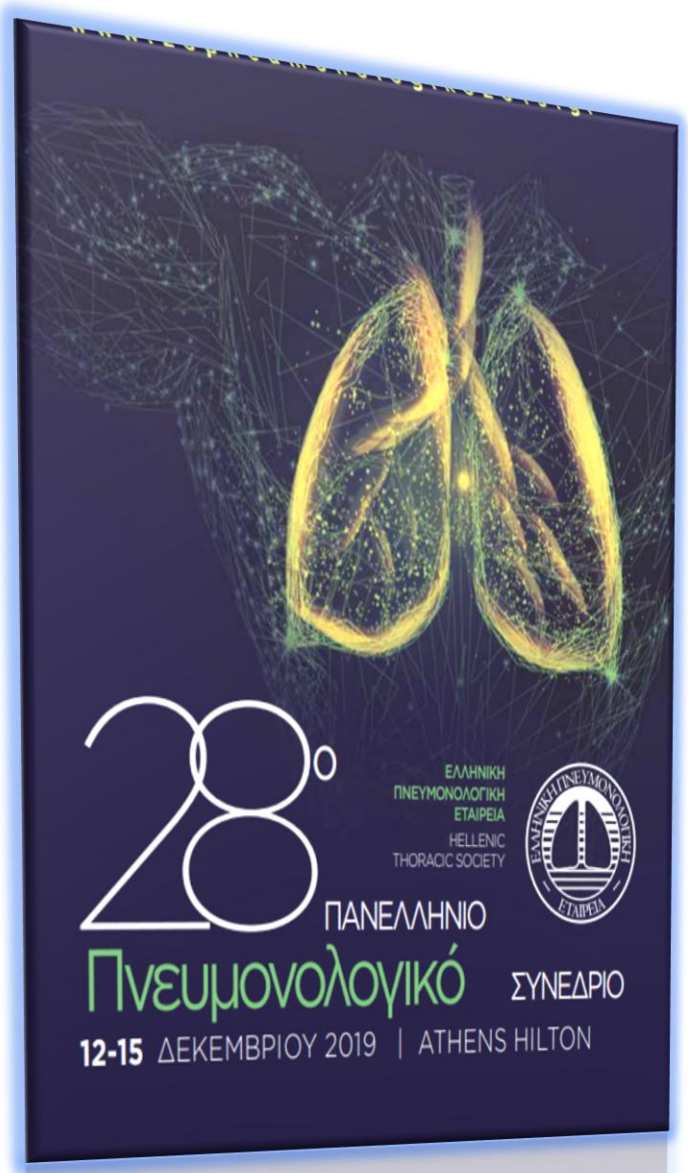


Βιοδείκτες λοιμώξεις αναπνευστικών. Πού βρισκόμαστε; Τι προσδοκούμε;

Σταματούλα Τσικρικά

Πνευμονολόγος-Φυματιολόγος

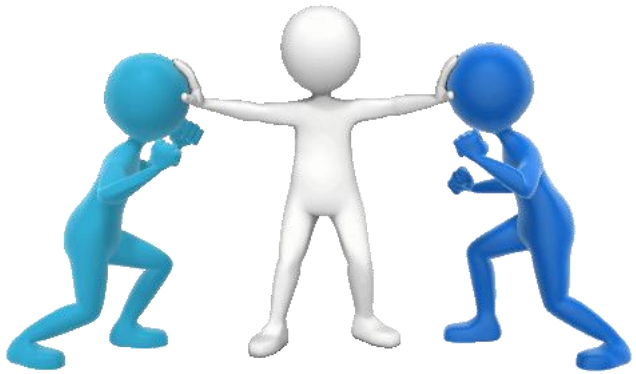
MSc Δημόσιας Υγείας

MSc Διεθνής Ιατρική- Διαχείριση Κρίσεων Υγείας

Διδάκτωρ ΕΚΠΑ

Εξ. ΜΕΘ Σισμανογλείου

ΚΑΜΙΑ ΣΥΓΚΡΟΥΣΗ ΣΥΜΦΕΡΟΝΤΩΝ

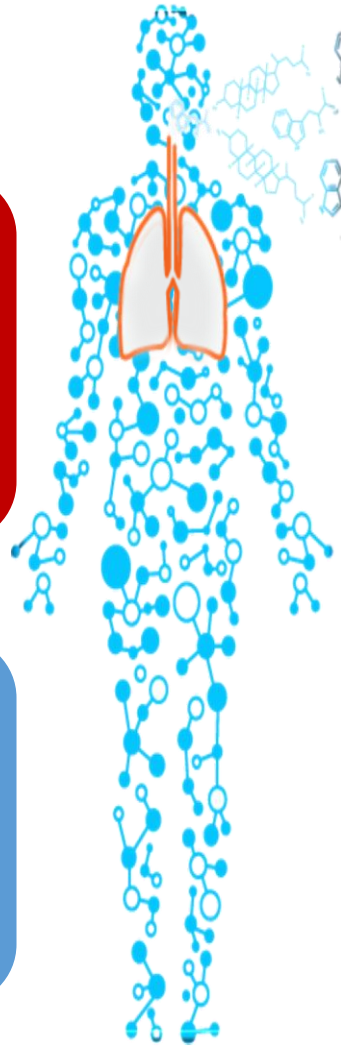


Τι καλούμε βιολογικό δείκτη?

Μετρήσιμες ουσίες σε ένα βιολογικό σύστημα που οι διαφορές στη συγκέντρωσή τους αντανακλούν διαταραχές στην φυσιολογική λειτουργία του συστήματος

Sankar V, et al. J Anesth 2013

Δίνουν απάντηση για τις ενδεχόμενες επιδράσεις ευεργετικές ή μη ενός φαρμάκου ή μιας θεραπευτικής αγωγής, σε συγκεκριμένους ασθενείς, ώστε οι γιατροί να γνωρίζουν εκ των προτέρων πριν προχωρήσουν σε χορήγηση της όποιας θεραπείας



Biomarkers working group, 2001

Ιδανικός βιοδείκτης…

Ως εργαλείο…

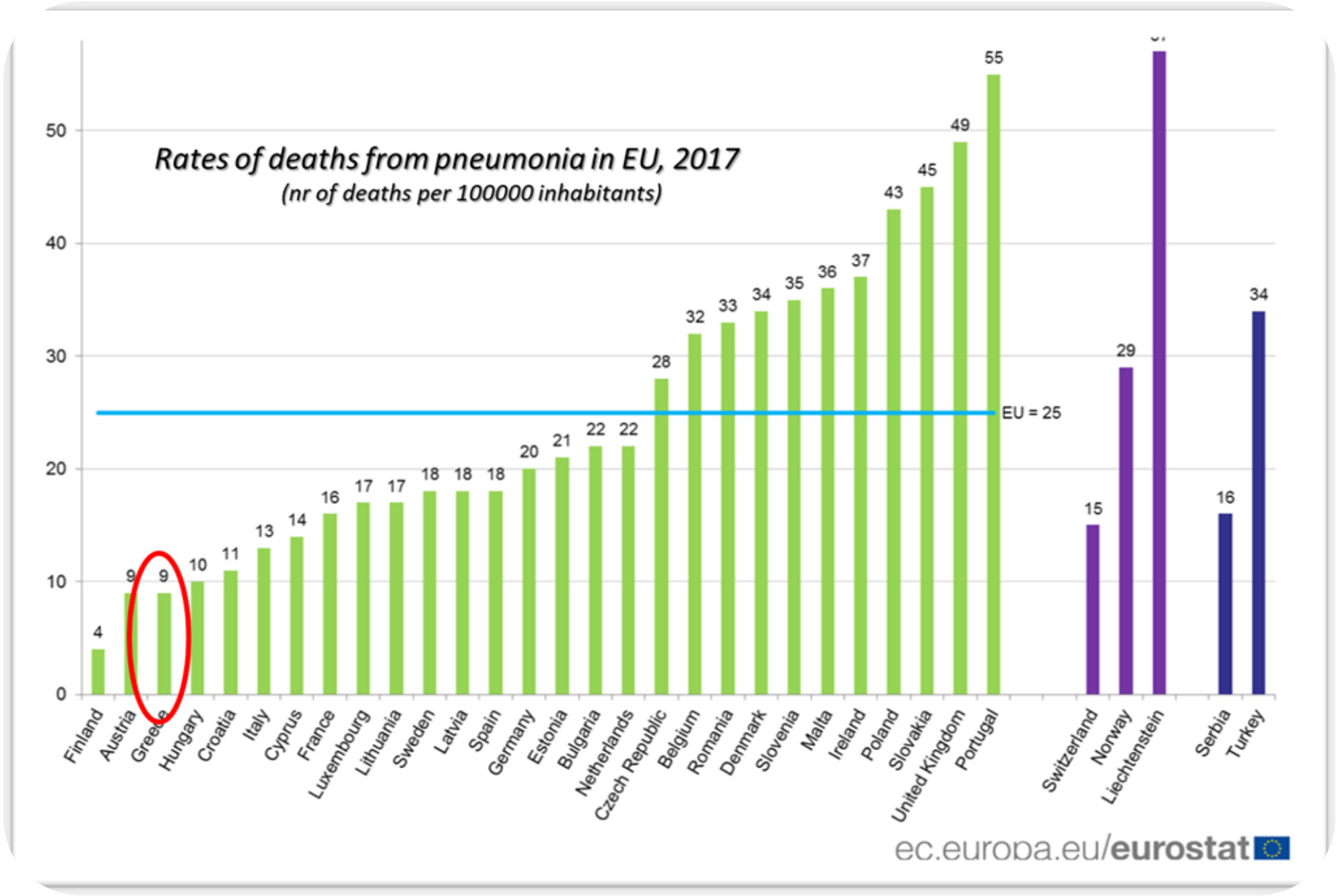
- Εύκολα μετρήσιμος
- Υψηλή ειδικότητα
- Υψηλή ευαισθησία
- Άμεση συσχέτιση με την κλινική κατάσταση και την πρόγνωση του ασθενούς
- Χωρίς αυξημένο κόστος

