Use of procalcitonin assay to streamline antibiotic usage

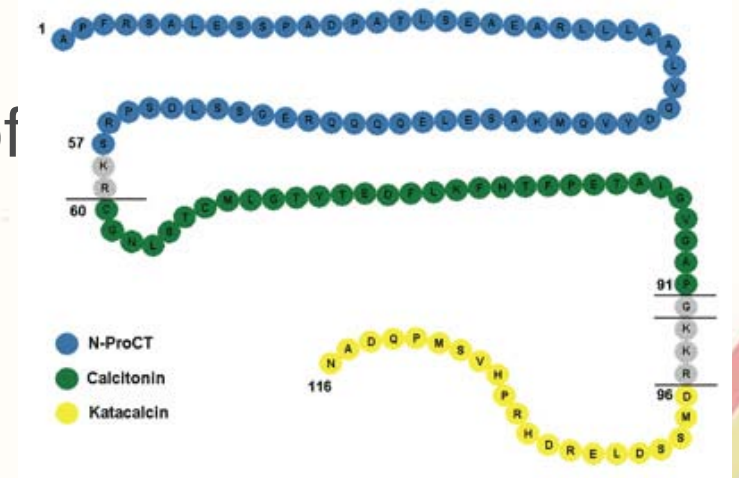
Dr Kristine Luk

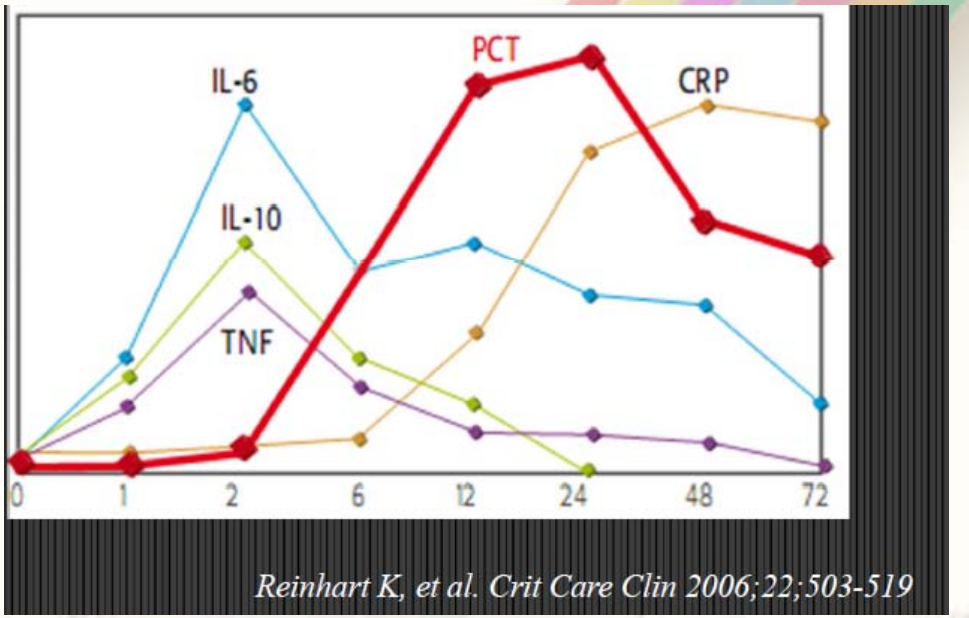
Outline

- Procalcitonin – physiology & kinetics
- Limitations
- Different settings
  - primary care & AED
  - critically ill patients
  - neutropenic febrile patients
  - autoimmune diseases
  - neonates
- Local experience

Procalcitonin – kinetics

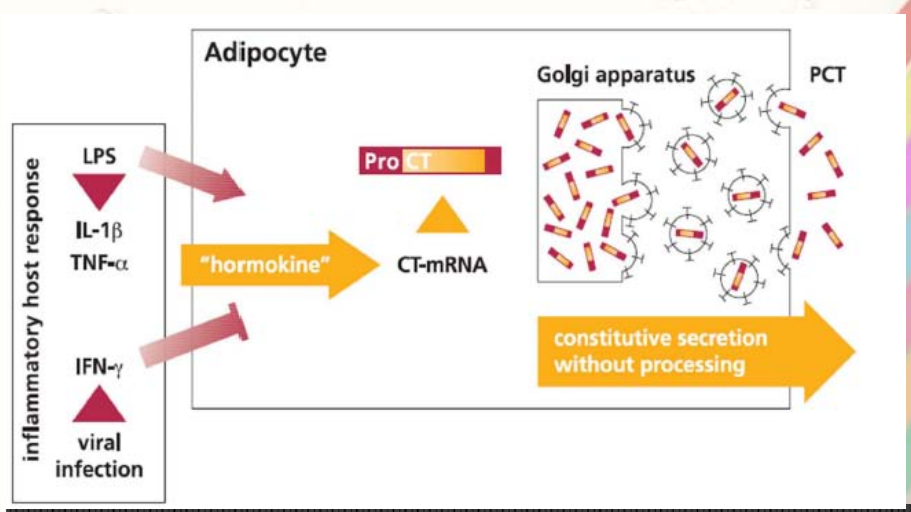
- 116 amino acid precursor polypeptide of calcitonin
- Half-life 24 hrs, independent of renal function
- Calcitonin level would not increase as enzymatic cleavage of calcitonin is bypassed.
- Greater sensitivity & NPV than CRP





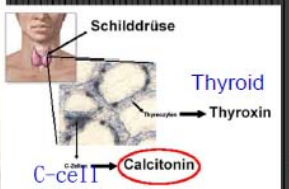
Physiology

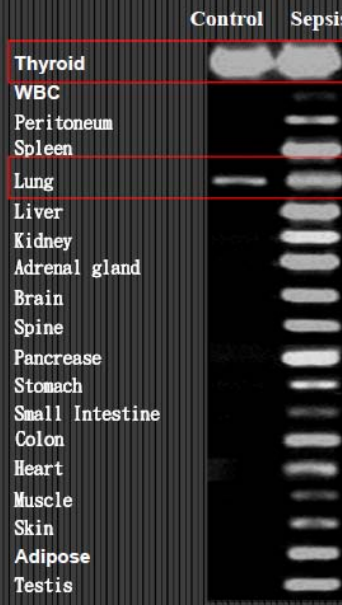
- In animal models of sepsis, PCT administration increased mortality
- Expression in WBCs is only increased transiently during the differentiation from monocytes to macrophages
- Neutropenic bacteremic patients have no deficiency in generating a PCT response



