AMS: biomarkers to initiate and to shorten the duration of antimicrobial treatment

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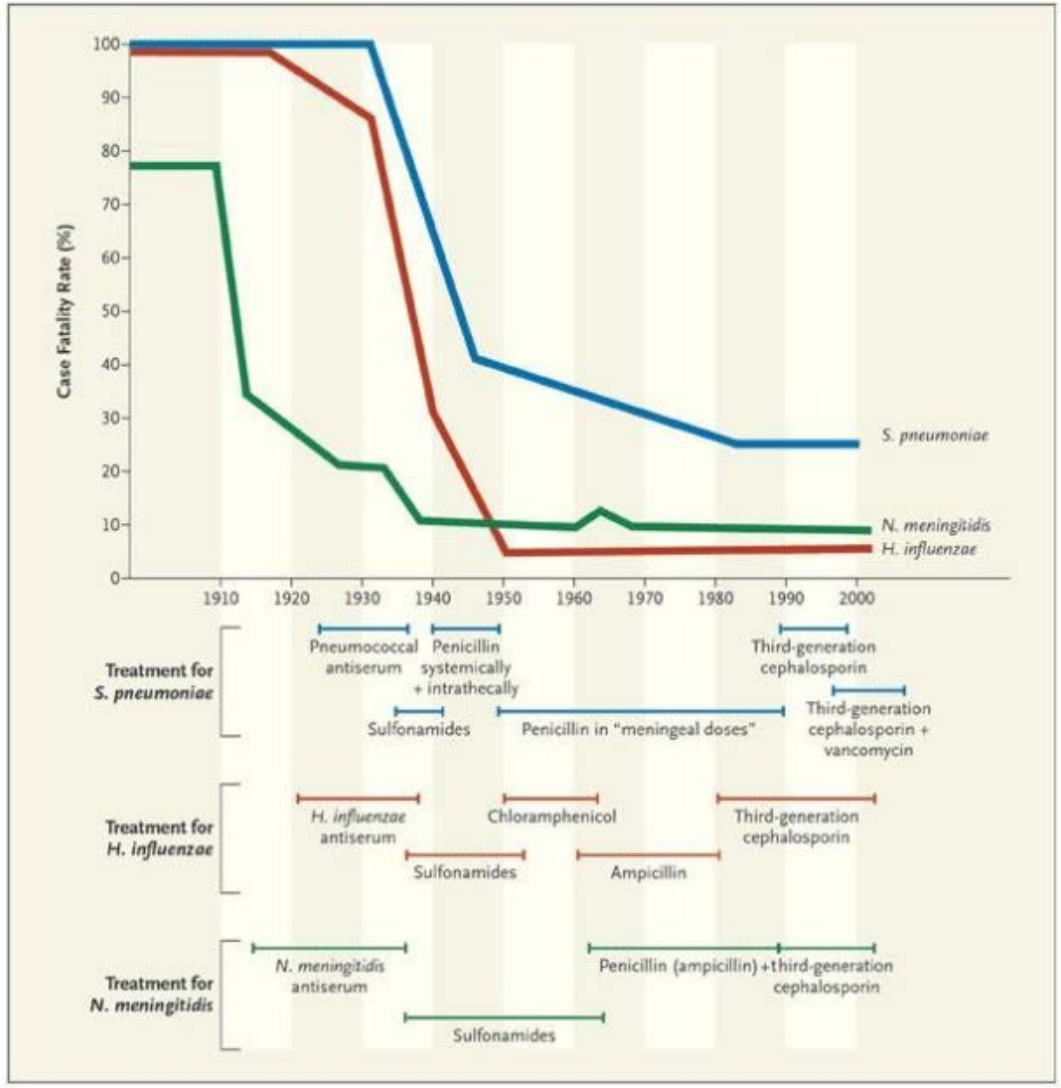
Antibiotic treatment

Disease	Mortality before antibiotics (%)	Mortality in the antibiotic era (%)	Difference in survival rate (%)
Community acquired pneumonia	~35	~10	~25
Hospital acquired pneumonia	~60	~30	~30
Infective endocarditis	~100	~25	~75
Skin and soft tissue infections	~11	~0,5	~10

Clin Infect Dis 2008;47: S249-65; Lancet 1935;226:383-4; Lancet 1938;231:733-4; Am J Med 1948;5:402-18;
Clin Infect Dis 2009;49:383-91.

Introduction



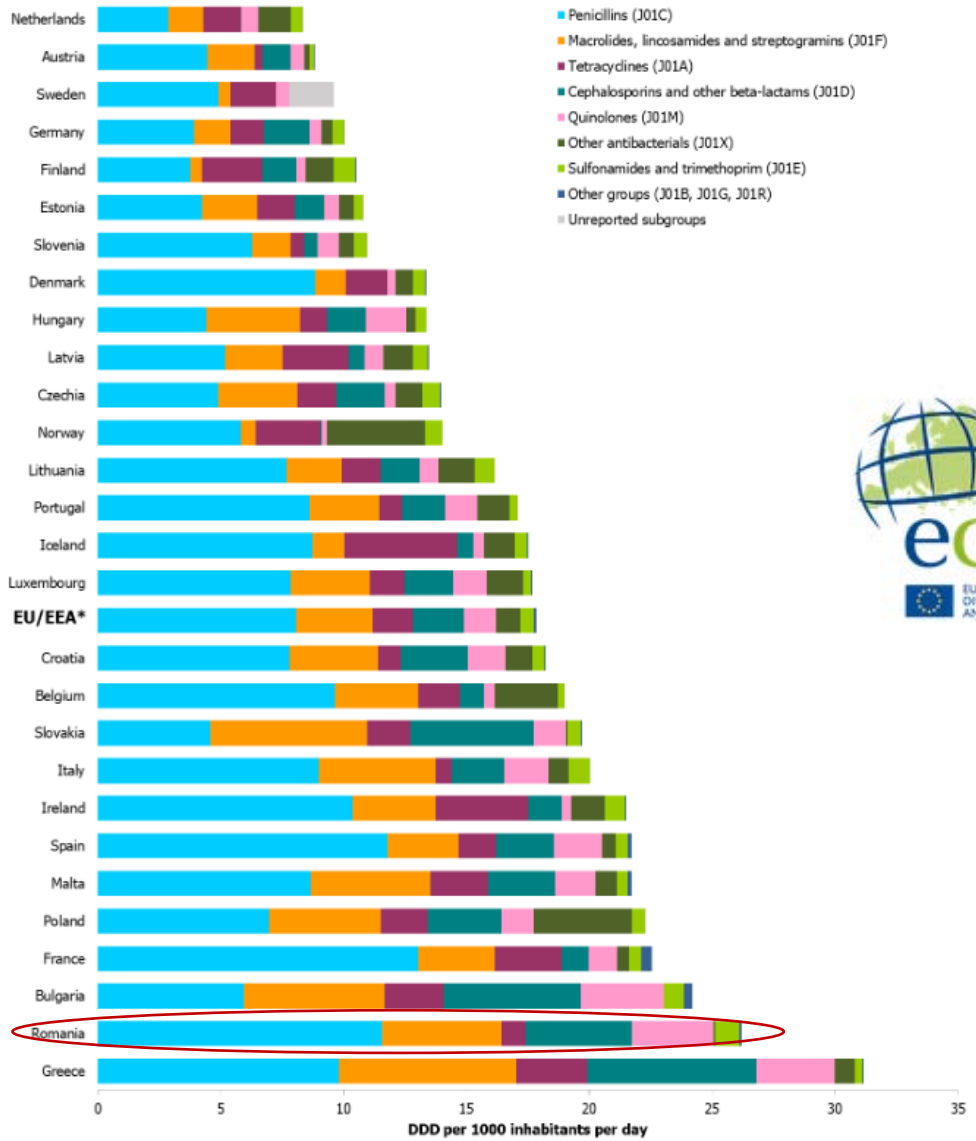
Pitfalls in antibiotic use

- No evidence of bacterial infections
- No clear indication for infection
- No microbiological tests or other relevant procedures
- No de-escalation strategy to narrow the spectrum in case of germ identification
- Prescribing antibiotics more time than necessary (too long course)
- Forgotten to stop AB if they are not needed
- Treating colonisation or contamination