McNerney et al.2012

Σε σχέση με τη νόσο…

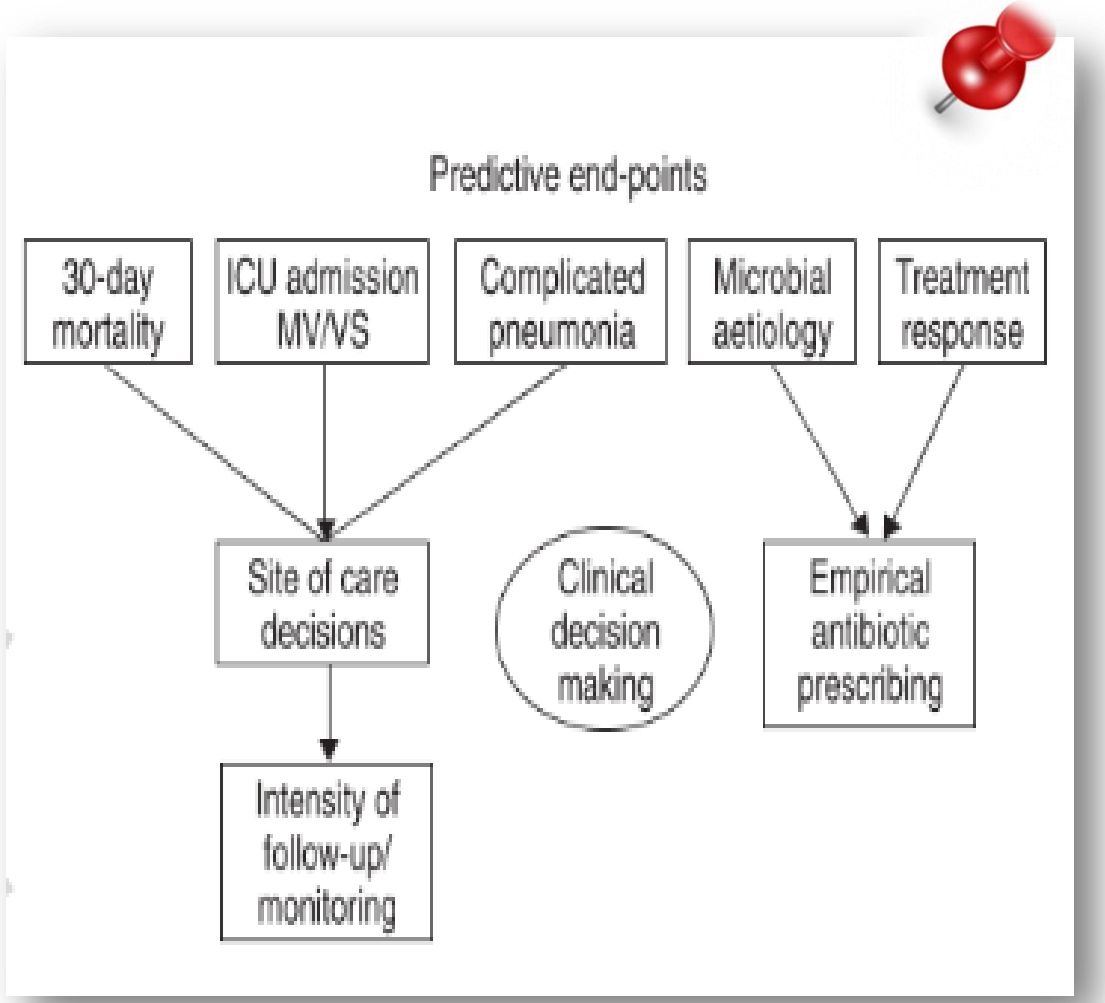
- Ανίχνευση ασθένειας
- Δείκτης κλινικής παρακολούθησης
- Δείκτης εργαστηριακής παρακολούθησης
- Δείκτης σταδιοποίησης
- Δείκτης πρόγνωσης

Wallis et al., 2010


Rates of deaths from pneumonia in EU, 2017
(nr of deaths per 100000 inhabitants)
EU = 25
Finland 4
Austria 9
Greece 9
Hungary 10
Croatia 11
Italy 13
Cyprus 14
France 16
Luxembourg 17
Lithuania 17
Sweden 18
Latvia 18
Spain 18
Germany 20
Estonia 21
Bulgaria 22
Netherlands 22
Czech Republic 28
Belgium 32
Romania 33
Denmark 34
Slovenia 35
Malta 36
Ireland 37
Poland 43
Slovakia 45
United Kingdom 49
Portugal 55
Switzerland 15
Norway 29
Liechtenstein
Serbia 16
Turkey 34
0
10
20
30
40
50
ec.europa.eu/eurostat

Τι προσδοκώ από τον βιοδείκτη στις λοιμώξεις αναπνευστικού?

- Διαφοροδιάγνωση
- Βαρύτητα της νόσου/Διαστρωμάτωση κινδύνου
- Διάρκεια της αγωγής/Αντιμικροβιακή αντοχή
- Πιθανότητα υποτροπής/επιπλοκές
- Θνησιμότητα



Ann Thorac Med. 2019

Procalcitonin
C-reactive protein
Proadrenomedullin
D-dimer
Brain natriuretic peptide
Copeptin
Pro-endothelin 1
White blood cell count
Others
- Cortisol
- Midregional proatrial natriuretic peptide
- Genomic bacterial load
- Pro-atrial natriuretic peptide
- Inflammatory cytokines (IL-6, TNF-α)
- Prothrombin fragment 1.2
- Thrombin–antithrombin complex
- Fibrinogen

IL: interleukin; TNF: tumour necrosis factor.

Int J Mol Sci. 2019

CURB-65 score

CURB(S) 65

↓

Saturation

ERJ 2012

CRB-65

↓

misclassified deaths as low risk patients

CURB-65	Clinical Feature	Points
C	Confusion	1
U	Urea > 7 mmol/L	1
R	RR ≥ 30	1
B	SBP ≤ 90 mm Hg OR DBP ≤ 60 mm Hg	1
65	Age ≥ 65	1

CURB-65 Score	Risk group	30-day mortality	Management
0–1	1	1.5%	Low risk, consider home treatment
2	2	9.2%	Probably admission vs close outpatient management
3–5	3	22%	Admission, manage as severe

Thorax 2003

PSI (Pneumonia Severity Index)

Κριτήρια εισαγωγής στο νοσοκομείο

Score	Risk	Disposition
≤70	Low risk	Outpatient care
71-90	Low risk	Outpatient vs. Observation admission
91-130	Moderate risk	Inpatient admission
>130	High risk	Inpatient admission

Patient characteristics	Number of points
Demographic factors	
Age	
Men	Age in years
Women	Age in years-10
Nursing home resident	Age plus ten
Coexisting illnesses (definitions listed below)	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination findings	
Altered mental status	20
Respiratory rate >30/min	20
Systolic blood pressure <90 mHg	20
Temperature <35◦C (95◦F) or >40◦C (104◦F)	15
Pulse rate >125/min	10
Laboratory and roentgenographic findings	
Arterial pH <7.35	30
Blood urea nitrogen >30 mg/dL (11 mmol/L)	20
Sodium <130 mmol/L	20
Glucose >250 mg/dL (14 mmol/L)	10
Hematocrit <30%	10
Partial pressure of arterial oxygen <60 mmHg	10
Pleural effusion	10