Tissue that Secrete Procalcitonin

- In healthy person, only thyroid and lung secrete procalcitonin and then processed into calcitonin
- During bacterial infection, all parenchymal tissues could secrete procalcitonin into blood stream





Müller B. et al., JCEM 200

Limitations:
Non bacterial causes of increased in PCT

Neuroendocrine tumor	Systemic inflam-mation	Trauma (2-20 µg/L)	Autoimmune diseases	Other infections
Medullary thyroid cancer	Inhalational injury	Mechanical injury	Adult onset Still's disease	Fungi (0.69 – 103 µg/L)
SCC lung	Pulmonary aspiration	Burns	Vasculitis?	Malaria (662 µg/L)
Carcinoid	Pancreatitis	Extensive surgery	SLE?	
	cirrhosis	Cardiogenic shock		
	Mesenteric infarction			
	Heat stroke			
	Neonate < 48hs			

Limitations: Intracellular bacteria?

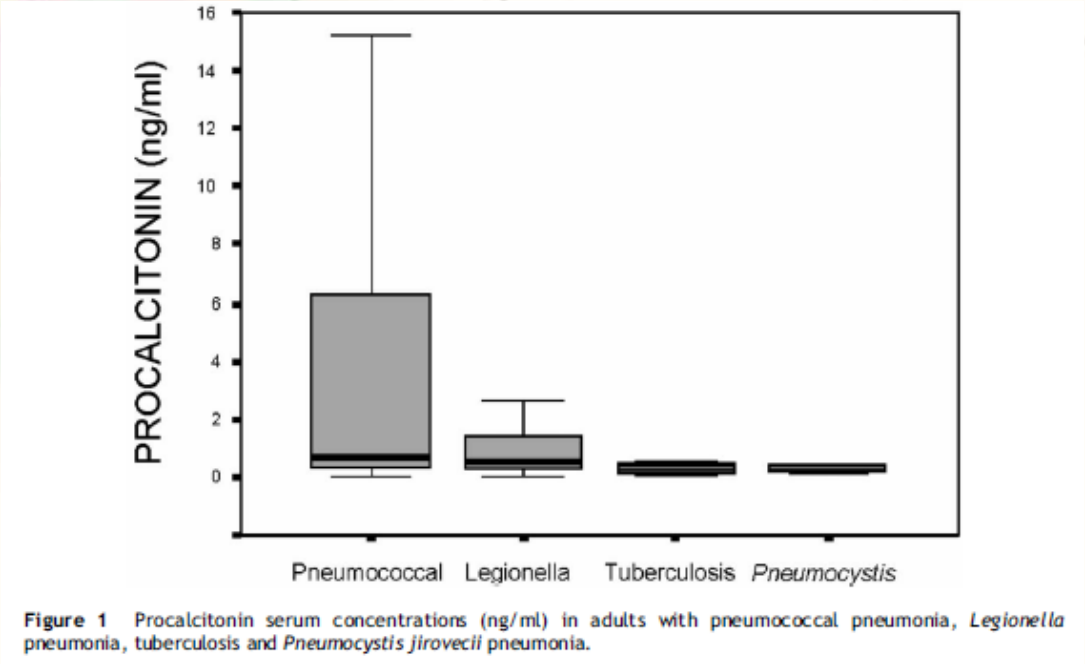


Figure 1 Procalcitonin serum concentrations (ng/ml) in adults with pneumococcal pneumonia, *Legionella* pneumonia, tuberculosis and *Pneumocystis jirovecii* pneumonia.

Journal of Infection (2006) 52, 169-177

- 75 patients presented with PTB, only 41.3% have a PCT value > 0.5 µg/L (range 0.02-1.09 µg/L)

Jpn J Infect Dis 2006; 59:164-167.

Primary care / AED patients

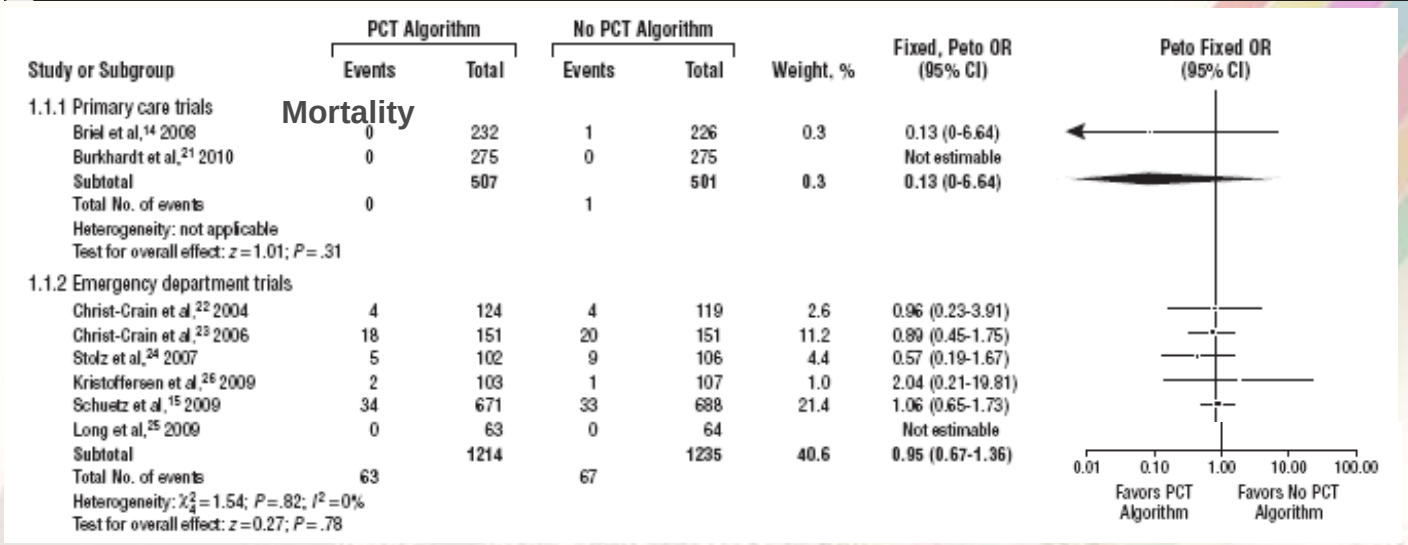
Table 2. Overview of Design and Content of the RCTs Grouped by Study Setting

