McLeod Health

Procalcitonin or No Calcitonin in the Guidance of Antimicrobial Therapy

A presentation for HealthTrust Members
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Abbreviations

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APACHE II- The Acute Physiology and Chronic Health Evaluation
CAP- community acquired pneumonia
CRP- C reactive protein
DNR- do not resuscitate
ESR- erythrocyte sedimentation rate
HAP- hospital acquired pneumonia
ICU- intensive care unit
IL- interleukin
INF- interferon
IV- intravenous
LRTI- lower respiratory tract infection
MICU- medical ICU
mL- milliliters
ng- nanograms
PCT- procalcitonin
RBC- red blood cell
RCT- randomized controlled trial
SAPS II- Simplified Acute Physiology Score
SIRS- Systemic inflammatory response syndrome
SOC- standard of care
SOFA- Sequential Organ Failure Assessment
TNF- tumor necrosis factor
UK- United Kingdom
VAP- ventilator associated pneumonia

Learning Objectives

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- Recall the advantages of procalcitonin as a diagnostic biomarker in bacterial infections
- Recognize how procalcitonin levels can be used as negative predictive values
- Identify clinical situations in which procalcitonin could be falsely elevated in bacterial infections

What is Procalcitonin

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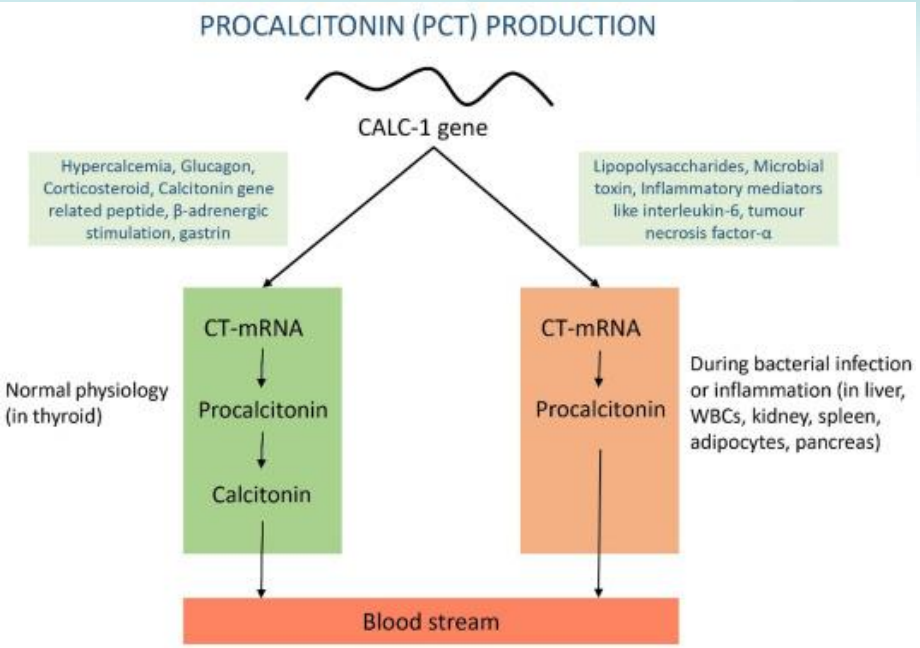
- Peptide precursor of the hormone calcitonin
- Levels
  - Under normal physiologic conditions concentrations are undetectable
  - Systemic inflammation → production of PCT activated in cell types that are unable to process PCT into calcitonin → accumulation of PCT



Sources: Allison B Chambliss, et al. *The Journal of Applied Laboratory Medicine*. 2023;8(3):598–634.
What is Procalcitonin (PCT)? - Creative Diagnostics

Pathophysiology

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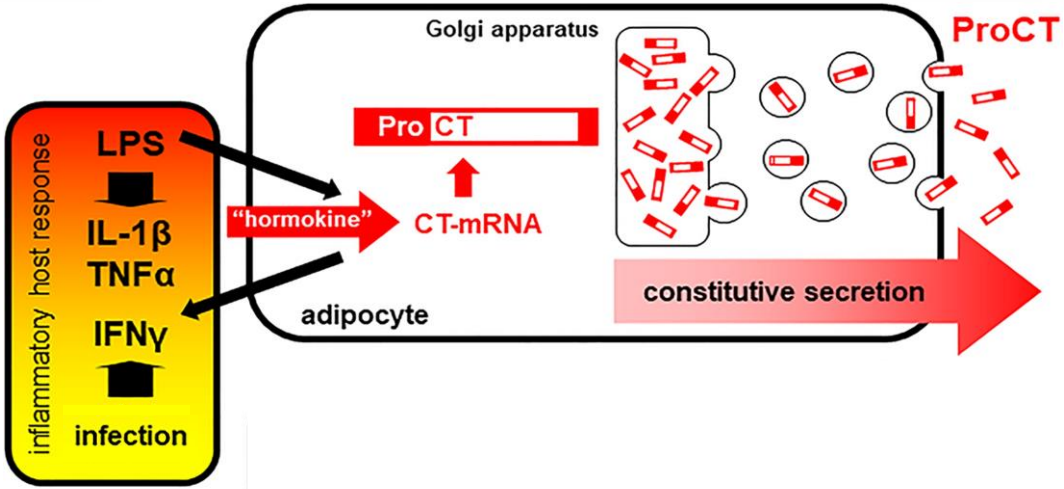
Bacterial infection → cytokine mediated: IL-1β, TNF-α, and IL-6 → activate PCT production



Sources: Allison B Chambliss, et al. *The Journal of Applied Laboratory Medicine*. 2023;8(3):598–634.
Lee H. *Korean J Intern Med.* 2013;28(3):285-291.
J Appl Lab Med, Volume 8, Issue 3, May 2023, Pages 598–634

Pathophysiology

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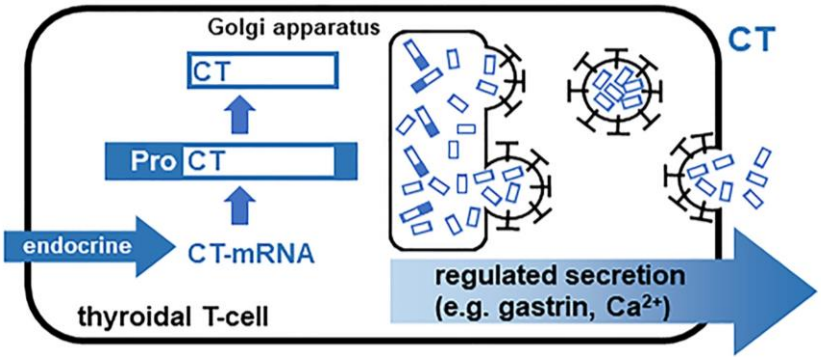
Viral infection → INF-γ secreted → counter regulates PCT expression



Sources: Allison B Chambliss, et al. *The Journal of Applied Laboratory Medicine*. 2023;8(3):598–634.
Lee H. *Korean J Intern Med.* 2013;28(3):285-291.
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Procalcitonin Levels

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- PCT increases within hours of the inflammatory insult
  - Peaks at ~ 12 hours
  - Half-life of ~ 24 hours
- Normal: ≤ 0.25 µg/L
- Possible infection: > 0.25 µg/L
- The extent of the initial and peak PCT level correlates with disease severity
- Decreasing concentrations indicate disease resolution
- PCT is a small protein eliminated primarily by the kidneys

Source: Allison B Chambliss, et al. *The Journal of Applied Laboratory Medicine*. 2023;8(3):598–634.

Other Biomarkers: CRP

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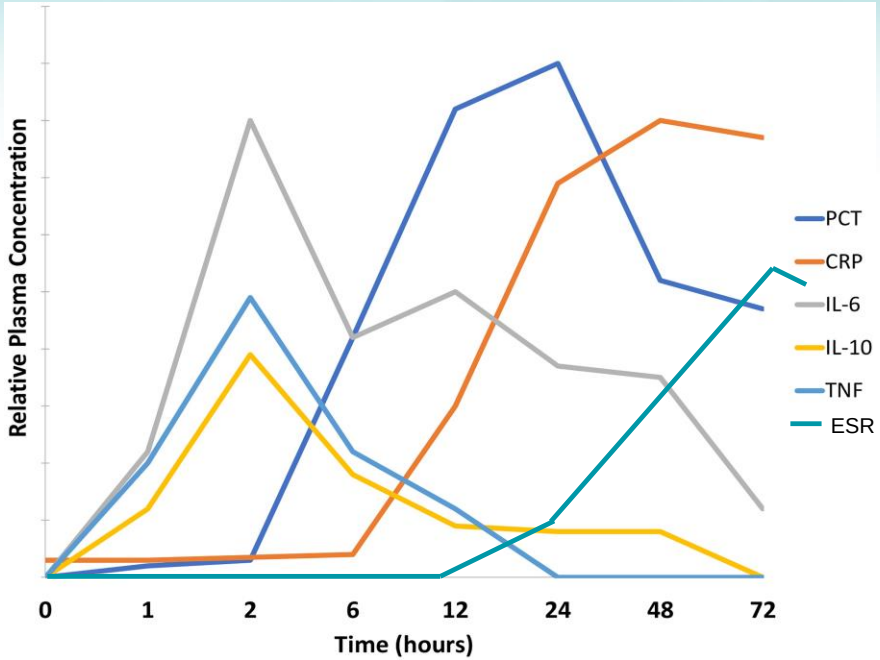
CRP is an acute phase reactant produced by the liver

- Upregulated in response to inflammation
- Longer half-life than PCT
  - Antibiotic monitoring is limited
- Less expensive than PCT
- Nonspecific for bacterial infection
- Typically used to identify inflammation



Sources: Allison B Chambliss, et al. *The Journal of Applied Laboratory Medicine*. 2023;8(3):598–634.
J Appl Lab Med, Volume 8, Issue 3, May 2023, Pages 598–634

Other Biomarkers: IL-6

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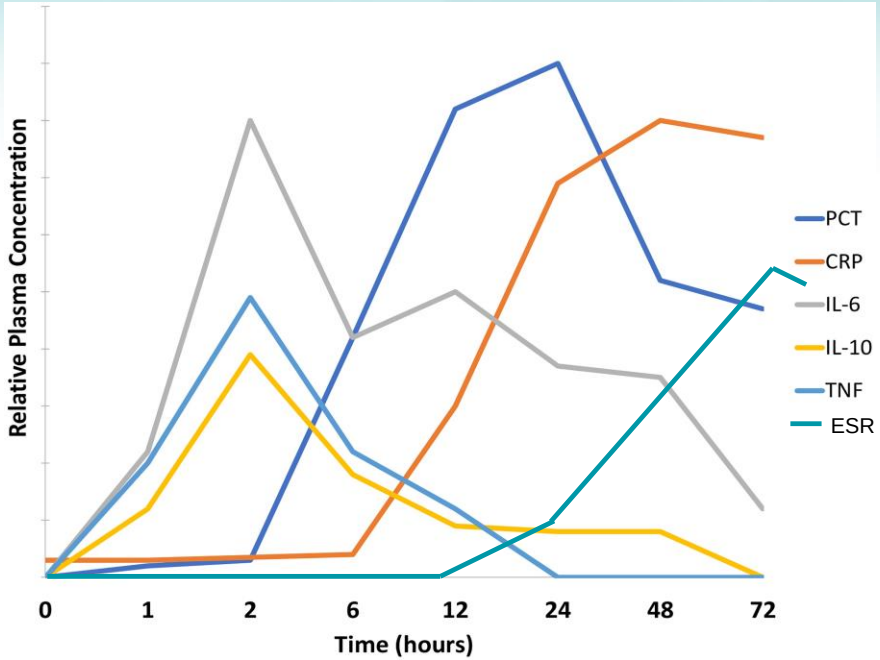
IL-6 is a proinflammatory cytokine

- Upregulated in response to inflammation
- Short half-life
- Correlates with the extent of the tissue damage
- Nonspecific to infection
- Typically used to assess severity of acute inflammation



Sources: Weidhase L, *et al*. *BMC Infect Dis*. 2019;19(1):150.
J Appl Lab Med, Volume 8, Issue 3, May 2023, Pages 598–634