N Engl J Med 1997

SMART-COP

SMRT-COP

⇩

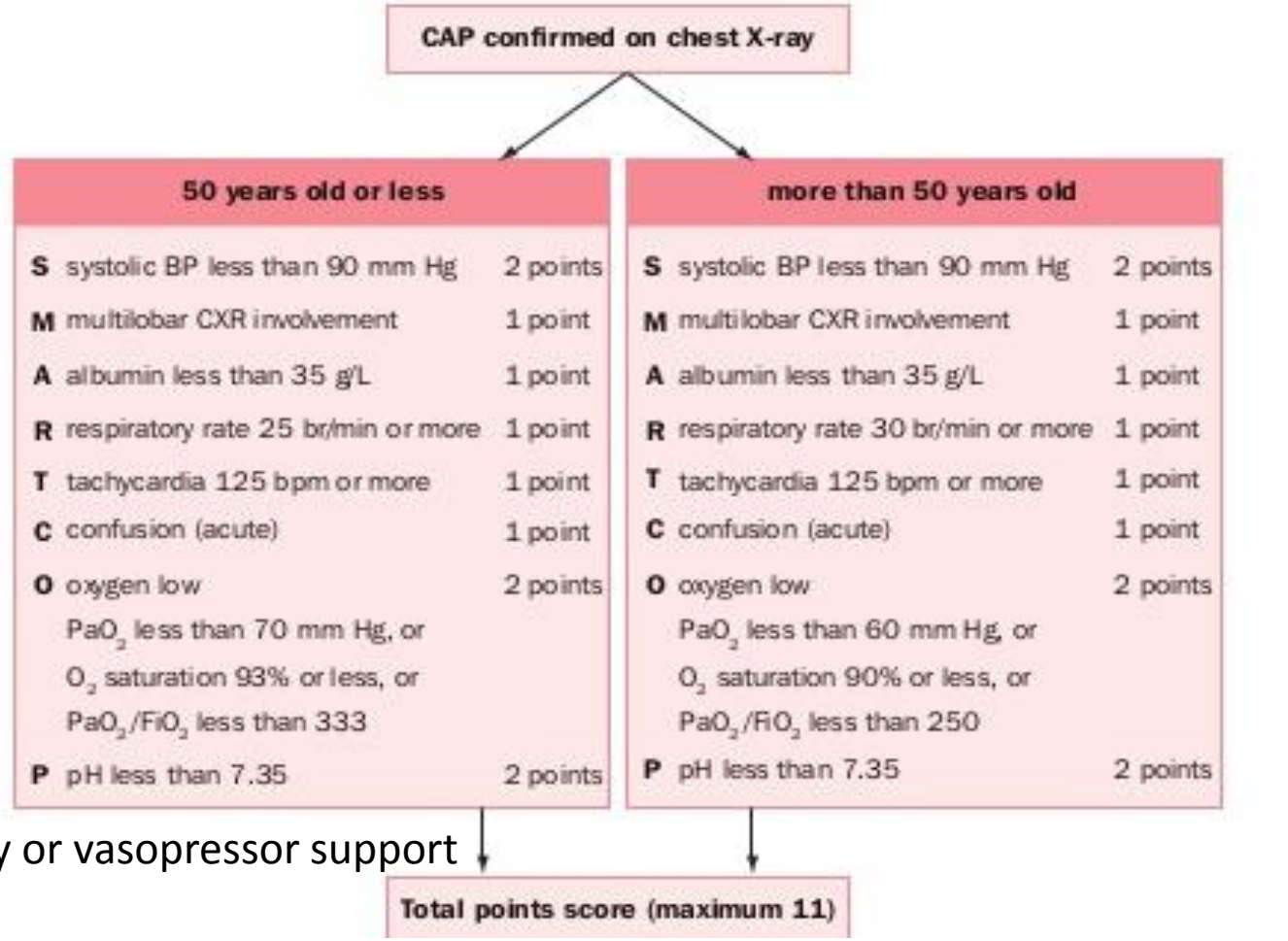
No albumin test

SMRT-CO

⇩

No albumin test

No ph test



IRVS: intensive respiratory or vasopressor support

Interpretation of SMART-COP score

0 to 2 points—low risk of needing intensive respiratory or vasopressor support (IRVS)

3 to 4 points—moderate risk (1 in 8) of needing IRVS

5 to 6 points—high risk (1 in 3) of needing IRVS

7 or more points—very high risk (2 in 3) of needing IRVS

Severe CAP = a SMART-COP score of 5 or more points.

Clin Infect Dis. 2008

IDSA/ATS 2007

Simplified Minor Criteria	Modified Minor Criteria
Confusion	Confusion
Uremia	Uremia
Respiratory rate ≥30 breaths/min	Respiratory rate ≥30 breaths/min
$PaO_2/FiO_2 \leq 250$ mmHg	$PaO_2/FiO_2 \leq 250$ mmHg
Multilobar infiltrates	Multilobar infiltrates
	Age ≥65 years

The modified version best predicted mortality
More suitable for clinic and ER department

Box 1 : ATS/IDSA criteria for ICU admission in CAP.

Criteria for ICU Admission

Major criteria

- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

Minor criteria

- Confusion, disorientation
- BUN >20 mg/dL
- RR>30 breaths/min
- Hypotension requiring aggressive fluid resuscitation
- PaO_2/FiO_2 ratio <250
- Multilobar infiltrates
- White blood cell count <4000 cells/mm^3
- Platelet count <100.000 cells/mm^3
- Core temperature <36°C (96.8°F)

Direct admission to ICU is recommended if the patient has 1 major criterion (strong recommendation) or 3 minor criteria (moderate recommendation).

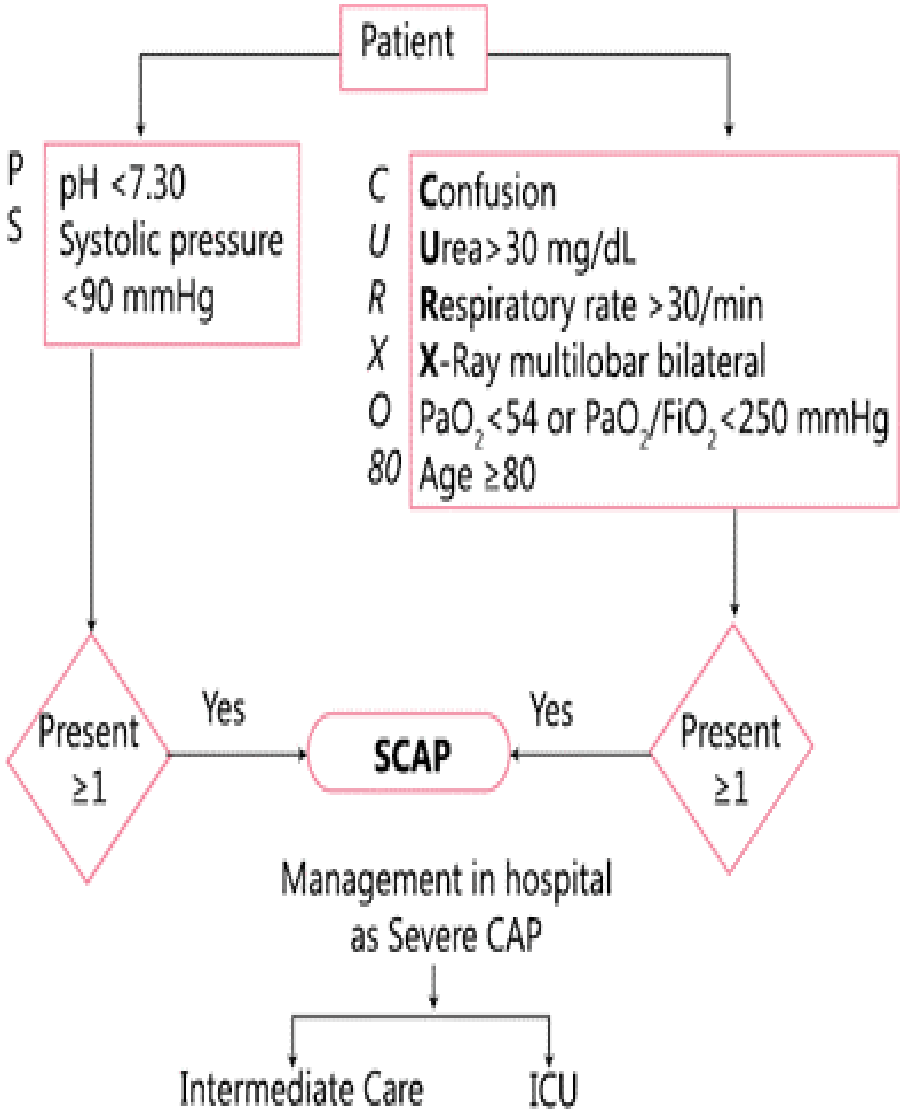
CAP-PIRO Score

P	**Comorbidities** (COPD or Imunnocompromised)	☐ 1 point
	Age > 70 yrs	☐ 1 point
I	**Bacteremia**	☐ 1 point
	Multilobar opacities	☐ 1 point
R	**Shock**	☐ 1 point
	Severe Hypoxemia	☐ 1 point
O	**ARDS**	☐ 1 point
	Acute renal failure	☐ 1 point