Noninfectious causes of fever

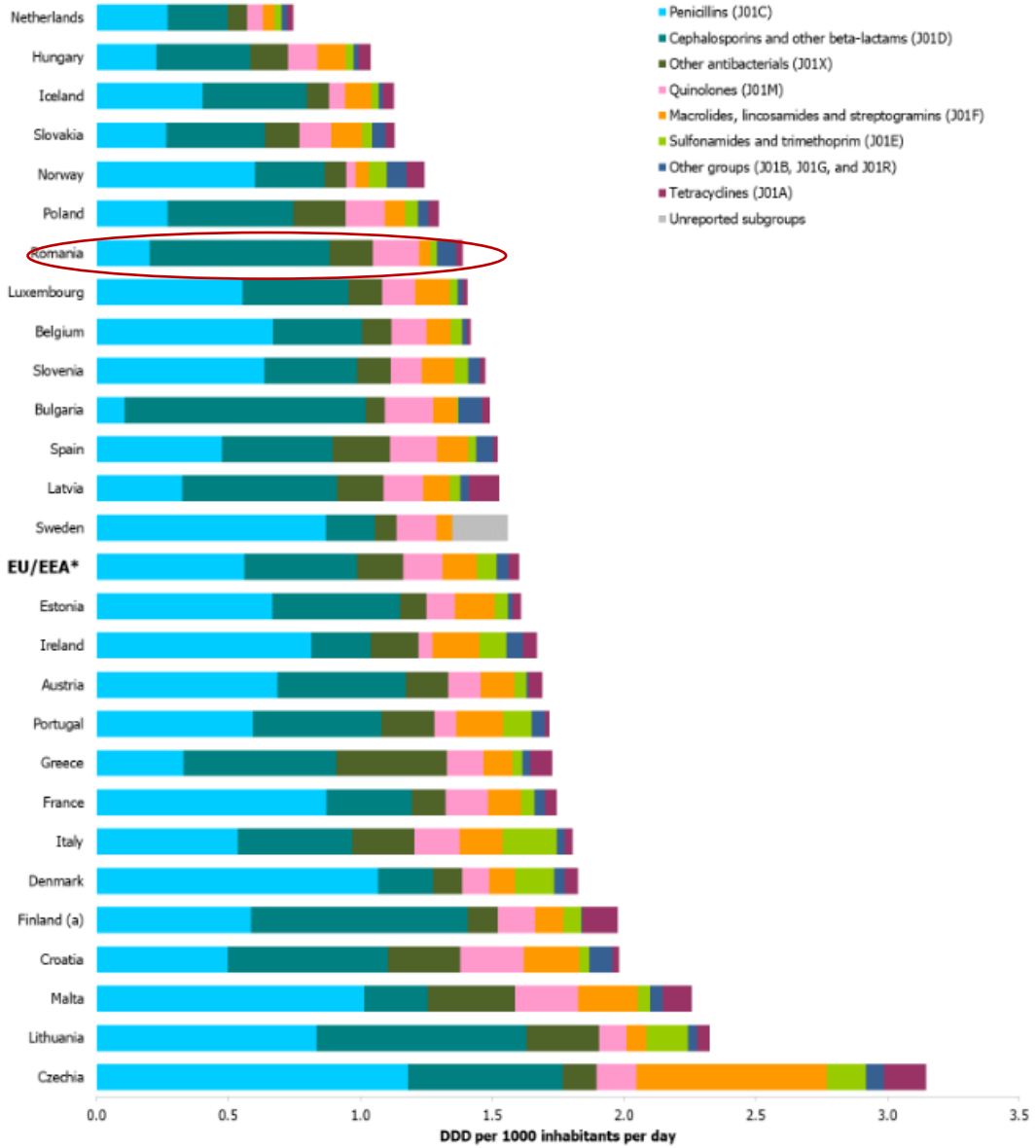
Inflamation	Malignancy	Miscellaneous
Adult Still disease SLE Sarcoidosis Giant cell arteritis	Leukemia Lymphoma Hepatocellular carcinoma Renal cell carcinoma	Drug induced Thyroiditis Thrombembolic events Factitious fever

Community consumption of antibacterials for systemic use



EU/EEA refers to the population-weighted mean consumption, based on countries that provided community sector data for 2022 (28 countries).

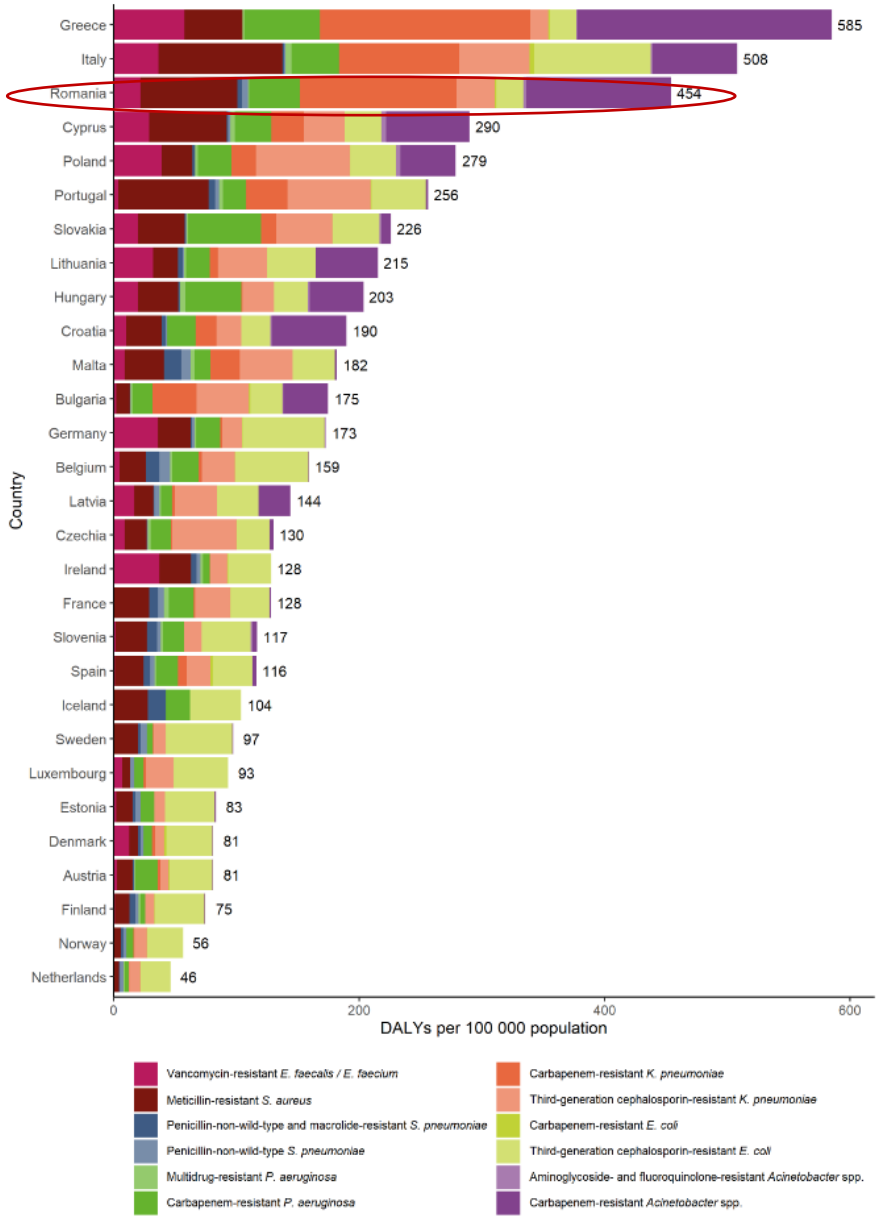
Hospital sector consumption of antibacterials for systemic use



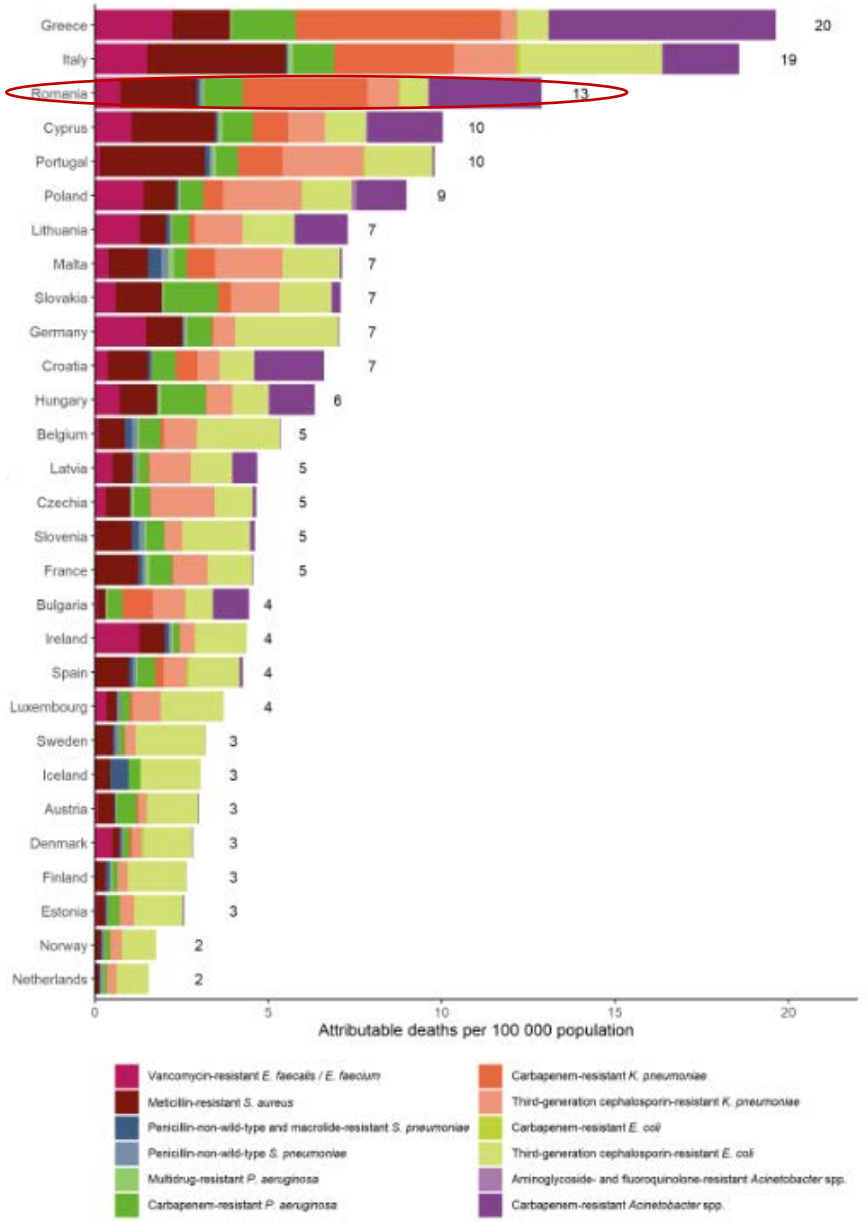
EU/EEA refers to the population-weighted mean consumption based on countries that provided hospital sector data for 2022 (27 countries).

(a) Finland: data include consumption in remote primary healthcare centres and nursing homes.

