostic specificity for dx of sepsis

- PCT indicates systemic inflammation, most likely coming from bact. infection

- Despite, PCT is a marker of non-bacterial inflammation as well

- Correlation with severity and risk of sepsis/MODS
The course of PCT and CRP (day 0-4) in survivors/non-survivors with VAP
## 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)</td>
<td>44% (n = 7/16)</td>
<td>0.019</td>
</tr>
<tr>
<td>Duration of Tx (days)</td>
<td>6 (3-26)</td>
<td>11 (4-32)</td>
<td>0.09</td>
</tr>
<tr>
<td>MOSF-Score</td>
<td>15 (5-49)</td>
<td>18 (2-36)</td>
<td>0.19</td>
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<tr>
<td>PRISM-Score</td>
<td>2 (0-4)</td>
<td>2 (1-4)</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>
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</table>
Time Course of Induction of various Mediators of the Systemic Inflammatory Response

Delta Procalcitonin Is a Better Indicator of Infection Than Absolute Procalcitonin Values in Critically Ill Patients: A Prospective Observational Study

Domonkos Trásy, Krisztián Tánczos, Márton Németh, Péter Hankovszky, András Lovas, András Mikor, Edit Hajdú, Angelika Osztroluczki, János Fazakas, and Zsolt Molnár

<table>
<thead>
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<th>One-year study period</th>
<th>Post hoc</th>
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<td>24 hours before t⁻¹</td>
<td>Infection</td>
</tr>
<tr>
<td>Suspicion of infection t₀</td>
<td>No infection</td>
</tr>
<tr>
<td>Available data</td>
<td></td>
</tr>
<tr>
<td>Start empiric antibiotics</td>
<td></td>
</tr>
</tbody>
</table>

(i) PCT  
(ii) CRP  
(iii) WBC  
(iv) Body temperature

(i) Demographics  
(ii) Signs of infection  
(iii) Suspected source  
(iv) Microbiology  
(v) PCT, CRP, WBC, body temperature
Delta-PCT absolute values and percentage increase:

Delta-PCT between day-1 and day-0 of dx of infection.
Day 1-3 Rules:
Daily measurement of PCT when antibiotics are started

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?
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

- **Half-Life in Plasma:**
  - 25-30hrs (1 Day)
  - Measure 1x per Day
PCT is produced by adherent monocytes for 3-5 hrs. PCT later also inhibits the migratory response after contact with PCT, the migratory response of monocytes is rapidly deactivated.

PCT acts as a chemokine and attracts further monocytes. PCT later also inhibits the migratory response.

PCT modulates cytokine response: decreases LPS induced TNF production.

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

Vascular smooth muscle cells: Initially PCT inhibits iNOS production.

Systemic Response:

Local Response:

1. 1st stimulus: infection, sepsis, trauma, cytokines:
   - Adhesion of monocytes

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

3. PCT stimulates iNOS and hence NO production after preincubation with LPS, TNF, IFNγ.

4. PCT acts as a chemokine and attracts further monocytes.

2. After preincubation with LPS, TNF, IFNγ, adherent monocytes produce PCT for 3-5 hrs.

6. PCT modulates cytokine response: decreases LPS induced TNF production.

Vascular smooth muscle cells: Initially PCT inhibits iNOS production.

Systemic Response:
The Basics: Why Procalcitonin (PCT) ?

- Increase and decrease of PCT indicates activity of systemic inflammation
- Higher diagnostic specificity for dx of sepsis
- Correlation with severity and risk of sepsis/MODS
- PCT indicates systemic inflammation, most likely coming from bact. infection
- Despite, PCT is a marker of non-bacterial inflammation as well
Diagnosis of Sepsis, Severe Sepsis and Septic Shock

Early Treatment of (Severe) Sepsis is important!

Cerebral insult

Myocardial infarction

Early Diagnosis of Sepsis is important!

Sepsis
Severe Sepsis
Septic Shock

Multiple trauma
Onset of Organ dysfunction

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

Patients (n)

Organdysfunction (hours after admission)
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*

*= Dx. includes Organ Dysfunction

Rangel-Frausto et al. (JAMA 1995)
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.
Time is survival: Kumar et al., CCM 2006:

Each hour of delay of Antibiotic Treatment increases Lethality > 7%
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 is important!