Other Biomarkers: IL-10

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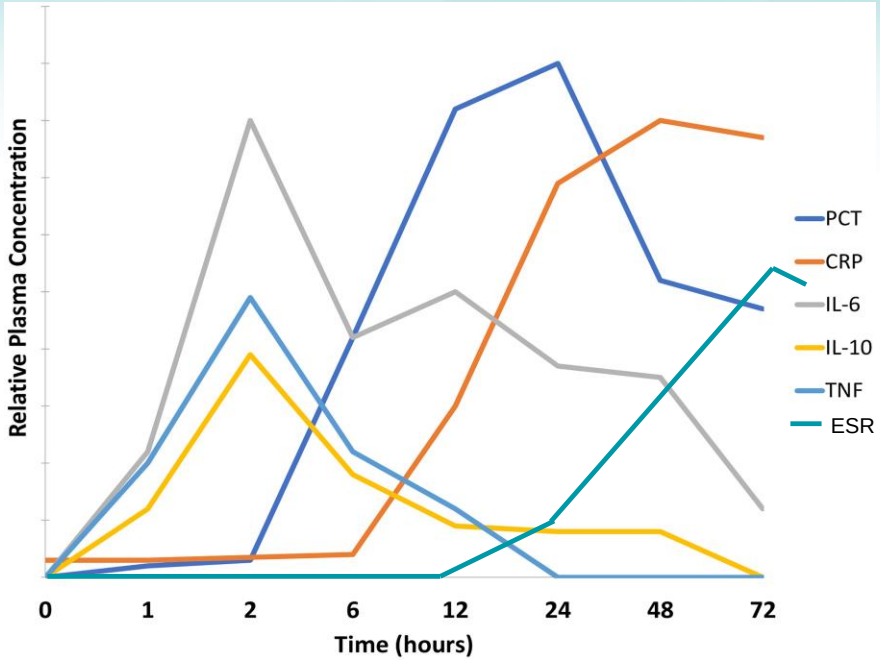
IL-10 is an anti-inflammatory cytokine

- Upregulated in response to inflammation
- Blocks the production of cytokines by immune cells to reduce inflammation
- Less specific for infectious causes
  - Rising in autoimmune disease
- Typically used for immune regulation and chronic inflammatory conditions



Sources: Moore KW, et al. Annu Rev Immunol. 2001;19:683-765.
J Appl Lab Med, Volume 8, Issue 3, May 2023, Pages 598–634

Other Biomarkers: TNF-α

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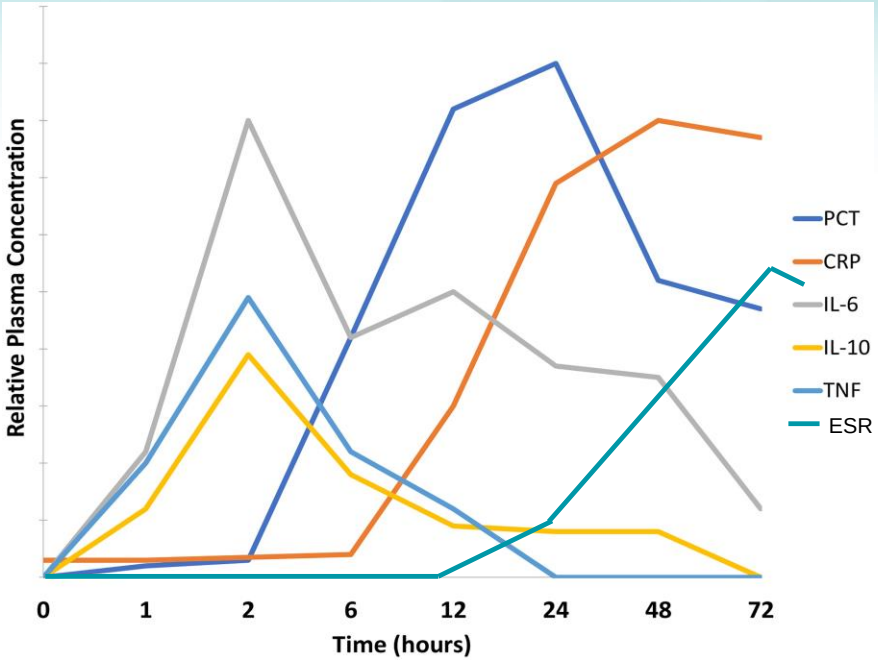
TNF-α is a cytokine that initiates the cytokine cascade

- Upregulated in response to inflammation
- Shorter half-life than PCT
- Nonspecific for bacterial infection
- Typically used to identify immune regulatory response and active inflammation



Sources: Liu C, *et al. Oncol Lett*. 2014;8(6):2747-2751.
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Other Biomarkers: ESR

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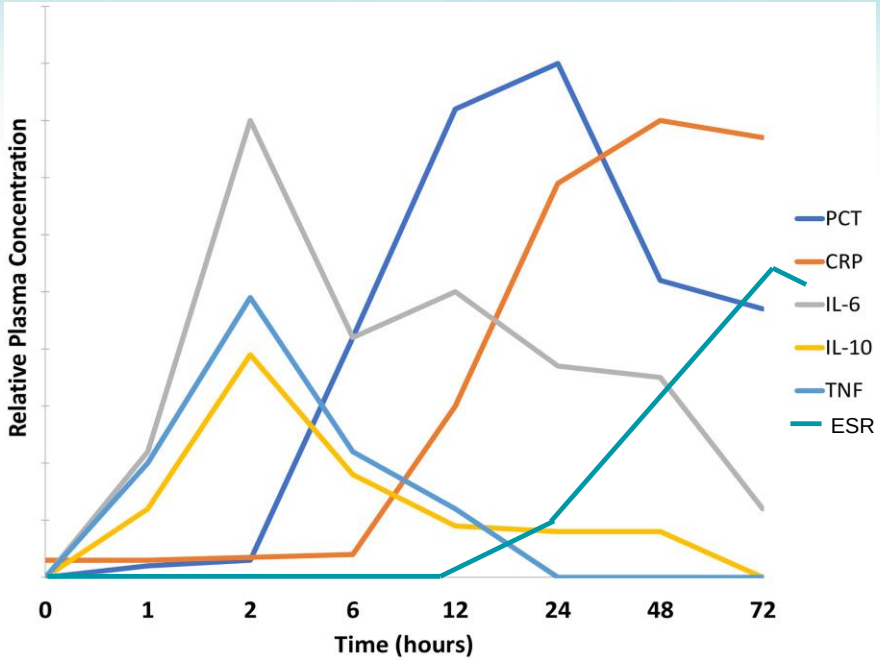
ESR is an indirect measure of acute phase reactants

- The rate at which RBCs settle in a tube, affected by the constituents of the patient's serum
- The main acute phase reactant is fibrinogen, but concentrations of others contribute
- Nonspecific to bacterial infections
- Typically used in acute or chronic inflammation



Source: Gauger J. *Emergency Medicine Tamed*. https://www.tamingthesru.com/blog/2016/10/2/esr-crp-procalcitonin-acute-inflammatory-markers-in-the-ed.

Biomarker Summary

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Biomarker	Use	Specific Indications	Comparison to PCT
CRP	Identify inflammation	Sepsis, pneumonia, UTI, arthritis, lupus, inflammatory bowel disease, post operative infection	Longer half life
IL-6	Severity of acute inflammation	Sepsis, pneumonia, meningitis, bacteremia, arthritis, lupus, trauma, or surgery	Shorter half life
IL-10	Immune regulation and chronic inflammatory conditions	HIV, hepatitis, arthritis, lupus, inflammatory bowel disease, ulcerative colitis, or Crohn's	Shorter half life
TNF-α	Immune regulatory response and active inflammation	Sepsis, systemic bacterial infections, tuberculosis, and bacterial pneumonia, HIV, hepatitis, arthritis, lupus, Crohn's, psoriasis, cancer	Shorter half life
ESR	Acute or chronic inflammation	Osteomyelitis, tuberculosis, endocarditis, hepatitis, mononucleosis, chronic infections, or autoimmune disorders	Longer half life

Nonbacterial Causes of Elevated Procalcitonin

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- Stress response
- Cardiogenic shock
- Compromised renal function
- Neonates after birth
- Malaria and some fungal infections
- Acute graft-versus-host disease
- Immunotherapy
- Autoimmune diseases
- Vasculitis and paraneoplastic disease

Sources: Allison B Chambliss, et al. *The Journal of Applied Laboratory Medicine*. 2023;8(3):598–634.
Lee H. *Korean J Intern Med.* 2013;28(3):285-291.

Guidelines for Procalcitonin Use

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Disease State	Recommendation	Guidelines
Sepsis	Antibiotic de-escalation Bacterial vs viral cause	2021 Surviving Sepsis Campaign Guidelines 2022 Guidelines for the Use of Procalcitonin for Rational Use of Antibiotics
CAP, HAP, and VAP	Antibiotic de-escalation Bacterial vs viral cause	2019 Guidelines for Diagnosis and Management of Community and Hospital Acquired Pneumonia 2015 Guidelines for Management of Community Acquired Pneumonia 2016 Management of Adults With Hospital Acquired and Ventilator Associated Pneumonia
Neutropenic Infections	Bacterial vs viral cause	2018 Guidelines for the Management of Sepsis in Neutropenic Cancer Patients
Rhinosinusitis	Bacterial vs viral cause	2018 Guideline for Rhinosinusitis
COPD	Need for antibiotics	2018 Guideline for the Diagnosis and Treatment of COPD Patients

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PRO-calcitonin Evidence

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Use of Procalcitonin to Reduce Patients' Exposure to Antibiotics in Intensive Care Units (PRORATA trial)

Bouadma L, Luyt C-E, Tubach F, Cracco C, Alvarez A, Schwebel C, *et al.* *Lancet Lond Engl.* 2010;375: 463-74.

PRORATA Study Design

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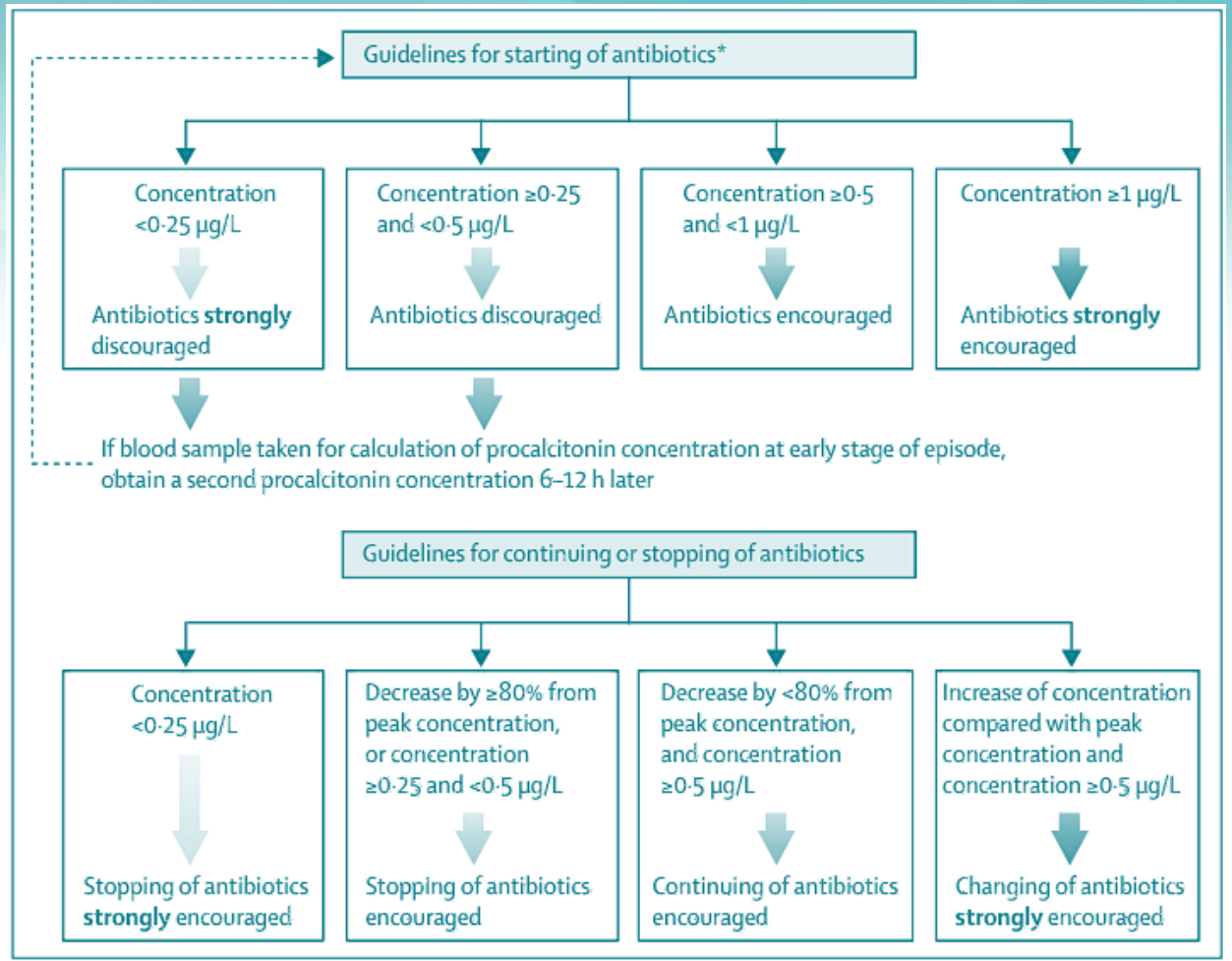
- Multicenter, prospective, parallel-group, open-label trial
- France
- June 2007 to May 2008
- Randomized into 2 groups in 1:1

Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Methods



Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Inclusion Criteria

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Inclusion Criteria	• Suspected bacterial infections • > 18 years old • Patients who developed sepsis during their stay in the ICU
Exclusion criteria	• Received antibiotics prior to admission • ICU < 3 days • Bone-marrow transplant or chemotherapy induced neutropenia • Long-term antibiotic treatment • SAPS II score > 65 points at screening • DNR orders

Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Outcomes

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Primary endpoints:

- Death from any cause by days 28 and 60
- Number of days without antibiotics at 28 days

Secondary outcome measures:

- Percentage of patients with relapse or superinfection
- Number of days without mechanical ventilation
- Length of stay in the ICU and hospital

Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Baseline Characteristics

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	PCT Group (n= 307)	SOC Group (n=314)
Age: mean (SD)	61 (15.2)	62.1 (15.0)
SOFA Score: mean (SD)	7.5 (4.4)	7.2 (4.4)
Pulmonary Infection: n (%)	183 (71%)	211 (74%)
Mechanical Ventilation: n (%)	211 (69%)	208 (66%)
Septic Shock: n (%)	138 (45%)	129 (41%)
Positive Blood Cultures: n (%)	55 (18%)	53 (17%)

Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Results

McLeod Health

	PCT Group (n= 307)	SOC Group (n=314)	P Value
28 day mortality: n (%)	65 (21.2%)	64 (20.4%)	-
60 day mortality: n (%)	92 (30%)	82 (26.1%)	-
Number of days without antibiotics: mean (SD)	14.3 (9.1)	11.6 (8.2)	<0.0001
Number of days without mechanical ventilation: mean (SD)	16.2 (11.1)	16.9 (10.9)	0.47
Length of stay in ICU: mean (SD)	15.9 (16.1)	14.4 (14.1)	0.23
Length of stay in hospital: mean (SD)	26.1 (19.3)	26.4 (18.3)	0.87
Days of antibiotic exposure per 1000 days	653	812	<0.0001

Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Results

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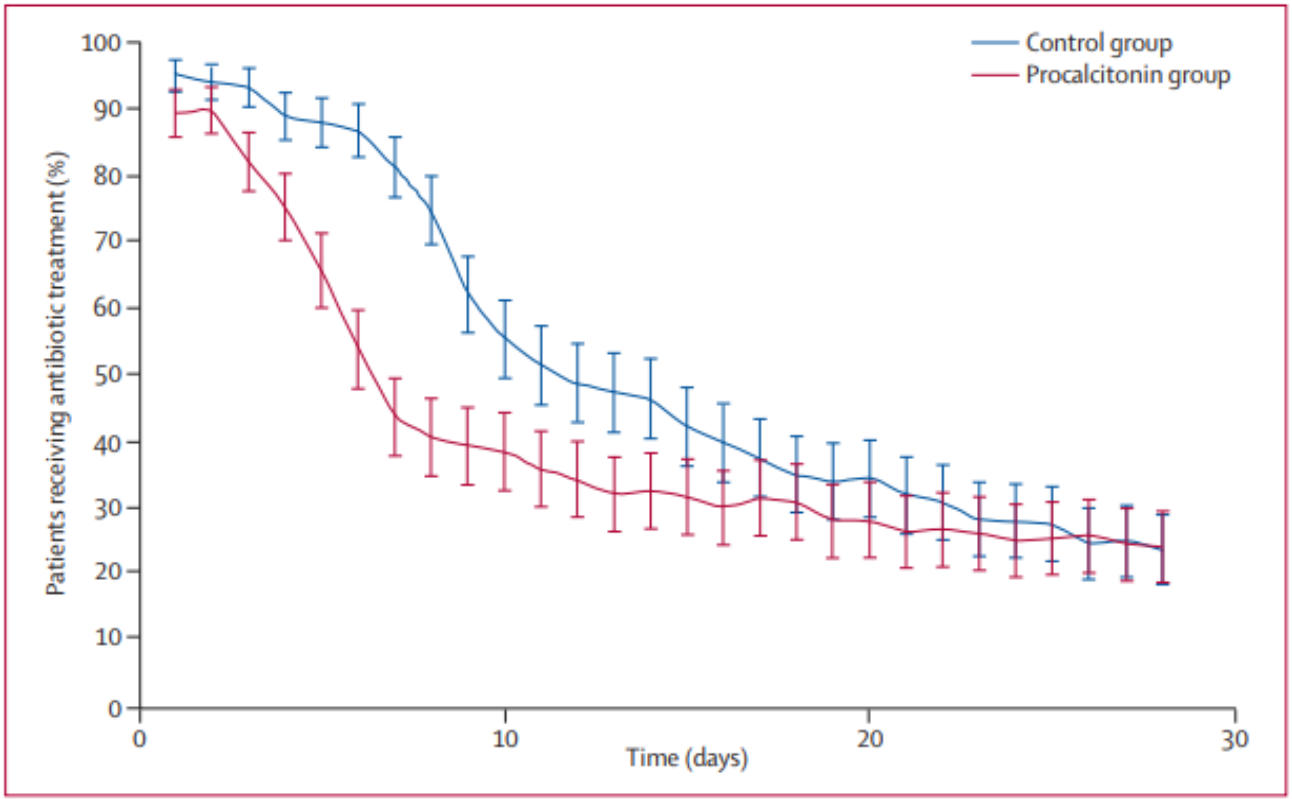
Absolute difference in the % of patients receiving antibiotics:

- Day 1: 5.6%
- Day 5: 22.2%
- Day 7: 37.6%
- Day 15: 10.5%
- Day 20: 6.2%



Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Results

McLeod Health

Duration of First Episode Antibiotic Treatment	PCT Group (n= 307)	SOC Group (n=314)	P Value
Overall population	307 (100%); 6.1 (6.0)	314 (100%); 9.9 (7.1)	<0.0001
Community acquired pneumonia	79 (26%); 5.5 (4.0)	101 (32%); 10.5 (6.4)	<0.0001
Ventilator associated pneumonia	75 (24%); 7.3 (5.3)	66 (21%); 9.4 (5.7)	0.0210
Urinary tract infection	24 (8%); 7.4 (6.3)	18 (6%); 14.5 (9.3)	0.0053
Infection with positive blood cultures	55 (18%); 9.8 (7.7)	53 (17%); 12.8 (8.1)	0.06

number of patients (%); days (SD)

Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

PRORATA Take Away

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Author's Conclusions

- In septic ICU patients a PCT guided treatment algorithm is beneficial for discontinuation strategies

Evaluation

- Specific benefit seen in pneumonia groups
- Most reduction seen at around 5-7 days
- Study design and size
- Open label design
- Final decision was at physician digression
- Limited surgical population

Source: Bouadma L, *et al. Lancet Lond Engl*. 2010;375: 463-74.

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Efficacy and Safety of Procalcitonin Guidance in Reducing the Duration of Antibiotic Treatment in Critically Ill Patients

de Jong E, van Oers JA, Beishuizen A, *et al. Lancet Infect Dis.* 2016;16(7):819-827

de Jong Study Design and Methods

McLeod Health

The Stop Antibiotics on Procalcitonin Guidance Study (SAPS)

Prospective, multicenter, randomized, controlled, open-label intervention trial

15 hospitals in the Netherlands

Sept 18, 2009 through July 1, 2013

Source: de Jong E*, et al. Lancet Infect Dis*. 2016;16(7):819-827

de Jong Methods

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Daily lab draws

SOC group

PCT group

Followed guideline recommendations

Continue antibiotics: PCT > 0.5 µg/L or decreased by < 80% of peak value

Discontinue antibiotics: PCT decreased by > 80% of its peak value or to < 0.5 µg/L

Source: de Jong E*, et al. Lancet Infect Dis*. 2016;16(7):819-827

de Jong Inclusion Criteria

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Inclusion Criteria	• Critically ill patients • 18 years or older • Admitted to the ICU • Received their first dose of antibiotics < 24 h before inclusion
Exclusion Criteria	• Prophylactic antibiotics • Prolonged antibiotic therapy • Severe immunosuppression • Severe infections • Moribund patients

Source: de Jong E, *et al. Lancet Infect Dis*. 2016;16(7):819-827

de Jong Outcomes

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Primary outcome:

- Antibiotic consumption
  - Daily defined doses
  - Duration of treatment
  - Antibiotic free days

Safety endpoint:

- Mortality at 28 days and 1 year

Secondary outcomes:

- Percentage of patients who had a recurrent infection
- Length of stay in hospital and ICU

Source: de Jong E*, et al. Lancet Infect Dis*. 2016;16(7):819-827

de Jong Baseline Characteristics

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	PCT Group (n= 761)	SOC Group (n=785)
Age: mean	65	65
SOFA Score: mean	6.0	6.0
Pulmonary Infection: n (%)	491 (65%)	503 (64%)
Mechanical Ventilation: n (%)	617 (81%)	628 (80%)
Septic Shock: n (%)	138 (45%)	129 (41%)
CRP Level (mg/L): mean	202	204
PCT Level (µg/L): mean	1.9	-

Source: de Jong E*, et al. Lancet Infect Dis*. 2016;16(7):819-827

de Jong Results

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	PCT Group (n= 307)	SOC Group (n=314)	P Value
Antibiotic Consumption: mean (SD) Duration of treatment Antibiotic free days at 28 days	 5.0 (3.0-9.0) 7.0 (0-14.5)	 7.0 (4.0-11.0) 5.0 (0-13.0)	 <0.0001 0.0016
28 day mortality: n (%)	149 (19.6%)	196 (25.0%)	0.0122
Reinfection: mean (SD)	38 (5.0)	23 (2.9)	0.0492
Length of stay in ICU: mean (SD)	8.5 (5.0-17.0)	9 (4.0-17.0)	0.56
Length of stay in hospital: mean (SD)	22.0 (13.0-39.3)	22.0 (12.0-40.0)	0.77

Source: de Jong E, *et al. Lancet Infect Dis*. 2016;16(7):819-827

de Jong Results

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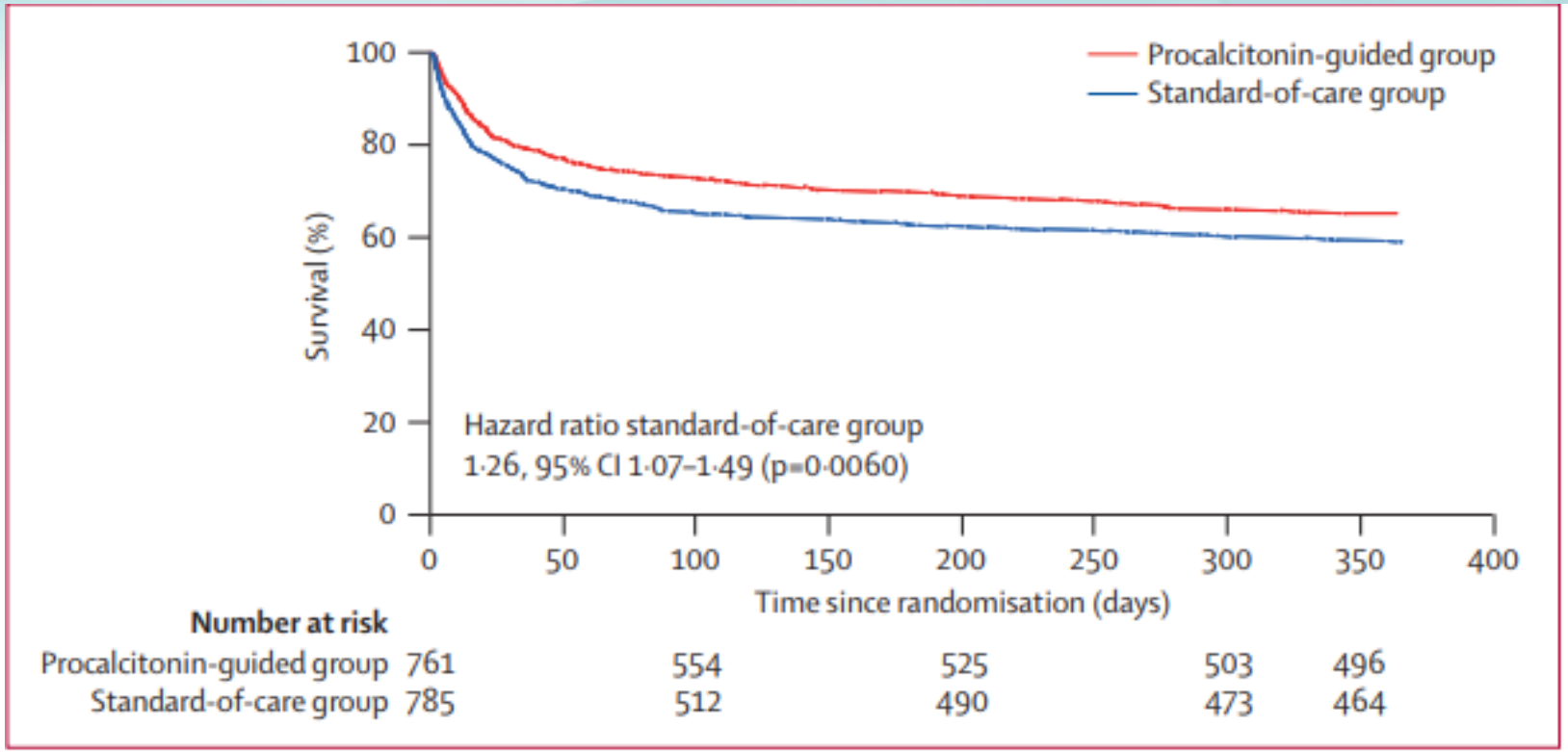