Source	Study Design[a]	Diagnosis	Research Question	Algorithm by PCT Level, µg/L	Outcome
			Primary Care Setting		
Briel et al,[14] 2008	Multicenter, noninferiority	Upper and lower RTI	Safety and reduction of Abx with repeated PCT-level measurement?	<0.10, SRAA; 0.10-0.25, RAA; >0.25, RFA; recheck PCT level at 6-24 h if no Abx initiated	Primary: days with restricted activity in first 14 d Secondary: Abx exposure, adverse events at day 28
Burkhardt et al,[21] 2010	Multicenter, noninferiority	Upper and lower RTI	Safety and reduction of Abx with single PCT-level measurement?	<0.25, RAA; >0.25, RFA	Primary: days with significant health impairment at day 14 Secondary: Abx exposure
			ED Settings		
Christ-Crain et al,[22] 2004	ED only, single center	CAP, AECOPD, bronchitis	Reduction of Abx for lower RTI with repeated CAP in ED with single PCT-level measurement?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; recheck PCT level after 6-24 h if no Abx initiated	Primary: Abx prescriptions at day 14 Secondary: readmission, relapse, QOL, cost
Christ-Crain et al,[23] 2006	ED and inpatient, single center	CAP	Reduction of Abx for CAP with repeated PCT-level measurements?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RAA; >0.50, SRFA; recheck PCT level every 2 d; discontinue Abx with same cutoffs	Primary: duration of Abx at day 28 Secondary: mortality, adverse outcomes
Stolz et al,[24] 2007	ED and inpatient, single center	AECOPD	Reduction of Abx for AECOPD with repeated PCT-level measurements?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; retest PCT level every 2 d; discontinue Abx with same cutoffs	Primary: Abx use in hospital and first 6 mo Secondary: ICU, death, LOS, AECOPD recurrence rate
Long et al,[25] 2009	ED at 2 centers	CAP	Reduction of Abx for CAP in outpatients with repeated PCT-level measurements?	<0.25, RAA; ≥0.25, RFA; if no Abx, retest PCT at 8-12 h, recheck PCT every 3 d; discontinue Abx with same cutoffs	Primary: Abx use within 28 d Secondary: clinical recovery, treatment failure, cost of Abx
Kristoffersen et al,[26] 2009	ED and inpatient, single center	Lower RTI	Reduction of Abx for lower RTI with single PCT-level measurement?	<0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA	Primary: Abx use Secondary: adherence to algorithm, mortality, ICU
Schuetz et al,[15] 2009	ED and inpatient, multicenter	CAP, AECOPD, bronchitis	Safety, Abx use, and feasibility in CAP, AECOPD, and bronchitis?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; retest PCT level every 2 d; discontinue Abx with same cutoffs	Primary: noninferiority of adverse outcomes at day 28 Secondary: duration of Abx

Therapy decisions – start / withhold antibiotics

Table 3. Primary and Secondary Outcomes of the Different RCTs, Grouped by Study Setting

Source	Diagnoses	Total No.	Mortality, Control vs PCT Groups, No. Dead/Total (%)	Abx Use, Control vs PCT	Relative Reduction, %	Key Findings
			Primary Care Settings			
Briel et al,[14] 2008[a]	Upper and lower RTI	458	1/226 (0.4) vs 0/232 (0)	Prescription: 97% vs 25% Duration (mean): 7.1 vs 6.2 d	Prescription: –74 Duration: –13	Reduction of Abx without additional days of restricted activity
Burkhardt et al,[21] 2010	Upper and lower RTI	550	0/275 (0) vs 0/275 (0)	Prescription: 36.7% vs 21.5% Duration (mean): 7.7 vs 7.8 d	Prescription: –42 Duration: 1	Reduction of Abx without causing heath impairment
			ED Settings			
Christ-Crain et al,[22] 2004	CAP, AECOPD, bronchitis	243	4/119 (3.4) vs 4/124 (3.2)	Prescription: 83% vs 44% Duration (mean): 12.8 vs 10.9 d	Prescription: –47 Duration: –15	Reduction of Abx prescriptions
Christ-Crain et al,[23] 2006	CAP	302	20/151 (13.2) vs 18/151 (11.9)	Prescription: 99% vs 85% Duration (mean): 12.9 vs 5.8 d	Prescription: –14 Duration: –55	Reduction of initiation and duration of Abx without adverse outcomes
Stolz et al,[24] 2007	AECOPD	208	9/106 (8.5) vs 5/102 (4.9)	Prescription: 72% vs 40%	Prescription: –44	Reduced Abx exposure without adverse outcome
Long et al,[25] 2009	CAP	127	0/64 (0) vs 0/63 (0)	Prescription: 97% vs 86% Duration (median): 10 vs 6 d	Prescription: –11 Duration: –40	Reduction of Abx use and shorter Abx duration
Kristoffersen et al,[26] 2009	Lower RTI	210	1/107 (0.9) vs 2/103 (1.9)	Prescription: 79% vs 85% Duration (mean): 6.8 vs 5.1 d	Prescription: 8 Duration: –25	Reduction of duration of Abx use
Schuetz et al,[15] 2009	CAP, AECOPD, bronchitis	1359	33/688 (4.8) vs 34/671 (5.1)	Prescription: 87.7% vs 75.4% Duration (median): 8.7 vs 5.7 d	Prescription: –14 Duration: –34	Noninferiority for clinical outcomes and decreased Abx use



Proposed algorithm for low-acuity non-pneumonic and moderate-acuity pneumonic infections

A

Evaluation at time of admission

PCT result	<0.10 µg/L	<0.25 µg/L	≥0.25 µg/L	>0.50 µg/L
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia, are at high risk (ie, COPD GOLD III-IV), or need hospitalization			
Follow-up/other comments	Follow-up only needed if no symptom resolution after 1 to 2 days; if clinical situation is not improving; consider Abx if PCT level increases to ≥0.25 µg/L		Clinical reevaluation as appropriate	