Interpretation

0–2 point	Low risk (1 in 30) for ICU mortality
3 points	Mild risk (1 in 8) for ICU mortality
4 points	High risk (2 in 5) for ICU mortality
5–8 points	Very high risk (3 in 4) for ICU mortality

Crit Care Med. 2009



J Infect. 2010

Δείκτες διαστρωμάτωσης κινδύνου

- A-DROP: AGE, DEHYDRATION, RESPRIRATORY FAILURE, ORIENTATION DISTURBANCE, SAP

  Sci Rep. 2018

- NEWS: National Early Warning Score

  BMJ Open. 2016

- CLCGH: Creatinine, Leukocyte, C-reactive protein, GCS≤9, HCO_3^-

  Eur J Intern Med. 2017

- CURSI: Confusion, Urea, Respiratory rate, Shock Index

  BMC Infect Dis. 2014

- SOAR: Systolic blood pressure, Oxygenation, Age, Respiratory rate

  Age Ageing. 2006

Severity scoring systems for pneumonia: current understanding and next steps. Curr Opin Pulm Med. 2018

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Score	Original purpose[a]	Original primary outcome in the development cohort
PSI [4]	'identify patients with community-acquired pneumonia who are at low risk of dying within 30 days of presentation'	30-day hospital mortality
CURB-65/CRB-65 [6]	'enable stratification of patients presenting to hospital with CAP into mortality risk groups that might be suitable for different management options'	30-day mortality
IDSA/ATS 2007 [7][b]	Distinguish patients with severe CAP who might benefit from ICU admission from those who would not directly benefit from ICU care	Direct admission to an ICU or high-level monitoring unit
SMART-COP [8]	'identify patients with CAP who require IRVS' (i.e., invasive or noninvasive mechanical ventilation or infusions of vasopressors for blood pressure support)	Need for intensive respiratory or vasopressor support
SCAP [9]	'identify, at first evaluation, patients at increased risk of complicated community-acquired pneumonia evolution'	Hospital mortality, mechanical ventilation, and/or septic shock
qSOFA [10▪▪]	'identify adult patients with suspected infection who are likely to have poor outcomes'	Hospital mortality

Η ει

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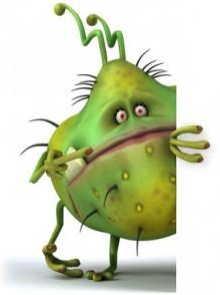
ΑΙΤΙΕΣ ΕΙΣΑΓΩΓΗΣ ΑΣΘΕΝΩΝ ΧΑΜΗΛΟΥ ΚΥΝΔΥΝΟΥ

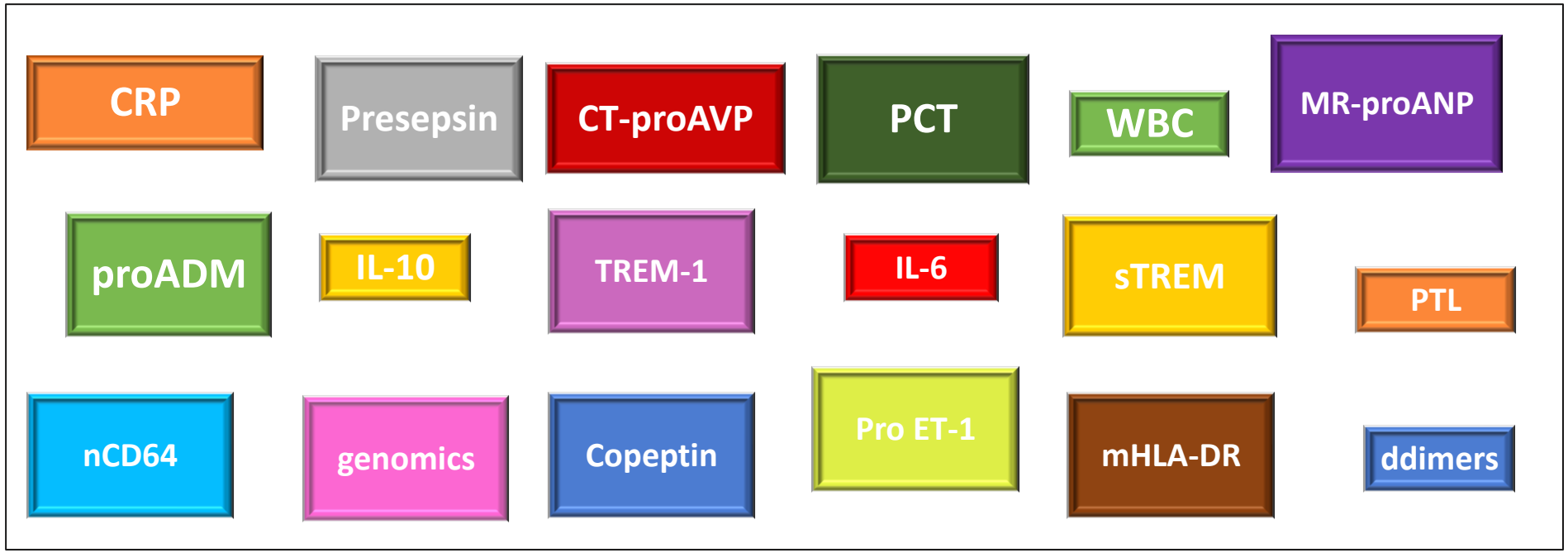
- Επιπλοκές (ίδιο ή έτερο σύστημα)
- Παρόξυνση προυπάρχουσας νόσου
- Μη συμμόρφωση του ασθενούς
- Αδυναμία κοινωνικού ιστού

Τα προγνωστικά μοντέλα δεν υποκαταστούν, αλλά συνεπικουρικούν στην κλινική εκτίμηση!!

Biomarkers in lower respiratory tract infections. Pulm Pharmacol Ther. 2010



Biomarkers LRTIs: Diagnosis & prognostic severity & treatment duration indicators



Chest. 2019

BMC Infect. Dis 2019

PCT and CRP levels in BAL did not differentiate between confirmed and not confirmed VAP

MR-pro-ANP & CT-pro- AVP strong predictor of mortality when compared with CRP-PCT

Copeptin useful marker of early mortality in ICU admission

Diagnostic Biomarkers	Prognostic Biomarkers	Antibiotic Guidance Biomarkers
Procalcitonin (PCT) [32]	C-reactive protein (CRP) predicts the absence of severe complications [60]	PCT guidance significantly reduces initiation and duration of antibiotic therapy [51]
CRP indicates inflammation intensity [40,58]	Interleukin 6 (IL-6) predicts treatment failure and mortality [39]	
Neutrophil CD64 (nCD64) used for the diagnosis of bacterial infection and sepsis [83,84,85,86,87,88,89,90]	Neutrophil-to-lymphocyte ratio (NLR) predicts mortality [74]	
D-dimer levels increased in patients with severe community-acquired pneumonia (CAP) [98]	Monocyte-to-lymphocyte ratio (MLR) indicates disease severity [75,76,77]	
Triggering receptor expressed on myeloid cells 1 (TREM-1) is a good predictor of ventilator-associated pneumonia (VAP) [103]	Platelets indicate CAP severity [78] and predict mortality [79]	
Atrial natriuretic peptide (ANP) levels increase during sepsis [115,116,117,118]	Monocyte human leukocyte antigen-DR (mHLA-DR) decreases rapidly in correlation to the severity and outcome of septic shock [94,95]; nonsurvivors express reduced levels of mHLA-DR [96]	