Estimations of the burden of infections with antibiotic-resistant bacteria presented as disability-adjusted life years (DALYs) per 100 000 population by country*



Estimations of the burden of infections with antibiotic-resistant bacteria presented as attributable deaths per 100 000 population



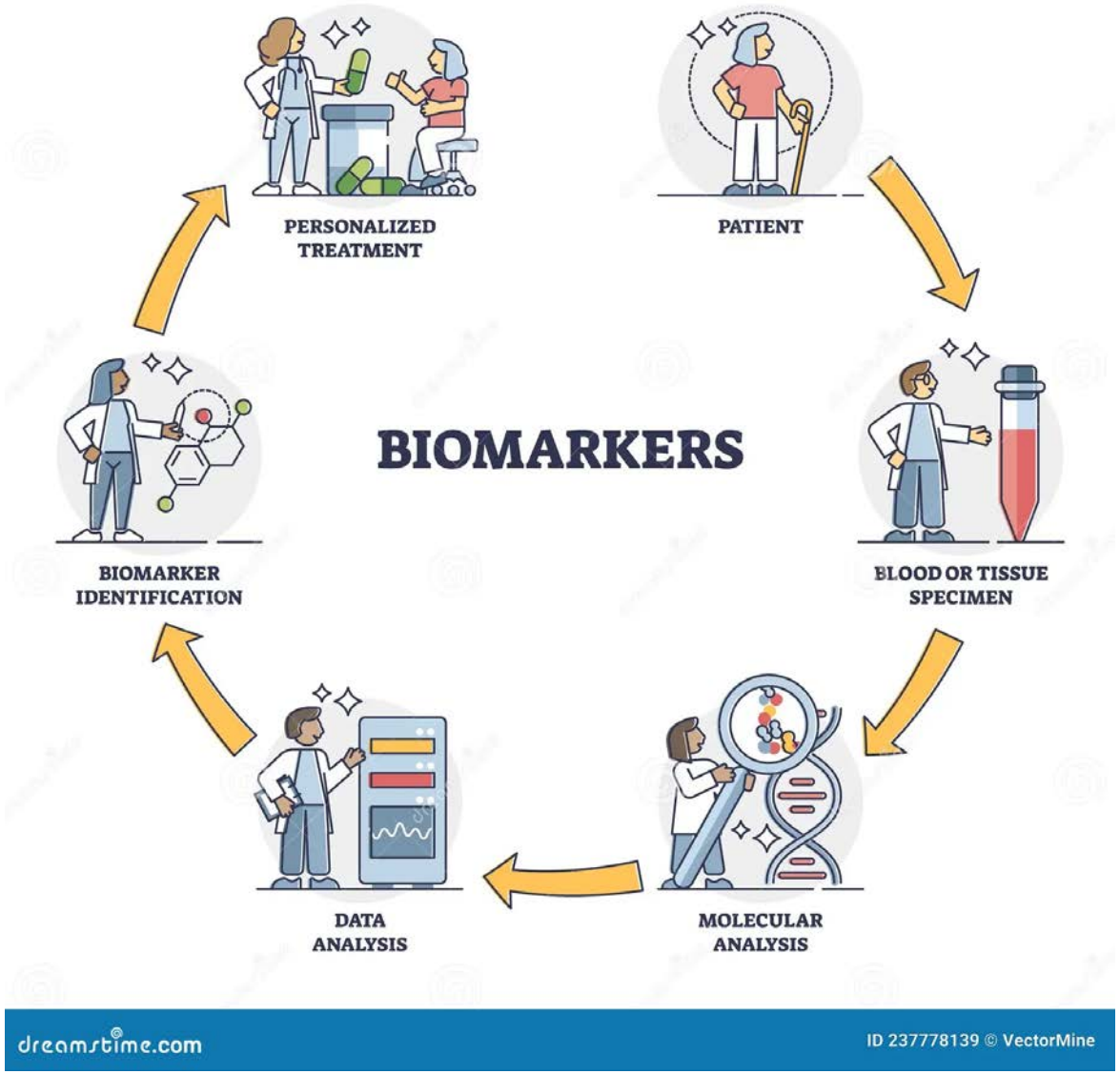
Biomarkers...let's start from definition

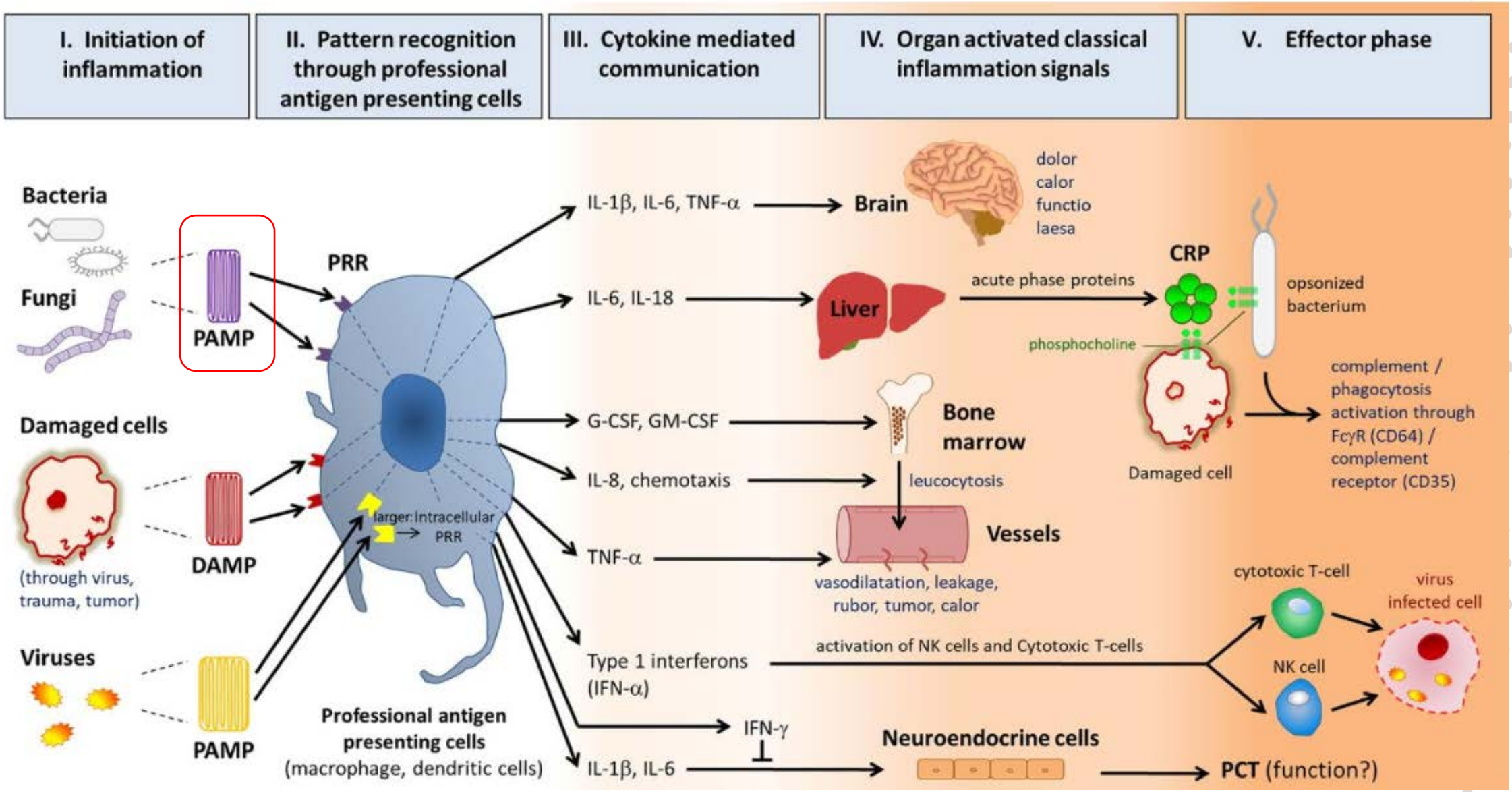
WHO: The term "biomarker" is used in a broad sense to include almost any measurement reflecting an interaction between a biological system and an environmental agent, which may be chemical, physical or biological.

In medicine is used to identify risk of disease, diagnose disease and its severity, guide intervention strategies and monitor patient responses to therapy.

For sepsis: 258 markers identify till now. Most of the biomarkers have not been well-studied apart of CRP and PCT ; in particular, the clinical role of these biomarkers needs to be better evaluated.

Barichello T, et al. *Crit Care* 2022; 26: 14.
Pierrakos C, et al. *Crit Care* 2020; 24: 287


BIOMARKERS
PERSONALIZED TREATMENT
PATIENT
BLOOD OR TISSUE SPECIMEN
MOLECULAR ANALYSIS
DATA ANALYSIS
BIOMARKER IDENTIFICATION
dreamstime.com
ID 237778139 © VectorMine


I. Initiation of inflammation
II. Pattern recognition through professional antigen presenting cells
III. Cytokine mediated communication
IV. Organ activated classical inflammation signals
V. Effector phase
Bacteria
Fungi
PAMP
PRR
Damaged cells
(through virus, trauma, tumor)
DAMP
larger: Intracellular PRR
Viruses
PAMP
Professional antigen presenting cells (macrophage, dendritic cells)
IL-1β, IL-6, TNF-α
Brain
dolor
calor
functio laesa
IL-6, IL-18
Liver
acute phase proteins
CRP
opsonized bacterium
phosphocholine
Damaged cell
complement / phagocytosis activation through FcγR (CD64) / complement receptor (CD35)
G-CSF, GM-CSF
Bone marrow
IL-8, chemotaxis
leucocytosis
TNF-α
Vessels
vasodilatation, leakage, rubor, tumor, calor
Type 1 interferons (IFN-α)
activation of NK cells and Cytotoxic T-cells
cytotoxic T-cell
NK cell
virus infected cell
IFN-γ
IL-1β, IL-6
Neuroendocrine cells
PCT (function?)

