PROCALCITONIN and Markers of Infection

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PARIS, FRANCE
MARKERS of INFECTION to complete clinical analysis?

- Positive predictive value
  - Diagnosis of bacterial infection
  - Diagnosis of viral infection +++

- Negative predictive value +++

STOP ANTIBIOTIC TREATMENT
AVOID UNNECESSARY ANTIBIOTIC TREATMENT
AVOID UNNECESSARY INVESTIGATIONS
Markers of infection are required to complete clinical analysis before results.
**BioMarkers of Sepsis**

### Increase of normal Proteins
- **Acute phase proteins**
  - CRP
  - Fibrinogen (ESR)

- **ProHormones**
  - **Procalcitonin**
  - Poadrenomedulin

- **Cytokines**
  - TNF, IL1, IL2, IL6, IL8 ….

### Markers produced by immune response
- **Presepsin**
  - CD14 on monocytes, (linked to LPS)

- **sTREM1**
  - Soluble receptor on myeloid cells

- **suPAR**
  - Soluble urokinase-type plasminogen activator receptor,

- **Interferons**
  - Viral infections
High serum procalcitonin concentrations in patients with sepsis and infection

Marcel Assicot  Dominique Gendrel  Hervé Carsin
Josette Raymond  Jean Guilbaud  Claude Bohuon

Bacterial vs viral infections

Found by chance!
Maturation of CALCITONIN

Pro-Calcitonin

N proCALCITONIN 1-57

C proCALCITONIN 60-116

Only in thyroidal C-cells

Katacalcin

Mature Calcitonin
During sepsis only ProCalciTion in blood without calcitonin

Experimental sepsis: mRNA of calcitonin and precursors, or cytokines

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Calcitonin</th>
<th>TNF-α</th>
<th>IL-6</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Sepsis</td>
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<td>Thyroid</td>
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<td>Perit. Macrophage</td>
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<td>Small Intestine</td>
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<td>Colon</td>
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<td>Heart</td>
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<td>Skin</td>
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<td>Visceral Fat</td>
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<td>Testes</td>
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(Mueller et al, JCEM 2001)
MARKERS after INTRAVENOUS ENDOTOXIN

modified from Dandona & Bohuon, JCEM, 1994
Procalcitonin is a marker of severity in septic shock

Schröder et al
Langenbeck’s arch surg 1999; 384 33-8
LOW PCT in VIRAL INFECTIONS

No production of PCT in presence of interferon

PCT concentrations of cells treated either with IL-1β or IL-1β and INF-γ (adapted from Linscheid et al. 2003)
Differentiate viral and bacterial infections

Blood collection in 360 feverish children at hospital admission
(St Vincent de Paul Children Hospital, PARIS, France)

Procalcitonin, C Reactive protein, Interleukin 6

Interferon α (Biological assay on MBDK cells)
Emergency room: Bacterial vs Viral infections

PCT > CRP or IL6, CRP = IL6

Bacterial vs viral infections in 360 children

Gendre et al. PEDI 1999

Gendre et al. PEDI 1999
PROCALCITONIN is the BEST predictor to differentiate bacterial and viral infections in hospitalized feverish children.
Procalcitonin validated as the best predictor of serious bacterial infection in pediatric emergency rooms (Europe, Asia, America)

**ORIGINAL RESEARCH CONTRIBUTION**

Procalcitonin as a Marker of Serious Bacterial Infections in Febrile Children Younger Than 3 Years Old

Prashant Mahajan, MD, MPH, MBA, Mary Grzybowski, PhD, MPH, Xinguang Chen, MD, PhD, Nirupama Kannikeswaran, MD, Rachel Stanley, MD, MHSA, Bonita Singal, MD, John Hoyle, Jr., MD, Dominic Borgia, MD, MPH, Elizabeth Duffy, MA, and Nathan Kuppermann, MD, MPH

**CONCLUSIONS**

Procalcitonin appears to be a more accurate marker than the white blood cell count, the absolute neutrophil count, or the absolute band count in identifying young febrile infants and children with serious bacterial infections. Further study on a larger cohort is required to
The negative predictive value of PCT is probably the most important

- Low PCT in viral infections
- Low PCT in inflammatory diseases with elevated usual markers
Procalcitonin secretion is independent of Interferon–α production during viral infections

Method: biological assay – incubation MBDK cells 48h
no INF-α in serum of normal patients

