ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΠΜΣ
«ΑΝΑΠΝΕΥΣΤΙΚΗ ΑΝΕΠΑΡΚΕΙΑ ΚΑΙ ΜΗΧΑΝΙΚΟΣ ΑΕΡΙΣΜΟΣ»
ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΕΚΠΑ

GUIDELINES: ΑΝΤΙΜΙΚΡΟΒΙΑΚΗ ΑΓΩΓΗ ΣΤΗΝ ΠΝΕΥΜΟΝΙΑ ΠΟΥ ΣΧΕΤΙΖΕΤΑΙ ΜΕ ΜΗΧΑΝΙΚΟ ΑΕΡΙΣΜΟ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΑΝΑΠΝΕΥΣΤΙΚΗ ΑΝΕΠΑΡΚΕΙΑ ΚΑΙ ΜΗΧΑΝΙΚΟΣ ΑΕΡΙΣΜΟΣ»

Γ’ ΕΞΑΜΗΝΟ

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Ορισμοί

Πνευμονία	**Νέο διήθημα στον απεικονιστικό έλεγχο του πνεύμονα** **+** **Συμπτώματα: Πυρετός, Πυώδεις αναπνευστικές εκκρίσεις, Πτώση Οξυγόνωσης** **Ή** **Εργαστηριακά ευρήματα: Λευκοκυττάρωση**
Σχετιζόμενη με το μηχανικό αερισμό (ventilator-associated)	**Που συμβαίνει > 48 ώρες μετά την ενδοτραχειακή διασωλήνωση και την έναρξη του μηχανικού αερισμού**

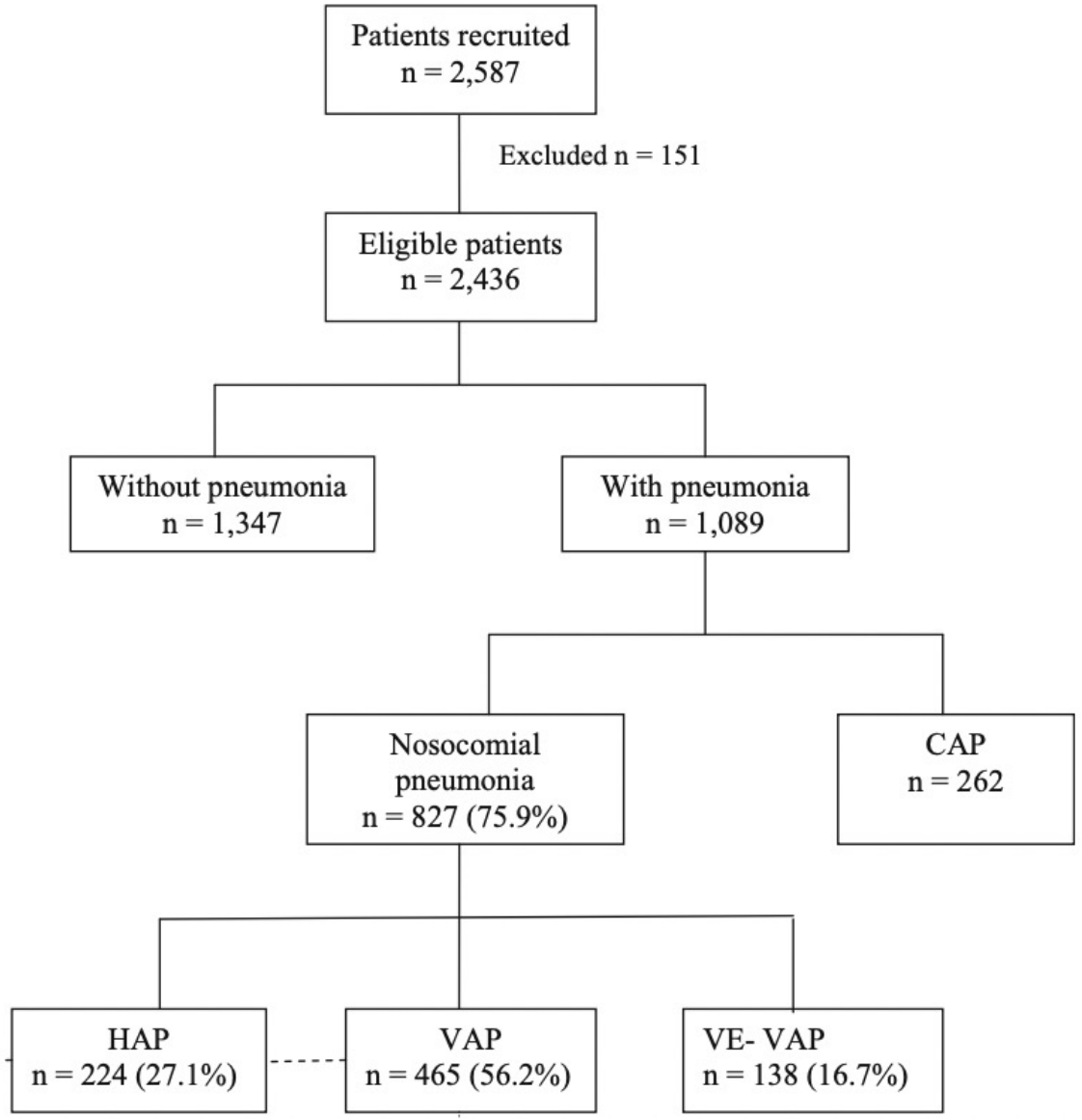
Νοσοκομειακή πνευμονία: πνευμονία που εκδηλώνεται ≥ 48 ώρες μετά την είσοδο στο νοσοκομείο και **δεν** υπήρχαν ενδείξεις επώασης κατά την εισαγωγή

Τραχειοβρογχίτιδα σχετιζόμενη με μηχανικό αερσιμό (VAT): Σημεία λοίμωξης αναπνευστικού, *χωρίς διήθημα*, σε ασθενή που βρίσκεται σε μηχανικό αερισμό για ≥ 48 ώρες

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. Eur Respir J. 2017;50(3):1700582.

Επίπτωση VAP

- Μελέτη παρατήρησης από 27 ΜΕΘ στην Ευρώπη (EU-VAP/CAP)
- 18.3 επεισόδια ανά 1000 ημέρες μηχανικού αερισμού
- Στο 89.1 % η διάγνωση τέθηκε εντός των 10 ημερών από την εισαγωγή στη ΜΕΘ
- Πρώιμη: (2-4 ημέρες από την εισαγωγή) 41.5%
- Όψιμη: (≥ 5 ημέρες από την εισαγωγή) 52.8%



Koulenti D, et al. Eur J Clin Microbiol Infect Dis. 2017;36(11):1999-2006.

« VAP is back »: επίπτωση της VAP σε COVID-19 ασθενείς

Study ID	N	Incidence (%)	Diagnostic tool	Recurrence (%)
Rouze, 2021	568	36	ETA	
Garcia Vidal, 2021	144	25		
Pickens, 2021	179	44	BAL	
Gragueb-Chatti, 2021	151	60	ETA/BAL	37
Maes, 2021	81	48	ETA/BAL	
Blonz, 2021	188	49	ETA/BAL	
Razazi, 2020	90	64	ETA/BAL	25
Llitjos, 2021	176	52	ETA/BAL	21
Rouyer, 2021	79	53	ETA/BAL	28
Giacobbe, 2021	586	29	ETA/BAL	
Grasselli, 2021	774	50	ETA/BAL	
D'Humières, 2021	77	84	ETA/BAL	23
Beaucoté, 2021	161	73	ETA/BAL	

Wicky PH, et al. Curr Opin Infect Dis. 2022;35(2):170-175.

Μικροβιολογική διάγνωση της VAP

- We suggest noninvasive sampling with semiquantitative cultures to diagnose VAP, rather than invasive sampling with quantitative cultures and rather than noninvasive sampling with quantitative cultures *(weak recommendation, low-quality evidence)*.
- For patients with suspected VAP whose invasive quantitative culture results are below the diagnostic threshold for VAP, we suggest that antibiotics be withheld rather than continued *(weak recommendation, very low-quality evidence)*.

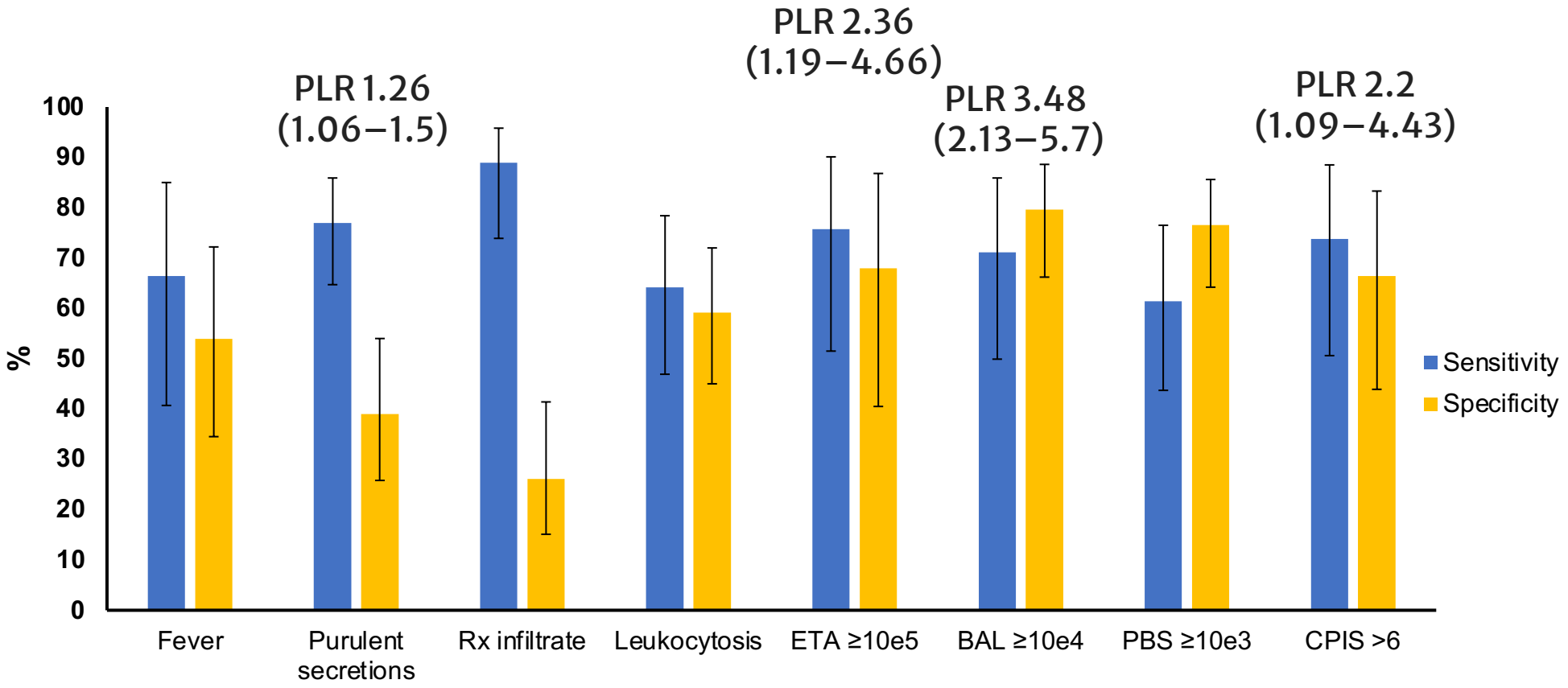
- We suggest obtaining distal quantitative samples (prior to any antibiotic treatment) in order to reduce antibiotic exposure in stable patients with suspected VAP and to improve the accuracy of the results. (Weak recommendation, low quality of evidence.)
- We recommend obtaining a lower respiratory tract sample (distal quantitative or proximal quantitative or qualitative culture) to focus and narrow the initial empiric antibiotic therapy. (Strong recommendation, low quality of evidence.)

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. Eur Respir J. 2017;50(3):1700582.

Μια δύσκολη διάγνωση

- SMRA up to September 2019
- N=25 studies

PICO criteria
- Adults mainly, ICU, ≥48h of MV
- Fever, purulent secretions, leukocytosis, Rx, ETA ≥10^5, PSB ≥10^3, BAL ≥10^4 CFU/ml
- Reference Standard: histolpathologic diagnosis or BAL ≥10^4 CFU/ml of a pathogen known to cause VAP

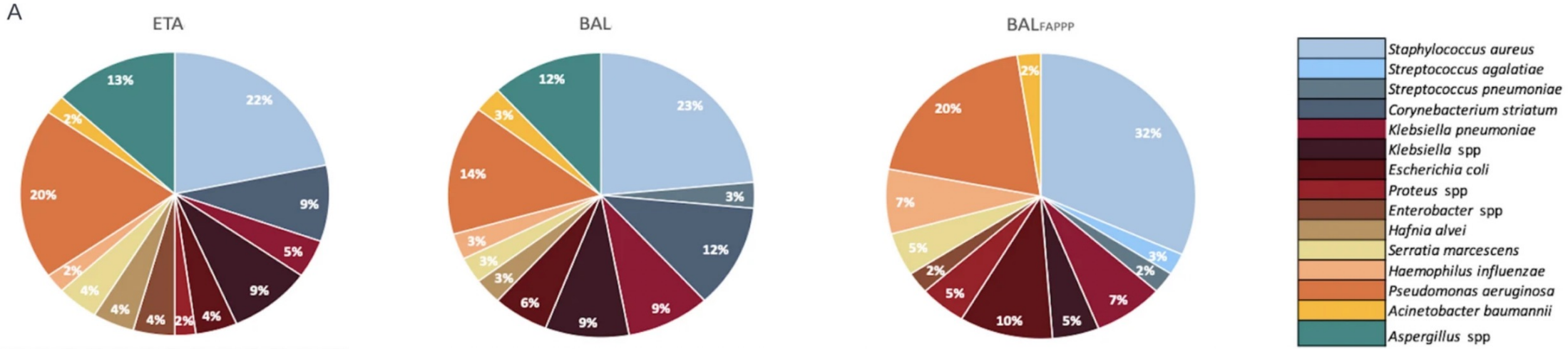


Fernando SM, et al. Intensive Care Med. 2020;46(6):1170-1179.

VAP σε COVID-19 ασθενείς: BE ή BAL;

n=79 ασθενείς σε MYA (Ιταλία)

A



positive test	35/49	71.4%
polymicrobial isolates	9/35	25.7%
total number of isolates	46	
MDR isolates	1/46	2.2%

positive test	27/49	55.1%
polymicrobial isolates	7/27	25.9%
total number of isolates	34	
MDR isolates	1/34	2.9%

positive test	28/49	57,1%
polymicrobial isolates	11/28	39,2%
total number of isolates	41	
MDR isolates	3/41	7,3%

Incidence 33.1% (22-44)

Incidence 20.1% (12.5-27.7)

Concordance in 79.4%

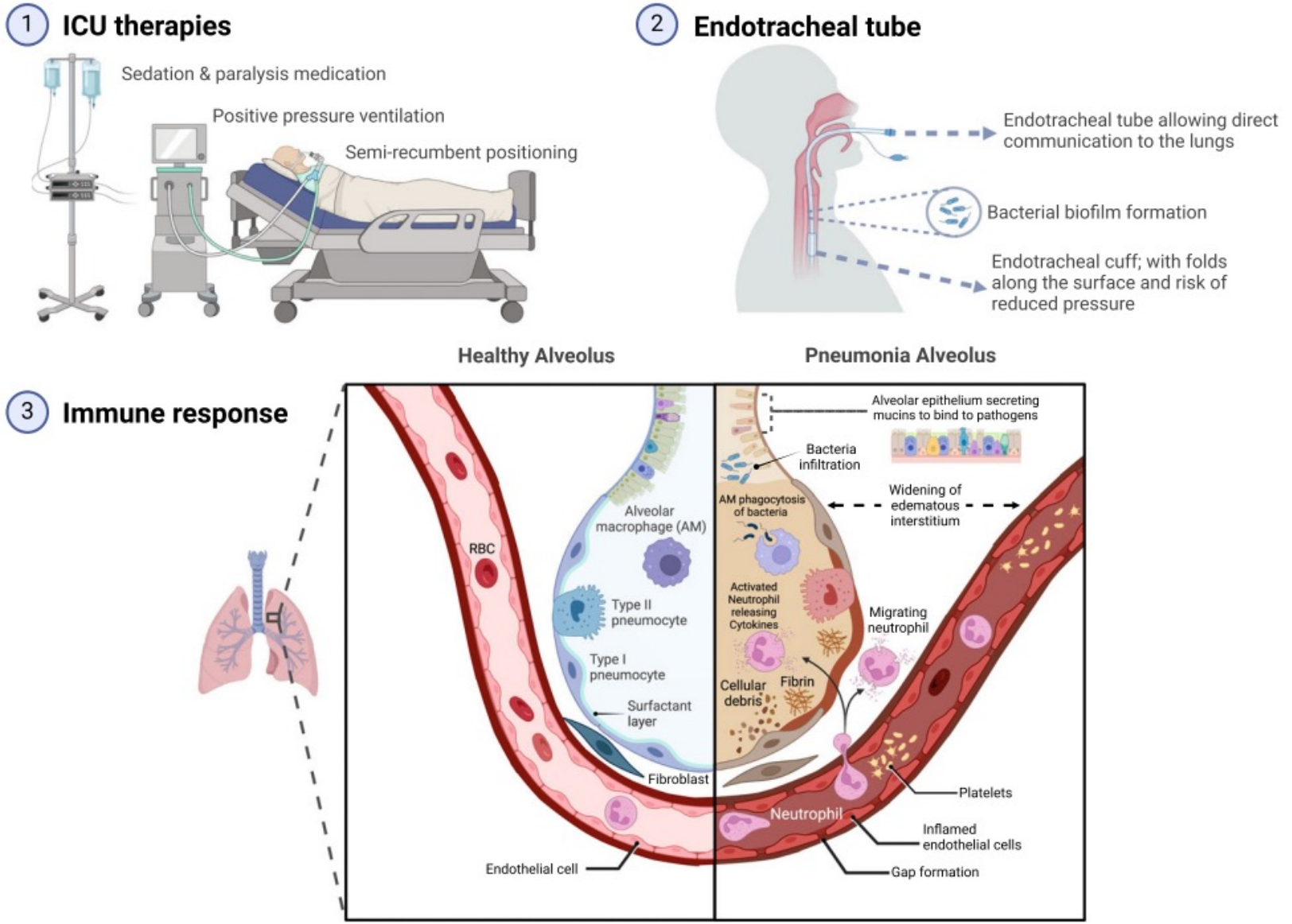
Sensitivity: 88.9%, Specificity 50%

Sensitivity: 95.0%, Specificity 69%

Mangioni D, et al. Crit Care. 2023;27(1):369.