- **PCT**
  - **no SIRS**: 32.9
  - **SIRS**: 42.2
  - **Sepsis**: 6
  - **Severe Sepsis**: 6
  - **Septic Shock**: 6

- **CRP**
  - **no SIRS**: 150
  - **SIRS**: 200
  - **Sepsis**: 250
  - **Severe Sepsis**: 300
  - **Septic Shock**: 350

- **Lactate**
  - **no SIRS**: 0
  - **SIRS**: 2
  - **Sepsis**: 4
  - **Severe Sepsis**: 6
  - **Septic Shock**: 8

*Castelli et al. Critical Care 2004*
PCT and Severity of Organ Dysfunction
Correlation with Disease Severity (Organ Dysfunction)

Harbarth S et al. AJRCC Med. 2001;164:396-402
Day 3 – 7 Rules = Follow-up rules

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

+ add a General Stop Rule of Day 7
  = stop tx latest on day 7 (unless other reasons are discussed*)

* other reasons:
Staph. aureus bacteremia („SAB“), endocarditis, osteomyelitis, focus not cured, tuberculosis.
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, Stopping antibiotics encouraged
- [PCT] ≥ 0.5 μg/l, Continuing antibiotics encouraged
- [PCT] / [PCT] previous ≥ 80%, Changing antibiotics strongly encouraged

Bouadma, Lancet 2010; 375(9713):463-474
Verlaufsgrafik von Patient: Türke
Antibiotics: Ceftriaxone 13.3. - 19.3.2017 (6 Days)
Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients

Nobre et al, Am J Respir Crit Care Med. 2008;177(5):498-505
Study of Nobre et al: 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
The 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
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
1. Antibiotic Resistance is a Problem
2.

Any Day of Antibiotic Use produces a more resistant Environment for the Patient
How to Do?

By an „Individual, Patient-adapted Antibiotic Therapy“

(„IPAT“)
Combine both Clinical Data AND PCT Data

Algorithm for onset and initial success of therapy (Day 1-3)

Algorithm to stop therapy (Day 3-7)
Our Aim for Today
Daily Re-assessment of AB-Tx:

We need Procalcitonin
for this purpose
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

630 Randomized

- 311 Assigned to the PCT Group
  - 4 withdrew consent
  - 307 Included in Analysis (1 lost to follow-up on day 15)

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

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

Main Goals:
To demonstrate that
...a Strategy including PCT Cineic in the Management of the Infection in the ICU ...

- ... leads to a increase of AB free days during the 1st 28 days
- ... without impact on Mortality at Day 28 and Day 60
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
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- [PCT] < 0.25 μg/l: Stopping antibiotics strongly encouraged
- 0.25 ≤ [PCT] < 0.5 μg/l: Stopping antibiotics encouraged
- [PCT] max and [PCT] < 80% of [PCT] max: Continuing antibiotics encouraged
- [PCT] max and [PCT] ≥ 80% of [PCT] max: Changing antibiotics strongly encouraged

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

23% less Exposure to Antibiotics

Bouadma, Lancet 2010; 375(9713):463-474
Why a “Maximum of 7 Days ?
**Prospective interventional trial**

**Guidance of Antibiotic Treatment in Patients with Community acquired Pneumonia (CAP)**

- **ProCAP Study**

**Primary endpoint:**
Duration of Antibiotic use

---

**CAP**
Prospective interventional trial

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

- Randomization

- ProCT group
  - 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

STOP or continue
Based on same cutoffs as above

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

- **Standard group** vs. **ProCT group**

  - Antibiotic duration (days)
    - Standard group: 13
    - ProCT group: 6

- Significance: $p < 0.001$

- Antibiotic prescription (%)
  - AB started
  - >4d
  - >6d
  - >8d
  - >10d
  - >14d
  - >21d

**Shorter AB-Courses $\Rightarrow$ 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

Safe reduction of average treatment duration from 13 to 5 days

Same outcome in both groups!

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

Christ-Crain M et al. Am J Respir Crit Care Med. 2006; 174: 84-93
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Same outcome in both groups!