B

Evaluation at time of admission

PCT result	<0.10 µg/L	<0.25 µg/L	≥0.25 µg/L	>0.50 µg/L
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Consider alternative diagnosis, or Abx if patients are clinically unstable, are at high risk for adverse outcome (eg, PSI classes IV-V, immunosupression), or have strong evidence of a bacterial pathogen			
Follow-up/other comments	Reassess patients' condition and recheck PCT level after 6 to 12 hours if no clinical improvement is observed		Recheck PCT level every 2 to 3 days to consider early cessation of Abx	

Follow-up evaluation every 2 to 3 days

PCT result	<0.10 µg/L	<0.25 µg/L	≥0.25 µg/L	>0.50 µg/L
Recommendation regarding use of Abx	Cessation of therapy strongly encouraged	Cessation of therapy encouraged	Cessation of therapy discouraged	Cessation of therapy strongly discouraged
Overruling the algorithm	Consider continuation of Abx if patients are clinically not stable			
Follow-up/other comments	Clinical reevaluation as appropriate		Consider treatment to have failed if PCT level does not decrease adequately	

Critically ill patients

- Pooled 1602 SIRS patients
- Unlikely to be helpful in assisting clinical decision (with a pretest probability of sepsis of 40%, PCT would only raise the post-test probability to 66%)
- NLR 0.43 (reduce the post-test probability to 23%, not enough to rule out an infection)

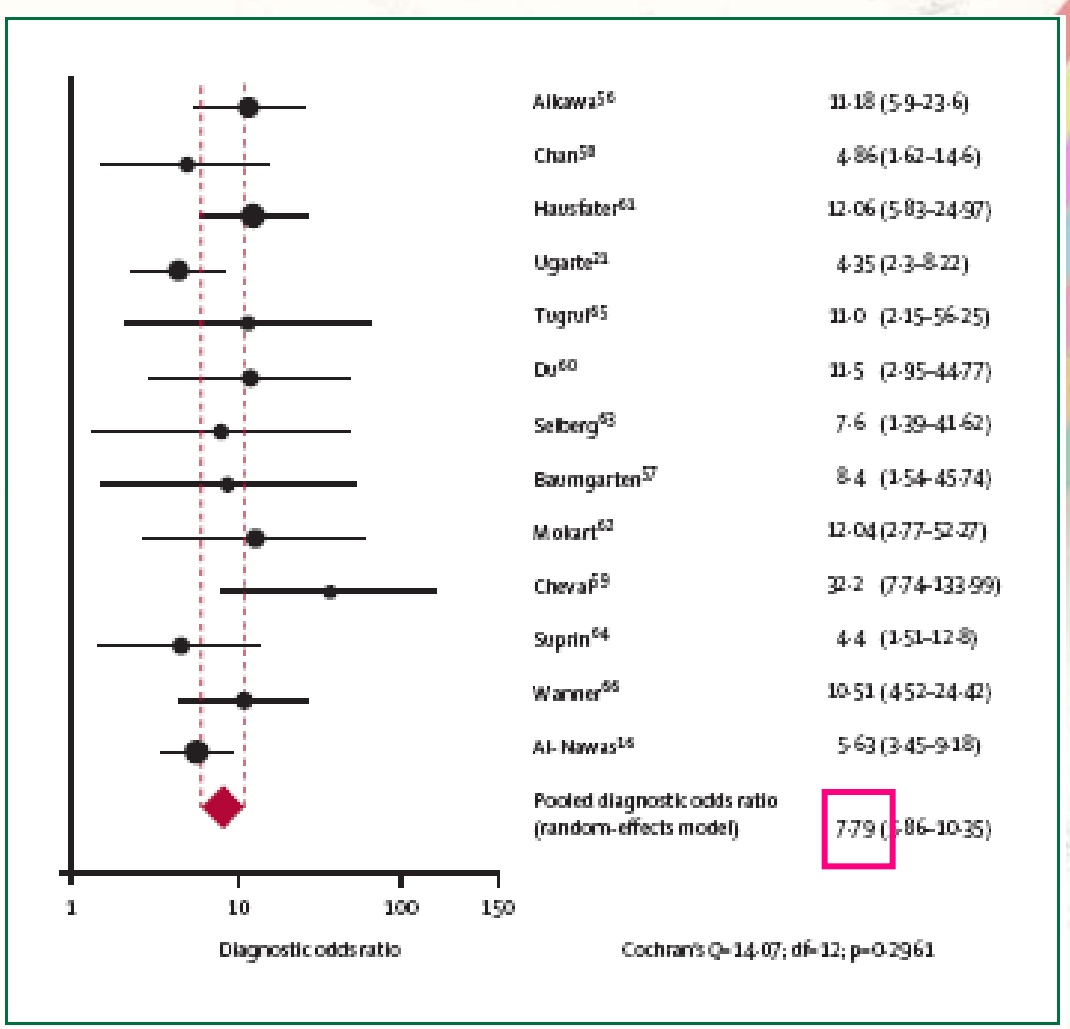


Figure 2: Diagnostic odds ratios of group 1 studies
Circles represent individual studies. Error bars represent 95% CIs. Diamond represents pooled diagnostic odds ratio, with dashed lines representing its 95% CI. Size of circles is proportional to weighting by inverse variance. SE=standard error.

VAP?

Table 1 Studies Evaluating Procalcitonin Concentration as a Diagnostic Marker of Ventilator-Associated Pneumonia

Reference	Number of Subjects		Cut-off	Sensitivity	Specificity
	VAP	No VAP	(ng/mL)	(%)	(%)
Duflo et al, 2002[22]	44	52	3.9	41	100
Ramirez et al, 2008[26]	9	11	2.99	78	97
Luyt et al, 2008[23]	32	41	2	41	61
Charles et al, 2009[24]	47	23	0.44	65	83
Jung et al, 2010[25]	48	38	0.5	54	39

VAP, ventilator-associated pneumonia.