Παθογένεση

« Gut-lung » axis
State of dysbiosis



Howroyd F, et al. Nat Commun. 2024;15(1):6447.
Bourdiol A, et al. Semin Respir Crit Care Med. 2022;43(2):271-279.

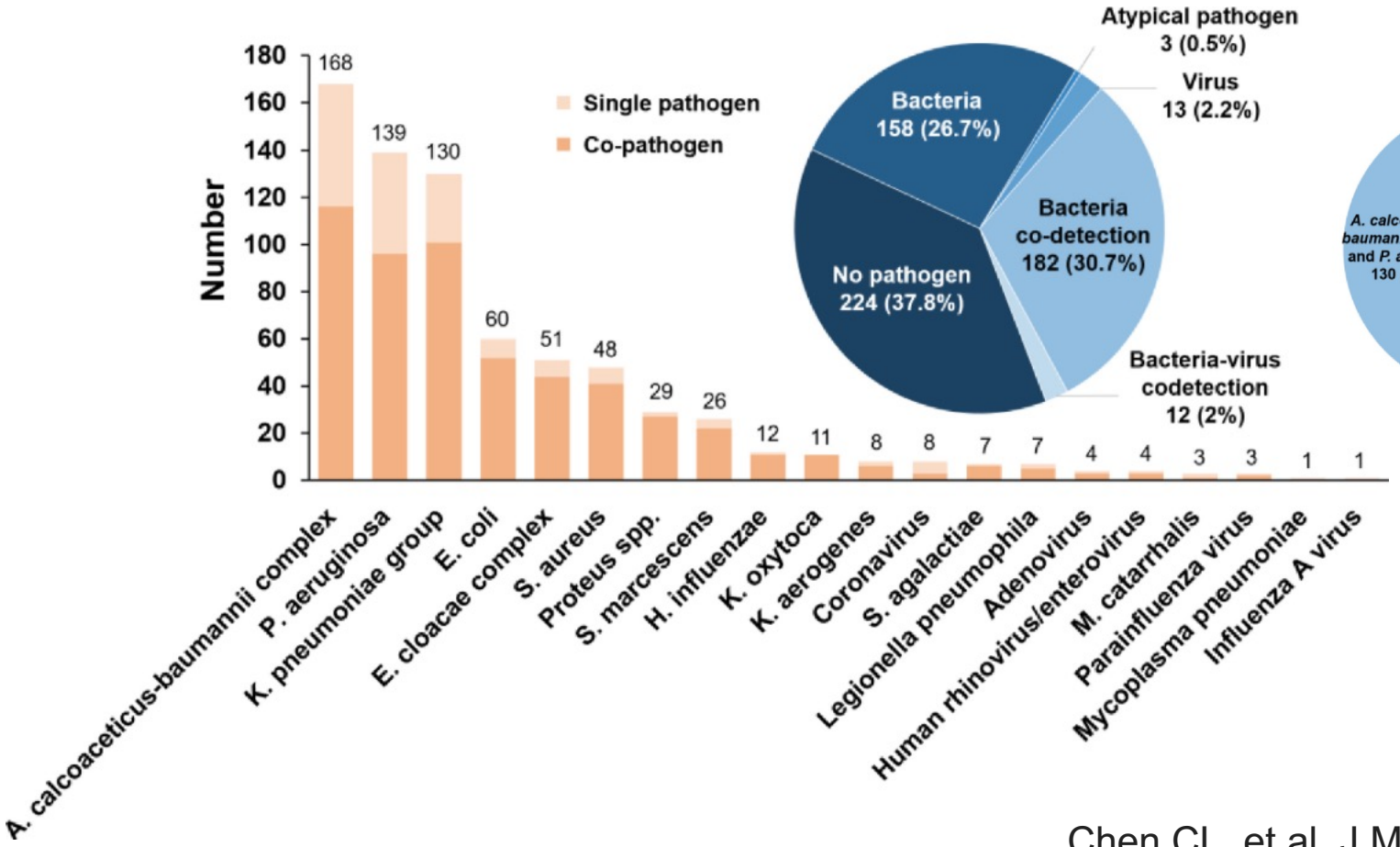
Συχνότερα παθογόνα

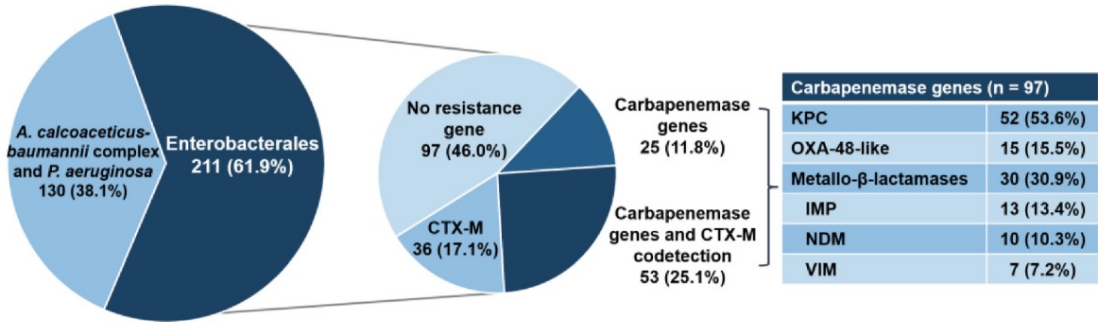
	HAP patients (*n* = 104)	VAP patients (*n* = 84)	*P*
Etiology of episodes, *n* (%)			
Staphylococcus aureus	42/104 (40.4%)	18/84 (21.4%)	**<0.01**
*Methicillin-resistant *Staphylococcus aureus*	18/42 (42.9%)	8/18 (44.4%)	0.909
Enterobacterales	37/104 (35.6%)	33/84 (39.3%)	0.601
Pseudomonas aeruginosa	15/104 (14.4%)	29/84 (34.5%)	**<0.01**
Acinetobacter baumannii	4/104 (3.8%)	2/84 (2.4%)	0.570
Stenotrophomonas maltophilia	1/104 (1.0%)	2/84 (2.4%)	0.440
Other microorganisms	5/104 (4.8%)	0/84 (0.0%)	0.066
**Multidrug-resistant microorganisms*	13/57 (22.8%)	10/66 (15.2%)	0.278
**Difficult-to-treat Gram-negative bacilli*	2/57 (3.5%)	2/66 (3.0)	0.881
Multidrug-resistant microorganisms	31/104 (29.8%)	18/84 (21.4%)	0.193
Polymicrobial infection, *n* (%)	6/104 (5.8%)	6/84 (7.1%)	0.702
Positive respiratory samples, *n* (%)			
Bronchial aspirate	61/104 (58.7%)	74/84 (88.1%)	<0.01
Sputum	26/104 (25.0%)	0%	<0.01
Other (bronchoalveolar lavage and pleural fluid)	17/104 (16.3%)	10/84 (11.9%)	0.388

Bouza E,et al. Microbiol Spectr. 2023;11(6):e0151723.

Συχνότερα παθογόνα σε ζώνες υψηλής αντοχής

N=592 pathogens recovered from n=467 critically ill patients with HAP/ VAP, using multiplex molecular panel

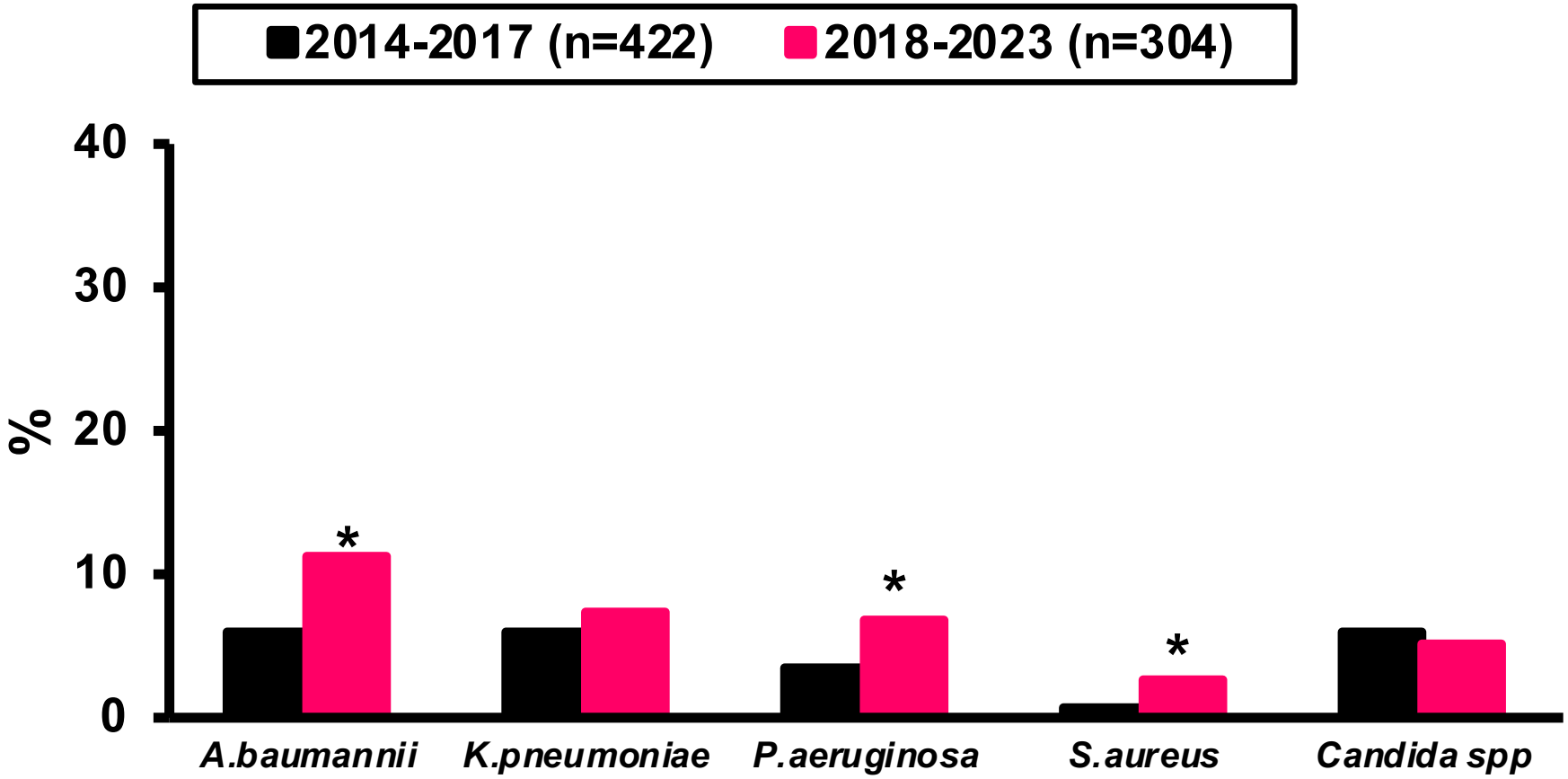




Carbapenemase genes (n = 97)	
KPC	52 (53.6%)
OXA-48-like	15 (15.5%)
Metallo-β-lactamases	30 (30.9%)
IMP	13 (13.4%)
NDM	10 (10.3%)
VIM	7 (7.2%)

Chen CL, et al. J Microbiol Immunol Infect. 2024 Jun;57(3):480-489.

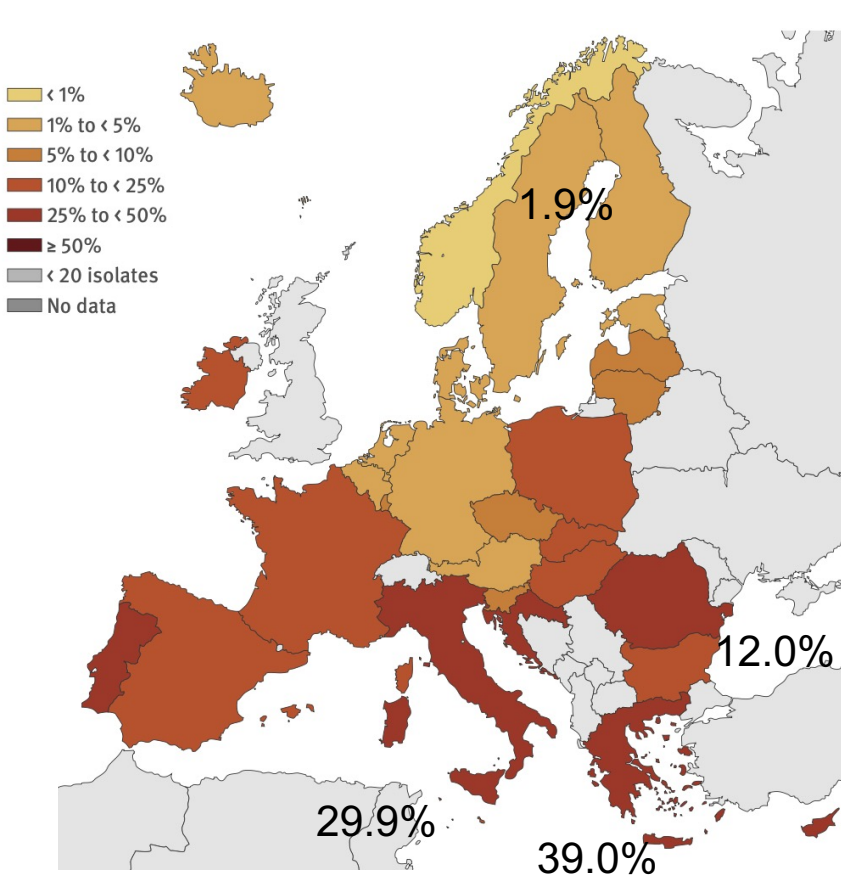
Συχνότερα παθογόνα στις ελληνικές ΜΕΘ



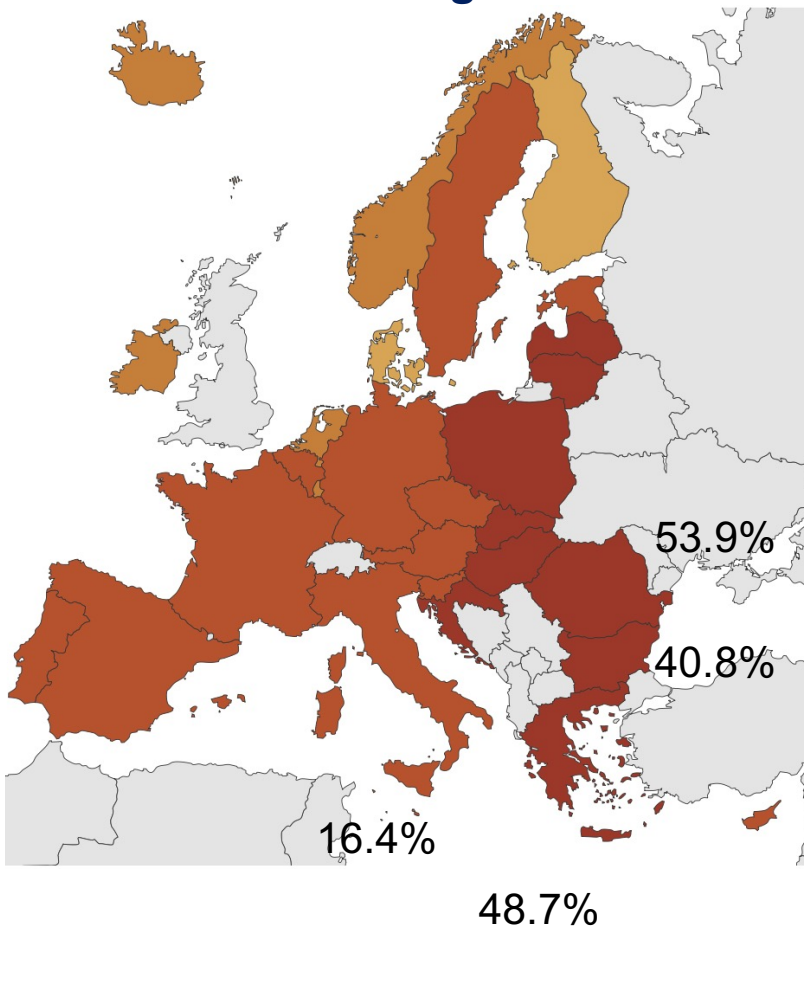
https://sepsis.gr/wp-content/uploads/2023/10/HISS_Booklet_on_Sepsis_2023.pdf