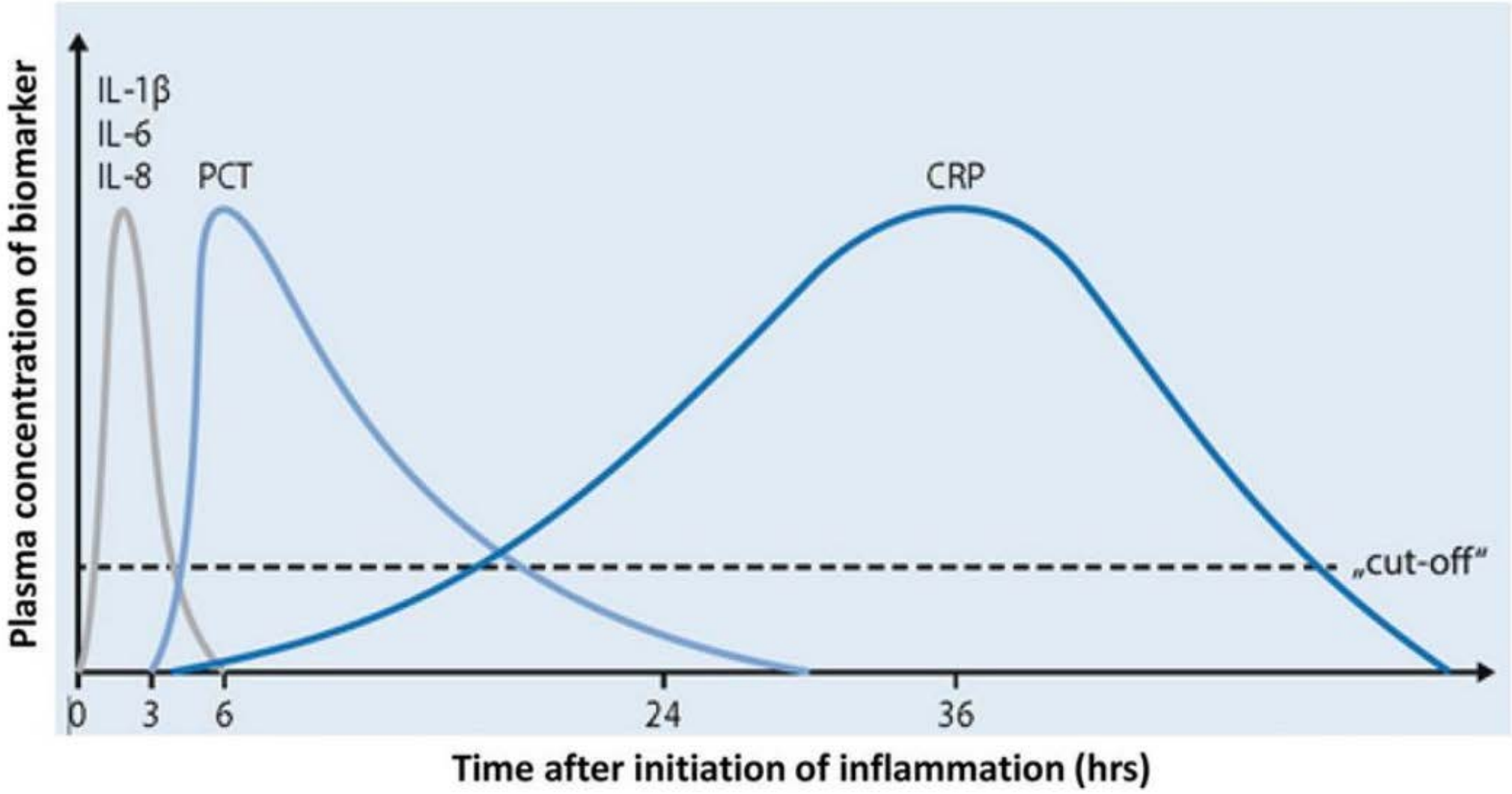
Biomarkers

Diagnostic test	**General: known preanalytic and analytic variability, integrated in the interpretation of assay results** **High predictive values** **Ability to differentiate sepsis and noninfectious events (specificity)** **Ability to differentiate bacterial from viral infection**
Prognostic test	**Early detection of patients at risk of a complicated course** **Levels associated with the inflammatory response** **Predictor of mortality**
Therapeutic test	**Follow-up of the efficacy of a therapy (e.g., rapid kinetics, independent of organ dysfunction**
Accessibility	**Routinely available** **Non- invasive** **Rapid turnaround time** **Technically feasible** **Validated** **Low cost**

Biomarkers for bacterial infections

Type	Comment
CRP	Widely introduced in the clinic, limited specificity, delayed increase in blood
WBC	Low specificity
PCT	Rapid increase in blood, mostly evaluated for sepsis, pneumonia, meningitis, urinary tract infection
CD 14, CD 64, TREM-1, Pentrexin-3, pro ADM, Copeptin, Syndecan-4…	Mostly evaluated for sepsis, some for pneumonia
Interleukins (IL1, IL6, IL-8, IL-10, IL-12, IL-17, and TNF-α…)	Rapid increase in blood, mostly evaluated for sepsis
mRNA transcriptomi /genomic biomarkers / proteomic biomarkers	Promising, high sensitivity and high specificity, use of multiple protein markers at the same time to distinguish the cause of fever, not yet commercially available

The kinetics of the different biomarkers



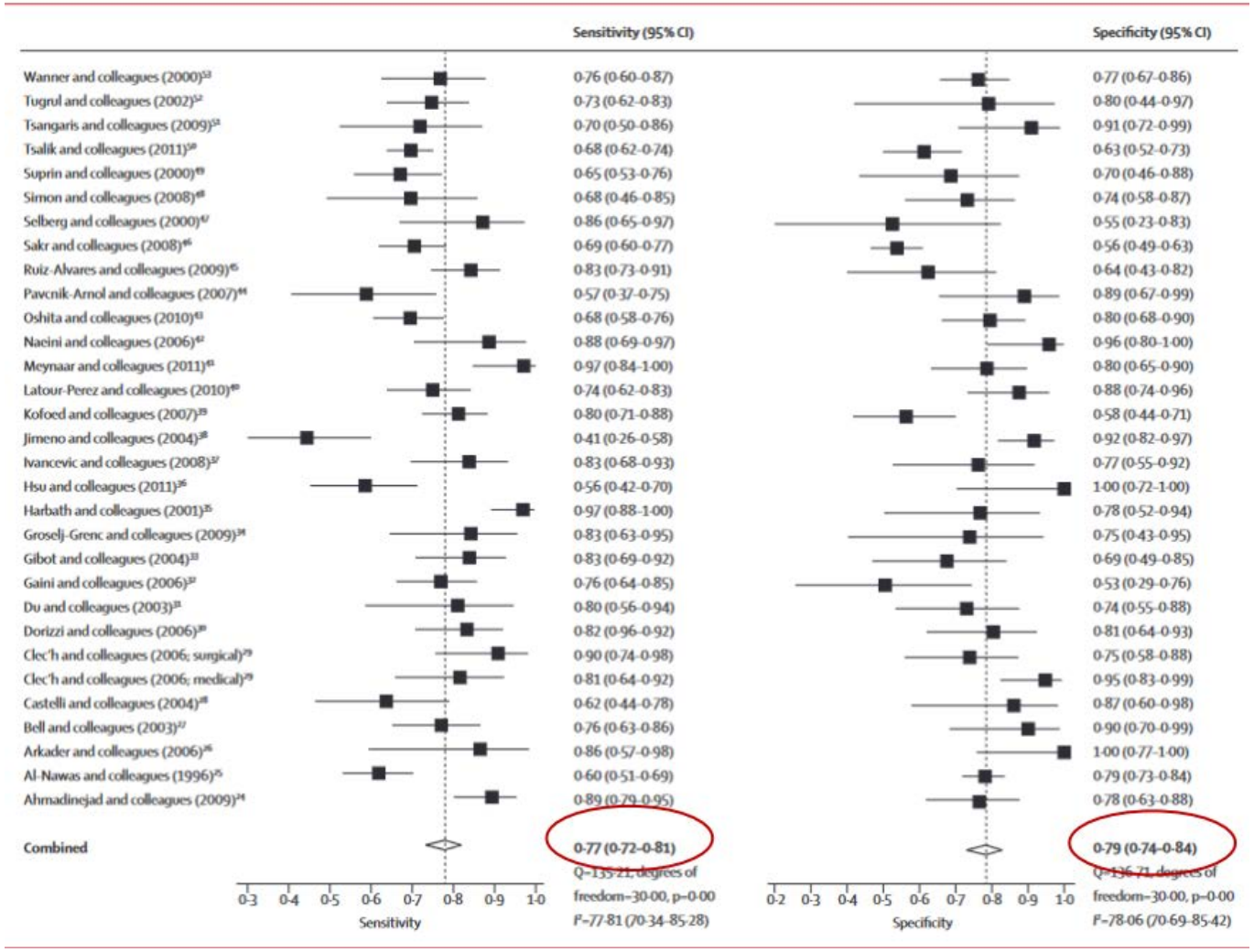
Biomarkers and bacterial infections

Serum Procalcitonin and C-Reactive Protein Levels as Markers of Bacterial Infection: A Systematic Review and Meta-analysis

	Procalcitonin markers				C-reactive protein markers			
	No. of results		Sensitivity,	Specificity,	No. of results		Sensitivity,	Specificity,
Study	TP/FN	FP/TN	% (95% CI)	% (95% CI)	TP/ FN	FP/TN	% (95% CI)	% (95% CI)
Aouifi et al. [117]	46/2	8/41	96 (85–99)	84 (70–92)	50/33	4/10	60 (49–71)	71 (42–90)
Enguix et al. [118][a]	19/3	1/23	86 (64–96)	96 (77–100)	19/4	1/22	83 (61–94)	96 (76–100)
Hatherill et al. [119][a]	103/3	9/40	97 (91–99)	82 (68–91)	73/0	37/43	100 (95–100)	54 (42–65)
Muller [121][a]	52/3	6/40	95 (84–99)	87 (73–95)	41/9	17/34	82 (68–91)	67 (52–79)
Penel et al. [122][a]	43/14	0/5	75 (62–85)	100 (48–100)	43/24	0/1	64 (52–75)	100 (3–100)
Rothenburger et al. [123][a]	12/2	3/42	86 (56–97)	93 (81–98)	14/30	1/14	32 (19–48)	93 (66–100)
Selberg et al. [125]	19/5	3/6	79 (57–92)	67 (31–91)	19/9	3/2	68 (48–83)	40 (7–83)
Suprin et al. [126][a]	49/6	26/14	89 (77–95)	35 (21–52)	55/5	19/14	92 (81–97)	42 (26–61)
Ugarte et al. [127][a]	75/31	36/48	71 (61–79)	57 (46–68)	80/26	3/53	75 (66–83)	63 (52–73)
Viallon et al. [128][a]	19/2	2/38	90 (68–98)	95 (82–99)	13/3	8/37	81 (54–95)	82 (67–91)
Total[b]	…	…	88 (80–93)	81 (67–90)	…	…	75 (62–84)	67 (56–77)