- Incorporating into a clinical score (e.g. CPIS) did not improve its diagnostic value
- 89.6% receive antibiotics at inclusion and 65% received antibiotics despite PCT < 0.5 ng/mL (PRORATA trial)
- Kinetics might be useful

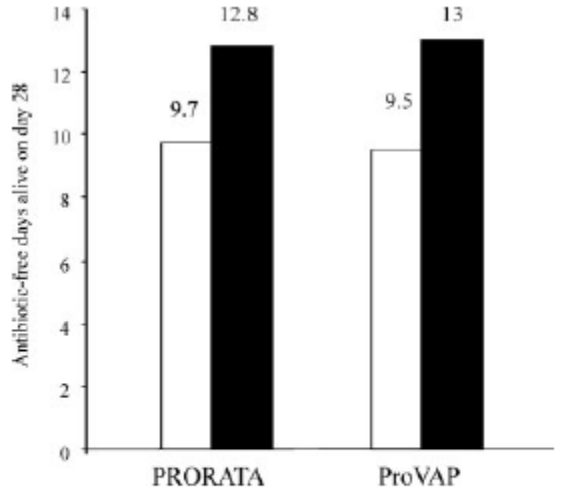


Figure 1 Number of antibiotic-free days alive on day 28 for patients with ventilator-associated pneumonia included in the PRORATA trial[30] or the ProVAP trial,[34] managed according to a procalcitonin algorithm (black bars) or a conventional control strategy (white bars).

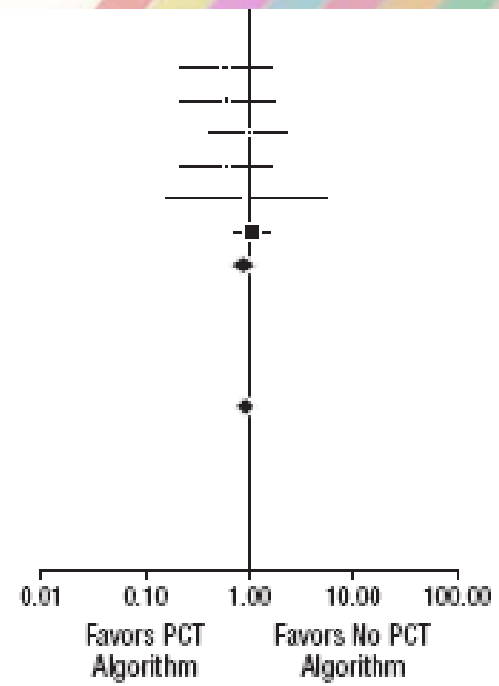
Therapy decision – shorten antibiotics duration

ICU and Inpatient Settings[b]					
Svoboda et al,[27] 2007	ICU, single center	Postop septic shock	Improvement of outcomes after multiple traumas or major surgery?	>2.00, change in use of Abx and catheters; <2.00, ultrasonography and CT, followed by surgery	Primary: ICU LOS, ICU mortality rate, SOFA score, days using ventilator
Nobre et al,[28] 2008	ICU, single center	Sepsis	Reduction of Abx in ICU patients with sepsis?	Discontinue Abx on day 5 when <0.25 or decrease of ≥90% from peak occurs	Primary: duration of Abx Secondary: mortality rate and LOS at day 28
Stolz et al,[29] 2009	European and US ICU, multicenter	VAP	Reduction of Abx in VAP in different ICUs?	<0.25, discontinue Abx; <0.50 or decrease of ≥80%, consider discontinuing Abx; >0.50 or decreased <80%, continue Abx; >1, continue Abx	Primary: Abx-free days alive
Hochreiter et al,[30] 2009	ICU, single center	Postop with infection	Reduction of Abx in postop ICU patients with infection?	Discontinue Abx if clinically improvement observed and <1.00 or if decrease to 25%-35% of initial value for 3 d observed	Primary: Abx use Secondary: LOS
Schroeder et al,[31] 2009	ICU, single center	Postop with severe sepsis	Reduction of Abx duration in severe sepsis in postop ICU patients?	Discontinue Abx if decrease to <1.00 or decrease by 25%-35% for 3 d observed	Primary: Abx use Secondary: LOS, mortality rate
Bouadma et al,[32] 2010	ICU, multicenter	Sepsis	Safety and reduction of Abx in ICU patients with sepsis?	<0.25, SRAA; 0.25-0.50, RAA; >0.50-1.00, RFA; >1.00, SRFA; retest PCT level in 6-12 h if Abx not initiated; discontinue Abx when <0.50 or decrease >80% from peak level observed	Primary: mortality rate at days 28 and 60, Abx use at day 28

Therapy decision – shorten antibiotics duration

				Inpatient and ICU Settings		
Svoboda et al,[27] 2007	Postop septic shock	72	13/34 (38.2) vs 10/38 (26.3)	NA	NA	Trend to decrease in SOFA and ventilator/ICU days
Nobre et al,[28] 2008	Sepsis	79	12/40 (30.0) vs 8/39 (20.5)	Duration (median): 9.5 vs 6.0 d	Duration: –37	Reduction in Abx duration and ICU LOS without adverse events
Stolz et al,[29] 2009	VAP	101	12/50 (24.0) vs 8/51 (15.7)	Abx-free days alive: 9.5 vs 13 Duration (median): 15 vs 10 d	Abx-free days alive: 27 Duration: –33	Decreased Abx use without increasing mortality rate
Hochreiter et al,[30] 2009	Postop patients with infection	110	14/53 (26.4) vs 15/57 (26.3)	Duration (mean): 7.9 vs 5.9 d	Duration: –25	Reduction in Abx duration and ICU LOS without adverse events
Schroeder et al,[31] 2009	Postop severe sepsis	27	3/13 (23.1) vs 3/14 (21.4)	Duration (mean): 8.3 vs 6.6 d	Duration: –20	Shorter Abx duration
Bouadma et al,[32] 2010[b]	Sepsis	621	64/314 (20.4) vs 65/307 (21.2)	Abx-free days alive: 11.6 vs 14.3 Duration (mean): 9.9 vs 6.6 d	Abx-free days alive: 19 Duration: –33	Reduction in Abx use without increase in mortality rate

Intensive care unit trials						
Svoboda et al,[27] 2007	10	38	13	34	5.3	0.58 (0.22-1.56)
Nobre et al,[28] 2008	8	39	12	40	5.1	0.61 (0.22-1.67)
Hochreiter et al,[30] 2009	15	57	14	53	7.2	0.99 (0.43-2.32)
Stolz et al,[29] 2009	8	51	12	50	5.4	0.60 (0.22-1.58)
Schroeder et al,[31] 2009	3	14	3	13	1.6	0.91 (0.15-5.42)
Bouadma et al,[32] 2010	65	307	64	314	34.4	1.05 (0.71-1.55)
Subtotal		**506**		**504**	**59.1**	**0.89 (0.66-1.20)**
Total No. of events	109		118			
Heterogeneity: $\chi^2_5 = 2.67$; $P = .75$; $I^2 = 0\%$						
Test for overall effect: $z = 0.76$; $P = .45$						
Total		**2227**		**2240**	**100.0**	**0.91 (0.73-1.14)**
Total No. of events	172		186			
Heterogeneity: $\chi^2_{11} = 5.22$; $P = .92$; $I^2 = 0\%$						
Test for overall effect: $z = 0.81$; $P = .42$						
Test for subgroup differences: $\chi^2_2 = 1.01$; $P = .60$; $I^2 = 0\%$						