Καλλιέργειες αίματος και πτυέλων

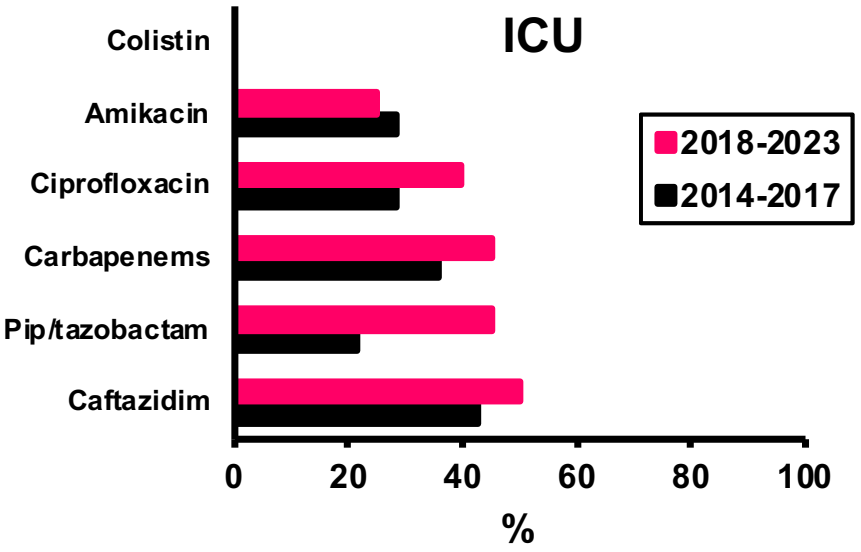
MRSA



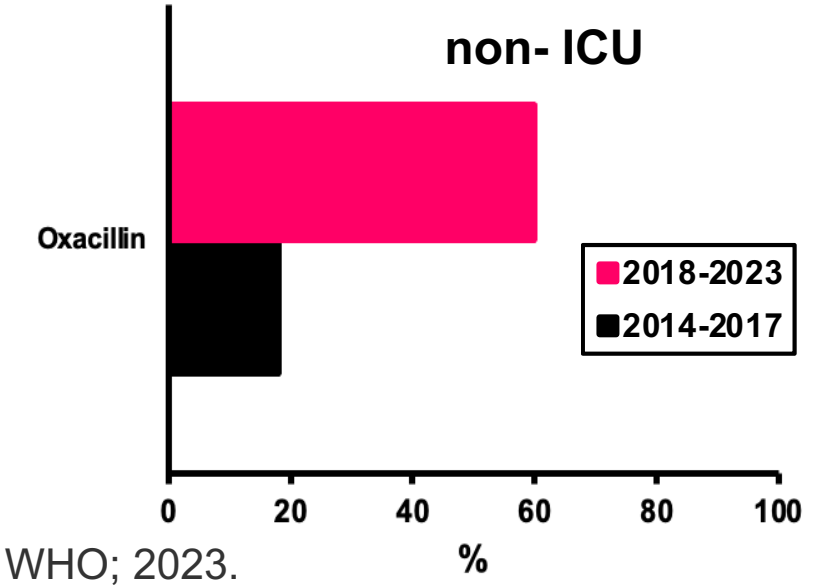
CR *P. aeruginosa*



Pseudomonas aeruginosa



S. aureus



Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.
https://sepsis.gr/wp-content/uploads/2023/10/HISS_Booklet_on_Sepsis_2023.pdf

The BIOFIRE® FILMARRAY® System

- *A. baumannii complex*
- *E. cloacae complex*
- *E. coli*
- *H. influenzae*
- *K. aerogenes*
- *K. oxytoca*
- *K. pneumoniae group*
- *M. catarrhalis*
- *Proteus spp*
- *P. aeruginosa*
- *S. marcescens*
- *S. aureus*
- *S. agalactiae*
- *S. pneumoniae*
- *S. pyogenes*

- *C. pneumoniae*
- *L. pneumophila*
- *M. pneumoniae*

- Adenovirus
- Coronavirus
- H metapneumovirus
- H enterovirus/rhinovorus
- Influenza A&B virus
- Parainfluenza virus
- RSV

- IMP/KPC/OXA48-like/NDM/VIM
- CTX-M
- *mec*A/C & MREJ

- *A. baumannii complex*
- *B. fragilis*
- *E. cloacae complex*
- *E. coli*
- *K. aerogenes*
- *K. oxytoca*
- *K. pneumoniae group*
- *Proteus spp*
- *Salmmonella spp*
- *S. marcescens*
- *H. influenzae*
- *N. meningitidis*
- *P. aeruginosa*
- *S. maltophilia*

- *E. faecalis*
- *E. faecium*
- *L. monocytogenes*
- *S. aureus*
- *S. epidermidis*
- *S. lugdunensis*
- *S. agalactiae*
- *S. pneumoniae*

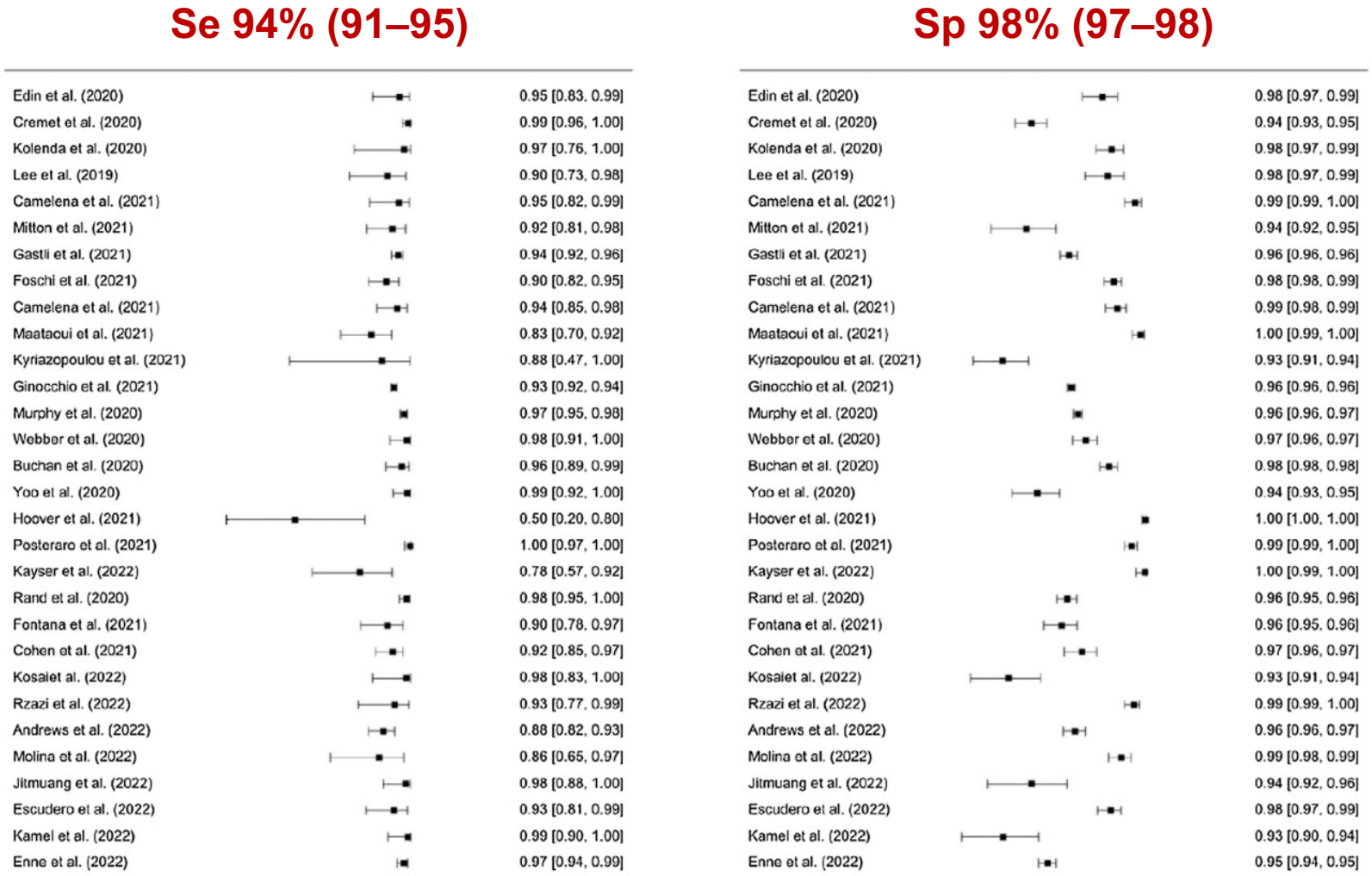
- *C. albicans*
- *C. auris*
- *C. glabrata*
- *C. kruzei*
- *C. parapsilosis*
- *C. tropicalis*
- *Cryptococcus (neoformans & gattii)*

- IMP/KPC/OXA48-like/NDM/VIM
- CTX-M
- *mec*A/C & MREJ
- *mcr*-1
- *van*A/B

https://www.biofiredx.com/products/the-filmarray-panels/

Diagnostic performance of FilmArray® Pneumonia plus

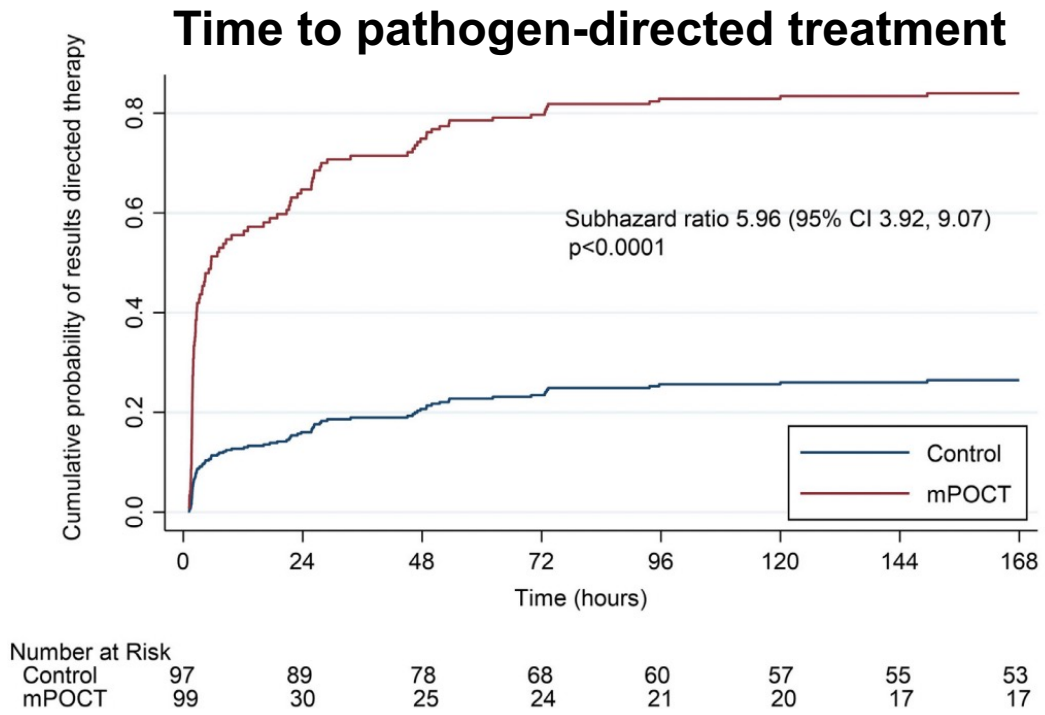
- Meta-analysis of 30 studies;
  8 968 samples



Moy AC, et al. Anaesth Crit Care Pain Med. 2023;42(6):101300.

Do molecular diagnostic tests change practice in VAP?

- single-center, open-label RCT
- UK
- N=200 critically ill with CAP/HAP/VAP
- Filmarray PP panel+ SOC vs SOC
- 23% VAP



Outcome	mPOCT group (n=100)	Control group (n=100)	Absolute difference (h)	P-value
Time to result	1.7 (1.6-1.9)	66.7 (56.7-88.5)	-65 (-68 to 62)	<0.0001
Patients with pathogen ID	71 (71)	51 (51)	20 (7 to 33)	0.004

Poole S, et al. J Infect. 2022;85(6):625-633.

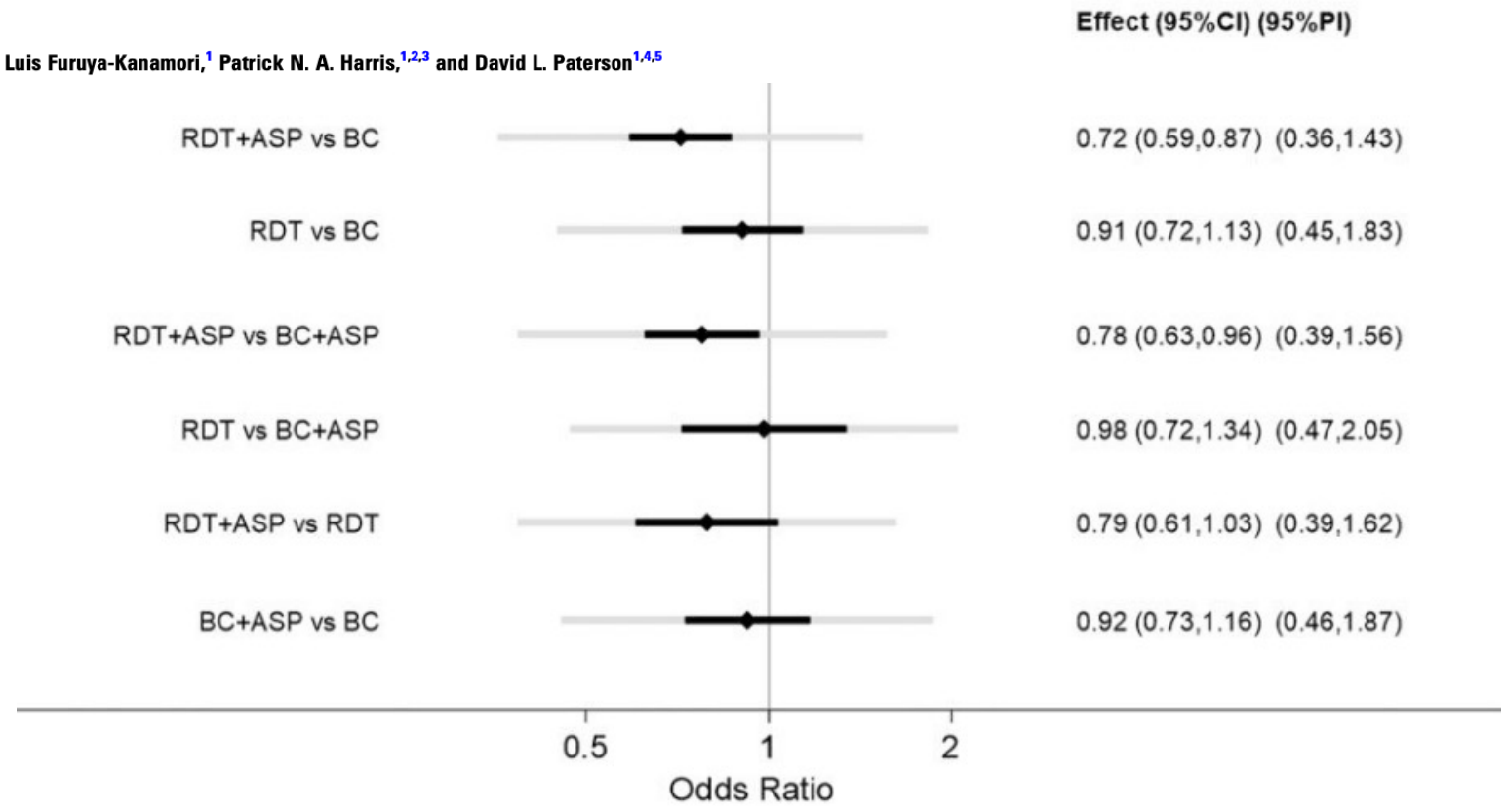
Clinical Infectious Diseases

MAJOR ARTICLE

Rapid Diagnostic Tests and Antimicrobial Stewardship Programs for the Management of Bloodstream Infection: What Is Their Relative Contribution to Improving Clinical Outcomes? A Systematic Review and Network Meta-analysis