Int J Mol Sci. 2019

Biomarkers That Indicate Direct Evidence of Infection	Biomarkers That Determine the Host Response to Infection
Presepsin is released in the blood during phagocytosis [97]	PCT, identifiable within 2–3 h with peak at 6 h [32]
TREM-1 expression is upregulated in the presence of extracellular bacteria and fungi [16]	CRP, identifiable within 4–6 h with peak at 36–50 h [40,59]
Diverse metabolomes specific for sepsis and CAP; putrescine is a predictor for CAP [132]	IL-6, immediate response to infection [44,69], more sensitive for localized infection (e.g., effusions) [44]
Exhaled breath contains volatile organic compounds (VOCs) that result from bacterial metabolism and/or host response to the environment [135]	NLR, PLR, and MLR indicate systemic inflammation and infection [72,73]
Specific patterns of lower airway microbiomes differently predict ICU admission and length of stay [142]	nCD64 increases during the proinflammatory state in response to infection and returns to normal when the stimulating factors disappear [80]

Int J Mol Sci. 2019

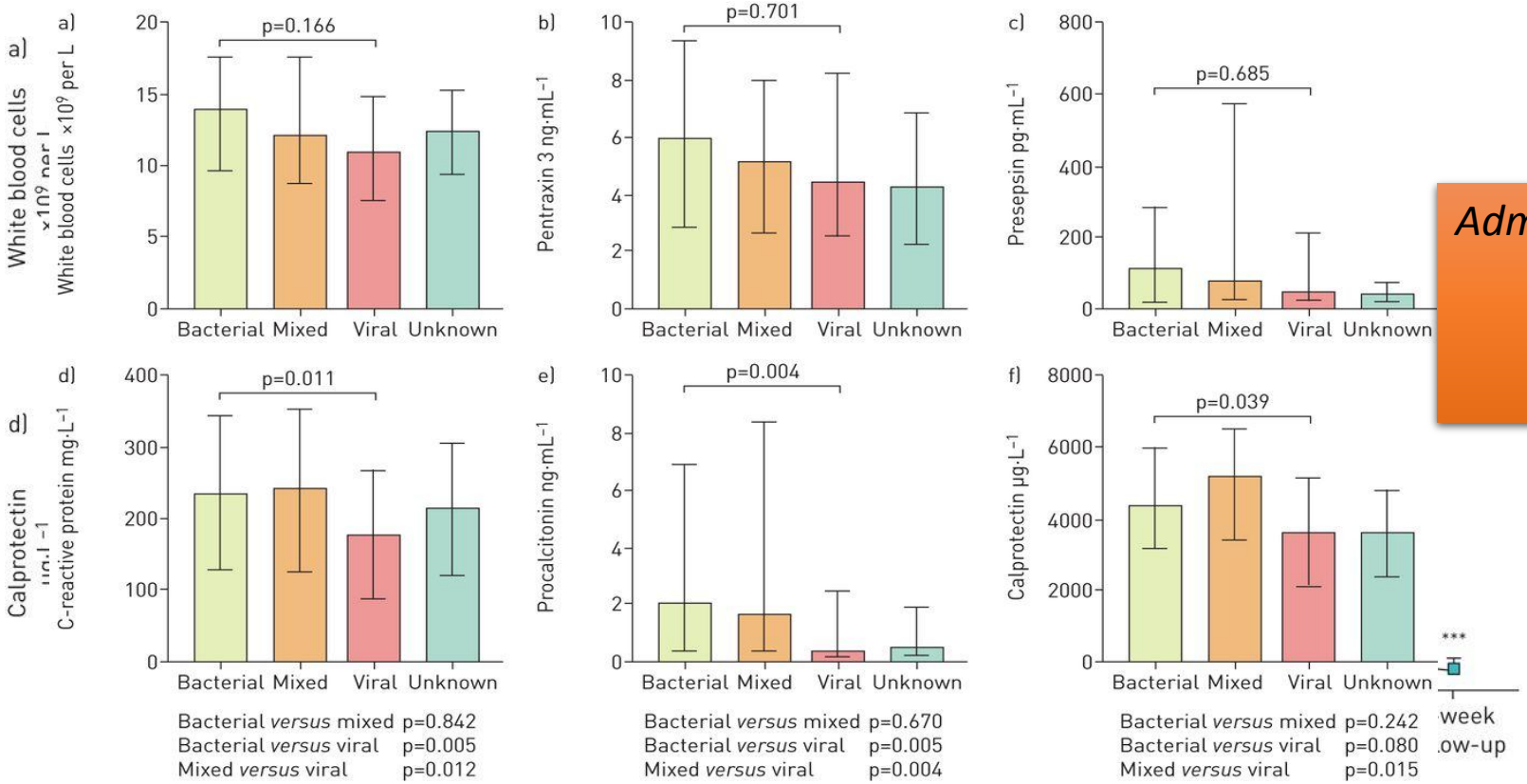
Inflammatory biomarkers are associated with etiology and predict outcomes in community-acquired pneumonia: results of a 5-year follow-up cohort study. ERJ Open Research 2019

CRP, PCT, calprotectin,PTX3, presepsin, WBCs → microbial aetiology & adverse outcomes

267 pts

admission, clinical stabilization, 6w follow-up

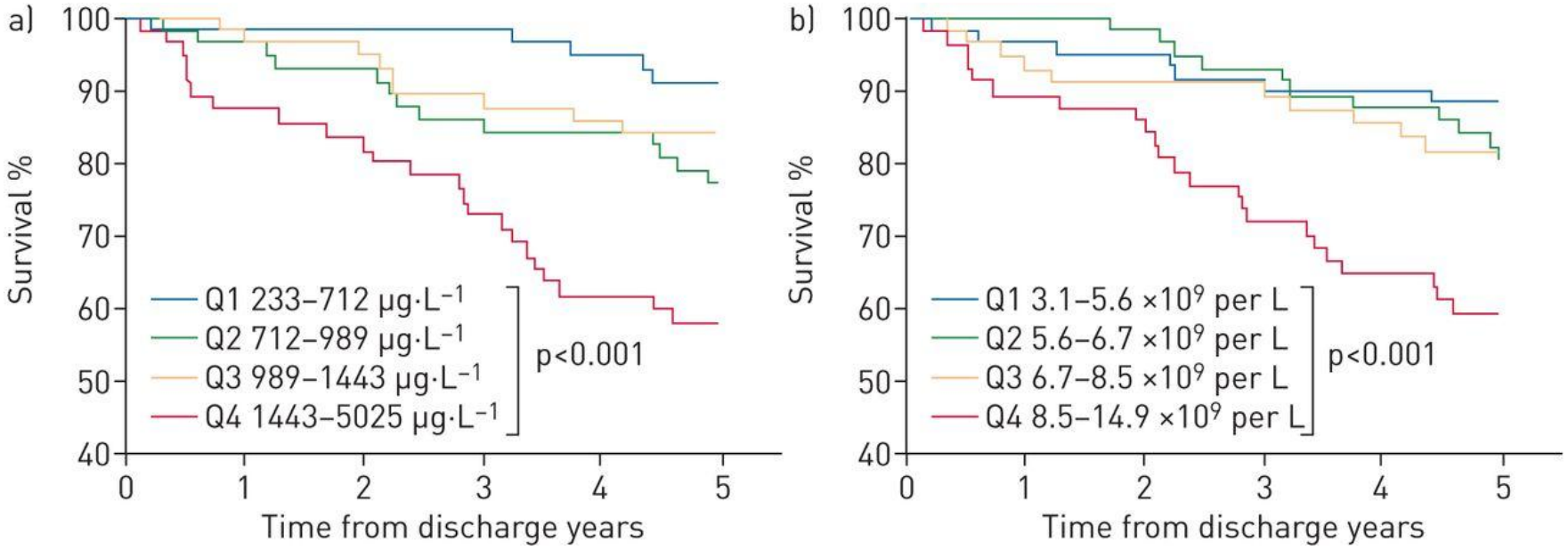
ICU admission and 30-day mortality



Admission: WBC, PTX3, presepsin similar
CRP, PCT significantly higher in bacterial and viral–bacterial CAP
Calprotectin higher in viral–bacterial

Inflammatory biomarkers are associated with etiology and predict outcomes in community-acquired pneumonia: results of a 5-year follow-up cohort study. ERJ Open Research 2019

6-week follow-up and associations to 5-year all-cause mortality



- ✓ Admission levels of PTX3 were associated with 5-year all-cause mortality
- ✓ 6-week follow up-Calprotectin + WBCs significantly associated with 5-year all-cause mortality
- ✓ Adverse short-term outcome had higher admission levels of PCT, PTX3, presepsin
- ✓ CURB-65 ≥3+PCT + PTX3 + presepsin discriminated patients with an adverse and nonadverse short-term outcome