Proposed algorithm for high-acuity infections in ICU settings

C

Evaluation at time of admission				
PCT result	<0.25 µg/L	<0.50 µg/L	≥0.50 µg/L	>1.0 µg/L
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Empirical therapy recommended in all patients with clinical suspicion of infection			
Follow-up/other comments	Consider alternative diagnosis; reassess patients condition and recheck PCT level every 2 days		Reassess patients' condition and recheck PCT level every 2 days to consider cessation of Abx	
Follow-up evaluation every 1 to 2 days				
PCT result	<0.25 µg/L or drop by >90%	<0.50 µg/L or drop by >80%	≥0.50 µg/L	>1.0 µg/L
Recommendation regarding use of Abx	Cessation of Abx strongly encouraged	Cessation of Abx encouraged	Cessation of Abx encouraged discouraged	Cessation of Abx strongly encouraged
Overruling the algorithm	Consider continuation of Abx if patients are clinically unstable			
Follow-up/other comments	Clinical reevaluation as appropriate		Consider treatment to have failed if PCT level does not decrease adequately	

Prognosis

In relation to 90-day mortality among critically ill septic patients

- PCT level 1-5 µg/L correlates with mortality of 11%
- 51-100 µg/L -> 42%

Curr Opin Crit Care 13:578-585

Neutropenic febrile patients

- N=158
- At a PCT cut-off of 1 ng/ml, sensitivity & specificity for bacteremia is 44.2% & 64.3%, respectively

	Category of infection					
	Bacteraemia	Localised bacterial infection	Severe sepsis	Clinically localised infection	Systemic mycosis	Fever of unknown origin
Number of patients	52 (32.1%)	14 (8.8%)	12(7.6%)	20 (12.7%)	5 (3.1%)	55 (34.0%)
Age in years (mean ± SD)	50.4 ± 18.2	53.3 ± 20.5	53.6 ± 15.0	52.3 ± 19.6	50.0 ± 20.9	49.1 ± 19.3
Male:female ratio	22:30	8:6	8:4	9:11	4:1	39:16
Underlying malignancy (number of patients)						
AML	32	5	7	11	2	30
NHL	7	4	2	2	–	11
ALL	11	3	1	4	2	11
Other	2	2	2	3	1	3
Underlying infection						
Primary bacteraemia	31	–	–	–	1	
UTI	1	7	3	–	–	
LRTI	3	3	5	9	3	
Central venous catheter	17	1	1	1	–	
Other	–	3	3	10	1	
Isolated pathogen						
CNS	26	1				
Streptococcus spp.	5	1				
Escherichia coli	6	7				
Pseudomonas aeruginosa	3	–				
Klebsiella pneumoniae	2	2				
Aspergillus spp.	–	–			4	
Other	10	1	3		1	

AML, acute myelogenous leukaemia; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia; LRTI, lower respiratory tract infection; UTI, urinary tract infection; CNS, coagulase-negative staphylococci.

Advent of fever	Mean (+/- SE) PCT level (ng/ml)
1st	1.17+/- 0.44
2nd	0.42 +/- 0.19
3rd	0.86 +/- 0.36
4th	0.39 +/- 0.18

Clinical Microbiology and Infection, Volume 10 Number 7, July 2004

Table 2. Daily follow-up of procalcitonin (PCT) levels of patients enrolled in the study, correlated with the category of infection

	Mean (± SE) PCT level (ng/mL)				
	Bacteraemia	Localised bacterial infection	Severe sepsis	Clinically localised infection	Fever of unknown origin
Afebrile neutropenia	0.85 ± 0.37	0.36 ± 0.10	0.47 ± 0.12	0.24 ± 0.02	0.59 ± 0.17
Advent of fever					
1st day	2.98 ± 1.03[a,b]	0.98 ± 0.24[c]	14.54 ± 5.05[d,e]	0.87 ± 0.23[g]	1.11 ± 0.27
2nd day	2.33 ± 0.54[a,b]	0.74 ± 0.17[c]	14.48 ± 6.08[d,f]	1.99 ± 1.59[g]	0.91 ± 0.32
3rd day	1.57 ± 0.37[a,b]	0.81 ± 0.34[c]	12.76 ± 6.15[d,f]	1.02 ± 0.31[g]	1.14 ± 0.49
4th day	1.04 ± 0.26[a,b]	0.53 ± 0.17[c]	8.91 ± 2.31[d,f]	0.47 ± 0.15[g]	1.17 ± 0.52
Afebrile	1.30 ± 0.37	0.39 ± 0.20	8.67 ± 5.65	0.53 ± 0.15	0.72 ± 0.16

[a]p NS (non-significant) when comparing the PCT levels of patients with bacteraemia to those of patients with fever of unknown origin (FUO).
[b]p NS when comparing the PCT levels of patients with bacteraemia to those of patients with localised bacterial infections.
[c]p NS when comparing the PCT levels of patients with localised bacterial infections to those of patients with FUO.
[d]p < 0.0001 when comparing the PCT levels of patients with severe sepsis to those of patients with localised infection.
[e]p 0.001 or [f]p < 0.0001 when comparing the PCT levels of patients with severe sepsis to those of patients with FUO.
[g]p NS when comparing the PCT levels of patients with clinically localised infections to those of patients with FUO.