Source: de Jong E*, et al. Lancet Infect Dis*. 2016;16(7):819-827

de Jong Take Away

McLeod Health

Author's Conclusions

- In ICU patients a PCT level of < 0.5 µg/L or level decreased by > 80% of its peak value can be used to facilitate discontinuation of antibiotics

Evaluation

- Mortality decreased
- Study design and size
- Levels around 5-6 days after initiation of antibiotics
- Open label, potential for bias
- Adherence

Source: de Jong E*, et al. Lancet Infect Dis*. 2016;16(7):819-827

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Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: The ADAPT-Sepsis Randomized Clinical Trial

Dark P, Hossain A, McAuley DF, *et al*. *JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Study Design and Methods

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Multicenter, prospective, blinded, noninferiority, randomized control trial

- Mortality noninferiority margin of 5.4%

January 1, 2018 to June 5, 2024

41 UK National Health Service ICUs

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Methods

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Strongly suggests stopping antibiotics:		Suggests stopping antibiotics:		Support usual care
PCT< 0.25 µg/L	CRP < 25 mg/L	PCT fall > 80% from baseline or < 0.5 µg/L	CRP fall 50% from baseline	Anything other than values listed above

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Criteria

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Inclusion

- 18 years or older
- Admitted to critical care of ICU
- IV antibiotics initiated within 24 hours and to be continued for 72+ hours

Exclusion

- Prolonged antibiotics
- Severely immunocompromised

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Outcomes

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Primary outcome:

- Total duration of antibiotic
- All cause mortality at 28 days

Secondary outcomes:

- Antibiotic duration for initial sepsis period
- Unscheduled escalation care or readmission
- Infection relapse or recurrence
- Critical care unit length of stay
- Hospital length of stay
- All cause mortality at 90 days

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Baseline Characteristics

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	PCT Group (n= 918)	SOC Group (n=918)
Age: mean	60.6	59.8
SOFA Score: mean	7.0	7.0
APACHE II: mean	17.5	17.2
Pulmonary Infection: n (%)	437 (48.3%)	451 (49.1%)
Intra-abdominal Infection: n (%)	230 (25.5%)	198 (21.8%)
Urinary Tract Infection: n (%)	124 (13.7%)	118 (21.8%)
Sepsis: n (%)	465 (50.8%)	466 (50.9%)
Septic Shock: n (%)	450 (49.2%)	450 (49.1%)

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Results

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	PCT Group (n= 918)	SOC Group (n=918)	P Value
Total antibiotic duration to 28 days: mean (SD) Intention to treat Per protocol	 9.8 (7.2) 9.8 (7.2)	 10.7 (7.6) 10.7 (7.6)	 0.01 0.02
28 day mortality: n (%) Intention to treat Per protocol	 184/879 (20.9%) 176/860 (20.5%)	 170/878 (19.4%) 166/864 (19.2%)	 0.02 0.02
Length of stay in ICU: mean (SD)	6.2 (3.1-12.3)	5.8 (3.0-12.4)	-
Length of stay in hospital: mean (SD)	12.6 (6.8)	12.7 (6.8)	-
Infection relapse requiring further antibiotics	15	5	-

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Results

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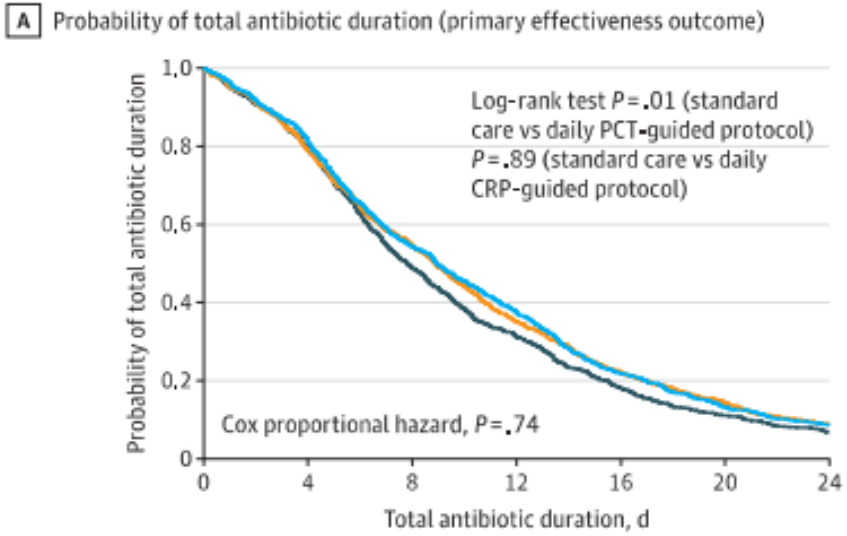
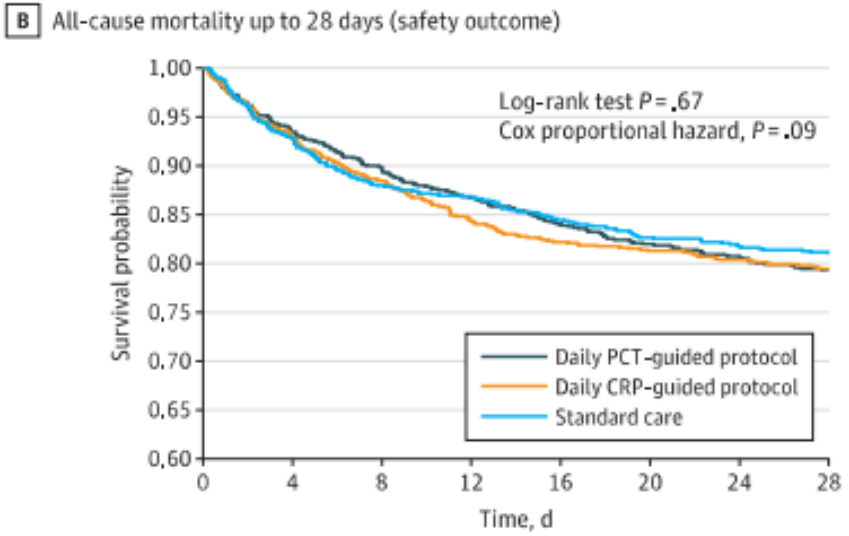


No. at risk

Guided protocol							
Daily PCT	897	713	438	280	163	99	61
Daily CRP	891	703	488	313	197	128	80
Standard care	904	737	491	339	199	119	78



No. at risk

Guided protocol								
Daily PCT	917	837	797	768	742	722	709	695
Daily CRP	923	831	783	742	720	710	701	691
Standard care	918	838	784	769	744	728	715	708

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

ADAPT- Sepsis Take Away

McLeod Health

Author's Conclusions

- In septic ICU patients a PCT guided discontinuation protocol can be used to safely facilitate discontinuation of antibiotics

Evaluation

- Study design and size
- Mortality- no difference
- Blinding
- Reduction was modest

Source: Dark P, *et al. JAMA*. Published online December 9, 2024.

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NO-calcitonin Evidence

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Procalcitonin-guided Interventions Against Infections to Increase Early Appropriate Antibiotics and Improve Survival in the Intensive Care Unit

Jensen JU, Hein L, Lundgren B, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Study Design and Methods

McLeod Health

Procalcitonin And Survival Study (PASS)

Randomized, controlled, open-label trial

September 1, 2006 to February 6, 2009

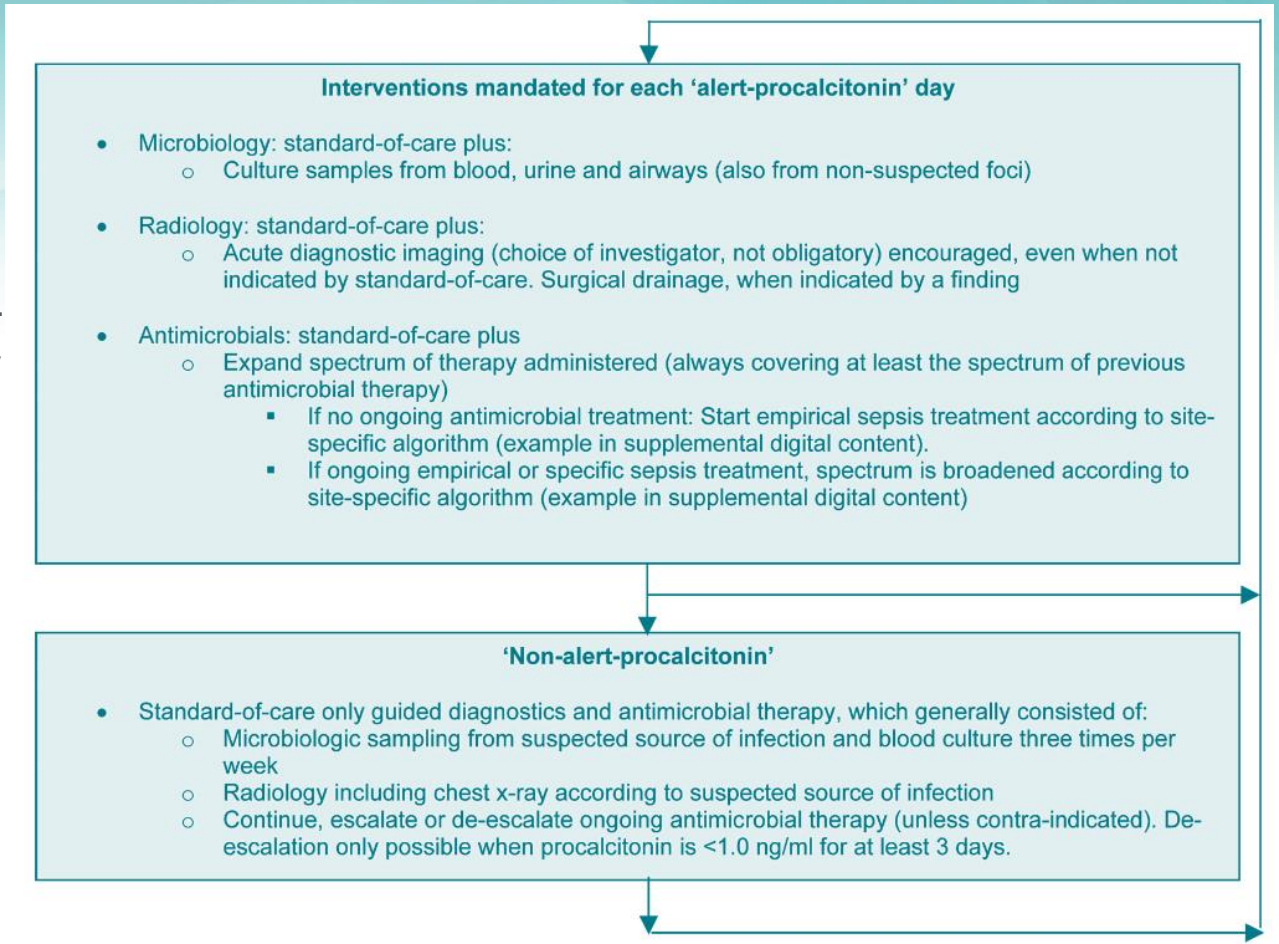
9 medical and surgical ICUs across Denmark

Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Methods

Daily labs

- Alert PCT > 1.0 µg/L or not decreasing by >10% from the previous day
- Goal of the alert PCT is to broaden antibiotics or increase diagnostic efforts



Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Criteria

McLeod Health

Inclusion:

- 18 years or older
- ICU stay ≥ 24 hours

Exclusion:

- Pregnant
- Harm from blood sampling
- Bilirubin > 40 mg/dL
- Triglycerides > 1000mg/dL

Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Outcomes

McLeod Health

Primary outcomes:

- 28 day survival

Secondary outcomes:

- Mechanical ventilation
- Median ICU length of stay
- Time to administration of appropriate antimicrobials

Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Baseline Characteristics

McLeod Health

	PCT Group (n= 604)	SOC Group (n=596)
Age: mean	67	67
APACHE II Score: mean	18	18
Surgical Patients: n (%)	227 (37.6%)	260 (43.6%)
Respiratory Failure: n (%)	410 (67.9%)	422 (70.8%)
Mechanical Ventilation: n (%)	401 (66.4%)	401 (67.3%)
Sepsis/ Septic Shock: n (%)	247 (35.6%)	212 (40.9%)
Alert Procalcitonin: n (%)	312 (51.7%)	279 (47.0%)
C reactive protein (mg/L): mean	161	152

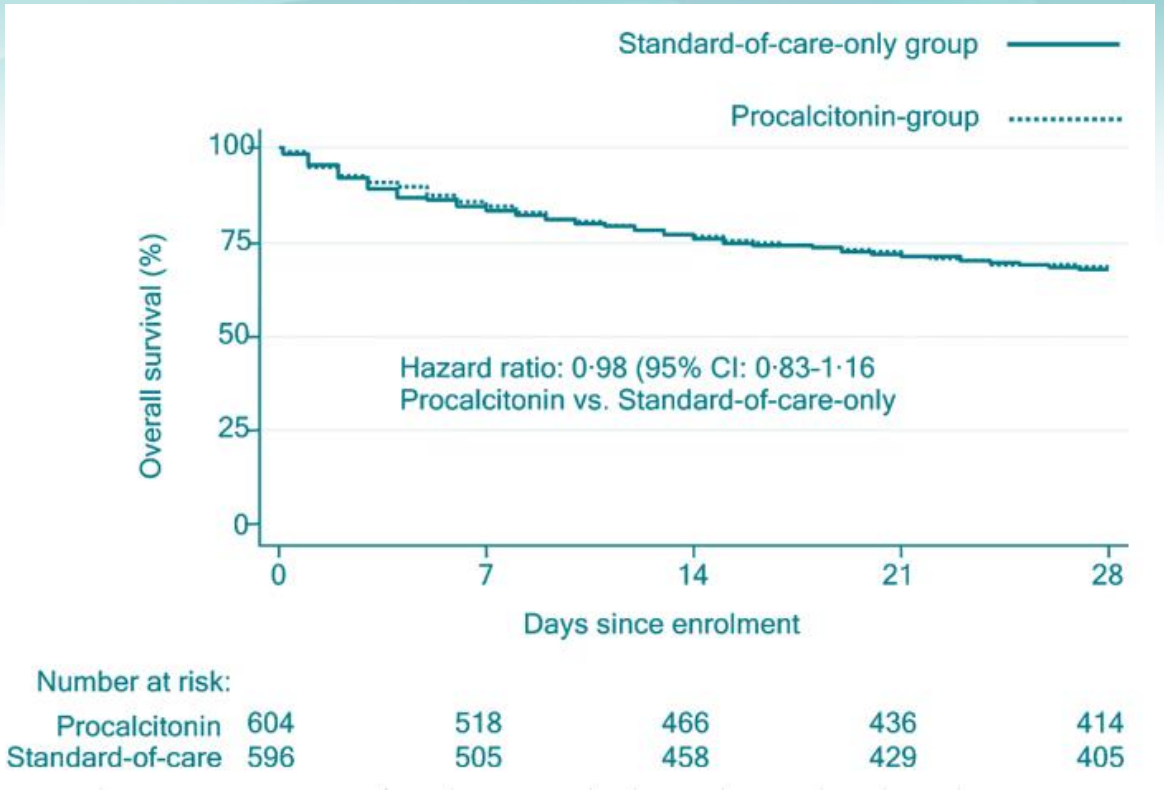
Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Results

McLeod Health

28 days after enrollment mortality occurred in:

- PCT: 190 participants
- SOC: 191 participants



Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Results

McLeod Health

	PCT Group (n= 604)	SOC Group (n=596)	P Value
Time to administration of appropriate antibiotics: days	-0.1	0.8	0.02
ICU days with mechanical ventilation: n (%)	3569 (65.5%)	2861 (60.7%)	<0.0001
ICU length of stay: days	6	4	0.004
60 day mortality: n (%)	220 (36.9%)	231 (38.2%)	-

Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

PASS Take Away

McLeod Health

Author's Conclusions

- PCT should NOT be used as a daily measure to broaden antibiotics or increase diagnostic efforts

Evaluation

- Study design and size
- Algorithm adherence
- No benefit in survival
- Prolonged length of stay in the ICU
- Longer time with mechanical ventilation

Source: Jensen JU, *et al*. *Crit Care Med*. 2011;39(9):2048-2058.

McLeod Health

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

Huang DT, Yealy DM, Filbin MR, *et al*. *N Engl J Med*. 2018;379(3):236-249.

ProACT Study Design and Methods

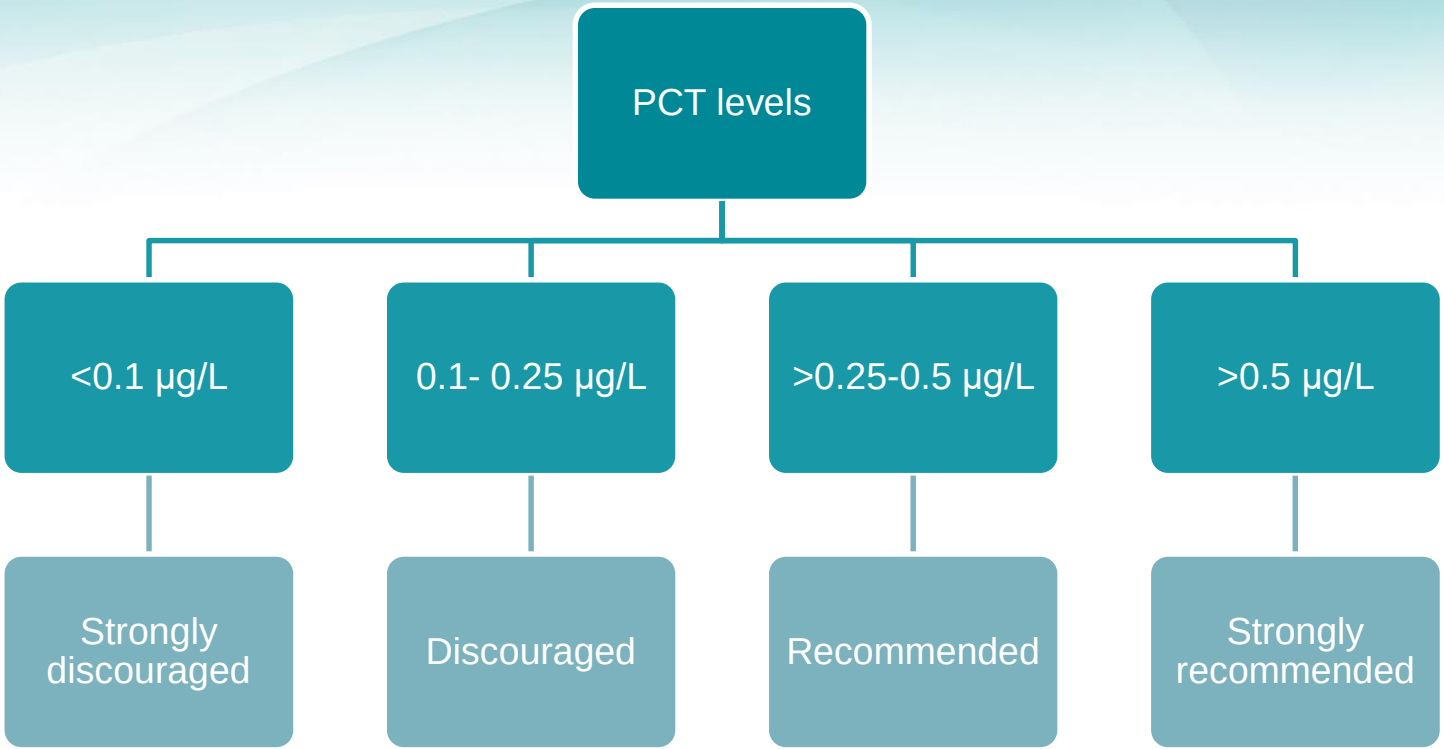
McLeod Health

- Procalcitonin Antibiotic Consensus Trial (ProACT)
- Multicenter, randomized, open-label controlled trial
- November 2014 to May 2017
- 14 hospitals in the United States

Source: Huang DT, *et al*. *N Engl J Med*. 2018;379(3):236-249.

ProACT Methods

McLeod Health



Source: Huang DT, *et al*. *N Engl J Med*. 2018;379(3):236-249.

ProACT Inclusion Criteria

McLeod Health

Inclusion Criteria:

- > 18 years old
- Initial diagnosis of acute lower respiratory tract infection
- Antibiotic prescribing not decided
- Antibiotic need uncertain
- Written consent

Source: Huang DT, *et al*. *N Engl J Med*. 2018;379(3):236-249.

ProACT Outcomes

McLeod Health

Primary outcome:	Primary safety outcome:	Secondary outcomes:
• Total antibiotic exposure	• Composite of adverse outcomes within 30 days after enrollment	• Prescription of antibiotics in the emergency department • Antibiotic receipt by day 30 • Antibiotic-days during the hospital stay

Source: Huang DT, *et al*. *N Engl J Med*. 2018;379(3):236-249.

ProACT Baseline Characteristics

McLeod Health

	PCT Group (n= 822)	SOC Group (n=823)
Age: mean	59.2	53.2
COPD: n (%)	267 (32.5%)	262 (31.8%)
Asthma: n (%)	312 (38.0%)	337 (40.9%)
Symptom Duration: days	5.5	5.5
Procalcitonin Level: n (%) <0.1 µg/L 0.1-0.25 µg/L 0.26-0.5 µg/L >0.5 µg/L	 588/808 (72.8%) 158/808 (19.6%) 27/808 (3.3%) 35/808 (4.3%)	 648/788 (82.2%) 72/788 (9.1%) 23/788 (2.9%) 45/788 (5.7%)
Final Diagnosis: n (%) Asthma COPD Bronchitis CAP	 310 (37.7%) 265 (32.2%) 208 (25.3%) 167 (20.3%)	 336 (40.8%) 259 (31.5%) 190 (23.1%) 161 (19.6%)

Source: Huang DT, *et al*. *N Engl J Med*. 2018;379(3):236-249.

ProACT Results

McLeod Health

	PCT Group (n= 826)	SOC Group (n= 830)	95% CI
Antibiotic days by day 30	4.2	4.3	-0.05 (-0.6-0.5)
Received any antibiotics by day 30: n (%)	471 (57%)	513 (61.8%)	-4.8 (-12.7-3.0)
Antibiotic prescription in ED: n (%)	282 (34.1%)	321 (38.7%)	-4.6 (-12.2-3.0)
Antibiotic-days during hospital stay	2.6	2.7	-0.1 (-0.8-0.6)
Hospital length of stay: days	5.0	4.7	0.3 (-0.2-0.9)

Source: Huang DT, *et al*. *N Engl J Med*. 2018;379(3):236-249.

ProACT Take Away

McLeod Health

Author's Conclusions

- PCT guided antibiotic prescription guidelines do not reduce the exposure to antibiotics in those presenting with LRTI

Evaluation

- Study design and size
- Patients with uncertain benefit from antibiotics
- Average symptoms per patient is 5 days
- PCT results were provided to the clinical team before decision making in most but not all instances
- Clinician guided

Source: Huang DT, *et al*. *N Engl J Med*. 2018;379(3):236-249.