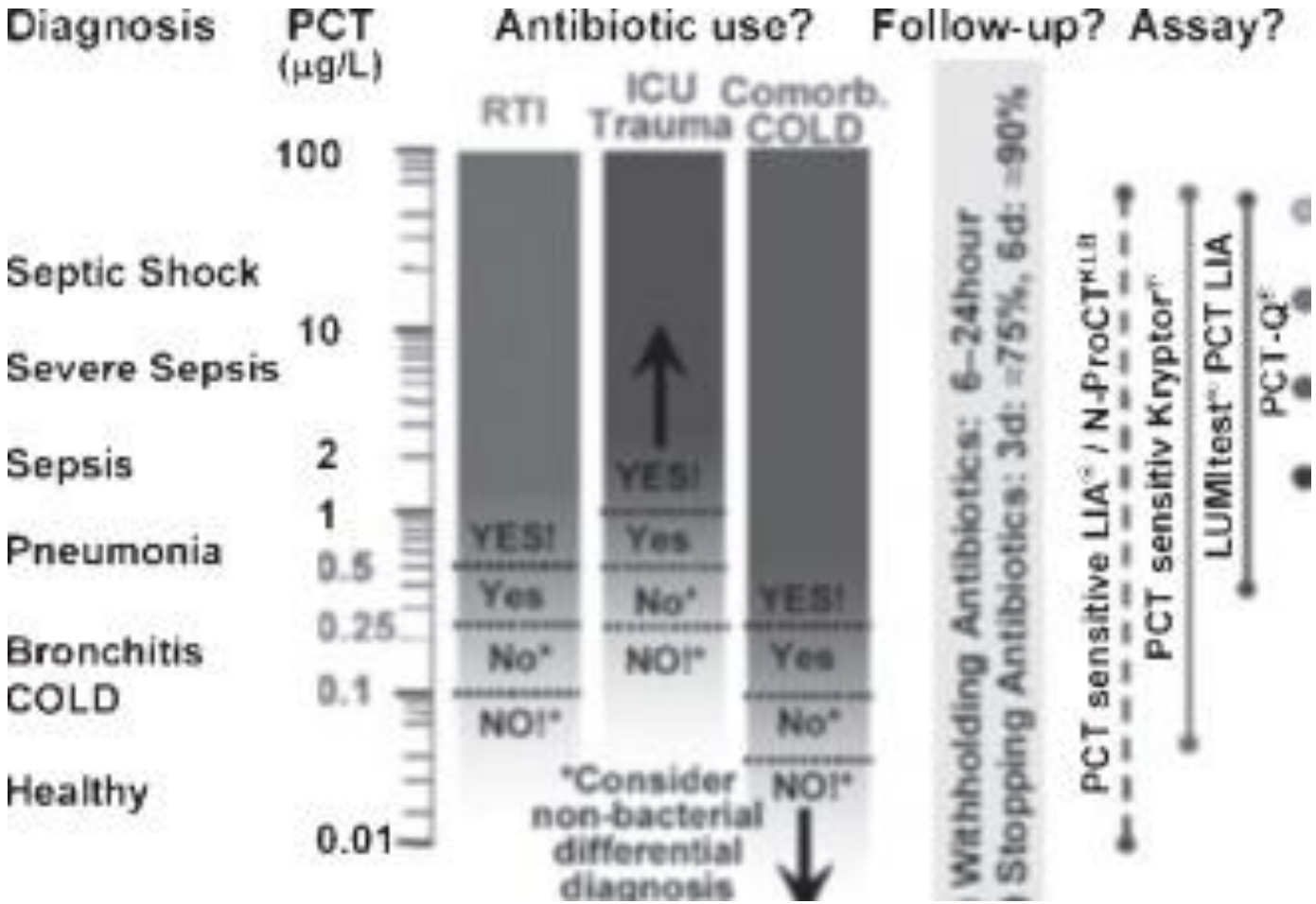
Markers of acute inflammation in assessing and managing lower respiratory tract infections: focus on procalcitonin. Clinical Microbiology and Infection 2006

- Most inflammatory cytokines is not useful in LRTI assessment, because of their short plasma half-life and rapid turn-over, the presence of blocking factors

  Chest. 2012

- Prohormones reflecting a specific pathophysiological pathway could enhance risk stratification in CAP, appear to be more reliable, because of their longer plasma half-lives, lesser variation in daily levels, and stability in vivo and ex vivo.

  Crit Care. 2010



ΑΛΓΟΡΙΘΜΟΣ ΕΝΑΡΞΗΣ ΑΝΤΙΜΙΚΡΟΒΙΑΚΩΝ (Lancet, 2004)

<0.1 μg/L **ΕΝΤΟΝΑ** ΑΠΟΘΑΡΡΥΝΕΤΑΙ	0.1-0.25 μg/L ΑΠΟΘΑΡΡΥΝΕΤΑΙ	0.25-0.5 μg/L ΕΝΘΑΡΡΥΝΕΤΑΙ	>0.5 μg/L **ΕΠΙΒΑΛΛΕΤΑΙ**

ΕΠΑΝΑΛΗΨΗ ΣΕ 6-12 ΩΡΕΣ

ΑΛΓΟΡΙΘΜΟΣ ΔΙΑΚΟΠΗΣ ΑΝΤΙΜΙΚΡΟΒΙΑΚΩΝ ΣΤΗ ΜΕΘ (Lancet, 2010)

<0.25 μg/L **ΕΝΤΟΝΑ** ΕΝΘΑΡΡΥΝΕΤΑΙ	0.25-0.5 μg/L Ή ≥80% ΑΡΧΙΚΗΣ ΕΝΘΑΡΡΥΝΕΤΑΙ	>0.5 μg/L Ή <80% ΑΡΧΙΚΗΣ **ΣΥΝΕΧΙΣΗ**	>0.5 μg/L + > **ΑΡΧΙΚΗ ΑΛΛΑΓΗ**

A model for predicting bacteremia in patients with community acquired pneumococcal pneumonia: a retrospective observational study.

BMC Pulm Med. 2018

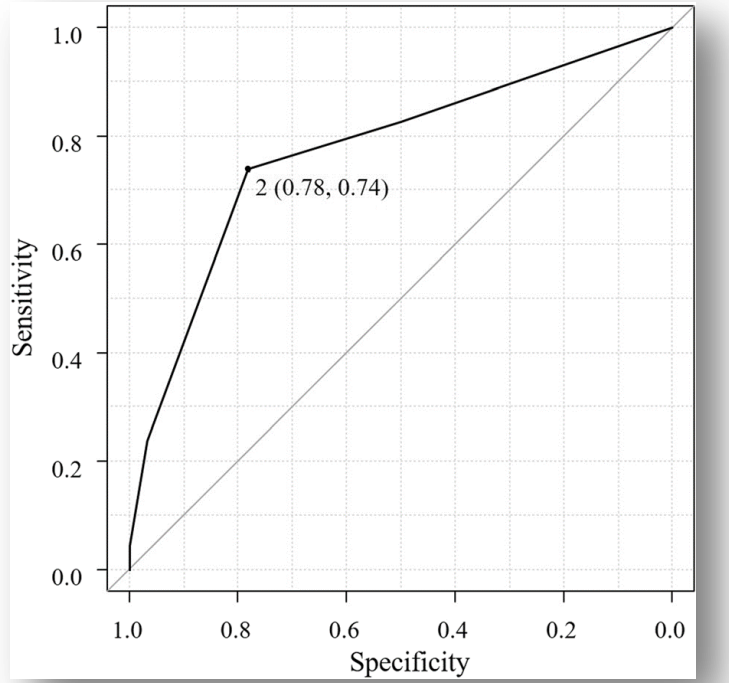
April 2007 -August 2015

3890pts

bacteremia

without bacteremia

age < 65 years
serum albumin level < 3.0 g/dL
intensive respiratory or vasopressor support (IRVS)
C-reactive protein level > 20 mg/dL



Risk factors	Bacteremia	No Bacteremia	Sensitivity	Specificity
0	8(17.4%)	174 (50.7%)	1.00	–
≥ 1	38 (82.6%)	169 (49.3%)	0.83	0.50
≥ 2	33 (71.7%)	75 (21.9%)	0.74	0.78
≥ 3	11 (23.9%)	9 (2.6%)	0.24	0.97
4	2 (4.3%)	0	0.043	1.00

Age < 65 yrs, hypoalbuminemia, IRVS, high CRP on admission are independent risk factors for the development of bacteremia

Time to Blood Culture Positivity as a Predictor of Clinical Outcomes and Severity in Adults with Bacteremic Pneumococcal Pneumonia. PLOS One. 2017

2003–2012: 4.639 hospitalized/419 + blood culture for *Streptococcus pneumonia*
early detection <9 h # late detection ≥9 h)