Table 3. Daily follow-up of C-reactive protein (CRP) levels of patients enrolled in the study, correlated with the category of infection

	Mean (± SE) CRP level (mg/L)				
	Bacteraemia	Localised bacterial infection	Severe sepsis	Clinically localised infection	Fever of unknown origin
Afebrile neutropenia	54.8 ± 20.9	50.6 ± 39.9	96.3 ± 26.9	24.0 ± 23.2	29.6 ± 8.2
Advent of fever					
1st day	89.7 ± 19.2[a,b]	94.9 ± 52.0[c]	228.6 ± 28.5[d,f]	51.1 ± 21.4[i]	82.5 ± 17.9
2nd day	123.9 ± 12.4[a,b]	90.6 ± 35.2[c]	214.2 ± 28.0[e,g]	129.0 ± 7.0[i]	76.1 ± 15.6
3rd day	123.8 ± 13.1[a,b]	90.1 ± 34.5[c]	205.0 ± 51.6[e,h]	102.0 ± 9.3[i]	87.3 ± 16.9
4th day	118.5 ± 26.5[a,b]	166.3 ± 69.9[c]	74.0 ± 4.0[g,h]	98.0 ± 15.0[i]	82.5 ± 20.0
Afebrile	77.7 ± 16.9	122.6 ± 33.9	86.7 ± 50.6	146.8 ± 53.2	53.2 ± 11.6

[a]p NS (non-significant) when comparing the CRP levels of patients with bacteraemia to those of patients with fever of unknown origin (FUO).
[b]p NS when comparing the CRP levels of patients with bacteraemia to those of patients with localised bacterial infections.
[c]p NS when comparing the CRP levels of patients with localised bacterial infections to those of patients with FUO.
[d]p 0.005 or [e]NS when comparing the CRP levels of patients with severe sepsis to those of patients with localised infection.
[f]p 0.039, [g]0.001 or [h]NS when comparing the CRP levels of patients with severe sepsis to those of patients with FUO.
[i]p NS when comparing the CRP levels of patients with clinically localised bacterial to those of patients with FUO.

Survived 9.79 +/- 1.29 ng/mL
Died 20.45 +/- 4.48ng/mL
(p<0.0001)

Bacteremia

Table 2
Diagnostic values in diagnosing bacteremia.

EngelAuthor	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Engel et al. [26]	PCT: 0.5 (ng/ml)	73	86	73	86
Giamarellos-Bourboulis et al. [40]	PCT: 1.0 (ng/ml)	78.6	63.6	84.6	–
Hambach et al. [27]	PCT: 1 (ng/ml)	70	61	54	76
	CRP: > 100 (mg/l)	83	61	58	85
von Lilienfeld-Toal et al. [41]	PCT: 0.62 (ng/ml)	72	77	62	84
	IL-6: 297 (pg/ml)	72	62	50	70
Persson et al. [35]	PCT: 1.3 (ng/ml)	79	87	63	94
	CRP: 143 (mg/l)	58	82	48	88
	IL-6: 71 (pg/ml)	68	72	41	89
Giamarellou et al. [30]	PCT: 1.0 (ng/ml)	44.2	64.3	82.1	18.8
	CRP: > 3.2 (mg/l)	34.6	21.4	62.1	8.3
Ruokonen et al. [31]	PCT: 0.5 (ng/ml)	54.5	88.2	–	–
Kitanovski et al. [42]	PCT > 1.04 (ng/ml)	87.5	80.8	58.3	95.5
	CRP > 124 (mg/l)	75	86.3	63.2	91.7
	IL-6 > 85.5 (pg/ml)	93.6	68.6	48.4	97.2
Secmeer et al. [44]	PCT: 0.4 (ng/ml)	33.3	92	50	92
	CRP: 50 (mg/l)	66.7	46.6	12	92

PCT: procalcitonin; CRP: C-reactive protein; IL-6: interleukin-6; PPV: positive predictive value; NPV: negative predictive value

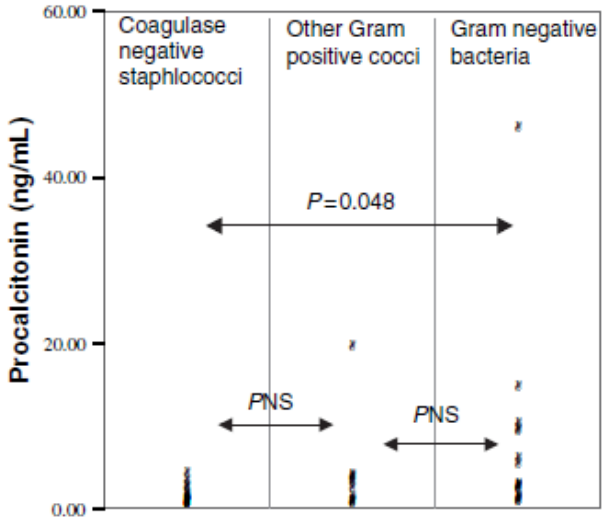


Fig. 1. Distribution of concentrations of procalcitonin at the time of fever manifestation among patients with bacteraemia caused by coagulase-negative staphylococci, other Gram-positive cocci and Gram-negative bacteria.

- Single vs serial measurements
- Type of organisms

Fungal infections

- Normal PCT levels at the onset with subsequent increases in patients with an unfavorable course

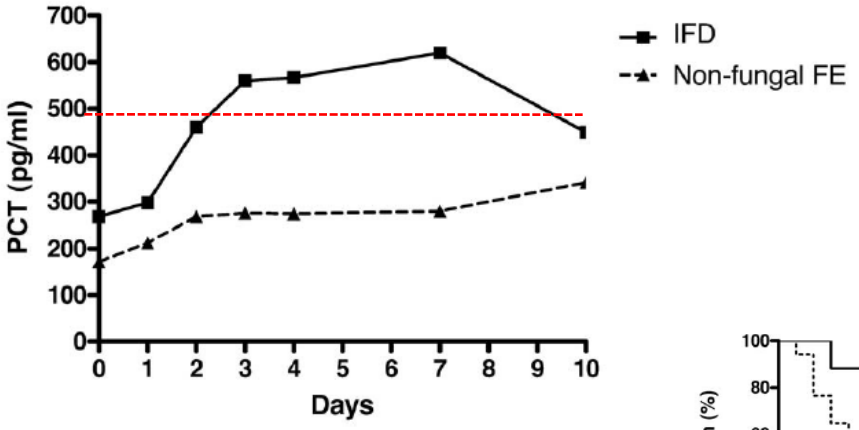


Figure 4. PCT kinetics in persistent neutropenic fever during more th
point are shown.