McLeod Health

Ineffectiveness of Procalcitonin-guided Antibiotic Therapy In Severely Critically Ill Patients: A Meta-analysis

Peng F, Chang W, Xie JF, Sun Q, Qiu HB, Yang Y. *Int J Infect Dis*. 2019;85:158-166

Peng Study Design and Methods

McLeod Health

Meta analysis

A total of 16 RCTs (6452 participants)

January 2004 and August 2018

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Criteria

McLeod Health

Inclusion Criteria:

- PCT-guided antibiotic therapy compared with SOC
- Critically ill adult patients
- Data reported for mortality
- LOS
- Duration of antibiotic use
- Randomized controlled study design

Exclusion criteria:

- Did not use PCT to guide antibiotic clinical decision-making
- Non RCTs
- Trials performed before 2004

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Outcomes

McLeod Health

Primary outcome:	• All cause mortality within 28 days
Secondary outcomes:	• Duration of antibiotics • Hospital LOS • ICU LOS

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Study Selection

McLeod Health

First Author	Diagnosis	Cohort	PCT algorithm	Antibiotic Duration
Annane, et al.	Suspected sepsis	31 each	Mixed- 0.25 µg/L	5 each
Bloos, et al.	Severe sepsis or septic shock	552 PCT 537 SOC	Cessation- < 0.1 µg/L or drop by > 50%	7 each
Bouadma, et al.	Suspected bacterial infection	307 PCT 314 SOC	Mixed- < 0.5 µg/L or drop by > 80%	10.3 PCT 13.3 SOC
Daubin, et al	Severe acute exacerbations of COPD	151 each	Mixed- < 0.1 µg/L or drop by > 90%	7.9 PCT 7.7 SOC
De Jong, et al.	Assumed or proven infection	761 PCT 785 SOC	Cessation- < 0.5 µg/L or drop by > 80%	5 PCT 7 SOC
Deliberato, et al.	Suspected sepsis, severe sepsis, or septic shock	42 PCT 39 SOC	Cessation- < 0.5 µg/L or drop by > 90%	10 PCT 11 SOC

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Study Selection

McLeod Health

First Author	Diagnosis	Cohort	PCT algorithm	Antibiotic Duration
Hochreiter, et al.	Confirmed or suspected bacterial infections	57 PCT 53 SOC	Cessation- < 1.0 µg/L or drop by > 65%	5.9 PCT 7.9 SOC
Jensen, et al.	Critically ill patients	604 PCT 596 SOC	Initiation- > 1.0 µg/L	6 PCT 4 SOC
Layios, et al.	Critically ill patients	258 PCT 251 SOC	Initiation- > 0.5 µg/L	–
Najafti, et al.	Critically ill patients with SIRS	151 each	Initiation- > 2.0 µg/L	–
Nobre, et al.	Severe sepsis or septic shock	49 PCT 45 SOC	Cessation- < 0.25 µg/L or drop by > 90%	6.0 PCT 9.5 CRP
Oliveria, et al.	Severe sepsis or septic shock	49 each	Cessation- < 0.1 µg/L or drop by > 90%	8.1 PCT 7.2 CRP

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

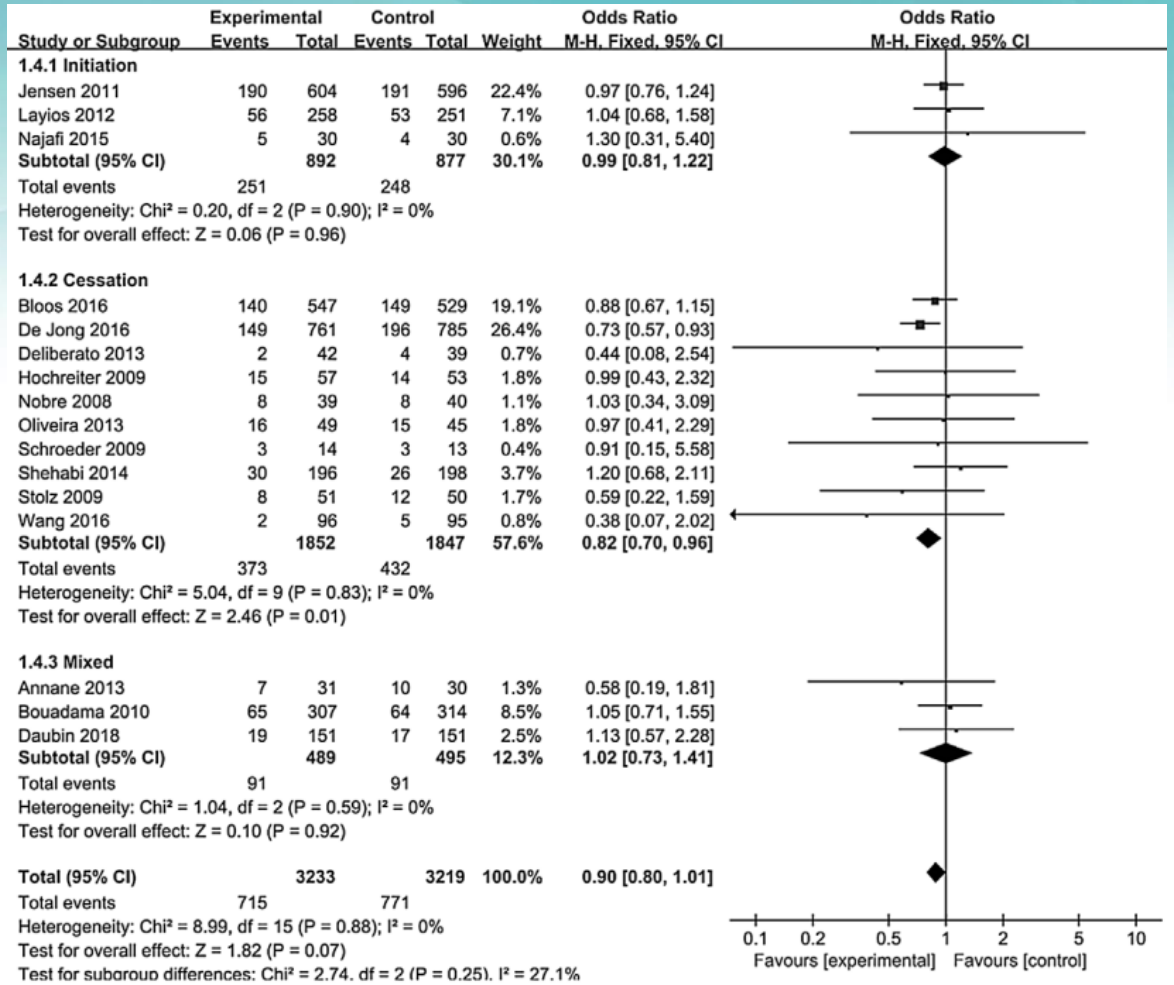
Peng Study Selection

McLeod Health

First Author	Diagnosis	Cohort	PCT algorithm	Antibiotic Duration
Schroeder, et al.	Severe sepsis	14 PCT 13 SOC	Cessation- < 1.0 µg/L or drop by > 65%	6.6 PCT 8.3 SOC
Shehabi, et al.	Suspected bacterial infection	196 PCT 198 SOC	Cessation- < 0.1 µg/L or drop by > 90%	6 PCT 4 SOC
Stolz, et al.	VAP	51 PCT 50 SOC	Cessation- < 0.25 µg/L or drop by > 80%	10 SOC 15 PCT
Wang, et al.	Acute exacerbations of COPD	95 PCT 96 SOC	Cessation- < 0.1 µg/L	17 PCT 12 SOC

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Results: Mortality



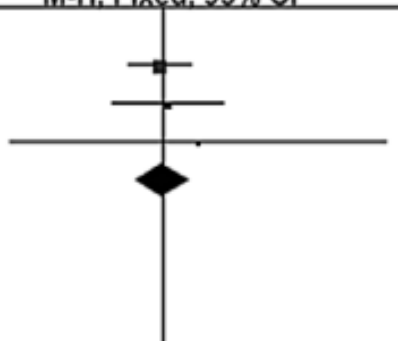
Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Figure 2. Forest plot of the effects of PCT-guided antibiotic strategies on short-term mortality.

Peng Results: Mortality

McLeod Health

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Initiation						
Jensen 2011	190	604	191	596	22.4%	0.97 [0.76, 1.24]
Layios 2012	56	258	53	251	7.1%	1.04 [0.68, 1.58]
Najafi 2015	5	30	4	30	0.6%	1.30 [0.31, 5.40]
Subtotal (95% CI)		**892**		**877**	**30.1%**	**0.99 [0.81, 1.22]**
Total events	251		248			
Heterogeneity: $Chi^2 = 0.20$, df = 2 (P = 0.90); $I^2 = 0\%$						
Test for overall effect: Z = 0.06 (P = 0.96)						

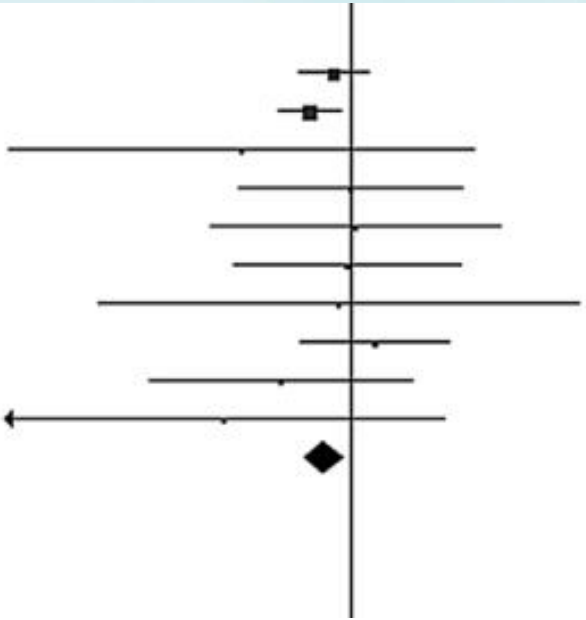


Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Results: Mortality

McLeod Health

1.4.2 Cessation						
Bloos 2016	140	547	149	529	19.1%	0.88 [0.67, 1.15]
De Jong 2016	149	761	196	785	26.4%	0.73 [0.57, 0.93]
Deliberato 2013	2	42	4	39	0.7%	0.44 [0.08, 2.54]
Hochreiter 2009	15	57	14	53	1.8%	0.99 [0.43, 2.32]
Nobre 2008	8	39	8	40	1.1%	1.03 [0.34, 3.09]
Oliveira 2013	16	49	15	45	1.8%	0.97 [0.41, 2.29]
Schroeder 2009	3	14	3	13	0.4%	0.91 [0.15, 5.58]
Shehabi 2014	30	196	26	198	3.7%	1.20 [0.68, 2.11]
Stolz 2009	8	51	12	50	1.7%	0.59 [0.22, 1.59]
Wang 2016	2	96	5	95	0.8%	0.38 [0.07, 2.02]
Subtotal (95% CI)		**1852**		**1847**	**57.6%**	**0.82 [0.70, 0.96]**
Total events	373		432			
Heterogeneity: $Chi^2 = 5.04$, df = 9 (P = 0.83); $I^2 = 0\%$						
Test for overall effect: Z = 2.46 (P = 0.01)						



Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

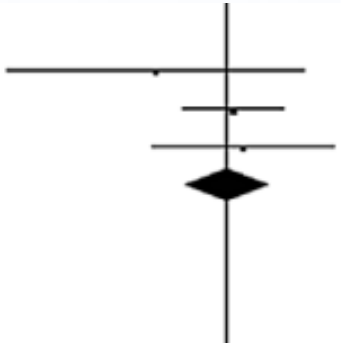
Peng Results: Mortality

McLeod Health

1.4.3 Mixed						
Annane 2013	7	31	10	30	1.3%	0.58 [0.19, 1.81]
Bouadama 2010	65	307	64	314	8.5%	1.05 [0.71, 1.55]
Daubin 2018	19	151	17	151	2.5%	1.13 [0.57, 2.28]
Subtotal (95% CI)		**489**		**495**	**12.3%**	**1.02 [0.73, 1.41]**
Total events	91		91			