Simon L, et al. Clin Infect Dis 2004;389:206-17

PCT in sepsis/critical ill patients: meta-analysis, 30 studies included (3244 patients)



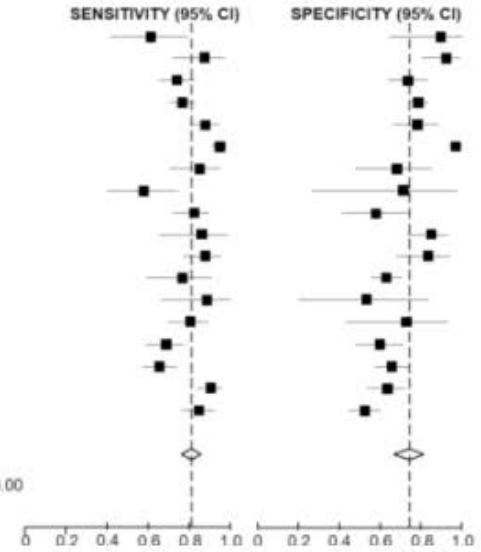
Conclusions:
Procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients.- Nevertheless, the results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment

Wacker C, et al. Lancet Infect Dis 2013;13:426-35

PCT and CD14 in sepsis: 3012 patients

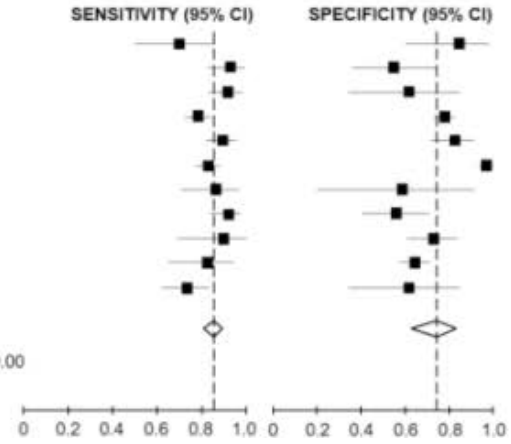
PCT

Author year	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)
Ali 2016	0.61 [0.42 - 0.77]	0.89 [0.65 - 0.99]
Bacil 2003	0.85 [0.71 - 0.94]	0.92 [0.80 - 0.98]
Bauer 2016	0.73 [0.64 - 0.81]	0.74 [0.64 - 0.83]
CakirMadenci 2014	0.75 [0.69 - 0.81]	0.79 [0.74 - 0.83]
Endo 2012	0.86 [0.78 - 0.92]	0.79 [0.67 - 0.87]
Enguix-Armada 2016	0.92 [0.88 - 0.95]	0.96 [0.92 - 0.99]
Gibot 2004	0.83 [0	
Godnic 2015	0.57 [0	
Klouche 2016	0.80 [0.71 - 0.87]	0.59 [0.43 - 0.74]
Leli 2016	0.84 [0.64 - 0.95]	0.84 [0.73 - 0.92]
Miglietta 2015	0.86 [0.75 - 0.93]	0.83 [0.69 - 0.93]
Romualdo 2014	0.76 [0.59 - 0.88]	0.64 [0.57 - 0.71]
Selberg 2000	0.86 [0.65 - 0.97]	0.55 [0.23 - 0.83]
Takahashi 2016	0.79 [0.69 - 0.87]	0.73 [0.45 - 0.92]
Ugarte 1999	0.68 [0.58 - 0.76]	0.61 [0.49 - 0.72]
vanderGeest 2016	0.65 [0.57 - 0.73]	0.66 [0.58 - 0.74]
Wong 2013	0.88 [0.82 - 0.93]	0.64 [0.55 - 0.72]
Yang 2016	0.83 [0.75 - 0.90]	0.54 [0.47 - 0.61]
COMBINED	0.80 [0.75 - 0.84]	0.75 [0.67 - 0.81]
	Q = 93.00, df = 17.00, p = 0.00	Q =132.11, df = 17.00, p = 0.00
	I2 = 81.72 [74.01 - 89.43]	I2 = 87.13 [82.21 - 92.05]



P-SEP

Author year	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)
Ali 2016	0.70 [0.51 - 0.84]	0.83 [0.59 - 0.96]
Behnes 2014	0.91 [0.82 - 0.97]	0.54 [0.34 - 0.72]
Behnes 2014	0.90 [0.81 - 0.96]	0.60 [0.32 - 0.84]
CakirMadenci 2014	0.77 [0.72 - 0.83]	0.77 [0.72 - 0.81]
Endo 2012	0.88 [0.80 - 0.93]	0.81 [0.70 - 0.90]
Enguix-Armada 2016	0.82 [0.76 - 0.86]	0.96 [0.92 - 0.99]
Godnic 2015	0.85 [0.70 - 0.94]	0.57 [0.18 - 0.90]
Klouche 2016	0.90 [0.82 - 0.95]	0.55 [0.39 - 0.70]
Leli 2016	0.88 [0.69 - 0.97]	0.72 [0.59 - 0.82]
Romualdo 2014	0.81 [0.65 - 0.92]	0.63 [0.56 - 0.70]
Takahashi 2016	0.73 [0.62 - 0.82]	0.60 [0.32 - 0.84]
COMBINED	0.84 [0.80 - 0.88]	0.73 [0.61 - 0.82]
	Q = 26.60, df = 10.00, p = 0.00	Q = 75.16, df = 10.00, p = 0.00
	I2 = 62.41 [37.85 - 86.97]	I2 = 86.69 [80.04 - 93.35]



Kondo Y, et al. J Int Care 2019;22:2-13.

Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult patients: a systematic review and meta-analysis

Metaanalysis – 19 studies were included

Conclusions:

The meta-analysis provided evidence that the diagnostic accuracy of procalcitonin and presepsin in detecting infection was similar and that both are useful for early diagnosis of sepsis and subsequent reduction of mortality in critically ill adult patients.

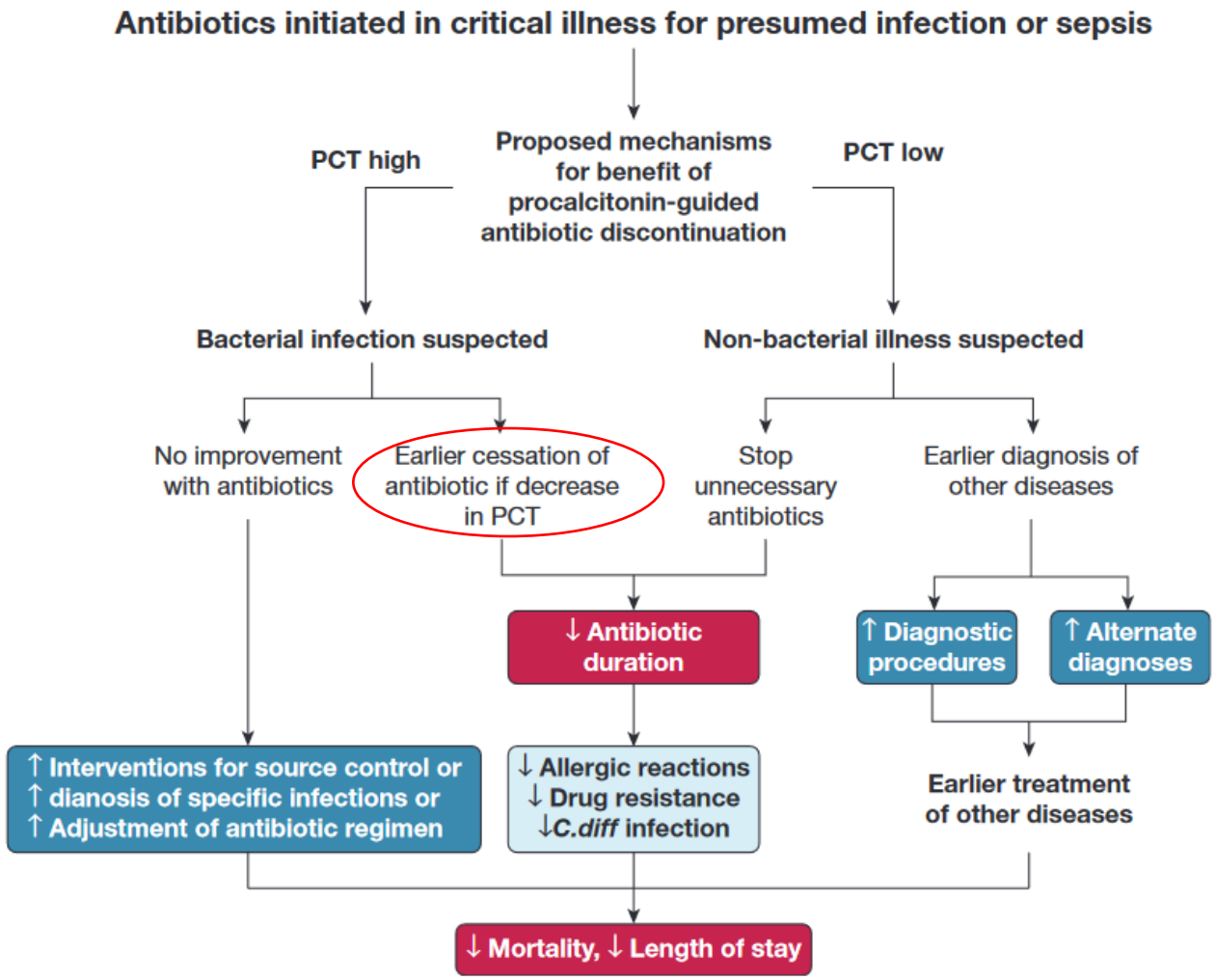
Biomarkers to start antibiotics in sepsis

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Critical Care Medicine

Recommendation
16. For adults with suspected sepsis or septic shock, we **suggest against** using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone *Weak recommendation, very low quality of evidence*

PCT-Guided Antibiotic Discontinuation and Mortality in Critically Ill Adults A Systematic Review and Meta-analysis



Pepper DJ, Sun J, Rhee C, Welsh J, Powers JH 3rd, Danner RL, Kadri SS. Chest. 2019 Jun;155(6):1109-1118

Biomarkers in meningitis. A systematic review and meta-analysis

(9 studies, 725 adult patients)

Conclusions:
Serum PCT is a highly accurate diagnostic test that can be used by physicians for rapid differentiation between bacterial and viral causes of meningitis in adults.