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: 84-93
Interventions to Stop Antibiotic Treatment 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.), corticosteroids 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

In 3 university medical centers and 12 teachings hospitals in the Netherlands

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)
Hazard ratio standard-of-care group
1.26, 95% CI 1.07–1.49 (p=0.0060)

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<th>Number at risk</th>
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Efficacy and Safety of Procalcitonin Guidance in reducing the Duration of Antibiotic Treatment in Critically ill Patients: a randomised, controlled, open-label Trial.

_Evelien de Jong, Jas A van Oers, Albertus Beishuizen, et al._

_Lancet Infect Dis_ 2016; 16: 758-60

**Antibiotic consumption:**

<table>
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<tr>
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<th>PCT-group</th>
<th>Standard-group</th>
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<tr>
<td>Duration of Tx</td>
<td>5.0 (3.0-9.0)</td>
<td>7.0 (4.0-11.0)</td>
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<tr>
<td>AB free days</td>
<td>7.0 (0.0-14.5)</td>
<td>5.0 (0.0-13.0)</td>
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<td>Repeated AB-courses</td>
<td>175 (23.0)</td>
<td>173 (22.0)</td>
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<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>
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<tr>
<td>Lenth of stay ICU</td>
<td>8.5 (5.0-17.0)</td>
<td>9.0 (4.0-17.0)</td>
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<tr>
<td>Lenth of stay hospital</td>
<td>22.0 (13.0-39.3)</td>
<td>22.0 (12.0-40.0)</td>
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</table>
The Basics: Why Procalcitonin (PCT)?
The Basics: Why Procalcitonin (PCT)?

- Higher diagnostic specificity for dx of sepsis
- PCT indicates systemic inflammation, most likely coming from bact. infection
- Despite, PCT is a marker of non-bacterial inflammation as well
- Correlation with severity and risk of sepsis/MODS
- Increase and Decrease indicates activity of systemic inflammation

-Guide of Antibiotic Therapy:
  - initial decline of peak values indicates success of therapy
  - further decline towards normal range indicates:
    AB are possibly not longer required!
    (use PCT-guided Algorithm e.g. from Bouadma)
„IPAT“ means:

- Treat only (short) periods of infection
  (3 days to a max. of 7 days)

- Treat only invasive infection
  (=do not treat colonisation/local infection)

- Treat only „proven“ infection, whenever possible
  (any „possible“, „likely“, „might be“ is not part of the concept)

- Document your decisions well
  („sepsis“, no infection, PCT,....)

- Communicate decisions with all doctors
  (your decision, knowledge of IPAT/PCT algorithm)
**Basic Rules:**

1. If PCT is very low (< 0.25-0.5 ng/ml), severe infection is unlikely and the need of antibiotics is questionable (<0.1 ng/ml, <0.25 ng/ml)
Basic Rules:

1. If PCT is very low (<0.25 - 0.3 ng/ml), severe infection is unlikely and the need of antibiotics should be questioned / re-evaluated.

2. The higher PCT is (> 0.5 - > 2 ng/ml), the more likely sepsis is: antibiotics are (urgently) recommended!
   - unless other reasons are clear and
   - a focus of sepsis/infection is excluded
PCT-Algorithm

A) Success-Rules (Day 1-3):

A) Day 1-3:
Questions to PCT and Follow-up Rules at Day 1-3:

1. If PCT declines, 
inflammation is controlled (Rule of Day 1-3) 
   - if not, inflammation continues (new/wrong Dx or Tx?)

2. Day 1-3 question as well: Is diagnosis correct?
B) Day 3 - 7: Follow-up Rules or „Stop-Rules“

Stop AB (Rule of Day 3-7)
- if focus has clinically cleared AND
- PCT-stop criteria apply (decline >80%, PCT < 0.3-0.5)

AND
Add general rule of maximum of 7 day treatment duration (Rule of Day 7)
= 
- stop rule of day 7 of Tx (unless reasons are discussed)
Case report II:
November 4, 2017:
26 year old lady, admitted after seizure with aspiration to hospital/ICU

Therapy started with Cefuroxime/Sulbactam

Procedure for AB-Stewardship
- initial PCT
- initial CXR

PCT: 0.05 ng/ml (Nov. 4, 2017)
Atelectasis or infiltrate on Chest-X-Rax
Staedt. KH Dresden-Neustadt
Kulow, Eva-Maria
15.06.1990 / 0140759601
Thorax
Bettaufnahme