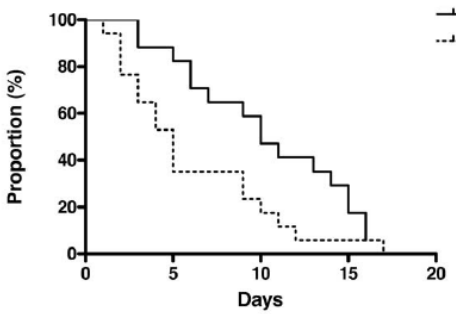


Figure 5. Percent of patients with PCT >500 pg/ml and fever (temperature >38°C) in follow-up of IFD. The T0 for PCT and fever is set on the time point at which the first positive PCT value (>500 pg/ml) has been documented.

PCT in neutropenia

- 0.5 – 1 ng/ml : local or uncomplicated systemic infections
- 1-2 ng/ml bacteremia or severe fungal infection
- >2 ng/ml severe sepsis and septic shock
- During early phase of fever (1st 24 h) normal values may be reported
- Coagulase negative Staphylococci bacteremia may cause no increase in PCT
- Sensitivity at most 88% for bacteremic infection

Infection 36 2008 No 5

PCT in autoimmune patients?

- Not enough data
- Conflicting results in the literature
- No correlation between PCT & disease activity;
- NSAIDs/steroid had no impact on PCT levels
- Different cut-off relating to different diseases entities?

Table 1 Differential diagnosis of non-infectious febrile diseases and relative values of CRP and PCT during steady state, exacerbation of underlying disease and bacterial infection (no change from baseline indicated by "–", relative elevation from baseline indicated by "↑" or "↑↑", insufficient data indicated by "⁇")

	Steady state		Exacerbation		Bact. infection	
	CRP	PCT	CRP	PCT	CRP	PCT
Auto-immune/systemic						
• RA	–	–	↑	–	↑↑	↑↑
• SLE	–	–	–/↑	–	↑↑	↑↑
• Arteriitis temporalis	↑/↑↑	–	n/a	n/a	n/a	n/a
• Vasculitis other	–/↑	–	–/↑↑	–	↑/↑↑	↑/↑↑
• Sarcoidosis	–/↑	⁇	–/↑	⁇	↑/↑↑	⁇
• Behcet's	–	–	↑	–	↑/↑↑	↑/↑↑
Auto-inflammatory						
• FMF	–	–	↑↑	–/↑	↑/↑↑	↑/↑↑
• TRAPS/HIDS	–	⁇	↑↑	⁇	⁇	⁇
• Still's disease	–	–	↑↑	↑↑	↑/↑↑	↑/↑↑
IBD						
• Crohn's disease	–	–	↑/↑↑	–	↑/↑↑	↑/↑↑
• Colitis ulcerosa	–	–	↑/↑↑	–	↑/↑↑	↑/↑↑
Malignancy	–/↑↑	–	n/a	n/a	–/↑↑	↑/↑↑
Tissue loss/ischemia	⁇	⁇	⁇	⁇	⁇	⁇
Endocrine	⁇	⁇	⁇	⁇	⁇	⁇

Journal of Infection (2010) 60, 409–416

Adult-onset Still's disease ->
elevated TNF α, higher cutoff 1.4 ng/ml

Neonates

- Physiological postnatal increase of serum PCT in healthy term & preterm neonates, with peak values at 24 h of age
- Meta-analysis 16 studies (1959 neonates) pooled sensitivity 81% specificity 79% for neonatal sepsis

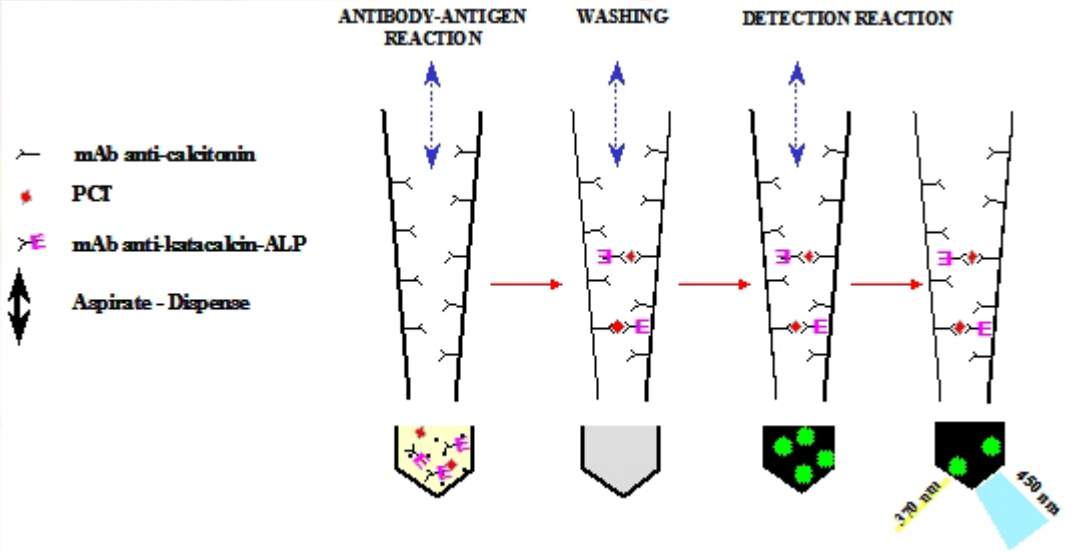
Table 3

PCT reference ranges for neonates of 0 – 48 hours of age (including 95% of all measurements)

Age in hours	PCT [µg/L]
0-6	2
6-12	8
12-18	15
18-30	21
30-36	15
36-42	8
42-48	2

Local experience

- Enzyme linked fluorescent immunoassay (ELFA)



- The reaction occurs within the interior of the solid phase receptade (SPR) whereby anti-calcitonin antibodies and conjugate form a sandwich.
- 4-MUP is cycled into SPR and conjugate enzyme catalyses the hydrolysis of the substrate into 4-Methyl-umbelliferone which is measured at 450nm.
- 20 minute incubation time
- Measurement range 0.09 – 200 µg/L
- $200-300 per test
- Review period (4/8/2010 – 26/5/2011) N=260

Conclusion

- PCT not sensitive enough to rule out bacterial infection in all setting
- Reassessment in cases in which antibiotics are withheld to ensure the clinical condition improves spontaneously
- Kinetics maybe more helpful to shorten antibiotics duration
- Supplement but not supplant clinical impressions
- Need to consider the cost-effectiveness

The End.

Questions?