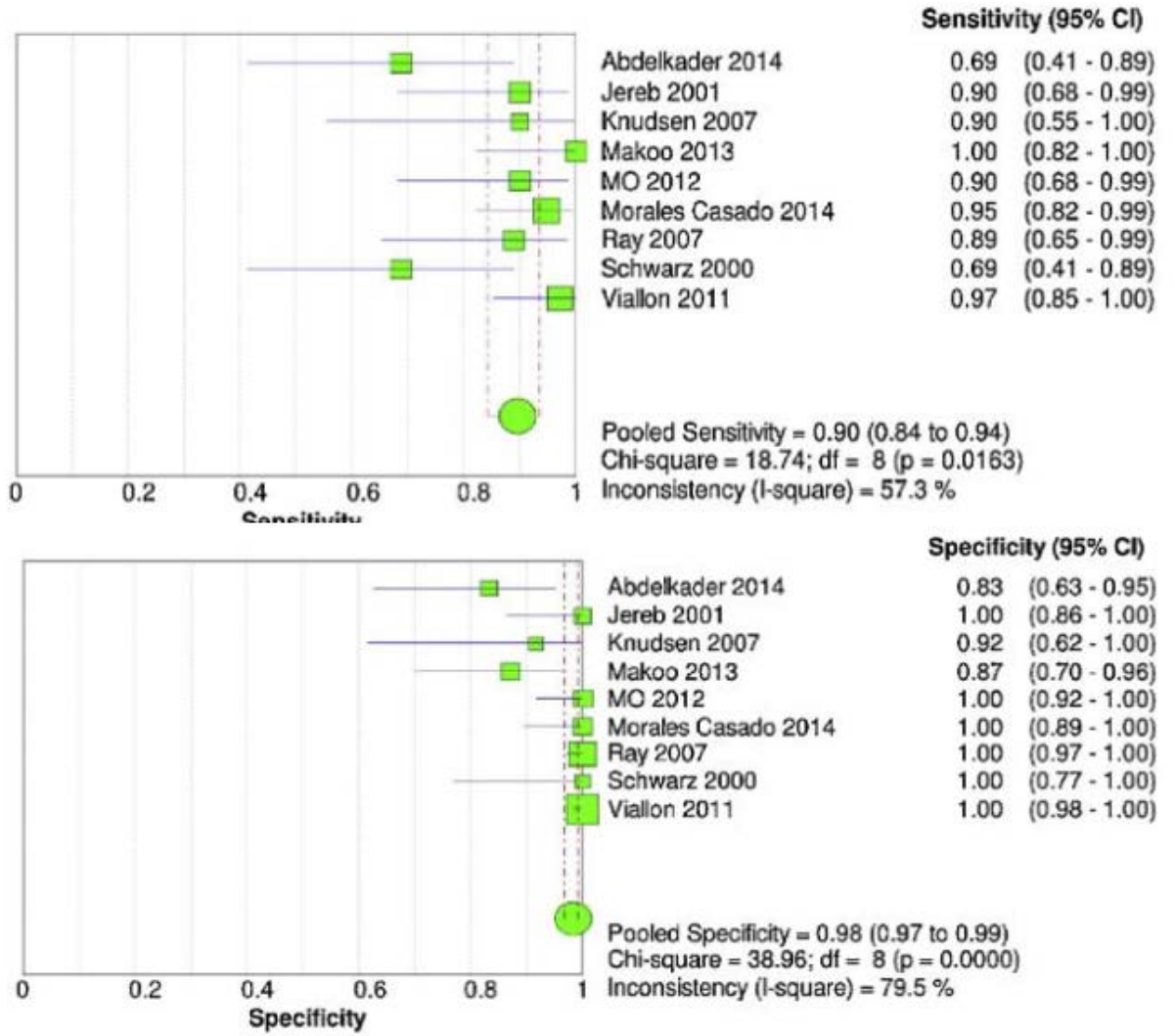


Figure 3. Pooled sensitivity (A) and specificity (B) for serum procalcitonin for the diagnosis of bacterial meningitis in adults.

Vikse J, et al. The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis. Intern J Infect Dis 2015;38:68-76

Biomarkers in respiratory infections

Accuracy of Biomarkers for the Diagnosis of Adult Community-acquired Pneumonia: A Meta-analysis

Studies (#)	Test and cutoff	Sensitivity	Specificity
3	CRP > 10 mg/L	0.90 (0.52–0.99)	0.48 (0.27–0.70)
6	CRP > 20 mg/L	0.80 (0.68–0.89)	0.62 (0.51–0.71)
2	CRP > 30 mg/L	0.76 (0.29–0.96)	0.70 (0.32–0.92)
1	CRP > 40 mg/L	0.89 (0.85–0.92)	0.52 (0.44–0.59)
9	CRP > 50 mg/L	0.71 (0.56–0.82)	0.80 (0.70–0.88)
1	CRP > 70 mg/L	0.69 (0.59–0.78)	0.66 (0.54–0.77)
6	CRP > 100 mg/L	0.58 (0.39–0.74)	0.90 (0.80–0.95)
1	CRP > 200 mg/L	0.36 (0.31–0.41)	0.96 (0.92–0.98)
2	PCT > 0.06–0.08 µg/L	0.60 (0.36–0.80)	0.75 (0.55–0.88)
3	PCT > 0.1 µg/L	0.74 (0.48–0.90)	0.69 (0.42–0.87)
4	PCT > 0.25 µg/L	0.44 (0.21–0.70)	0.91 (0.76–0.97)
4	PCT > 0.50 µg/L	0.28 (0.11–0.53)	0.96 (0.80–0.99)
1	PCT > 1.0 µg/L	0.43 (0.38–0.48)	0.96 (0.92–0.98)
5	WBCs > 9.5 × 10^9–10.5 × 10^9 cells/L	0.55 (0.45–0.66)	0.82 (0.78–0.86)

Conclusions:

The best evidence supports CRP as the preferred biomarker for diagnosis of outpatient CAP given its:

- Accuracy
- Low cost
- Point-of-care availability

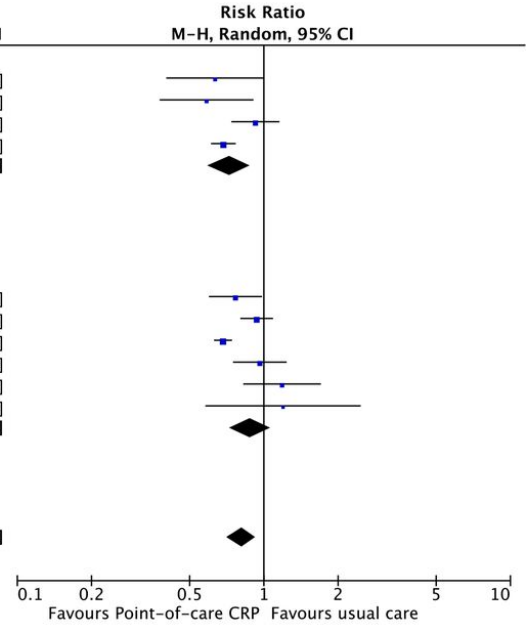
Ebel MH, et al. Academ Emerg Med 2020;27:195-206.

Impact of point-of-care C reactive protein in ambulatory care: a systematic review and meta-analysis

Conclusion:
performing point-of-care CRP could reduce immediate antibiotic prescription in adults and children.

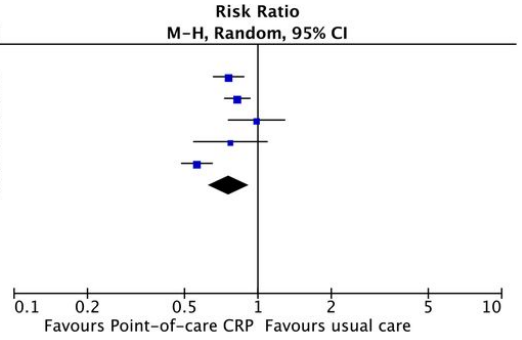
A

Study or Subgroup	Point-of-care CRP Events	Total	usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
cluster randomised trials						
Andreeva 2014	18	49	22	38	5.5%	0.63 [0.40, 1.00]
Cals 2009	20	65	31	59	5.8%	0.59 [0.38, 0.91]
Lemiengre 2014	117	455	106	381	11.5%	0.92 [0.74, 1.16]
Little 2013	304	920	407	844	15.5%	0.69 [0.61, 0.77]
Subtotal (95% CI)		**1489**		**1322**	**38.2%**	**0.73 [0.60, 0.88]**
Total events	459		566			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.62$, df = 3 (P = 0.08); $I^2 = 55\%$						
Test for overall effect: Z = 3.21 (P = 0.001)						
individually randomised trials						
Cals 2010	56	129	73	129	10.6%	0.77 [0.60, 0.98]
Diederichsen 2008	179	414	184	398	14.1%	0.94 [0.80, 1.09]
Do 2016	441	1017	647	1019	16.4%	0.68 [0.63, 0.74]
Melbye 1995	54	108	68	131	10.6%	0.96 [0.75, 1.24]
Rebnord 2017	36	138	57	259	7.3%	1.19 [0.82, 1.70]
Van den Bruel 2016	10	26	9	28	2.7%	1.20 [0.58, 2.47]
Subtotal (95% CI)		**1832**		**1964**	**61.8%**	**0.88 [0.73, 1.07]**
Total events	776		1038			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 24.04$, df = 5 (P = 0.0002); $I^2 = 79\%$						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**3321**		**3286**	**100.0%**	**0.81 [0.71, 0.92]**
Total events	1235		1604			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 31.82$, df = 9 (P = 0.0002); $I^2 = 72\%$						
Test for overall effect: Z = 3.21 (P = 0.001)						
Test for subgroup differences: $Chi^2 = 1.90$, df = 1 (P = 0.17), $I^2 = 47.5\%$						