Viral infections:
132 / 172 are producers of INF-α

Bacterial infections
6 / 70 are producers of INF-α
(viral + bacterial co-infections)

INF-α: Sensitivity 77% Specificity 90% for viral vs bacterial infections

PIDJ 1999
Man, 78 y, hypertension

**Referred for bacterial pneumonia**

Acute Thoracic Pain
39°5, cough
Bilateral crackles

10700 Blood cells, 80% PN
  • CRP 70

PCT 0.11 ng/ml

P Hausfater, SAU Pitié, PARIS
Bilateral pulmonary embolism
Referred for bacterial pneumonia, PCT 0.11
Meningitis: bacterial or viral?

**Bacterial meningitis**
- Prevalence = 6-10%
- Morbidity High
- Mortality 5-7%

**Viral Meningitis-Associated Hospitalizations in the United States, 1988–1999**

Nino Khetsuriani\(^a\)  Eva S. Quiroz\(^a,b\)  Robert C. Holman\(^c\)  Larry J. Anderson\(^a\)

*Respiratory and Enteric Viruses Branch, Division of Viral and Rickettsial Diseases (DVRD), Centers for Disease Control and Prevention (CDC)*, *Epidemic Intelligence Service, Epidemiology Program Office, CDC, and Office of the Director, DVRD, CDC, Atlanta, Ga., USA*

- Hospital stays:
  - Mean hospital stay: 5 days/patient
- Mean cost/patient: 5000 $
- Total cost/year: 200,000 days/year
  - 250 to 300 Million $

**Clinical and/or biological criteria**
Values at admission in bacterial (n = 23) and viral (n = 60) meningitis

Gendrel & al, Clin Infect Dis 1997
Stop antibiotic treatment if PCT< 0.5 ng/ml

2001 & 2001: PCT three times a week in St Vincent de Paul Hospital

2000: 69 patients with viral meningitis, 24 treated
- Intravenous antibiotic stopped:
  - Day 1: 10 pts, Day 2: 11 pts, Day 3: 3 pts
- Mean antibiotic treatment: **1.25 days** in the 24 pts

2001: 21 Viral meningitis, 9 treated
- Mean 1.7 days

Control group: no PCT in routine use (before 2000)
- 41 viral meningitis, 19 treated
- Mean antibiotic treatment: **4.8 days**

St Vincent de Paul Hospital

Clin Inf Dis 1997, Arch Ped 2002
Clinical Prediction Rule for Identifying Children With Cerebrospinal Fluid Pleocytosis at Very Low Risk of Bacterial Meningitis

BACTERIAL MENINGITIS SCORE
Gram, CSF neutrophils and proteins
Seizures, Blood neutrophils

Sensitivity 98%, Neg Pred Value 99%

Application of BMS to the French BM cohort published in Clin Inf Dis 2005
Sensitivity of the Bacterial Meningitis Score in 889 Children with Bacterial Meningitis

FRANÇOIS DUBOS, MD, FRANCE DE LA ROCQUE, MD, CORINNE LEVY, MD, EDOUARD BINGEN, MD, YANNICK AUJARD, MD, ROBERT COHEN, MD, GÉRARD BRÉART, MD; THE BACTERIAL MENINGITIS STUDY GROUP, DOMINIQUE GENDREL, MD, AND MARTIN CHALUMEAU, MD, PHD

(J Pediatr 2008:152:378-82)

889 children with BM

BMS Application

BM detected in 884 children

5 patients non diagnosed with BMS

4/5 Neisseria meningitis

• PCT high in 3, not done in 2

caught-up by PCT
Validation of negative predictive value of PCT

**Meningitest®**

**Acute meningitis (≥7 cells/mm³)**
- *Without exclusion criteria*

- **Purpura**
- **or Palsies**
- **or Toxic presentation**

- or **bacter in CSF (Gram color)**
- or **CSF prot ≥0.5 g/L**
- or **PCT ≥0.5 ng/mL**

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**Yes**

- **Hospitalisation and antibiotics**

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**No**

- **No hospitalisation, no antibiotics**

**PCT < .5 ng/ml and CSF prot < .5 g/l**

Meningitest avoid significantly more unnecessary antibiotic treatments

ADC 2010
A physiological rise of PCT is observed after delivery.

High PCT in cord blood is a marker of materno-fetal infection.