- 51% PSI IV-V
- 8% died within 30-days after admission

- severity of CAP (IDSA/ATS)
- *S. pneumoniae* serotype and LOS → CRP ≥15 mg/dl, PSI IV-V, ARDS and early detection
- in-hospital mortality rate
- 30-day mortality rate → age ≥65, acute renal failure, septic shock, ARDS, early detection
- ICU admission/ LOS/ mortality rate

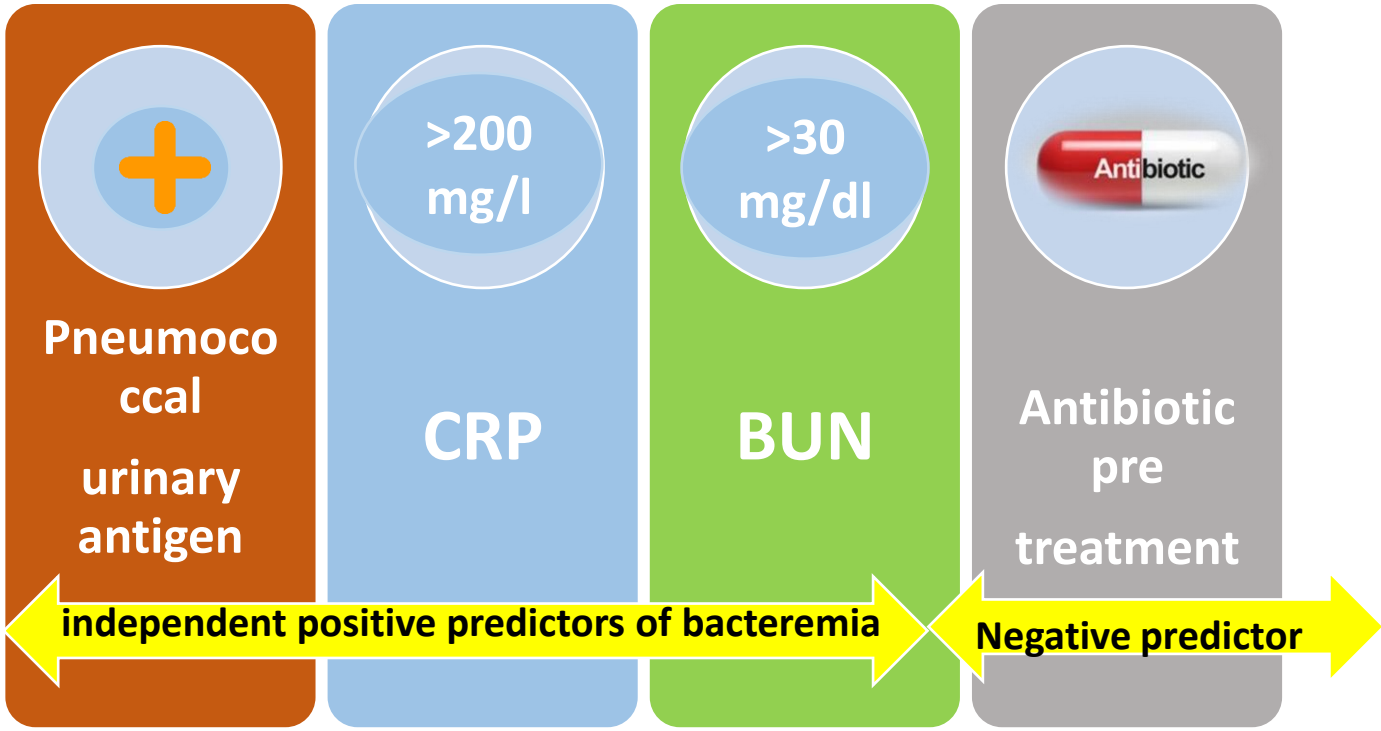
- non-SD differences in the use of previous antibiotics and pn.vaccine between groups
- early detection group presented a higher median PSI, more severe CAP, pulmonary complications
- early detection group had a longer LOS, higher rate of in-hospital mortality, higher rate of 30-day mortality
- no difference between groups in ICU admission, length of ICU stay or ICU mortality
- any association between TTP and pneumococcal serotype

Higher pneumococcal load with increased disease severity in CAP

Rate and Predictors of Bacteremia in Afebrile Community-Acquired Pneumonia.

Chest. 2019

- 2002-2016- cohort study **CAPNETZ**
- 11591 CAP pts/4349 BCs
- <37.8°C -2807pts
- all-cause 28-day mortality

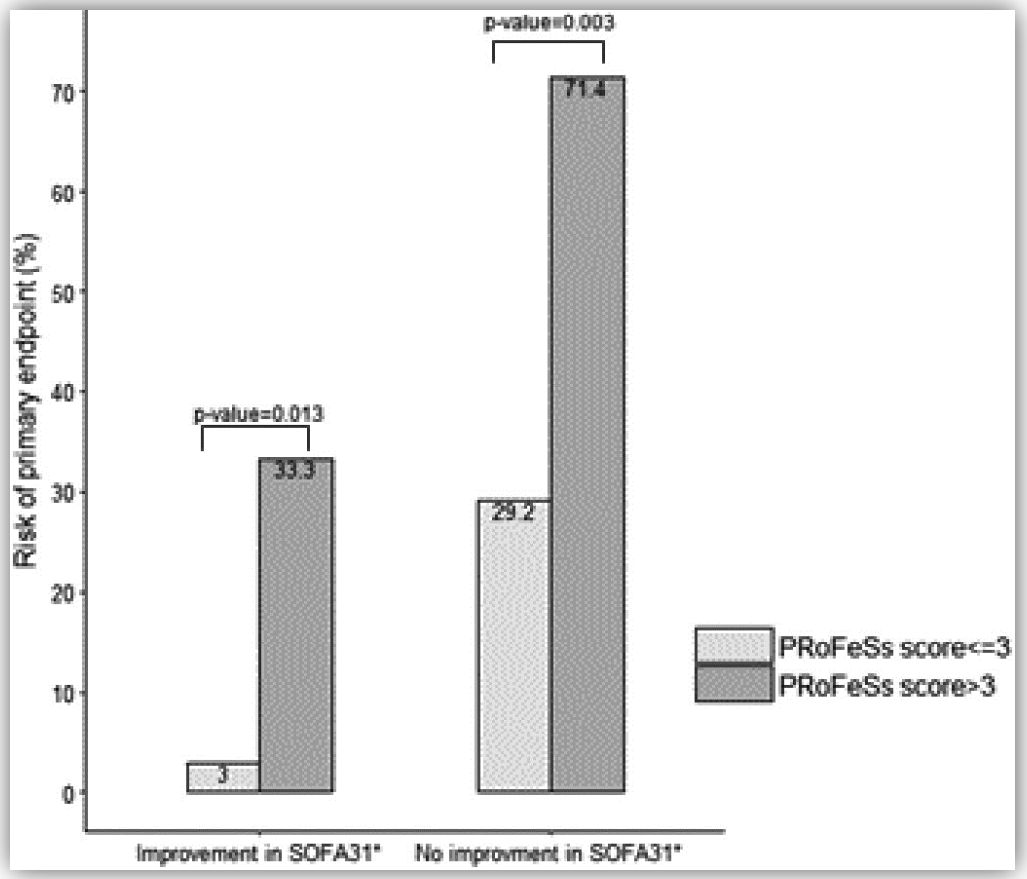


- ***x2 in afebrile bacteremia***
- ***Bacteremia presented in 5%***
- ***No sign.diff. in demography, comorbidities, severity of disease and inflammatory parameters***

Early prediction of treatment failure in severe community-acquired pneumonia: The PRoFeSs score (PRediction of Failure in SCAP score). J Crit Care. 2019

Biomarkers to provide a point score that, after 48 h of treatment, could early predict treatment failure at fifth day of ICU stay in severe community-acquired pneumonia patients.