B

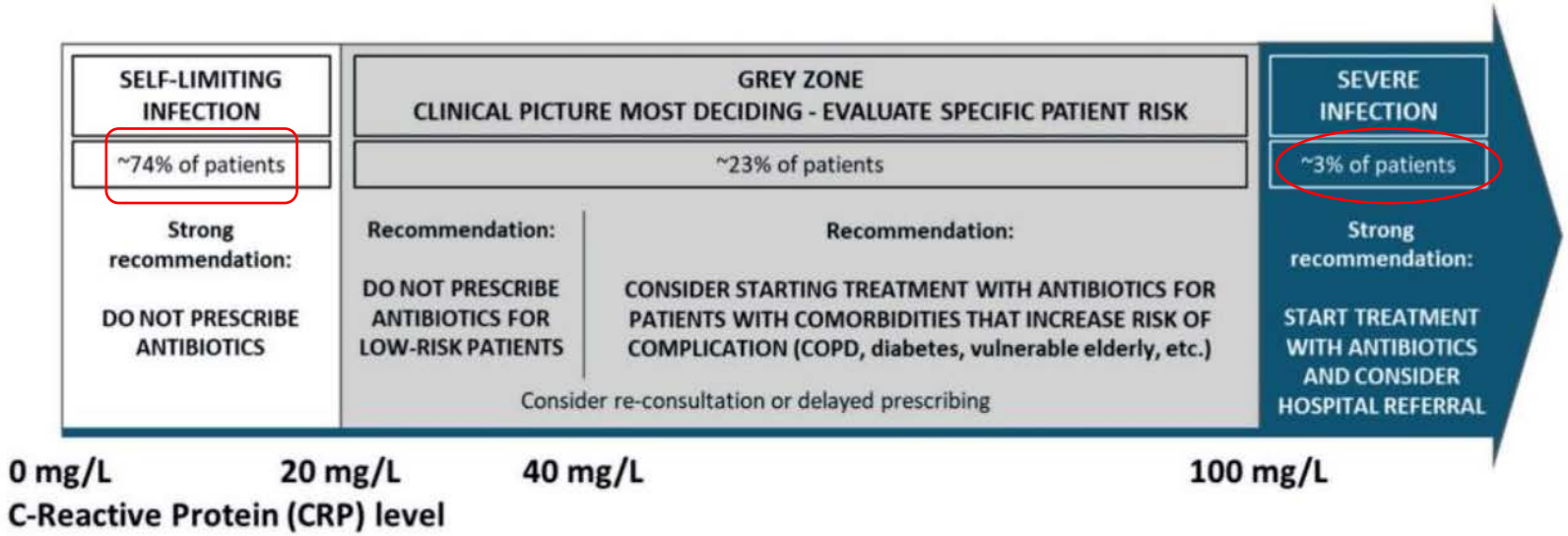
Study or Subgroup	Point-of-care CRP Events	Total	usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
observational studies						
Bjerrum 2004	166	281	67	86	22.7%	0.76 [0.65, 0.88]
Fagan 2001	87	122	175	202	23.7%	0.82 [0.73, 0.93]
Jakobsen 2010	129	372	46	131	17.1%	0.99 [0.75, 1.30]
Kavanagh 2011	27	60	35	60	13.7%	0.77 [0.54, 1.10]
Llor 2012	97	208	521	628	22.7%	0.56 [0.48, 0.65]
Subtotal (95% CI)		**1043**		**1107**	**100.0%**	**0.76 [0.63, 0.91]**
Total events	506		844			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 21.08$, df = 4 (P = 0.0003); $I^2 = 81\%$						
Test for overall effect: Z = 2.89 (P = 0.004)						
Test for subgroup differences: Not applicable						



Verbakel JY, et al. BMJ 2019

Biomarkers in lower respiratory tract infections

Guidance on C-reactive protein point-of-care testing and complementary strategies to improve antibiotic prescribing for adults with lower respiratory tract infections in primary care



Van Hecke O, et al. Frontiers Med 2023

PCT in respiratory tract infections

Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis

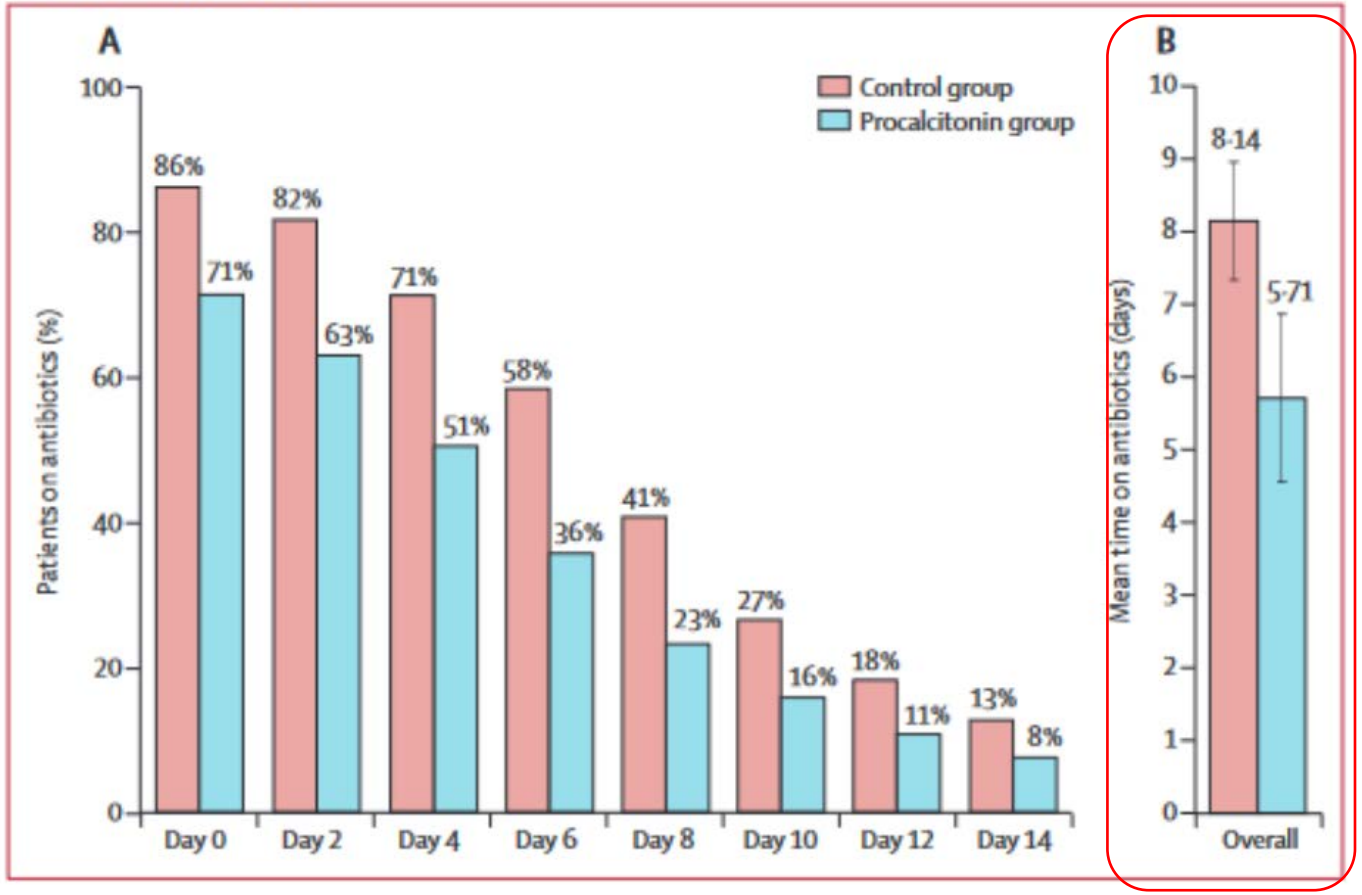
	Control (n=3372)	Procalcitonin group (n=3336)	Adjusted OR or difference (95% CI), p value*	$p_{interaction}$
Overall				
Initiation of antibiotics	2894 (86%)	2351 (70%)	0·27 (0·24 to 0·32), p<0·0001	..
Duration of antibiotics, days†	9·4 (6·2)	8·0 (6·5)	−1·83 (−2·15 to −1·5), p<0·0001	..
Total exposure of antibiotics, days‡	8·1 (6·6)	5·7 (6·6)	−2·43 (−2·71 to −2·15), p<0·0001	..
Setting-specific outcomes				
Primary care	501	507	..	..
Initiation of antibiotics	316 (63%)	116 (23%)	0·13 (0·09 to 0·18), p<0·0001	<0·0001
Duration of antibiotics, days†	7·3 (2·5)	7·0 (2·8)	−0·52 (−1·07 to 0·04), p=0·068	0·064
Total exposure of antibiotics, days‡	4·6 (4·1)	1·6 (3·2)	−3·02 (−3·45 to −2·58), p<0·0001	0·101
Emergency department	1638	1615	..	..
Initiation of antibiotics	1354 (83%)	1119 (69%)	0·49 (0·41 to 0·58), p<0·0001	<0·0001
Duration of antibiotics, days†	9·8 (5·4)	7·3 (5·1)	−2·45 (−2·86 to −2·05), p<0·0001	<0·0001
Total exposure of antibiotics, days‡	8·2 (6·2)	5·2 (5·4)	−3·02 (−3·41 to −2·62), p<0·0001	<0·0001
Intensive care unit	1233	1214	..	..
Initiation of antibiotics	1224 (99%)	1116 (92%)	0·02 (0·01 to 0·05), p<0·0001	<0·0001
Duration of antibiotics, days†	9·5 (7·4)	8·8 (7·8)	−1·23 (−1·82 to −0·65), p<0·0001	<0·0001
Total exposure of antibiotics, days‡	9·5 (7·4)	8·1 (7·9)	−1·44 (−1·99 to −0·88), p<0·0001	<0·0001

Schuetz P, et al. Lancet Infect 2018;18:95-106.