Umbilical cord blood procalcitonin level in early neonatal infections: a 4-year university hospital cohort study

J. Caillon, J.-C. Rozé, C. Gras-Le Guen
A new procalcitonin cord-based algorithm in early-onset neonatal infection: for a change of paradigm

S. Lencot · B. Cabaret · G. Sauvage · C. Laurans · E. Launay · J.-L. Orsonneau · J. Caillon · C. Boscher · J.-C. Roze · C. Gras-Le Guen

A cord-blood PCT algorithm allows to reduce by 25% neonates antibiotic exposure when compared to usual guidelines
Urinary Tract Infections

Antibiotic treatment is based on resistances

Prediction of REFLUX?
Prediction of RENAL SCARS?
Procalcitonin is a marker of severity of renal lesions in pyelonephritis

Results of initial CRP & PCT and DMSA scintigraphy in 60 children with urinary tract infection (Geneva & Paris)

Importance of renal scars is correlated with PCT and not with CRP, TNF, IL6 and IL8

Benador, Siegrist, Gendrel, et al
PEDIATRICS, 1998; 102 : 1422
PCT is a predictor of renal scars after UTI

Serum Procalcitonin for Prediction of Renal Parenchymal Involvement in Children with Urinary Tract Infections: A Meta-analysis of Prospective Clinical Studies

Elpis Mantadakis, MD, Eleni Plessa, MD, Evridiki K. Vouloumanou, MD, Drosos E. Karageorgopoulos, MD, Athanasios Chatzimichael, MD, and Mathew E. Falagas, MD, MSc, DSc

Conclusions In children with culture-proven UTI, a serum PCT value >0.5 ng/mL predicts reasonably well the presence of RPI, as evidenced by DMSA scintigraphy. PCT may aid in the identification of children with UTI necessitating more intense evaluation and management. (J Pediatr 2009;155:875-81)
Febrile urinary tract infection (UTI) in children

- Frequent: 2-7% before 6 years old
- Vesico-ureteral reflux (VUR):
  - 20-40% after a 1st UTI
  - relapsing UTI, renal scarring
    hypertension and renal failure
  - potential treatement

⇒ **Systematic voiding cystouretrograph (VCUG)**

Girardin, *Paediatr*, 2002
Ultrasonography cannot predict Vesico Ureteral Reflux

Imaging Studies after a First Febrile Urinary Tract Infection in Young Children

Alejandro Hoberman, M.D., Martin Charron, M.D., Robert W. Hickey, M.D., Marc Baskin, M.D., Diana H. Kearney, R.N., and Ellen R. Wald, M.D.

Figure 1. Frequency of Evidence of Dilatation of the Urinary Tract on the Initial Ultrasonogram, According to the Presence or Absence and Degree of Vescicoureteral Reflux (VUR) in Children with a First Urinary Tract Infection.
Systematic cystourethrogram after UTI
Bilateral VUR
grade 3-4

Normal ultrasonogram
CRP : 16 mg/l

Only one marker of severity

PCT : 2.5 ng/ml
Procalcitonin as a Predictor of Vesicoureteral Reflux in Children With a First Febrile Urinary Tract Infection

n = 136, 46% males
Mean age = 10 months
25% VUR, 9% VUR ≥ 3

p = 0.047
PCT European Validation for VUR

5 patients with grade 3 VUR misdiagnosed
3/5 abnormal ultrasonography

Leroy et al
J Pediatr 2007
Cost-analysis

PCT < 0.5 in UTI and normal ultrasonography:

1/3 - 1/2 of unnecessary cystographies could be avoided

VCUG

200€

PCT

10€

add side effects: pain, infection...
Severity of pneumococcal invasive infections

Pneumococcus is « the captain of all the men of death »

William OSLER

Mortality of pneumococcal pneumonia with and without antibiotics

Pneumococcal acute otitis media is non invasive
In acute bacterial otitis media, how to predict antibiotics efficacy?

**Spontaneous recovery is frequent**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Amox-clav 90mg/6.4mg bid</th>
<th>Placebo</th>
<th>Amox-clav 40mg/5.7mg bid</th>
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</thead>
<tbody>
<tr>
<td>Duration (days)</td>
<td>7 d</td>
<td>10 d</td>
<td>6-35</td>
<td>16 m</td>
</tr>
<tr>
<td>Age (months)</td>
<td>6-23 m</td>
<td>6-35</td>
<td>16 m</td>
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<td>Range Mean</td>
<td>≈10 m</td>
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<td>N of patients</td>
<td>291</td>
<td>359</td>
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<td>Failures</td>
<td>51%</td>
<td>16%</td>
<td>44.9</td>
<td>18.6</td>
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<tr>
<td>P</td>
<td>0.001</td>
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In acute otitis media, PCT is a predictor of severity not a predictor of bacterial origin.