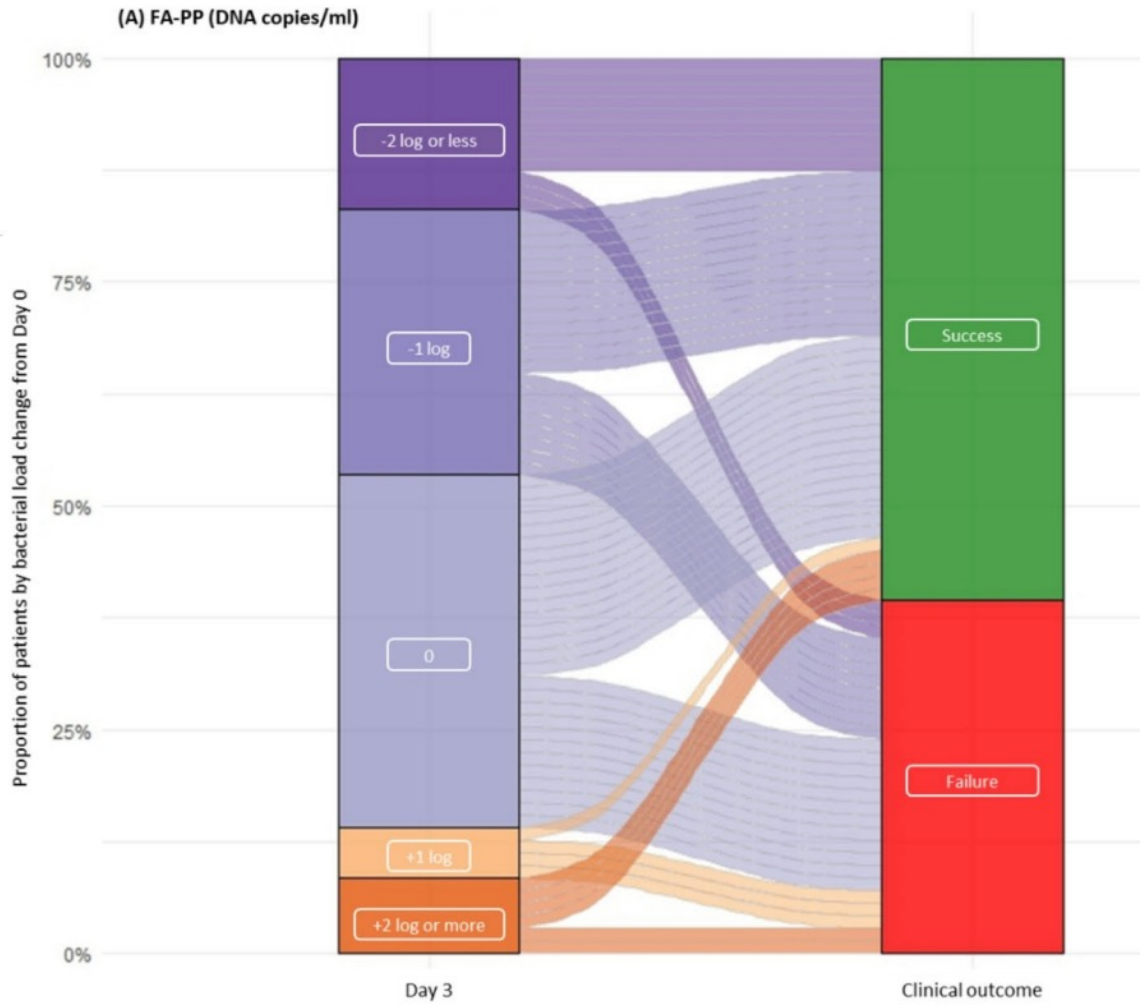
Anna Maria Peri,[1,©] Mark D. Chatfield,[1] Weiping Ling,[1] Luis Furuya-Kanamori,[1] Patrick N. A. Harris,[1,2,3] and David L. Paterson[1,4,5]

Outcome: mortality

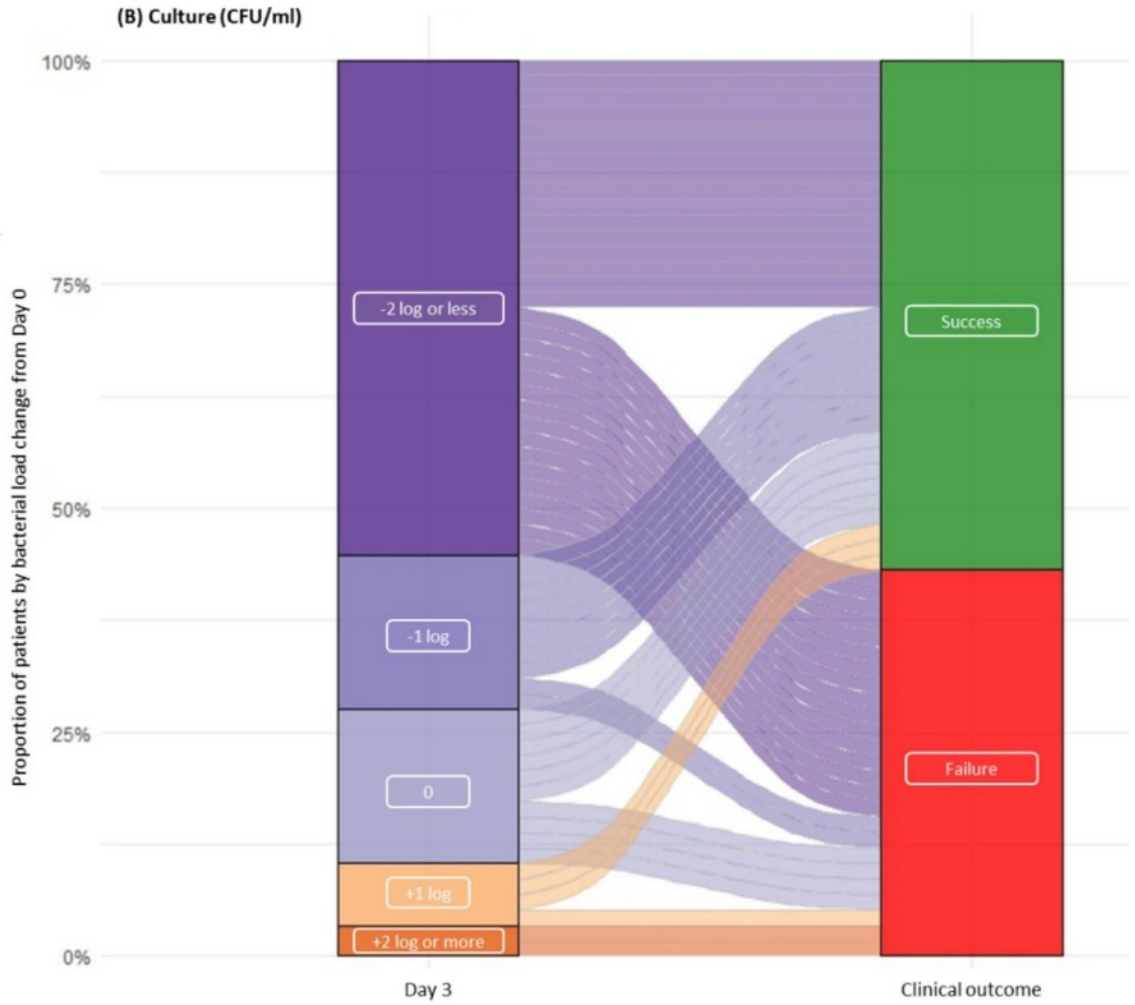


Peri AM, et al. Clin Infect Dis. 2024 Aug 16;79(2):502-515

Η μεταβολή του βακτηριακού φορτίου δε σχετίζεται με την πρόγνωση



OR 0.88 (0.45-1.72); p=0.71



OR 1.15 (0.67-1.16); p=0.61

Dessajan J, et al. Crit Care. 2025 Jul 12;29(1):301.

Η σημασία των βιοδεικτών στη VAP

- For patients with suspected HAP/VAP, we recommend using clinical criteria alone, rather than using serum **PCT** plus clinical criteria, to decide whether or not to initiate antibiotic therapy *(strong recommendation, moderate-quality evidence)*.
- For patients with suspected HAP/VAP, we suggest using clinical criteria alone, rather than using **CPIS** plus clinical criteria, to decide whether or not to initiate antibiotic therapy *(weak recommendation, low-quality evidence)*.

- Performing routine bedside clinical assessment (including ≥1 score like CPIS, SOFA, or APACHE II) in patients receiving antibiotic treatment for VAP or HAP represents good practice (Good practice statement).
- We do not recommend the routine measurement of serial serum PCT levels to reduce duration of the antibiotic course in patients with HAP or VAP when the anticipated duration is 7–8 days (Strong recommendation, moderate quality of evidence).
- The measurement of serial serum PCT levels together with clinical assessment in specific clinical circumstances with the aim of reducing antibiotic treatment duration represents good practice (Good practice statement).

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. Eur Respir J. 2017;50(3):1700582.

Clinical Pulmonary Infection Score (CPIS)

1. Temperature °C
   - ⩾ 36.5 and ⩽ 38.4 = 0 point
   - ⩾ 38.5 and ⩽ 38.9 = 1 point
   - ⩾ 39 or ⩽ 36.0 = 2 points
2. Blood leukocytes, mm^{-3}
   - ⩾ 4,000 and ⩽ 11,000 = 0 point
   - < 4,000 or > 11,000 = 1 point + band forms ⩾ 500 = +1 point
3. Tracheal secretions
   - < 1+ of tracheal secretions = 0 point
   - ⩾ 1+ of tracheal secretions = 1 point + purulent secretion = +1 point
4. Oxygenation: Pa_{O_2}/FI_{O_2}, mm Hg
   - > 240 or ARDS = 0 point
   - ⩽ 240 and no evidence of ARDS = 2 points
5. Pulmonary radiography
   - No infiltrate = 0 point
   - Diffused (or patchy) infiltrate = 1 point
   - Localized infiltrate = 2 points
6. Culture of tracheal aspirate (semiquantitative: 0-1-2 or 3+)
   - Pathogenic bacteria cultured ⩽ 1+ or no growth = 0 point
   - Pathogenic bacteria cultured > 1+ = 1 point + same pathogenic bacteria seen on the Gram stain > 1+ = +1 point

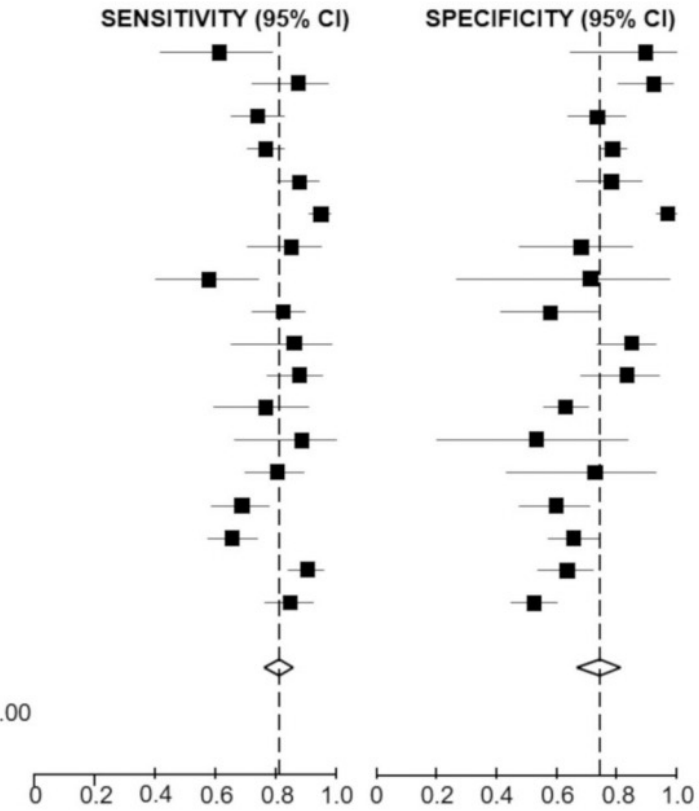
Volume (0-4+) of tracheal secretions
X
Number of aspirations in a day

>6 : διάγνωση πιθανή

Pugin J, et al. Am Rev Respir Dis. 1991 May;143(5 Pt 1):1121-9.

PCT in prediction of sepsis

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 [0.69 - 0.92]	0.69 [0.49 - 0.85]
Godnic 2015	0.57 [0.41 - 0.73]	0.71 [0.29 - 0.96]
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]

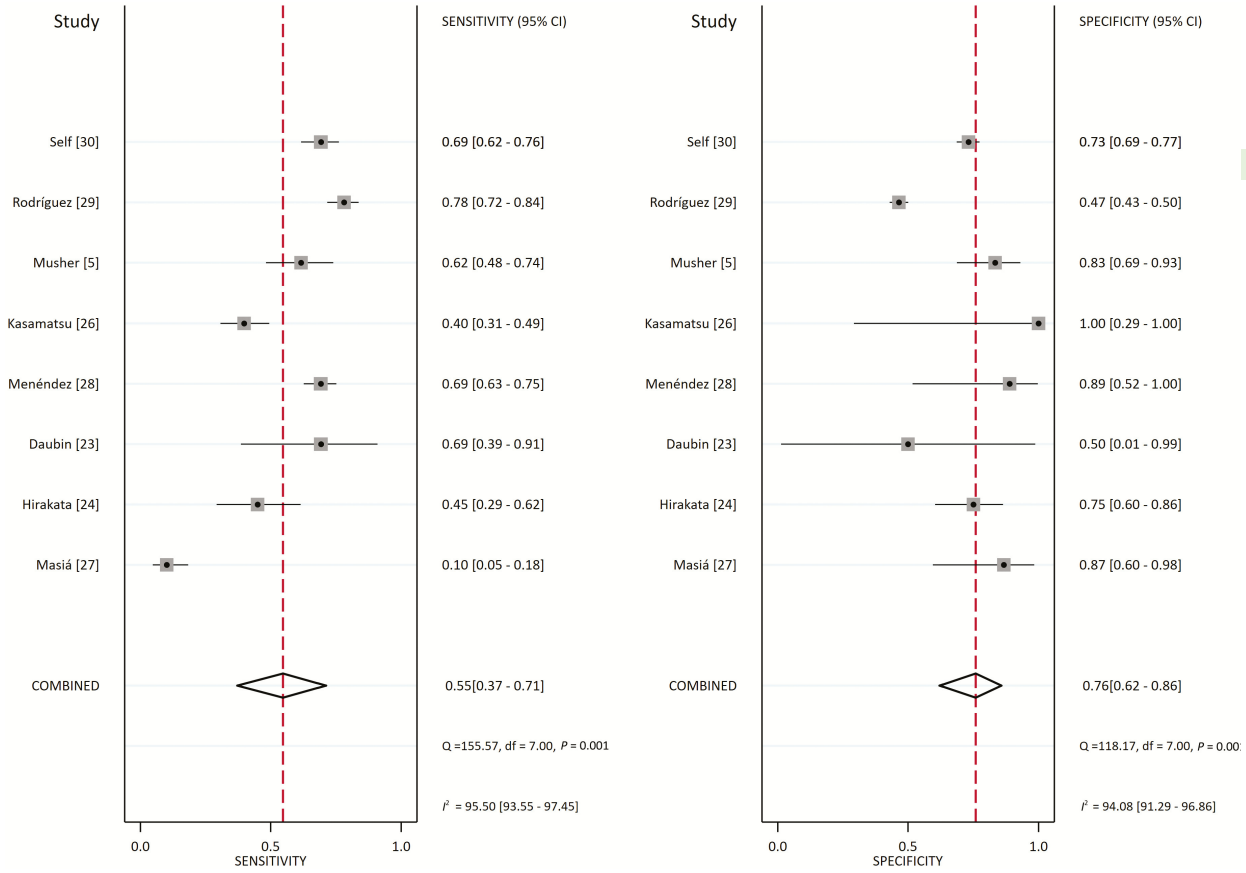


18 studies, observational only
Cutoffs used: varied between > 0.28 and > 4.5 ng/ml

Kondo Y, et al. J Intensive Care. 2019;7:22.