PCT in respiratory tract infections

Conclusions:
PCT to guide AB treatment in patients with acute respiratory infections
-reduces antibiotic exposure
-reduce side-effects
- improve survival.
Mortality rate at 30 days was significantly lower in PCT-guided patients than in control arm.

Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis



Schuetz P, et al. Lancet Infect 2018;18:95-106.

PCT in lower respiratory infection

Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay,* Grant W. Waterer,* Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I.

Am J Respir Crit Care Med. 2019 Oct 1; 200(7): e45–e67.

- „We recommend that empiric antibiotic therapy should be initiated in adults with clinically suspected and radiographically confirmed CAP regardless of initial serum procalcitonin level“.

PCT in the management of Community-Acquired Pneumonia in Hospitalized Adults

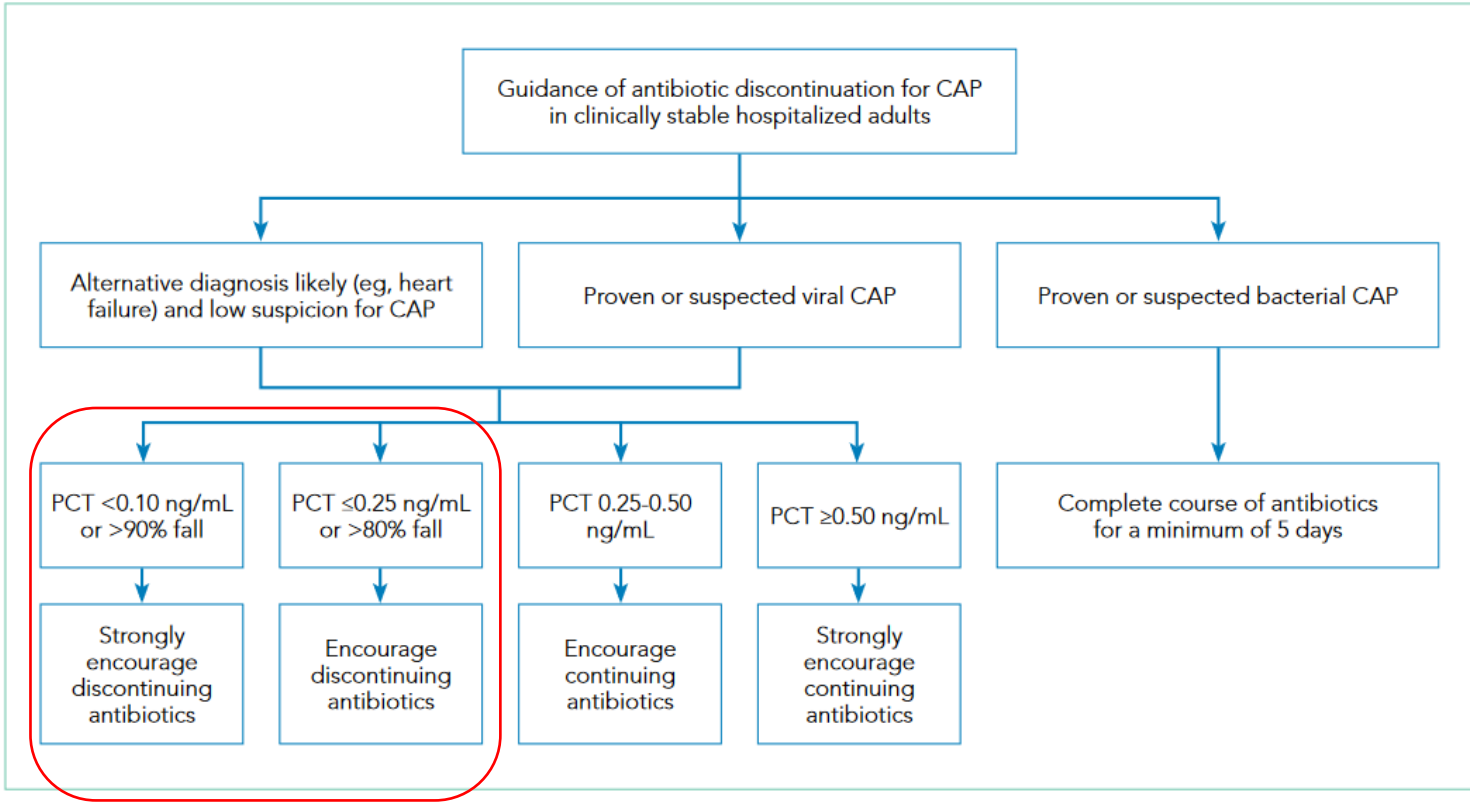


FIG. Procalcitonin Guidance for Antibiotic Discontinuation in Hospitalized Adults with CAP

The cut-off values and thresholds used in this algorithm are adapted from those used in the clinical trials included in the 2017 Cochrane review meta-analysis.[6]

Abbreviations: CAP, community acquired pneumonia, PCT, procalcitonin.

Choi JJ, J Hosp Med. 2019 Nov 1;14(11):691-693.

Conclusions

- Still no ideal biomarker available
- Sensibility and specificities differ between them
- Their usefulness in clinical practice differ depending on the site of infection
- Do **NOT** forget the clinical pictures and the comorbidities of the patients
- Most probably, in the future the decisions of prescribing antibiotics will be based on a combination of biomarkers… artificial intelligence could be a useful tool

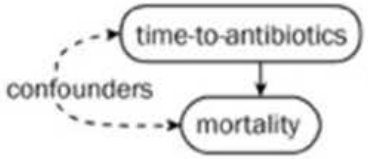
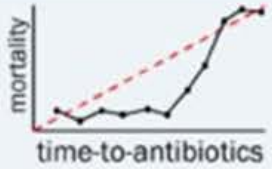
RISK OF MISLEADING CONCLUSIONS IN OBSERVATIONAL STUDIES OF TIME-TO-ANTIBIOTICS AND MORTALITY IN SUSPECTED SEPSIS

Pak et al., 2023 | *Clinical Infectious Diseases*

IDSA
Infectious Diseases Society of America

MOTIVATION Four analytical concerns are present in most cohort studies of time-to-antibiotics and sepsis outcomes.

OBJECTIVE Test for the effects of each of these concerns in a multi-hospital cohort of patients with suspected infection (N=104,248). We used logistic regression as in prior studies and varied the assumption underlying each concern.

ANALYTICAL CONCERN		TEST	RESULTS
Insufficient confounding adjustment		Add progressively more detailed covariates: basics → + comorbidities → + labs → + vitals	⚠ Changed
Including time-to-antibiotics outliers		Pts treated >6h are rare & different. Lower max time-to-antibiotics: 24h → 12h → 6h	⚠ Changed
Equating sepsis & septic shock		Separate analyses for: • suspected infection • suspected sepsis • suspected septic shock	⚠ Changed
Linearizing non-linearity		Remove the assumption of a linear relationship between time-to-antibiotics ↔ log odds of mortality	⚠ Changed

CONCLUSIONS

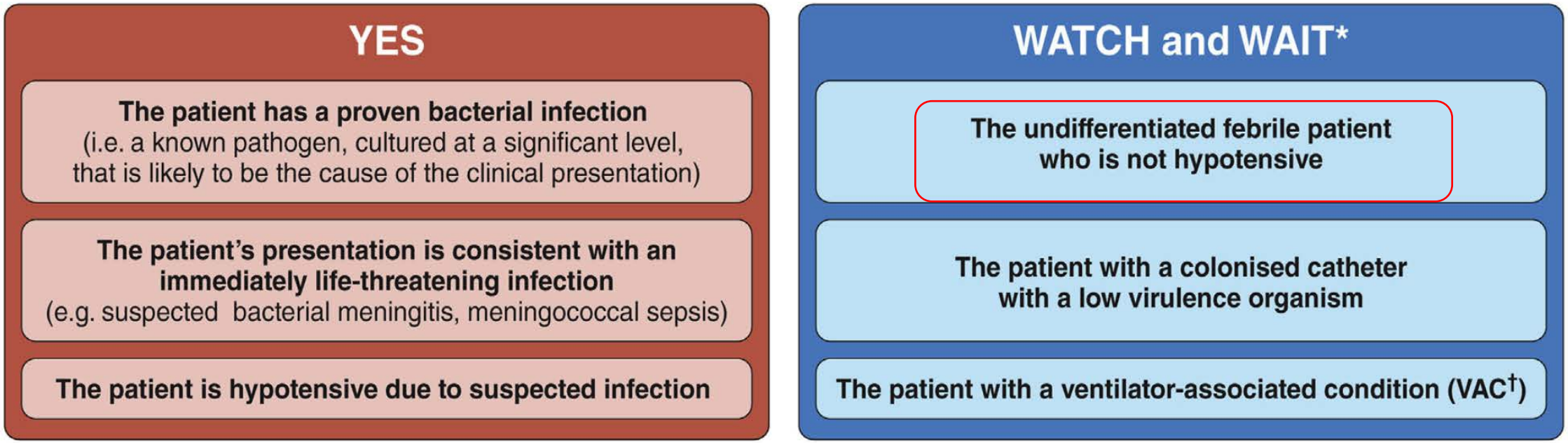
Each of these analytical choices can easily bias estimates of the time-to-antibiotics ↔ mortality association.

In our most defensible model (max adjustment, only time-to-antibiotics <6h) each additional hour until antibiotics was associated with the following changes in mortality:

COHORT		HOURLY aOR
Septic Shock	↑	1.07 (1.04–1.11)
Sepsis	NS	1.03 (0.98–1.09)
Infection	NS	0.99 (0.94–1.05)

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciad450

Do I Need to Give Antibiotics?



*Watch and Wait: Close monitoring of the patient in an high-dependency or intensive care setting for signs of deterioration whilst further investigations and attempts at source identification and control are carried out.

†VAC: An increase in the minimum PEEP during a 24-hour period of 3cm H_2O or an increase in the minimum FiO_2 during a 24 hour period of 20%, after a period of 48 hours of stable ventilator settings


Thank you!