PCT can be low in non invasive bacterial infection.

PCT in 8 children with pneumococcal acute otitis media

Gendrel et al, PIDJ 1999
12 years, 39°, cough, CRP 70 mg/l
Emergency Room 1st diagnosis: *Mycoplasma pneumoniae*

Emergency room PCT: 18 ng/ml
2 days after admission, Blood culture results: *Strept pneumoniae*
PCT is low in viral infection

39°C after 2 days amoxicillin trt

RSV in throat

PCT 0.4 ng/ml

CRP 45 mg/l
Community Acquired Pneumonia
88 children, 2m-12y

CRP at emergency room

Moulin F, Arch Dis Child 2001
Community Acquired Pneumonia
88 children, 2m-12y

PCT at emergency room

Moulin F, Arch Dis Child 2001
Procalcitonin is predictive of bacteremia in pneumonia

Chest, 2010

Procalcitonin Levels Predict Bacteremia in Patients With Community-Acquired Pneumonia

A Prospective Cohort Trial

Fabian Müller, MD; Mirjam Christ-Crain, MD; Thomas Bregenzer, MD; Martin Krause, MD; Werner Zimmerli, MD; Beat Mueller, MD; and Philipp Schuetz, MD; for the ProHOSP Study Group*

Procalcitonin is useful in identifying bacteraemia among children with pneumonia

Scandinavian Journal of Infectious Diseases, 2010; 42: 644–649

CRISTIANA M. NASCIMENTO-CARVALHO¹, MARIA-REGINA A. CARDOSO², ALDINA BARRAL³, CÉSAR A. ARAÚJO-NETO⁴, SYLVIE GUERIN⁵, ANNIIKA SAUKKORIIPI⁶, MIKA PALDANIIUS⁶, RAIIJA VAINIONPÄÄ⁷, PIERRE LEBON⁵, MAIJA LEINONEN⁶, OLLI RUUSKANEN⁸ & DOMINIQUE GENDREL⁵

| Typical bacterial (n = 48) | Atypical bacterial (n = 20) | Viral (n = 57) | Unknown (n = 34) |
Procalcitonin as marker of sepsis

- Graft: infection vs reject
- Febrile neutropenia
- Gangrenous appendicitis
- Post surgical infections
  etc …….
Procalcitonin is superior to other markers in severity of bacterial infection

Schröder et al
Langenbeck’s arch surg 1999; 384 33-8
Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial

Lancet 2004, 363(9409) : 600-607

Mirjam Christ-Crain, Daiana Jaccard-Stolz, Roland Bingisser, Mikael M Gencay, Peter R Huber, Michael Tamm, Beat Müller

Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia

A Randomized Trial

Mirjam Christ-Crain, Daiana Stolz, Roland Bingisser, Christian Müller, David Miedinger, Peter R. Huber, Werner Zimmerli, Stephan Harbarth, Michael Tamm, and Beat Müller

Am J Respir Crit Care Med Vol 174. pp 84-93, 2006
Same outcome in the two groups
Conclusions: Our results suggest that a protocol based on serial PCT measurement allows reducing antibiotic treatment duration and exposure in patients with severe sepsis and septic shock without apparent harm.
Use of procalcitinin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

Lila Bouadma, Charles-Edouard Luyt, Florence Tubach, Christophe Cracco, Antonio Alvarez, Carole Schwebel, Frédérique Schortgen, Sigismond Losocki, Benoît Veber, Monique Pehoux, Maguy Bernard, Blandine Pasquet, Bernard Régnier, Christian Brun-Buisson, Jean Chastre, Michel Wolff, for the PRORATA trial group

Lancet 2010; 375: 463-474

Stop antibiotics if PCT
- Low
- Dramatic decrease
A BIOLOGICAL MARKER IS ONLY A HELP FOR THE PHYSICIAN

PROCALCITONIN and other markers of infection:

- the field of application in routine use?
- a correct methodology in studies?