Procalcitonin is not enough to start antimicrobials

Distinguishing bacterial from viral CAP

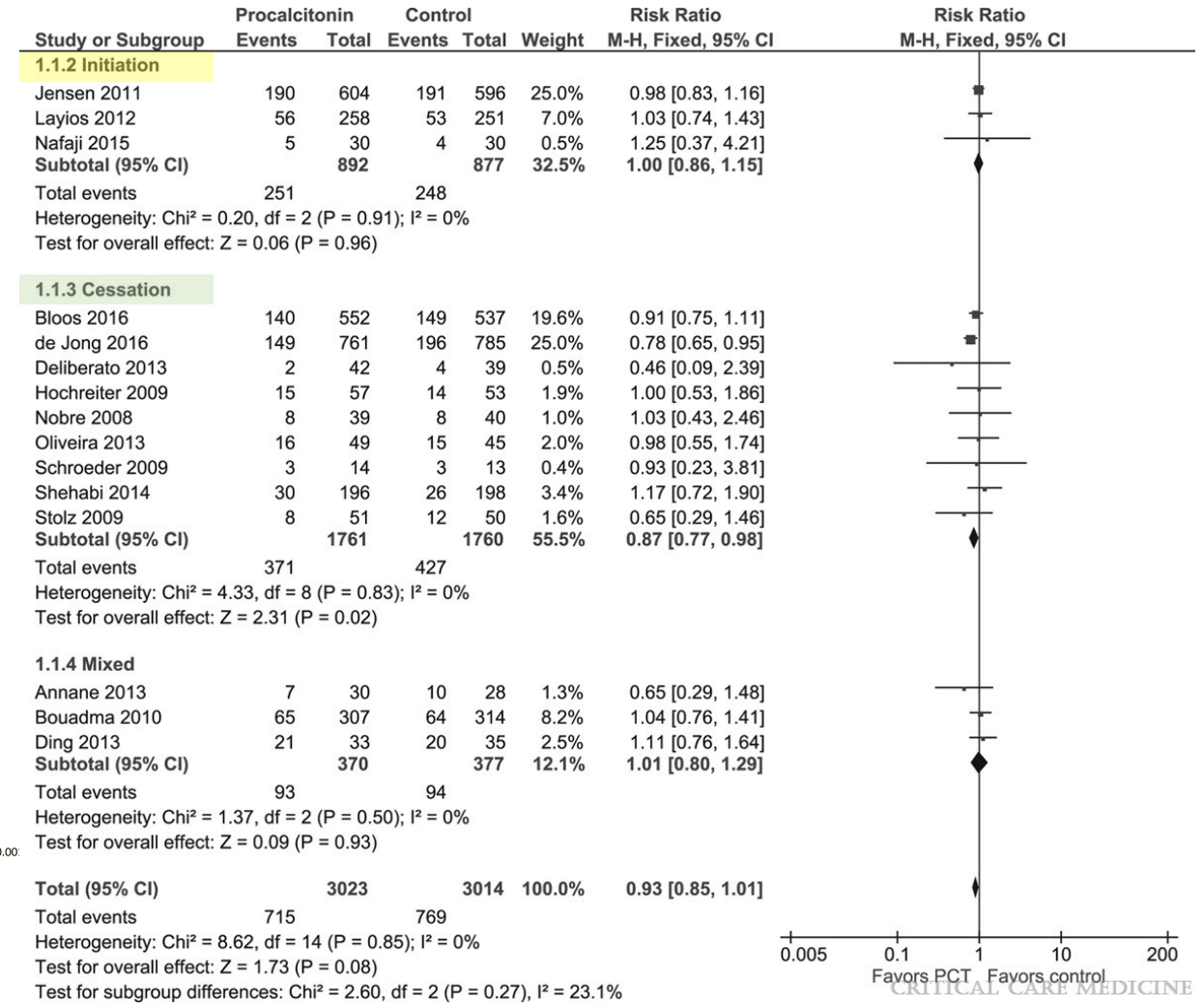


Se 0.55 (0.37-0.71)

Sp 0.76 (0.62-0.86)

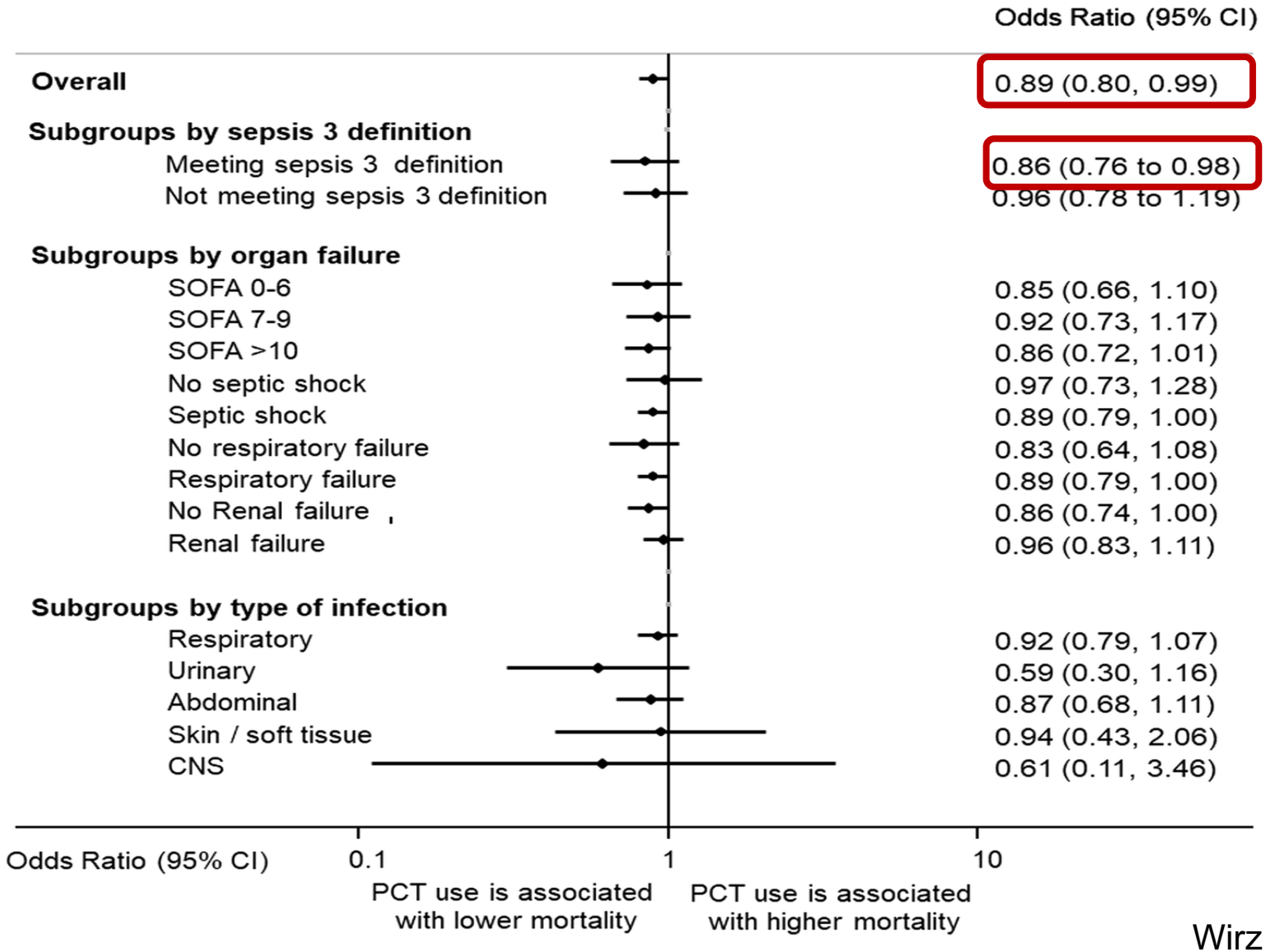
Kamat IS, et al. Clin Infect Dis. 2020;70(3):538-542.

PCT guidance in critically ill patients



Lam SW, et al. Crit Care Med. 2018;46(5):684-690.

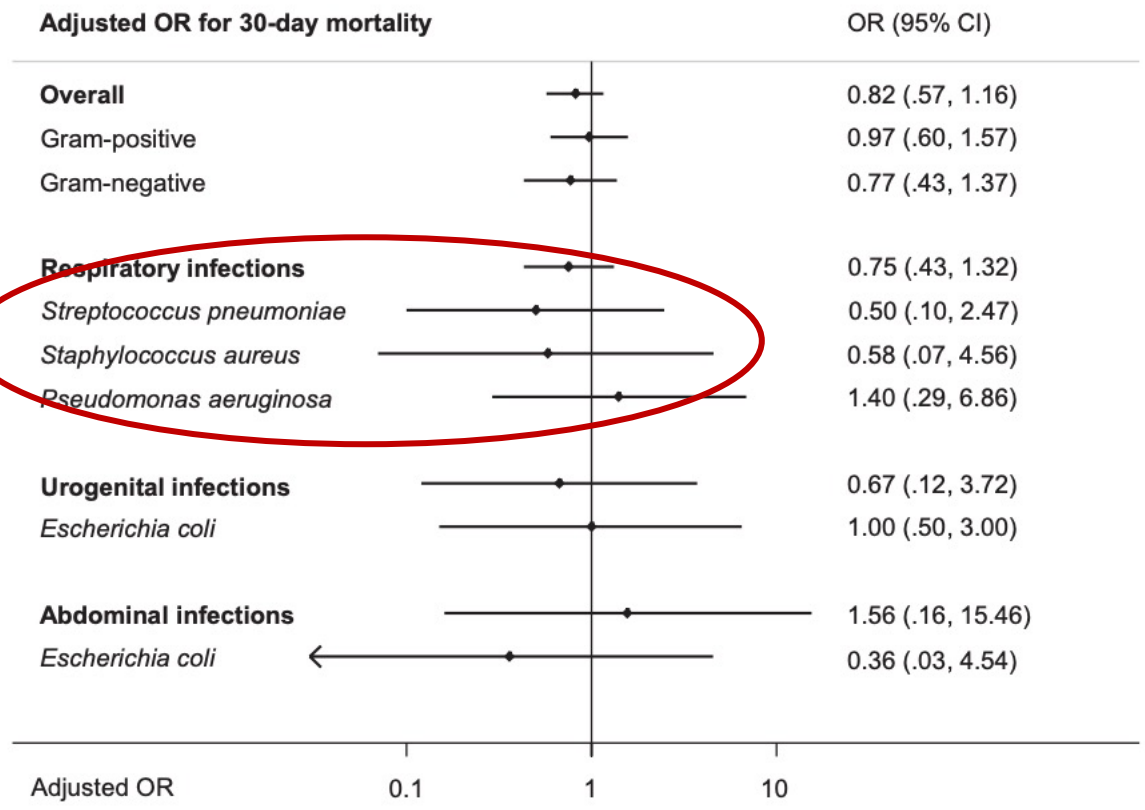
Procalcitonin-guided stewardship in sepsis may improve mortality

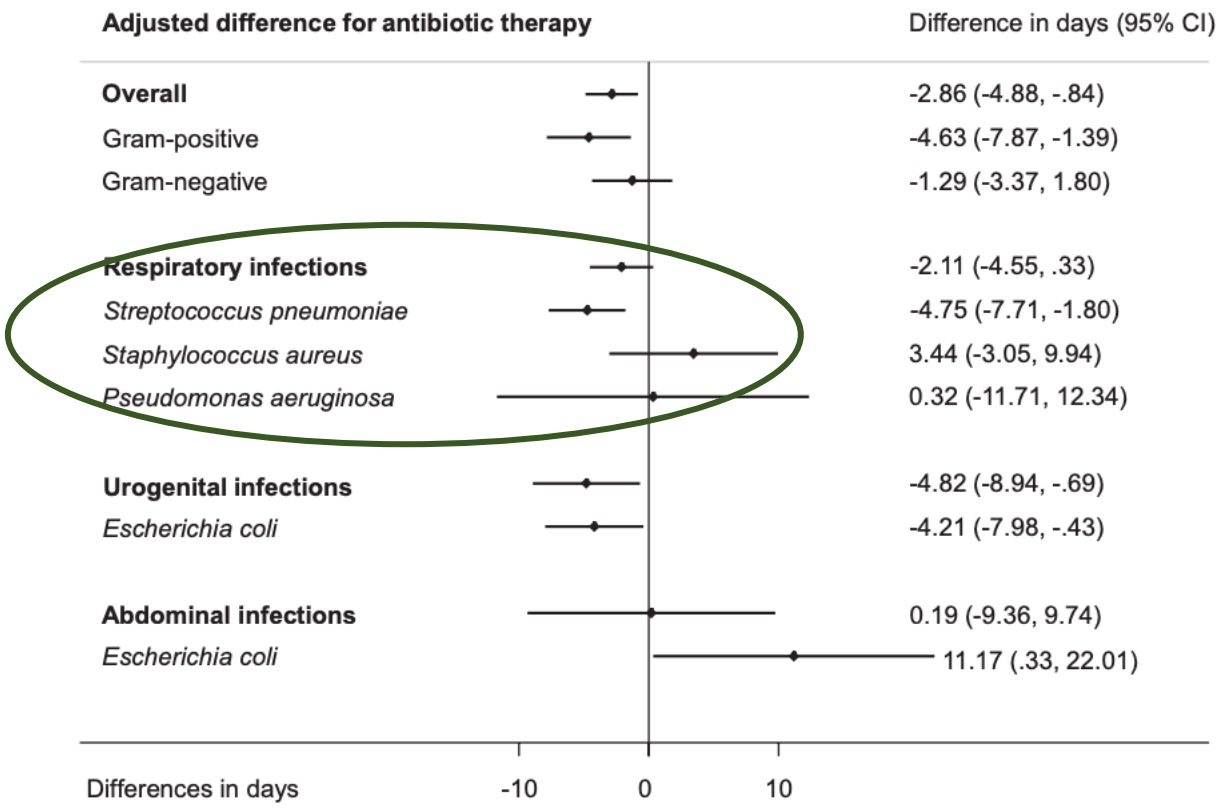


↓ treatment duration (days): -1.19, 95% CI -1.73 to -0.66; p <0.001

Wirz Y, et al. Crit Care. 2018;22(1):191.

Procalcitonin-guided ATB stop is safe in bacteremia





Meier MA, et al. Clin Infect Dis. 2019;69(3):388-396.

Αρχική θεραπεία: παραδοχές

- We recommend that all hospitals regularly generate and disseminate a local antibiogram, ideally one that is specific to their intensive care population(s) if possible.
- We recommend that empiric treatment regimens be informed by the local distribution of pathogens associated with VAP and their antimicrobial susceptibilities.

Focus on organ failure

High MDR risk: prior antibiotic use within 90 days, septic shock before, ARDS, ≥ 5 days of hospitalization, acute renal replacement therapy, high resistance rates (>10%–20%)

- A distinction should be made between patients with risk factors for antibiotic resistance and patients without these risk factors, and also between early (before 5 days) and late (after 5 days) episodes.

High MDR risk: *either septic shock and/or the following risk factors, hospital settings with high rates (>25%) of MDR pathogens, previous antibiotic use, recent prolonged hospital stay (>5 days) and previous colonisation with MDR pathogens.*

Focus on local ecology and septic shock

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. ERJ Open Res. 2018;4(2):00028-2018.

Αρχική θεραπεία

- In patients with suspected VAP, we recommend including coverage for *S. aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli in all empiric regimens (*strong recommendation, low-quality evidence*).
- We suggest including an agent active against MRSA for the empiric treatment of suspected VAP only in patients with any risk factor for antimicrobial resistance, including patients in units where the prevalence of MRSA is not known (*weak recommendation, very low-quality evidence*).

- We recommend initial empiric combination therapy for high-risk HAP/VAP patients to cover Gram-negative bacteria and include antibiotic coverage for MRSA in those patients at risk. (Strong recommendation, moderate quality of evidence.)

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. Eur Respir J. 2017;50(3):1700582.

Αρχική θεραπεία για Gram (+)

- If empiric coverage for MRSA is

  Indicated: we recommend vancomycin or linezolid *(strong recommendation, moderate-quality evidence)*

  Not indicated: we suggest piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem *(weak recommendation, very low-quality evidence)*.

- No further precision regarding *S. aureus*

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. Eur Respir J. 2017;50(3):1700582.

Αρχική θεραπεία για Gram (-)

ESCMID

IDSA Infectious Diseases Society of America

Combination therapy (2 classes):

- We suggest 2 antipseudomonal agents in patients with risk factors for antimicrobial resistance, including patients in an ICU where local antimicrobial susceptibility rates are not available *(weak recommendation, low-quality evidence)*.

- We recommend broad-spectrum empiric antibiotic therapy targeting *Pseudomonas aeruginosa* and extended-spectrum **β**-lactamase-producing organisms, in settings with a high prevalence of *Acinetobacter* spp., and other high-risk patients (Strong recommendation, low quality of evidence).

Monotherapy:

- We suggest one antipseudomonal agent in patients without risk factors for antimicrobial resistance *(weak recommendation, low-quality evidence)*.