04.11.2017, 16:49:03
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Kulow, Eva-Maria
15.06.1990 / 0140780001
Thorax
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07.11.2017, 07:58:33
Case report II:
November 4, 2017:
26 year old lady, admitted after seizure with aspiration to hospital/ICU

Therapy started with Cefuroxime/Sulbactam

Procedure for AB-Stewardship
- initial PCT, daily follow up of PC T
- initial CXR, CXR when decision to stop AB is ready

Course of Disease:
PCT: 0.05 ng/ml (Nov. 4, 2017), PCT 0.05 ng/ml on Nov. 6.
No infiltrates / no atelectasis no CXR on November 7.

Antibiotics stopped on November 6.
Guidelines
A large body of literature suggests that use of such algorithms (PCT-guided algorithms) can speed safe antimicrobial de-escalation compared to standard clinical approaches with reduced antimicrobial consumption without an adverse effect on mortality ....

R. Phillip Dellinger, MD\textsuperscript{1}; Mitchell M. Levy, MD\textsuperscript{2}; Andrew Rhodes, MB BS\textsuperscript{3}; Djillali Annane, MD\textsuperscript{4}; Herwig Gerlach, MD, PhD\textsuperscript{5}; Steven M. Opal, MD\textsuperscript{6}; Jonathan E. Sevransky, MD\textsuperscript{7}; Charles L. Sprung, MD\textsuperscript{8}; Ivor S. Douglas, MD\textsuperscript{9}; Roman Jaeschke, MD\textsuperscript{10}; Tiffany M. Osborn, MD, MPH\textsuperscript{11}; Mark E. Nunnally, MD\textsuperscript{12}; Sean R. Townsend, MD\textsuperscript{13}; Konrad Reinhart, MD\textsuperscript{14}; Ruth M. Kleinpell, PhD, RN-CS\textsuperscript{15}; Derek C. Angus, MD, MPH\textsuperscript{16}; Clifford S. Deutschman, MD, MS\textsuperscript{17}; Flavia R. Machado, MD, PhD\textsuperscript{18}; Gordon D. Rubenfeld, MD\textsuperscript{19}; Steven A. Webb, MB BS, PhD\textsuperscript{20}; Richard J. Beale, MB BS\textsuperscript{21}; Jean-Louis Vincent, MD, PhD\textsuperscript{22}; Rui Moreno, MD, PhD\textsuperscript{23}; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Table 1: Diagnostic Criteria for Sepsis

Plasma PCT more than two SD above the normal value.
Section D: Antimicrobial Therapy:

3. Use of low Procalcitonin levels.....

... to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (Grade 2 C)

Prevention, diagnosis, therapy and follow-up care of sepsis: 1st revision of S-2k guidelines of the German Sepsis Society (Deutsche Sepsis-Gesellschaft e.V. (DSG)) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI))

- In order to shorten the duration of antimicrobial therapy, serial procalcitonin (PCT) measurements may be considered.
  → Recommendation level C (evidence level IIb for [18])
Epidemiologie, Diagnostik, antimikrobielle Therapie und Management von erwachsenen Patienten mit ambulant erworbenen tiefen Atemwegsinfektionen (akute Bronchitis, akute Exazerbation einer chronischen Bronchitis, Influenza und andere respiratorische Virusinfektionen) sowie ambulant erworbener Pneumonie
13.2. Diagnostik bei hospitalisierten CAP-Patienten

1. Therapiedauer

In einer Studie bei CAP konnte durch eine mittels serieller Procalcitonin III - Bestimmung an den Behandlungstagen 0, 4, 6 und 8 gesteuerte Antibiotikatherapie die mediane Dauer der antimikrobiellen Therapie auf 5 Tage bei gleichem Therapieerfolg reduziert werden. Selbst bei schwerer Pneumonie war nur selten eine Therapie von mehr als 8 Tagen erforderlich [291]. Ein Procalcitonin-Spiegel von < 0,1 µg/L im Verlauf spricht daher bei klinischer Besserung für eine Beendigung der Antibiotikatherapie. Eine sinnvolle Strategie ist bei kürzerer Therapiedauer die tägliche klinische Überprüfung von Symptomen, die auf ein Rezidiv hinweisen können.
The End
Thank you for your attention!