Variables	Categories	Points
Charlson score (points)	0–1	0
	2–3	2
	4–5	3
	6–10	6
Lactate D3 (mmol/l)	≤1.10	0
	1.11–1.35	1
	1.36–1.80	2
	1.81–2.49	3
	2.50–3.49	5
	≥3.50	11
PCT D1 (ng/ml)	≤2.17	0
	2.18–7.23	−1
	7.24–9.42	−2
	9.42–15.40	−3
	15.41–27.20	−4
	27.21–47.90	−7
	47.91–76.10	−10
	≥76.11	−26
PCT D3 (ng/ml)	≤2.93	0
	2.94–8.64	1
	8.65–19.40	2
	19.41–27.40	4
	27.41–49.20	6
	≥49.21	12
D-dimer D3 (µg/ml)	≤3.04	0
	3.05–7.17	1
	7.18–9.14	2
	9.15–18.50	3
	18.51–32.6	7
	≥32.61	10
BNP D1 (pg/ml)	≤227.0	0
	227.1–809.0	−1
	809.1–2140.0	−2



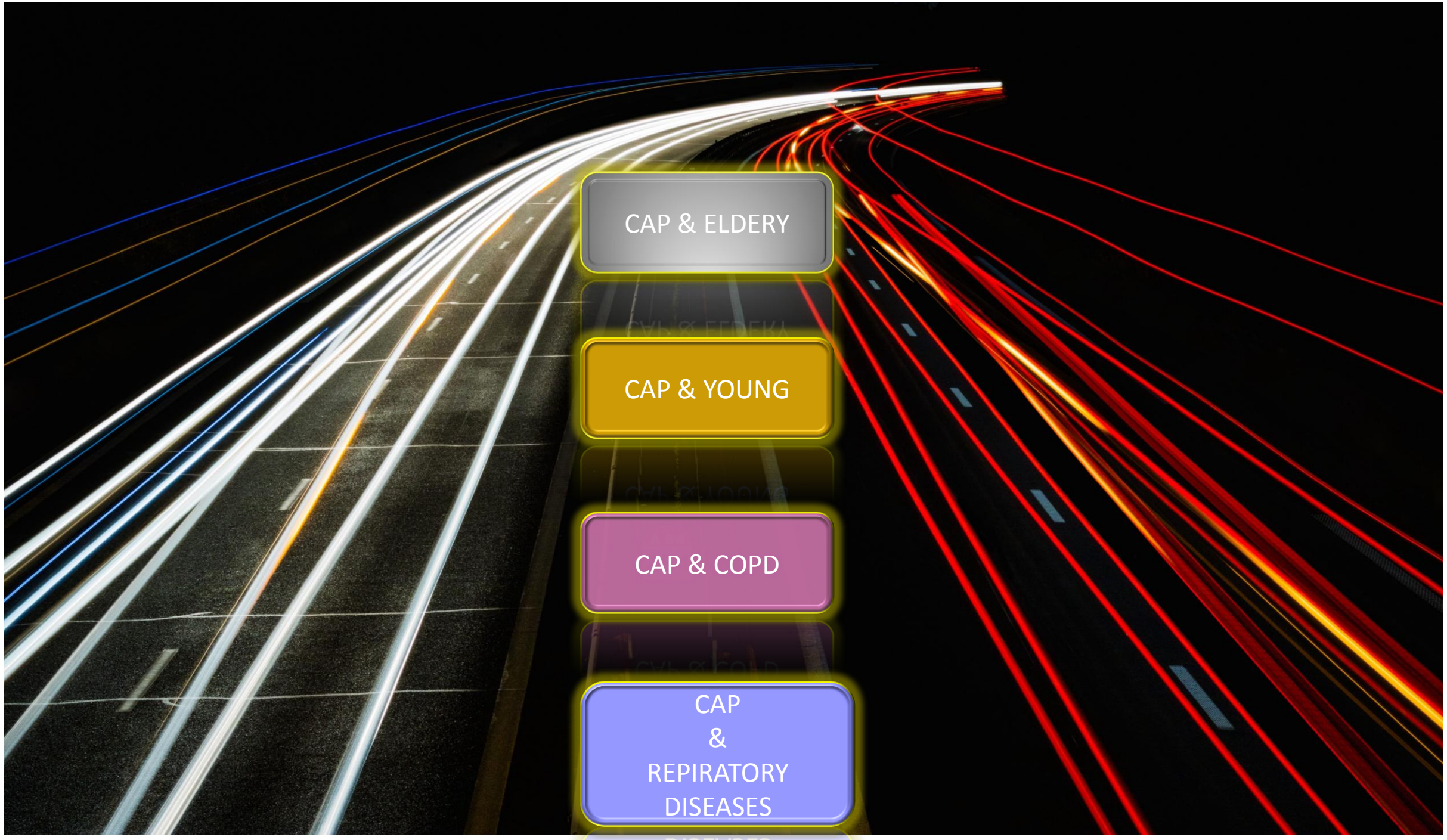
Outcomes associated with the use of a revised risk assessment strategy to predict antibiotic resistance in community-onset pneumonia: a stewardship perspective. J Antimicrob Chemother. 2018

- DRIP score: Drug Resistance In Pneumonia
- 102 patients
- >4 indicates a risk of MDR organisms

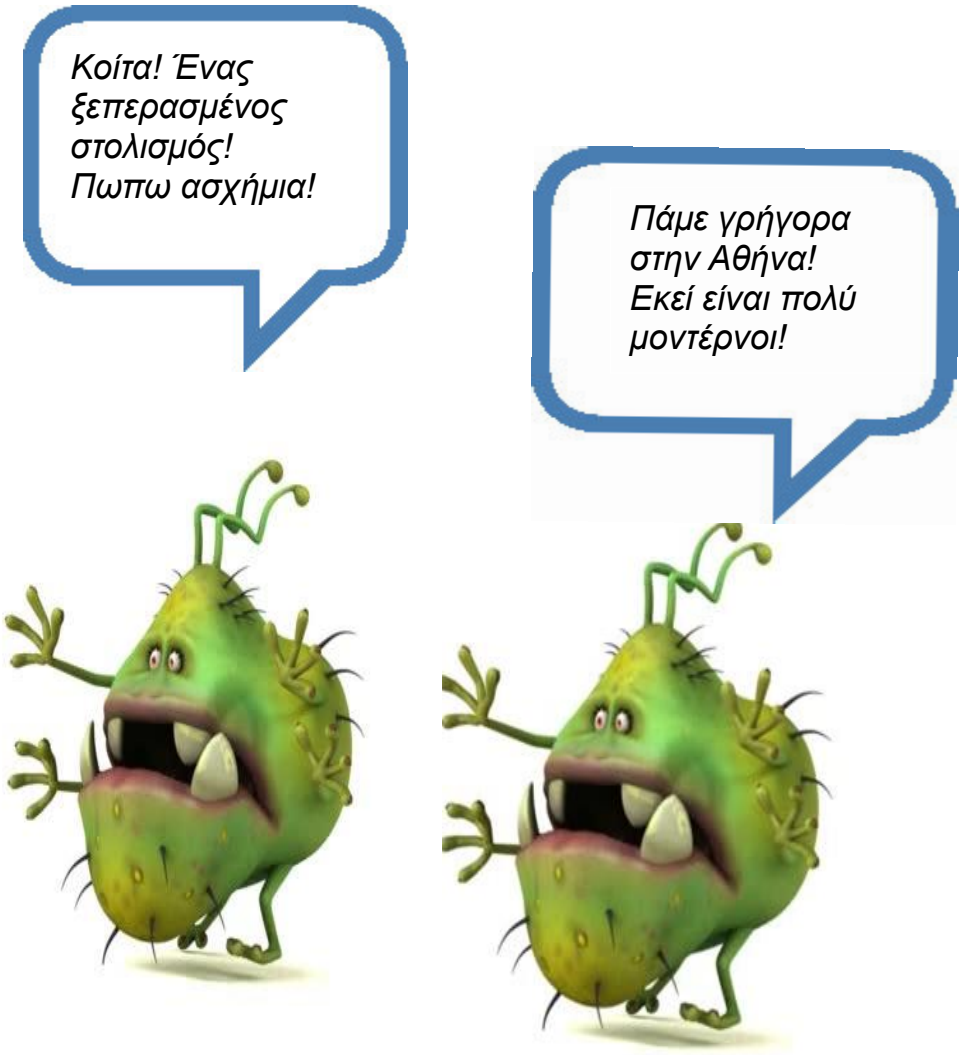
A sign. decrease in use of anti-pseudomonal & anti-MRSA antimicrobial agents

DRIP Score	
Major Risk Factors	Points
Antibiotic use <60 days	2
Long term care resident	2
Tube feeding	2
Prior DRP (1 year)	2
Minor Risk Factors	
Hospitalization <60 days	1
Chronic pulmonary disease	1
Poor functional status	1
Gastric acid suppression	1
Wound care	1
MRSA colonization (1 year)	1
Total Points Possible	14

Not associated with a significant difference on 30 day all-cause readmissions


CAP & ELDERY
CAP & YOUNG
CAP & COPD
CAP
&
REPIRATORY
DISEASES


Merry Christmas


Κοίτα! Ένας ξεπερασμένος στολισμός! Πωπω ασχήμια!
Πάμε γρήγορα στην Αθήνα! Εκεί είναι πολύ μοντέρνοι!