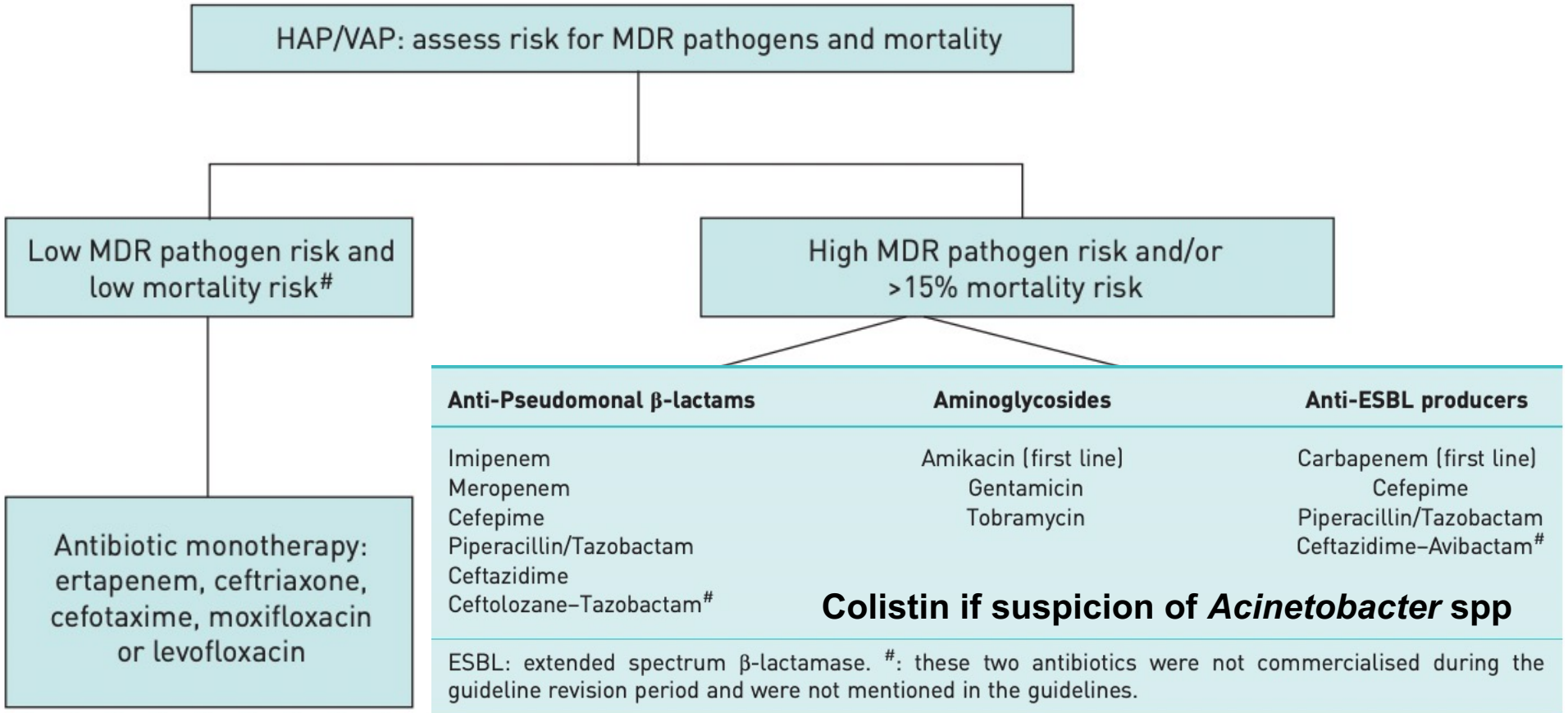
  avoid aminoglycosides (*weak, low*)
  avoid colistin (*weak, very low*)

- We suggest using narrow-spectrum antibiotics in patients with suspected low risk of resistance and early-onset HAP/VAP (Weak recommendation, very low quality of evidence).

  ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. Eur Respir J. 2017;50(3):1700582.

One or two agents?



Torres A, et al. ERJ Open Res. 2018;4(2):00028-2018.

One or two agents?

Clinical Microbiology and Infection 29 (2023) 1364–1366

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journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

Which trial do we need? One or two antimicrobials with anti-pseudomonal activity for the empirical treatment of ventilator-associated pneumonia due to Gram-negative bacteria

Erlangga Yusuf [1,*], Alexandre P. Zavascki [2], Henrik Endeman [3], Andre C. Kalil [4]

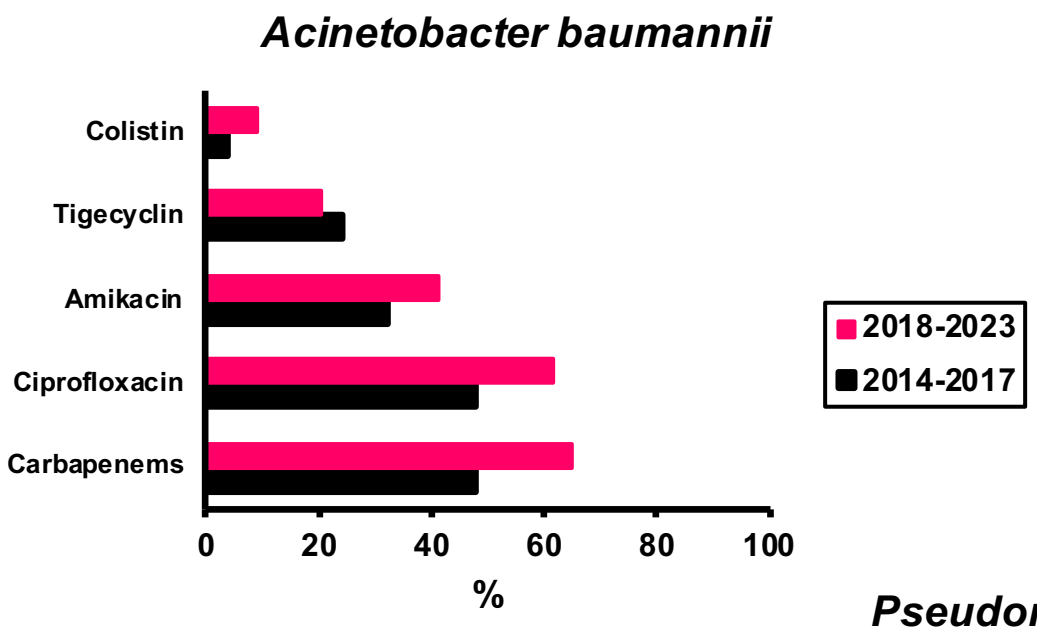
[1] *Department of Medical Microbiology and Infectious Disease, Erasmus MC, Rotterdam, the Netherlands*
[2] *Internal Medicine Department, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*
[3] *Department of Intensive Care, Erasmus MC, Rotterdam, the Netherlands*
[4] *Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE, USA*

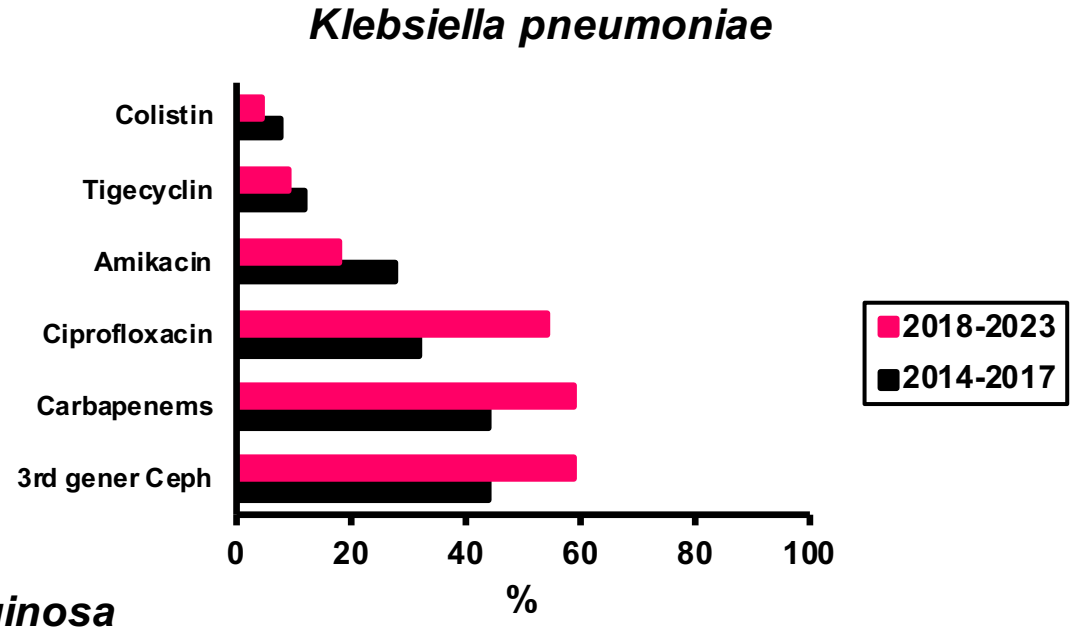
Στοχευμένη θεραπεία για Gram (-)

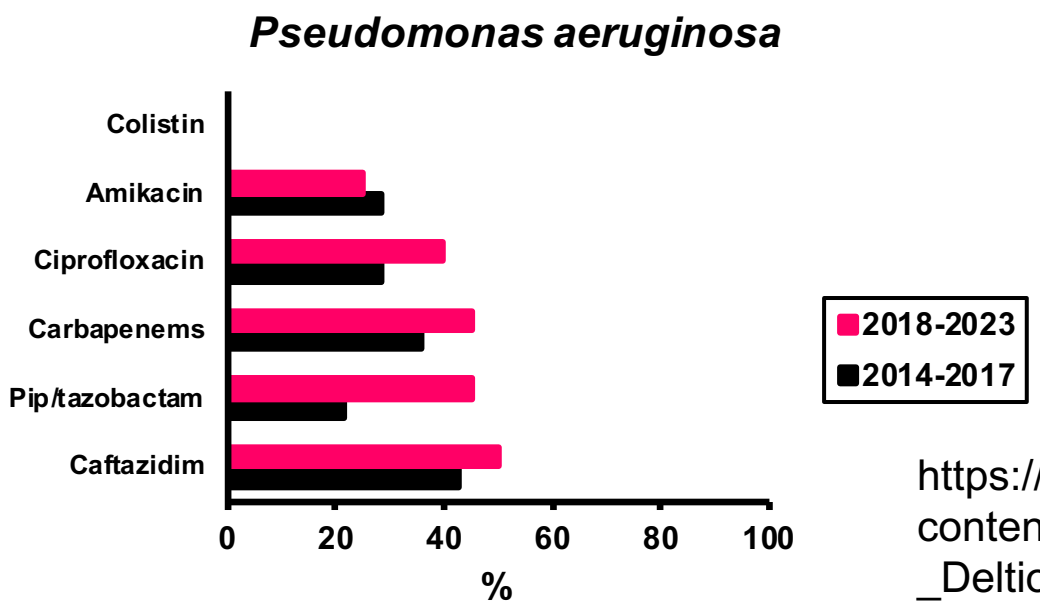
Pathogen	Recommendation	GRADE
P. aeruginosa	Therapy based upon results of AST	Strong, low
	No aminoglycoside monotherapy	Strong, very low
	If no septic shock AND low risk of death (<15%): monotherapy	Strong, low
	If septic shock or high risk of death (>25%): combination therapy	Weak, very low
ESBLs	Therapy based upon results of AST and patient factors (allergy, comorbidities prone to toxicity)	Strong, very low
A. baumannii	Treatment with either a carbapenem or ampicillin/sulbactam if susceptible	
	If only sensitive to colistin: intravenous polymyxin (colistin or polymyxin B) and adjunctive inhaled colistin	Strong, low Weak, low
	If only sensitive to colistin: no adjunctive rifampicin	Weak, moderate
	No tigecyclin	Strong, low
CREs	If only sensitive to colistin: intravenous polymyxin (colistin or polymyxin B) and adjunctive inhaled colistin	Strong, moderate Weak, low

Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.

Ελληνικά δεδομένα- η επιδημιολογία της σήψης







https://sepsis.gr/wp-content/uploads/2023/10/HISS_Enimerotiko_Deltio_Gia_Tin_Sipsi_2023.pdf

What to do with CREs and DTR PA?

	CRE, non-CPE	CRE, KPC +	CRE, OXA-48	CRE, MBL+	DTR PA
IDSA	extended-infusion Meropenem (or Imipenem-cilastatin) OR Ceftazidime-avibactam, Meropenem-vaborbactam, and Imipenem-cilastatin-relebactam	Meropenem-vaborbactam, Ceftazidim-avibactam, Imipenem-cilastatin-relebactam OR Cefiderocol as alternative	Ceftazidime-avibactam is preferred, Or Cefiderocol	Ceftazidime-avibactam in combination with Aztreonam, Or Cefiderocol	Ceftolozane-tazobactam, Ceftazidime-avibactam, Imipenem-cilastatin-relebactam OR Cefiderocol
ESCMID	Meropenem-vaborbactam or Ceftazidime-avibactam No data for Imirenem/ relebactam		Ceftazidime-avibactam	Cefiderocol	Ceftolozane-tazobactam No data for Imirenem/ relebactam

Adapted from Tamma PD, et al. Clin Infect Dis. 2024 Aug 7:ciae403.
Paul M, et al. Clin Microbiol Infect. 2022 Apr;28(4):521-547.

The Ambler molecular classification of beta-lactamase enzymes

Ambler Class	Type	Examples
A	Narrow spectrum β – lactamases (penicillinases)	PSE, CARB
	Broad spectrum β – lactamases	TEM-1, TEM-2, SHV-1
	Extended spectrum β – lactamases (ESBLs)	TEM-3, SHV-5, CTX-M1
	Class A carbapenemases	GES, KPC, SHV-38
B	Metallo β - lactamases	IMP, VIM, NDM
C	AmpC	DHA, CMY-1, ACT-1
D	Extended spectrum β – lactamases (ESBLs), Oxacillinases	OXA-1, OXA-10, OXA-11, OXA-15
	Carbapenem-hydrolysing class D β – lactamases (CHDLs)	OXA-23 (*A. baumannii*), OXA-48 (enterobacteriaceae)

Lawrence J, et al. Nat Commun. 2024 Oct 21;15(1):9070

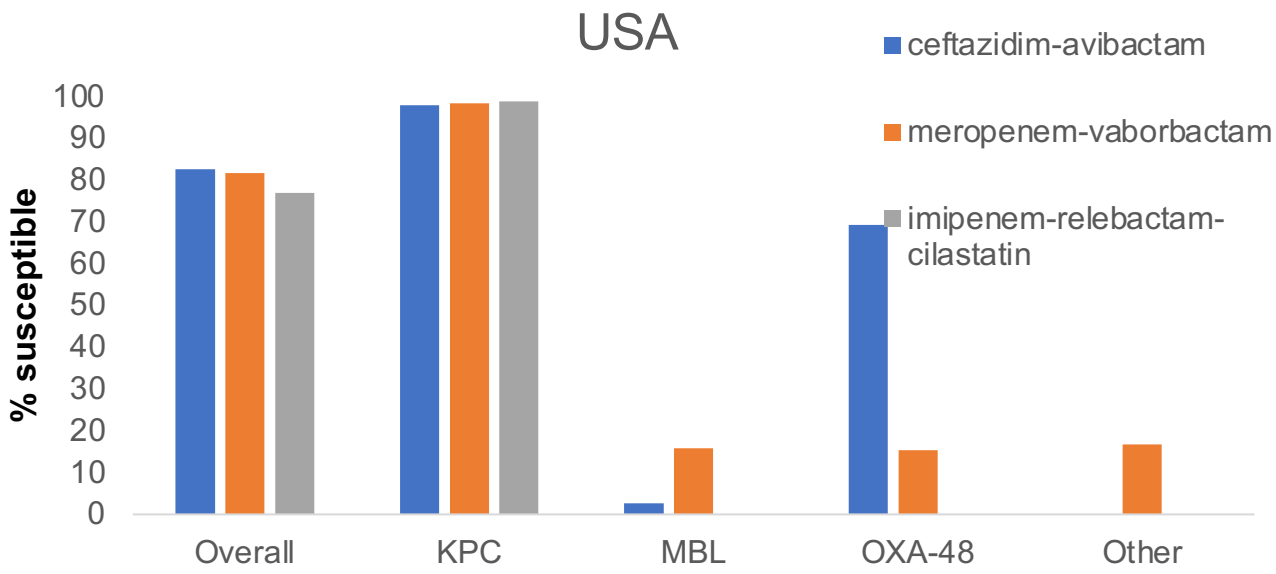
New approvals

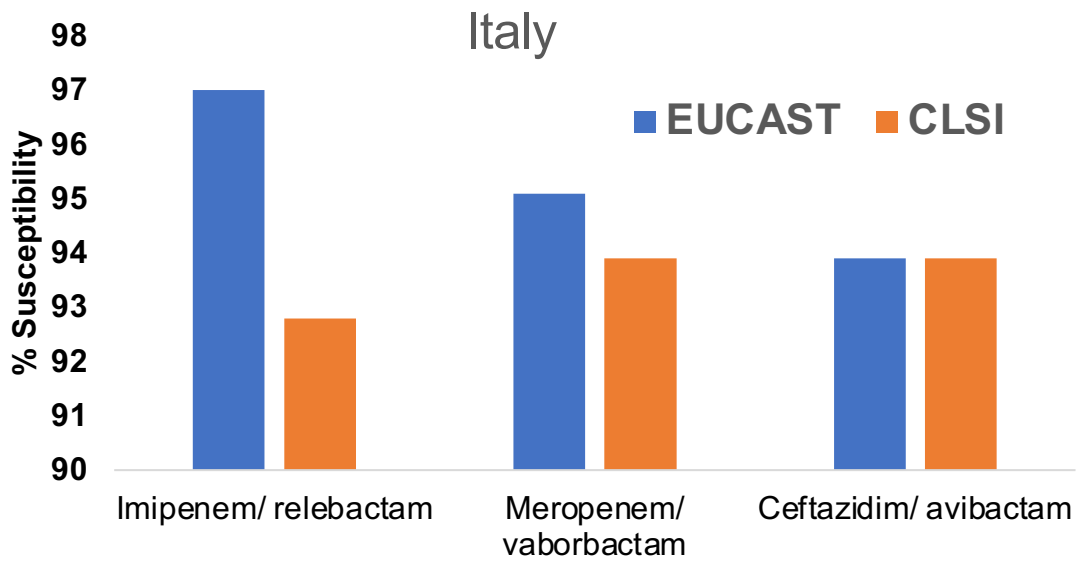
Drug	Spectrum	Labeled indications	Dosage for HAP/VAP
Ceftazidim-avibactam	**ESBL**, **KPC**, **AmpC**, and some **OXA** (e.g., OXA 48) producing Enterobacterales, MDR *P. aeruginosa*, MDR *A. baumannii*	FDA: **HAP/VAP**, cUTIs, cIAIs EMA: all those infections due to aerobic gram-negative organisms with limited treatment options	2.5 (2/0.5) gr x 3 by IV infusion over 2h
Ceftolozane-tazobactam	**ESBL**-producing Enterobacterales, **MDR *P. aeruginosa***, some anaerobes, Streptococcus spp., MSSA	FDA: **HAP/VAP**, cUTIs, cIAIs EMA: **HAP/VAP**, cUTIs, cIAIs	3 (2/1) gr x 3 by IV infusion over 1h
Meropenem-vaborbactam	**ESBL**, **KPC**, **AmpC**-producing Enterobacterales, non-MDR *P. aeruginosa*, non-MDR *A. baumannii*, Streptococcus spp. MSSA	FDA: cUTI, including pyelonephritis. EMA: cUTI (including pyelonephritis), **HAP, VAP**, cIAI, and infections due to aerobic GNB with limited treatment options	4 (2/2) gr x 3 by IV infusion over 3h
Imipenem-relebactam-cilastatin	**ESBL**, **KPC**-producing Enterobacterales, **MDR *P. aeruginosa***, Streptococcus spp., MSSA	FDA: **HAP/VAP**, cIAI, cUTI; EMA: infections due to aerobic GNB with limited or no other therapeutic options	1250 (500/500/250) mg x 4 by IV infusion over 30’
Cefiderocol	**ESBL**, **CRE** (class A, B, and D enzymes), CR *P. aeruginosa*, S. maltophilia, ***A. baumannii***, Streptococcus spp.	FDA: cUTI, **HAP/VAP** EMA: infections due to aerobic GNB with limited therapeutic options	2 gr x 3 by IV infusion over 3h

Adapted from Bassetti M, et al. Semin Respir Crit Care Med. 2022;43(2):280-294.