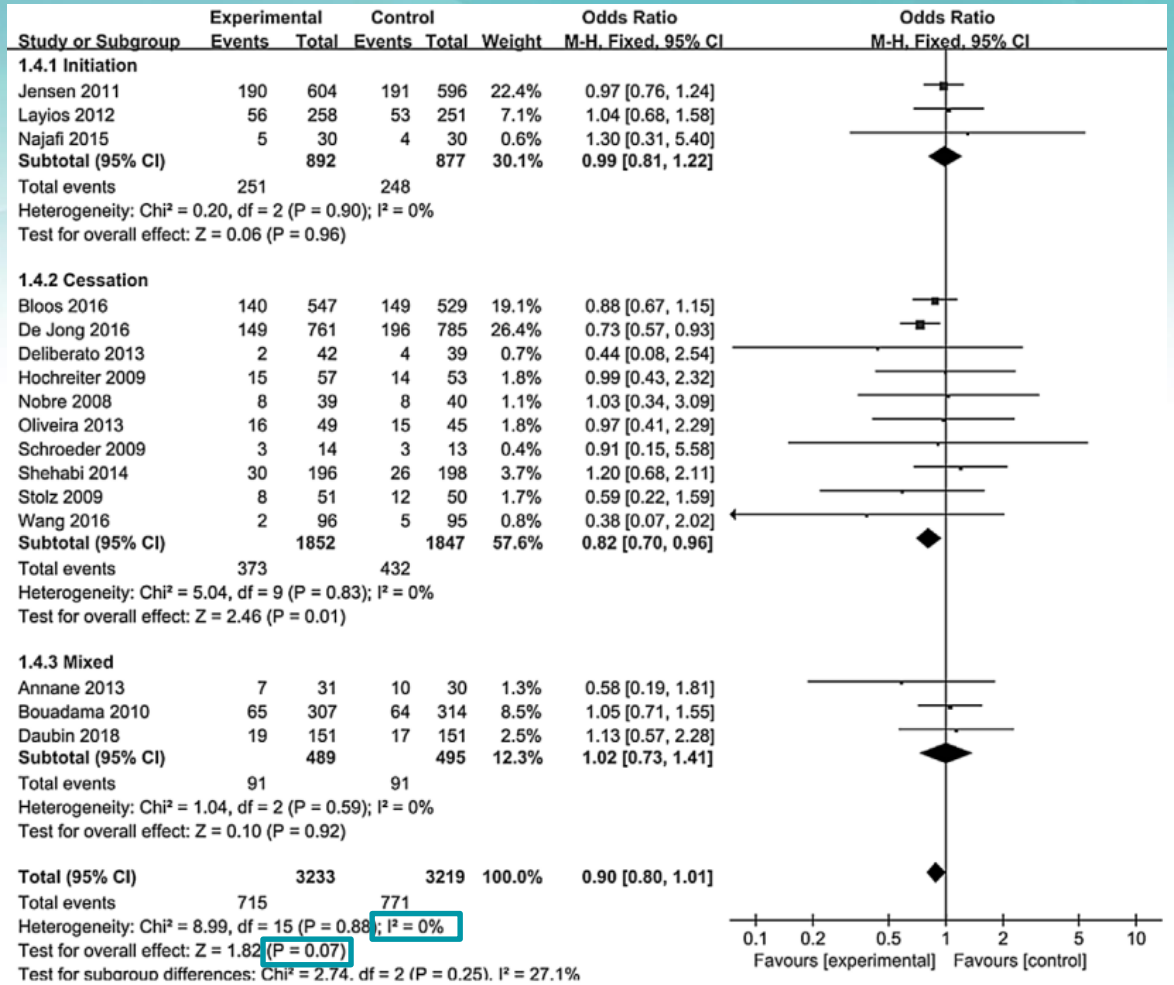
Heterogeneity: $Chi^2 = 1.04$, df = 2 (P = 0.59); $I^2 = 0\%$

Test for overall effect: Z = 0.10 (P = 0.92)



Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Results: Mortality



Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Figure 2. Forest plot of the effects of PCT-guided antibiotic strategies on short-term mortality.

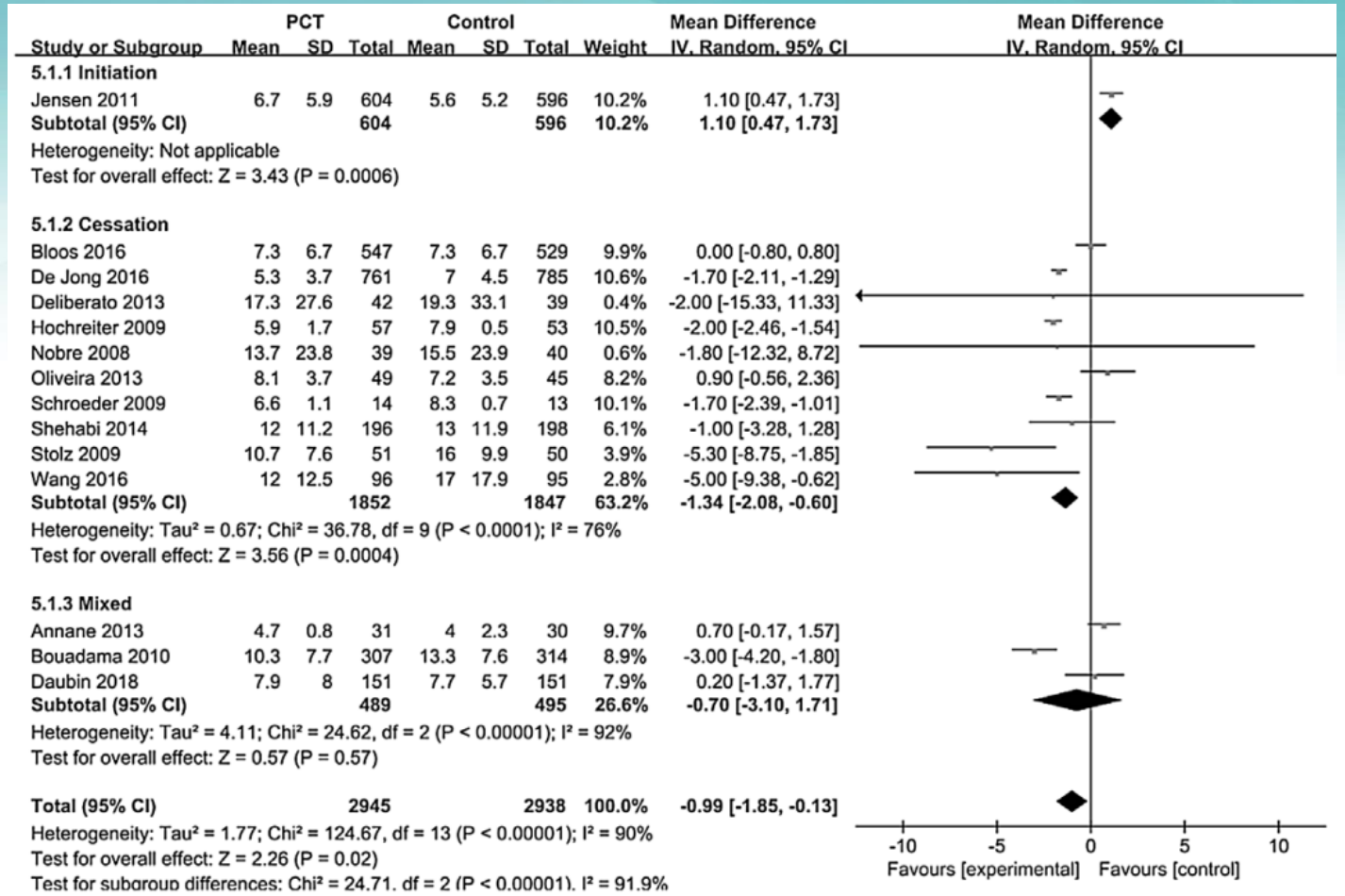
Peng Results

McLeod Health

Term of Mortality	Number of Trials	PCT	SOC	Pooled OR	P Value
28 Day Mortality	8	595/2509	652/2510	0.88	0.05
ICU Mortality	5	99/677	95/669	1.03	0.86
Hospital Mortality	9	83/556	89/548	0.90	0.52
Cessation	10	373/1852	432/1847	0.82	0.01
SOFA > 8 < 8	9 3 6	371/1756 151/612 220/1144	427/1752 164/592 263/1160	0.83 0.85 0.81	0.02 0.23 0.04
Adherence > 70% < 70%	10 4 6	373/1852 56/380 317/1472	432/1847 54/378 378/1469	0.95 1.03 0.79	0.01 0.9 0.007
All listed terms of mortality have a heterogeneity of 0% between all studies included					

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Results: Duration



Study or Subgroup	PCT Mean	PCT SD	PCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.1.1 Initiation								
Jensen 2011	6.7	5.9	604	5.6	5.2	596	10.2%	1.10 [0.47, 1.73]
Subtotal (95% CI)			**604**			**596**	**10.2%**	**1.10 [0.47, 1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								
5.1.2 Cessation								
Bloos 2016	7.3	6.7	547	7.3	6.7	529	9.9%	0.00 [-0.80, 0.80]
De Jong 2016	5.3	3.7	761	7	4.5	785	10.6%	-1.70 [-2.11, -1.29]
Deliberato 2013	17.3	27.6	42	19.3	33.1	39	0.4%	-2.00 [-15.33, 11.33]
Hochreiter 2009	5.9	1.7	57	7.9	0.5	53	10.5%	-2.00 [-2.46, -1.54]
Nobre 2008	13.7	23.8	39	15.5	23.9	40	0.6%	-1.80 [-12.32, 8.72]
Oliveira 2013	8.1	3.7	49	7.2	3.5	45	8.2%	0.90 [-0.56, 2.36]
Schroeder 2009	6.6	1.1	14	8.3	0.7	13	10.1%	-1.70 [-2.39, -1.01]
Shehabi 2014	12	11.2	196	13	11.9	198	6.1%	-1.00 [-3.28, 1.28]
Stolz 2009	10.7	7.6	51	16	9.9	50	3.9%	-5.30 [-8.75, -1.85]
Wang 2016	12	12.5	96	17	17.9	95	2.8%	-5.00 [-9.38, -0.62]
Subtotal (95% CI)			**1852**			**1847**	**63.2%**	**-1.34 [-2.08, -0.60]**
Heterogeneity: Tau² = 0.67; Chi² = 36.78, df = 9 (P < 0.0001); I² = 76%								
Test for overall effect: Z = 3.56 (P = 0.0004)								
5.1.3 Mixed								
Annane 2013	4.7	0.8	31	4	2.3	30	9.7%	0.70 [-0.17, 1.57]
Bouadama 2010	10.3	7.7	307	13.3	7.6	314	8.9%	-3.00 [-4.20, -1.80]
Daubin 2018	7.9	8	151	7.7	5.7	151	7.9%	0.20 [-1.37, 1.77]
Subtotal (95% CI)			**489**			**495**	**26.6%**	**-0.70 [-3.10, 1.71]**
Heterogeneity: Tau² = 4.11; Chi² = 24.62, df = 2 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 0.57 (P = 0.57)								
Total (95% CI)			**2945**			**2938**	**100.0%**	**-0.99 [-1.85, -0.13]**
Heterogeneity: Tau² = 1.77; Chi² = 124.67, df = 13 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 2.26 (P = 0.02)								
Test for subgroup differences: Chi² = 24.71, df = 2 (P < 0.00001), I² = 91.9%								

Figure 4. Forest plot of effects of PCT-guided antibiotic strategies on antibiotic duration.

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Results: Duration

McLeod Health

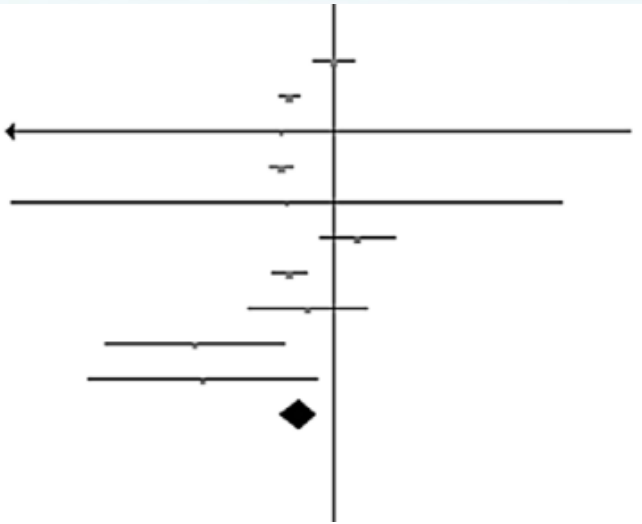
Study or Subgroup	PCT Mean	PCT SD	PCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.1.1 Initiation								
Jensen 2011	6.7	5.9	604	5.6	5.2	596	10.2%	1.10 [0.47, 1.73]
Subtotal (95% CI)			**604**			**596**	**10.2%**	**1.10 [0.47, 1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Results: Duration

McLeod Health

5.1.2 Cessation								
Bloos 2016	7.3	6.7	547	7.3	6.7	529	9.9%	0.00 [-0.80, 0.80]
De Jong 2016	5.3	3.7	761	7	4.5	785	10.6%	-1.70 [-2.11, -1.29]
Deliberato 2013	17.3	27.6	42	19.3	33.1	39	0.4%	-2.00 [-15.33, 11.33]
Hochreiter 2009	5.9	1.7	57	7.9	0.5	53	10.5%	-2.00 [-2.46, -1.54]
Nobre 2008	13.7	23.8	39	15.5	23.9	40	0.6%	-1.80 [-12.32, 8.72]
Oliveira 2013	8.1	3.7	49	7.2	3.5	45	8.2%	0.90 [-0.56, 2.36]
Schroeder 2009	6.6	1.1	14	8.3	0.7	13	10.1%	-1.70 [-2.39, -1.01]
Shehabi 2014	12	11.2	196	13	11.9	198	6.1%	-1.00 [-3.28, 1.28]
Stolz 2009	10.7	7.6	51	16	9.9	50	3.9%	-5.30 [-8.75, -1.85]
Wang 2016	12	12.5	96	17	17.9	95	2.8%	-5.00 [-9.38, -0.62]
Subtotal (95% CI)			**1852**			**1847**	**63.2%**	**-1.34 [-2.08, -0.60]**
Heterogeneity: Tau² = 0.67; Chi² = 36.78, df = 9 (P < 0.0001); I² = 76%								
Test for overall effect: Z = 3.56 (P = 0.0004)								



Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

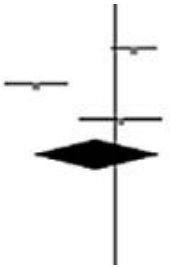
Peng Results: Duration

McLeod Health

5.1.3 Mixed								
Annane 2013	4.7	0.8	31	4	2.3	30	9.7%	0.70 [-0.17, 1.57]
Bouadama 2010	10.3	7.7	307	13.3	7.6	314	8.9%	-3.00 [-4.20, -1.80]
Daubin 2018	7.9	8	151	7.7	5.7	151	7.9%	0.20 [-1.37, 1.77]
Subtotal (95% CI)			489			495	26.6%	**-0.70 [-3.10, 1.71]**

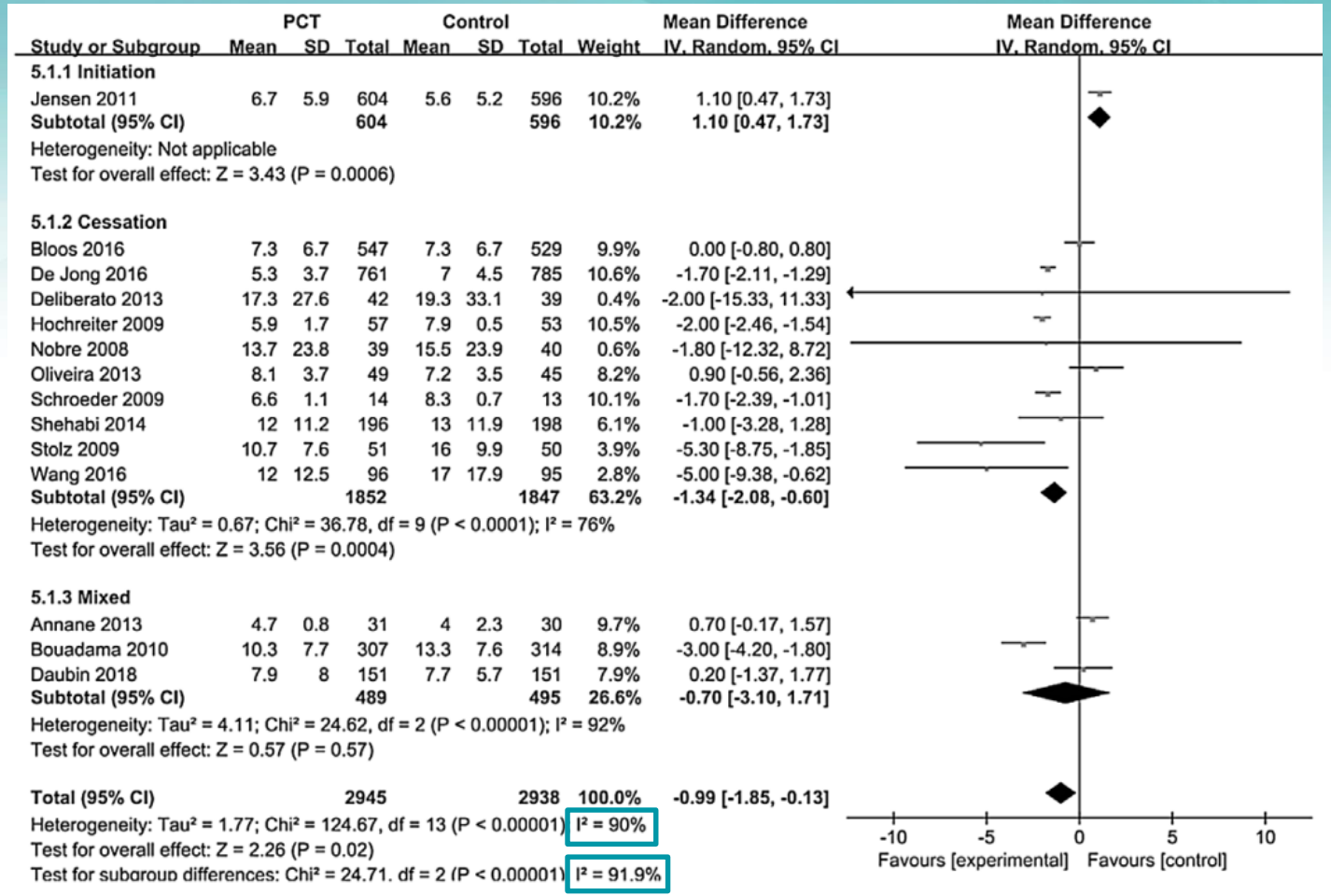
Heterogeneity: Tau² = 4.11; Chi² = 24.62, df = 2 (P < 0.00001); I² = 92%

Test for overall effect: Z = 0.57 (P = 0.57)



Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Results: Duration



Study or Subgroup	PCT Mean	PCT SD	PCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.1.1 Initiation								
Jensen 2011	6.7	5.9	604	5.6	5.2	596	10.2%	1.10 [0.47, 1.73]
Subtotal (95% CI)			**604**			**596**	**10.2%**	**1.10 [0.47, 1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								
5.1.2 Cessation								
Bloos 2016	7.3	6.7	547	7.3	6.7	529	9.9%	0.00 [-0.80, 0.80]
De Jong 2016	5.3	3.7	761	7	4.5	785	10.6%	-1.70 [-2.11, -1.29]
Deliberato 2013	17.3	27.6	42	19.3	33.1	39	0.4%	-2.00 [-15.33, 11.33]
Hochreiter 2009	5.9	1.7	57	7.9	0.5	53	10.5%	-2.00 [-2.46, -1.54]
Nobre 2008	13.7	23.8	39	15.5	23.9	40	0.6%	-1.80 [-12.32, 8.72]
Oliveira 2013	8.1	3.7	49	7.2	3.5	45	8.2%	0.90 [-0.56, 2.36]
Schroeder 2009	6.6	1.1	14	8.3	0.7	13	10.1%	-1.70 [-2.39, -1.01]
Shehabi 2014	12	11.2	196	13	11.9	198	6.1%	-1.00 [-3.28, 1.28]
Stolz 2009	10.7	7.6	51	16	9.9	50	3.9%	-5.30 [-8.75, -1.85]
Wang 2016	12	12.5	96	17	17.9	95	2.8%	-5.00 [-9.38, -0.62]
Subtotal (95% CI)			**1852**			**1847**	**63.2%**	**-1.34 [-2.08, -0.60]**
Heterogeneity: Tau² = 0.67; Chi² = 36.78, df = 9 (P < 0.0001); I² = 76%								
Test for overall effect: Z = 3.56 (P = 0.0004)								
5.1.3 Mixed								
Annane 2013	4.7	0.8	31	4	2.3	30	9.7%	0.70 [-0.17, 1.57]
Bouadama 2010	10.3	7.7	307	13.3	7.6	314	8.9%	-3.00 [-4.20, -1.80]
Daubin 2018	7.9	8	151	7.7	5.7	151	7.9%	0.20 [-1.37, 1.77]
Subtotal (95% CI)			**489**			**495**	**26.6%**	**-0.70 [-3.10, 1.71]**
Heterogeneity: Tau² = 4.11; Chi² = 24.62, df = 2 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 0.57 (P = 0.57)								
Total (95% CI)			**2945**			**2938**	**100.0%**	**-0.99 [-1.85, -0.13]**
Heterogeneity: Tau² = 1.77; Chi² = 124.67, df = 13 (P < 0.00001)	I² = 90%							
Test for overall effect: Z = 2.26 (P = 0.02)								
Test for subgroup differences: Chi² = 24.71, df = 2 (P < 0.00001)	I² = 91.9%							

Figure 4. Forest plot of effects of PCT-guided antibiotic strategies on antibiotic duration.

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

Peng Take Away

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Author's Conclusions

- No short-term mortality benefit seen with PCT use for initiation of antibiotics
- PCT guided cessation strategies decreased short term mortality and antibiotic durations

Evaluation

- Meta analysis design
- Size of study
- Diagnostic criteria of sepsis varied between the included studies
- Variance of strategies between studies
- Most benefit with adherence < 70%

Source: Peng F, *et al. Int J Infect Dis*. 2019;85:158-166

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Assessment Question 1:
Which of the following is an advantage of procalcitonin compared to other inflammatory markers?

a) Procalcitonin is specific to viral infection

b) Procalcitonin has no advantage over other inflammatory markers

c) Procalcitonin is rarely falsely elevated

d) Procalcitonin is not elevated in response to most viral infections

Assessment Question 1: Correct Response

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Which of the following is an advantage of procalcitonin compared to other inflammatory markers?

a) Procalcitonin is specific to viral infection

b) Procalcitonin has no advantage over other inflammatory markers

c) Procalcitonin is rarely falsely elevated

d) Procalcitonin is not elevated in response to most viral infections

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Assessment Question 2:
What procalcitonin level is a negative predictor for bacterial infection?

a) < 0.25 ng/mL

b) < 0.5 ng/mL

c) > 2.5 ng/mL

d) > 5 ng/mL

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Assessment Question 2: Correct Response

What procalcitonin level is a negative predictor for bacterial infection?

a) < 0.25 ng/mL

b) < 0.5 ng/mL

c) > 2.5 ng/mL

d) > 5 ng/mL

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Assessment Question 3:

Which situation could lead to a falsely elevated procalcitonin?

a) Antibiotic use

b) Augmented renal clearance

c) Viral infections

d) Trauma

Assessment Question 3: Correct Response

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Which situation could lead to a falsely elevated procalcitonin?

a) Antibiotic use

b) Augmented renal clearance

c) Viral infections

d) Trauma

Key Points

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PCT algorithm for initiation and discontinuation of antibiotics in septic patients

Draw PCT at admission and if on antibiotics at day 5

Most benefit seen in pulmonary infections

No benefit to broaden antibiotics or increase diagnostic efforts after initial diagnosis

Should not be used to differentiate between respiratory infection vs COPD or asthma exacerbation

Proposed Procalcitonin Algorithm

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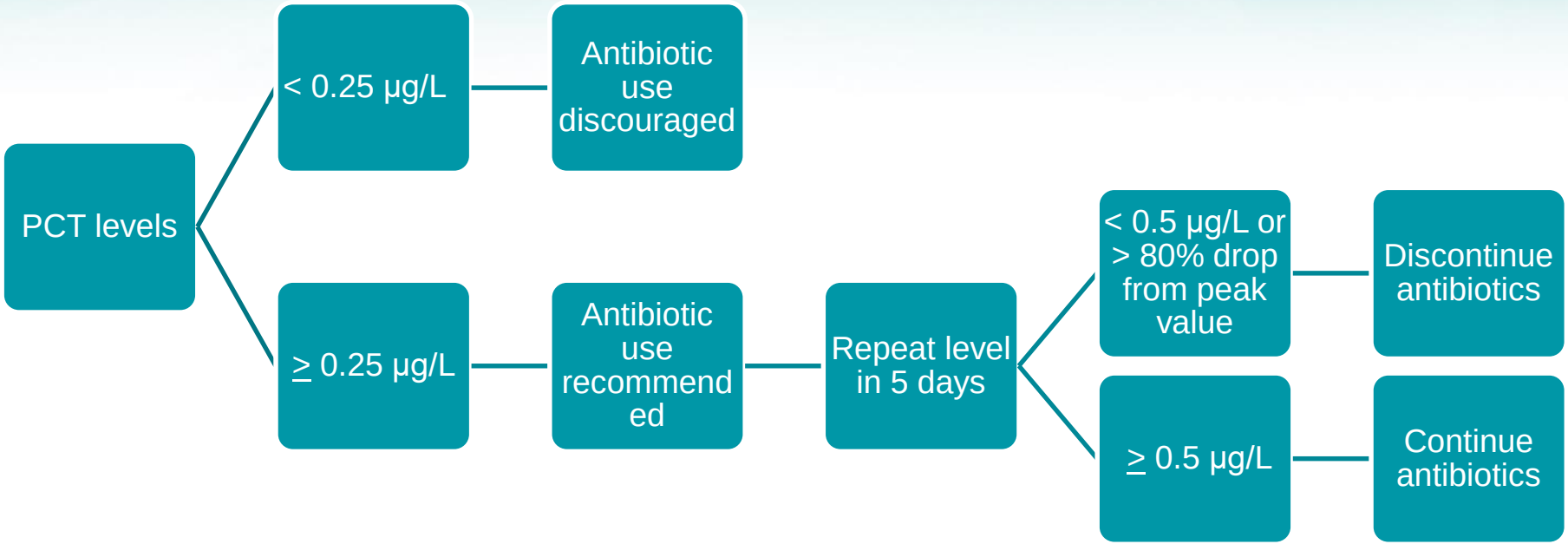

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Thank you!

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