Any difference?

Ouctome (%)	CZA (n=105)	MVB (n=26)	P-value
Clinical success	65 (61.9)	18 (69.2)	0.49
30-day mortality	20 (19.1)	3 (11.5)	0.57
90-day mortality	30 (28.6)	7 (26.9)	0.48
Recurrence	15 (14.3)	3 (11.5)	1.00
Resistance acquisition	**3 (20)**	**0 (0.0)**	**1.00**





Ackley R, et al. Antimicrob Agents Chemother. 2020;64(5):e02313-19.
Sader HS, et al. Diagn Microbiol Infect Dis. 2023;106(2):115945.
Bianco G, et al. J Antimicrob Chemother. 2025;80(2):583-592.

A comparison of novel BL/BLIs

	CAZ/ AVI	IMI/REL	MEM/VAB
Active against	CPE and P. aeruginosa producing ESBL, KPC, AmpC and certain OXA-48/ OXA-48-like	CPE and P. aeruginosa producing ESBL, KPC, AmpC (incl reduced porin mutations)	CPE producing ESBL, KPC, AmpC Carba-S P. aeruginosa
Inactive against	MBL, A. baumannii, Anaerobes Lower for respiratory P. aeruginosa than ceftolozan/ tazobactam (CACTUS)	Lower for OXA-48/ OXA-48-like, Non-morganellaceae enterobacterales, MBL, A. baumannii	OXA-48, MBL, A. baumannii, CRE P. aeruginosa
ELF / plasma	~30%	~55%	~70%
Potential for resistance induction	10-20%	?	Lower than caz/avi

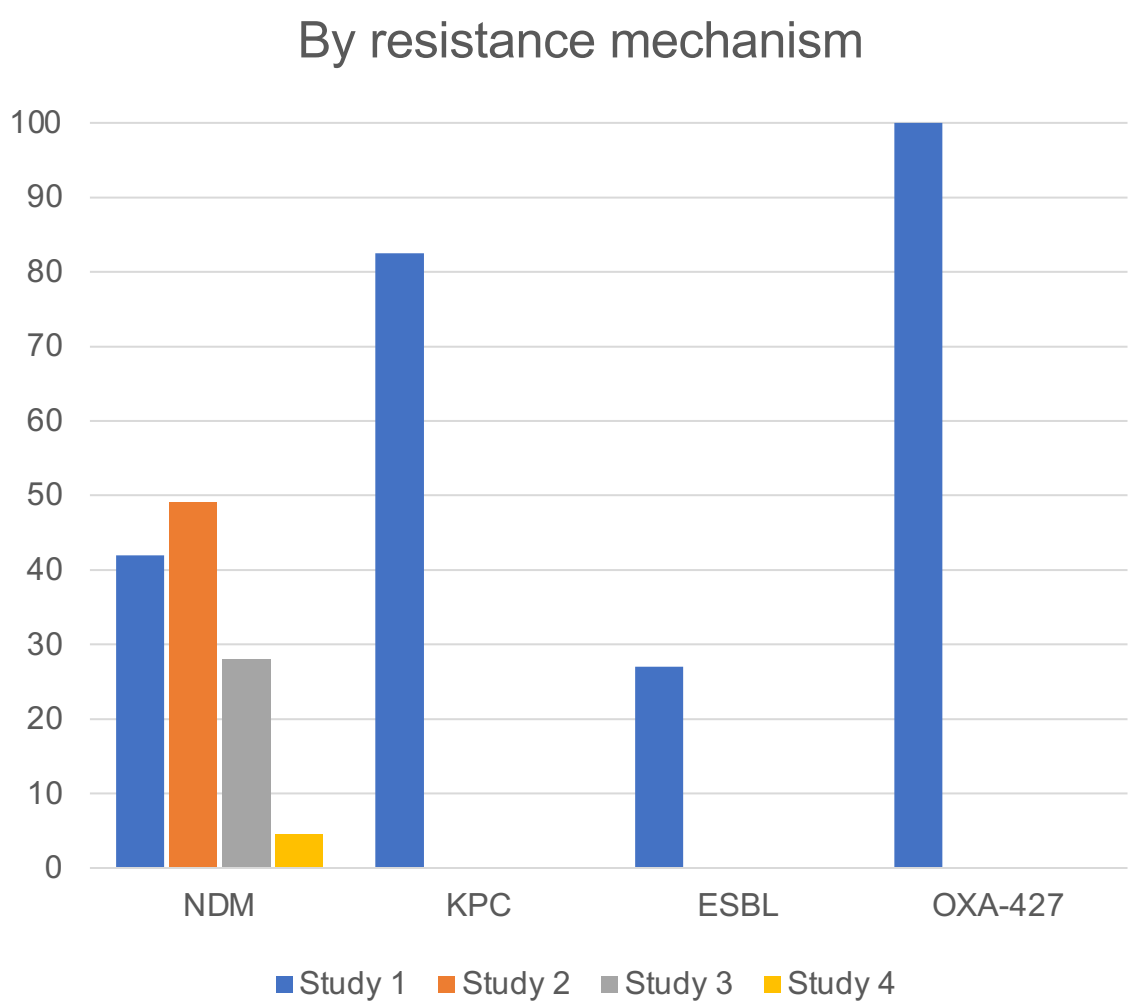
Adapted from Karaiskos I, et al. Antibiotics (Basel). 2025 May 21;14(5):528.

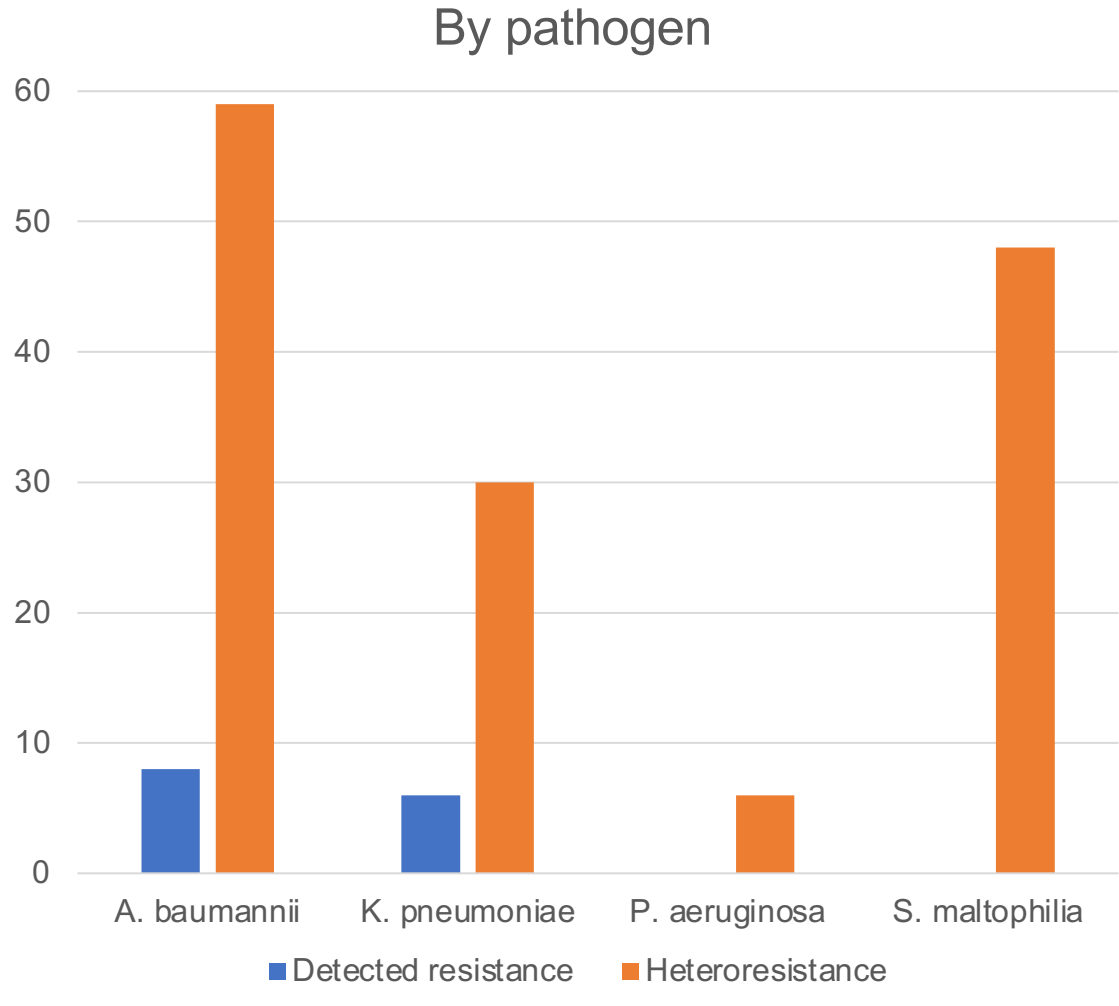
Cefiderocol for VAP

Study	APEKS-NP study	CREDIBLE-CR study	Falcone et al
Type	RCT	RCT open-label	Observational with IPTW
N of patients	292	150	124
VAP prevalence	122 (41.7)	59	35 (28.5)
Main pathogen	K. pneumoniae	A. baumannii	A. baumannii (100%)
Comparator	meropenem	BAT (mainly colistin)	colistin
Mortality (%)	12.4 (18/145)*	25 (25/101)	34 (14/39)
Mortality comparator (%)	11.6 (17/146)	18 (9/49)	55.8 (43/75)
Difference	0.8% (-6.6 to 8.2)	6.4% (-8.6 to 19.2)	0.44 (0.22–0.66); P =0.018

Wunderink RG, et al. Lancet Infect Dis. 2021;21(2):213-225.
Bassetti M, et al. Lancet Infect Dis. 2021;21(2):226-240.
Falcone M, et al. 2022;66(5):e0214221

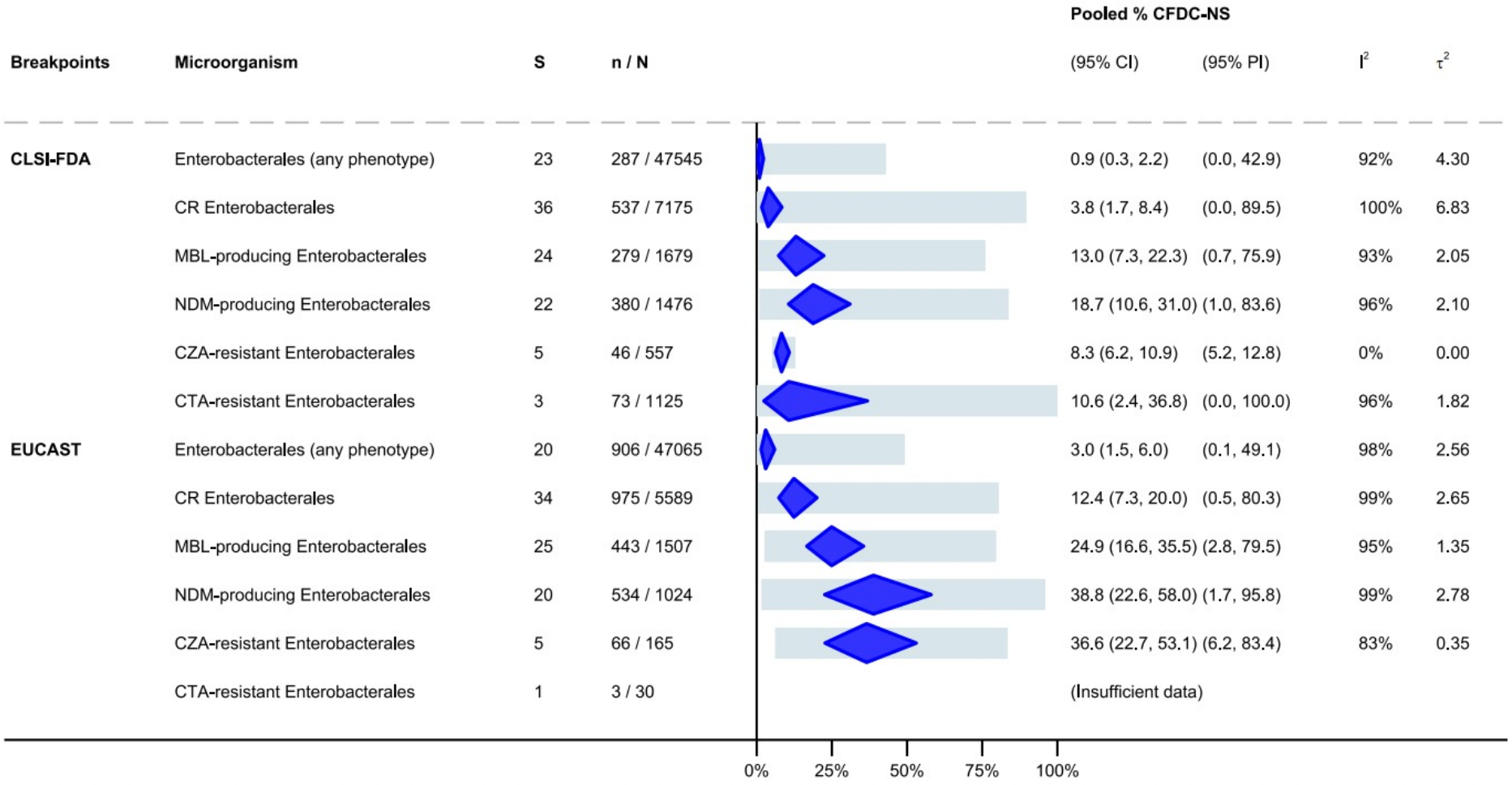
Heteroresistance in cefiderocol





Adapted from Karakonstantis S et al. Antibiotics (Basel). 2022;11(6):723.
Choby JE, et al. Lancet Infect Dis. 2021 May;21(5):597-598.

Resistance in cefiderocol



Karakonstantis S, et al. Clin Microbiol Infect. 2024;30(2):178-188.

What about Gram-positives?

Drug	Spectrum	Labeled indications	Dosage
Tedizolid	**PRP, VRE, MRSA, VRSA**	FDA: ABSSSI EMA: ABSSSI	200 mg x 1 PO or IV infusion over 60’
Lefamulin	***S. pneumoniae*** penicillin non-susceptible and macrolide R, **MRSA**, M. catarrhalis, H. influenzae, **atypicals**	FDA: CABP EMA: CABP Poster on MRSA and MSSA from HAP	600 mg x 2 PO or 150 mg x 2 IV infusion over 60’
Iclaprim	Gram (+) including **MRSA**, M. catarrhalis, H. influenzae	None (Qualified drug status for infectious diseases)	?
Ceftarolin	MSSA, **MRSA**, *Streptococcus pneumoniae* and non-β-lactamase-producing Enterobacterales	FDA: ABSSSI and CABP	600 mg x 2 IV infusion over 5-60’

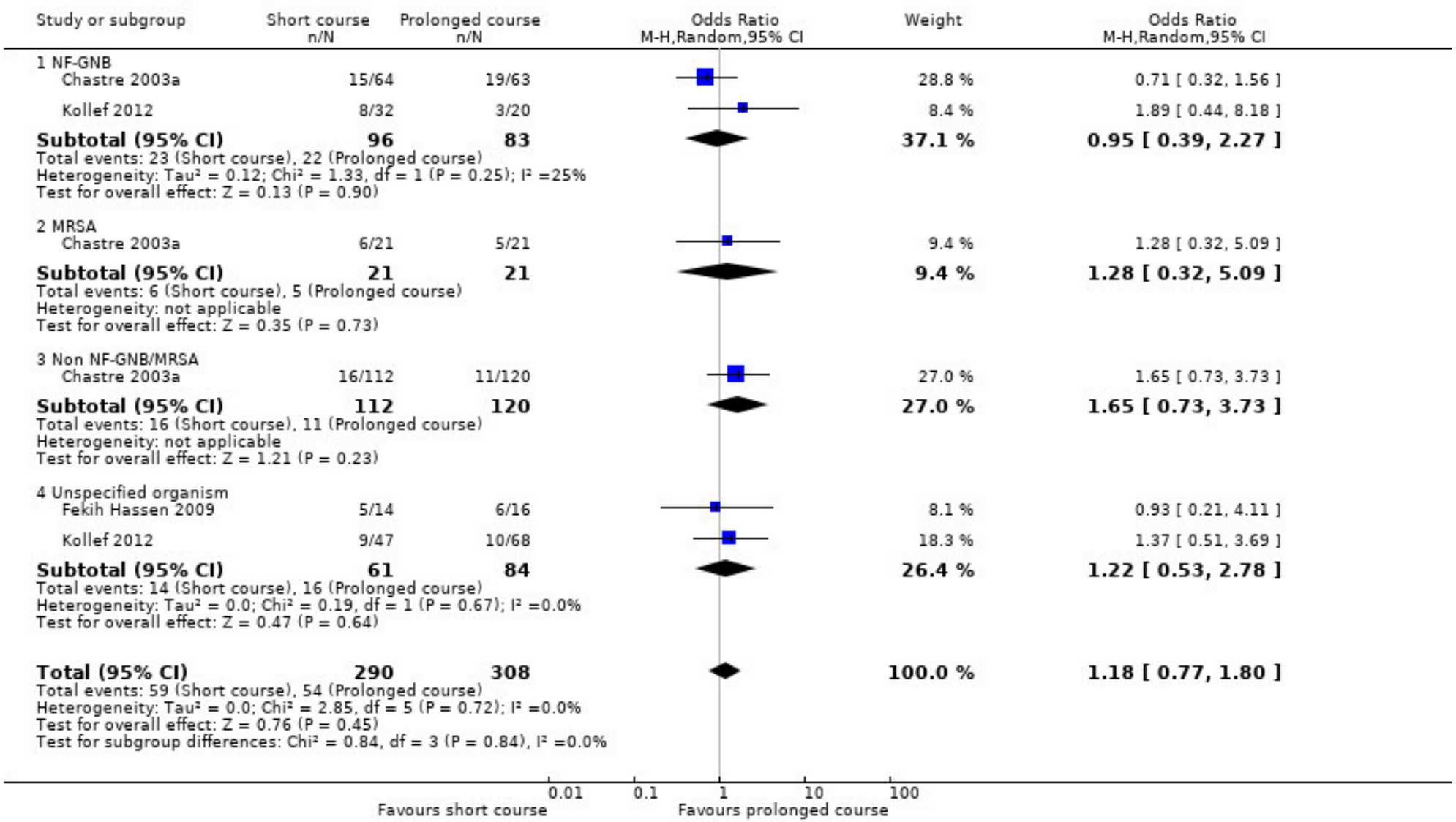
Deescalation

- For patients with HAP/VAP, we suggest that antibiotic therapy be de-escalated rather than fixed *(weak recommendation, very low-quality evidence)*.

- If initial combination therapy is started, we suggest continuing with a single agent based on culture results and only consider maintaining definitive combination treatment based on sensitivities in patients with extensively drug-resistant (XDR; *i.e.* susceptible to only one or two classes of antibiotics)/pan-drug-resistant (PDR; *i.e.* not susceptible to any antibiotics) nonfermenting Gram-negative bacteria and carbapenem-resistant *Enterobacteriaceae* (CRE) isolates. (Weak recommendation, low quality of evidence.)

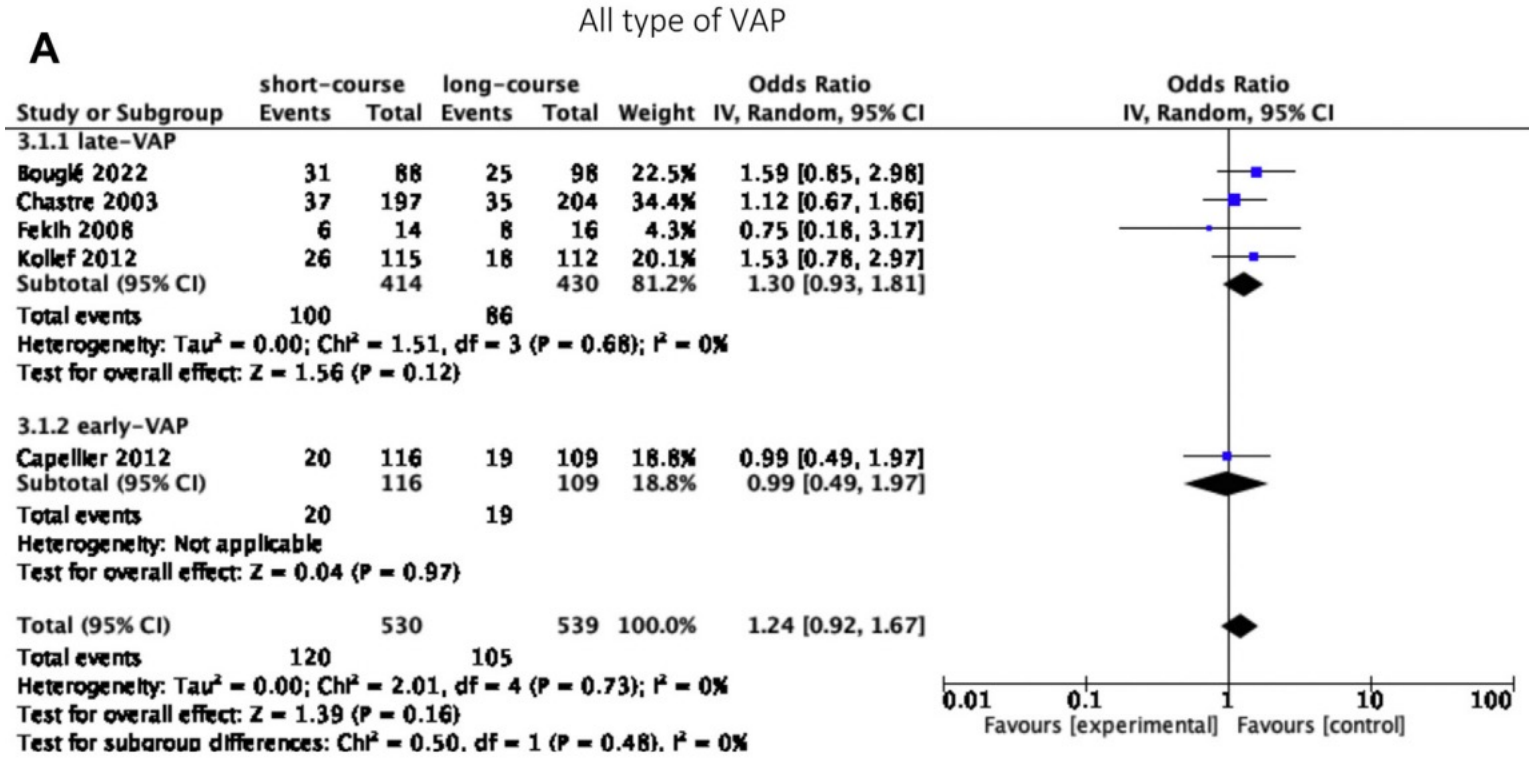
Kalil AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.
Torres A, et al. Eur Respir J. 2017;50(3):1700582.

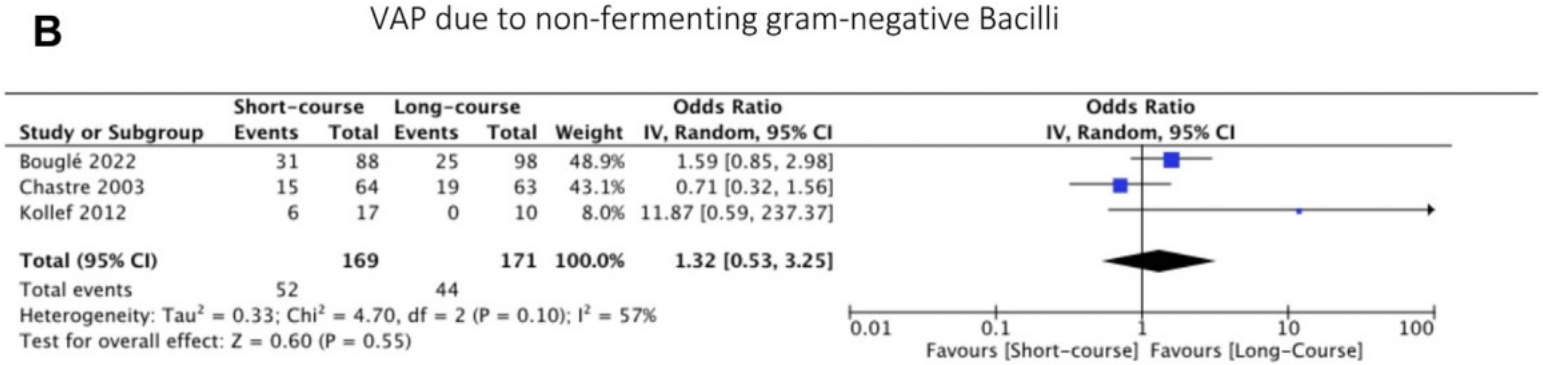
How long? (7-8 days vs 10-15)



Pugh R, et al. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD007577. doi: 10.1002/14651858.CD007577.pub3.

How long? (7-8 days vs 10-15)



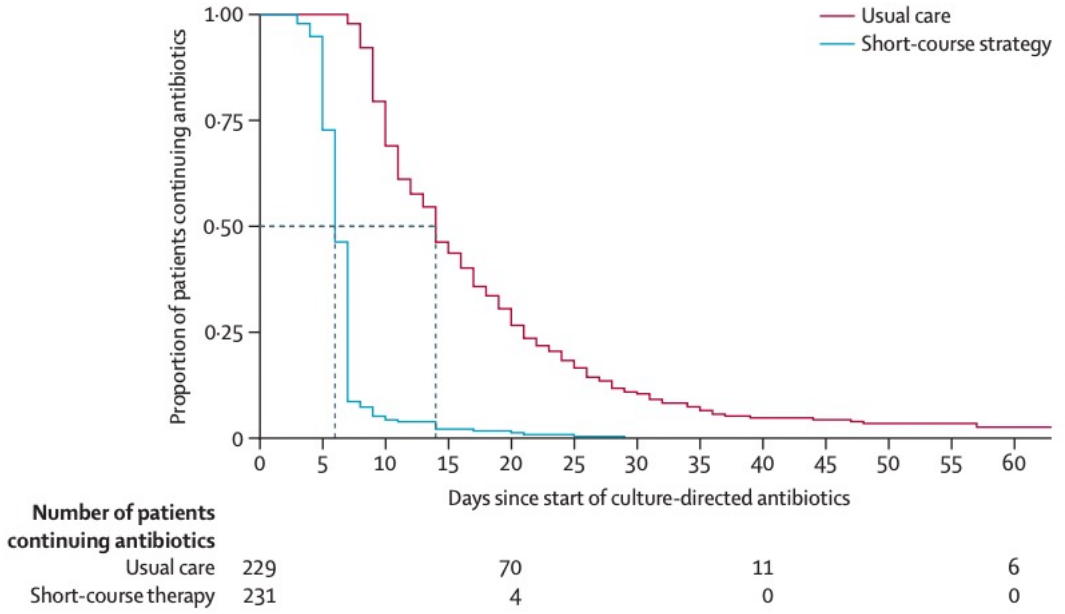


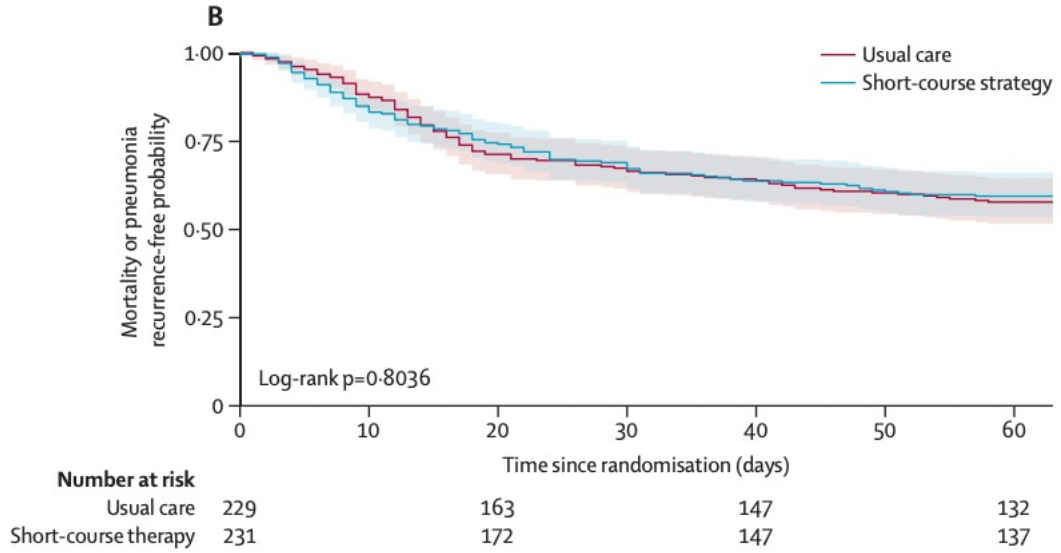
OR for recurrence/relapse:
1.45 (0.94-2.22); p=0.09;
I^2=0%
Similarly for non-fermenters

Daghmouri MA, et al. EClinicalMedicine. 2023;58:101880.

Less is more

- Τυχαιοποιημένη, ανοικτού τύπου πολυκεντρική μελέτη, μη κατωτερότητας
- 39 ΜΕΘ σε Νεπάλ, Σιγκαπούρη και Ταϊλάνδη
- N= 461 ασθενείς με VAP
- 3-5 ημέρες (και σίγουρα <7) vs ≥8 ημέρες αντιβιοτικών





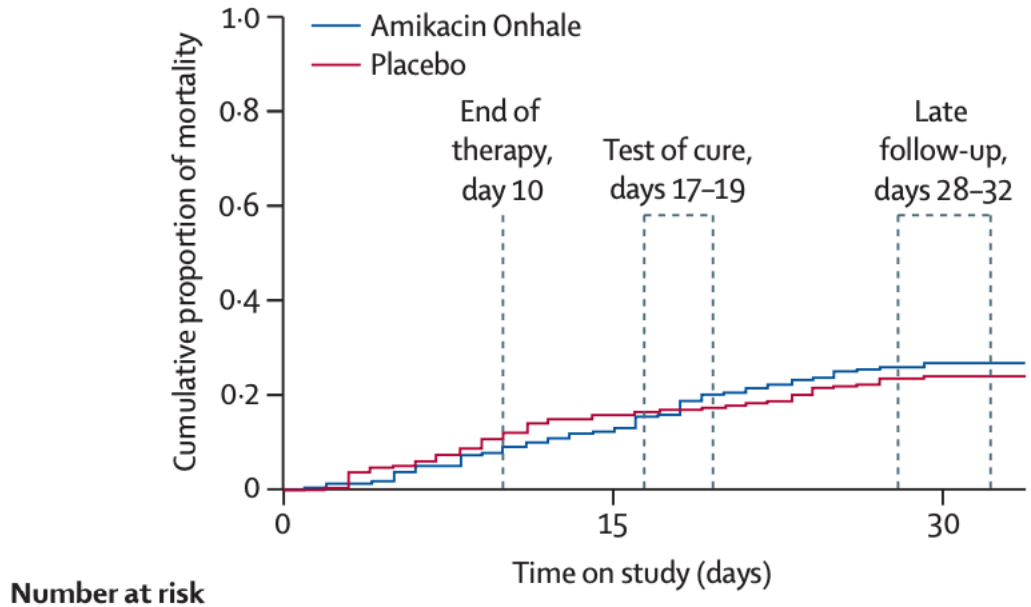
Mo Y, et al. Lancet Respir Med. 2024;12(5):399-408.

Εισπνεόμενα αντιβιοτικά

- Όφελος:
  - Αυξημένη συγκέντρωση στους αεραγωγούς= στην εστία της λοίμωξης
  - Βελτιωμένη φαρμακοκινητική → συμπληρωματική θεραπεία με συστηματική
  - Μικρότερη συστηματική απορρόφηση/ τοξικότητα
  - Μικρότερη διαταραχή του συνολικού μικροβιώματος
  - *Παράδειγμα:* κολιστίνη
- Ιδιαίτερης σημασίας για αντιβιοτικά με μικρή διείσδυση στο επιθηλιακό υγρό (epithelial lining fluid-ELF)
  - *Παράδειγμα:* αμινογλυκοσίδες
- Συμμετοχή στην αύξηση του προφίλ ανθεκτικότητας;

Εισπνεόμενα αντιβιοτικά και θνητότητα στη VAP

- Τυχαιοποιημένη, διπλή τυφλή, πολυκεντρική μελέτη
- 153 ΜΕΘ
- N= 725 ασθενείς με VAP και παράγοντες κινδύνου πολυανθεκτικών Gram (-)
- Εισπνεόμενη αμικασίνη vs εικονικό



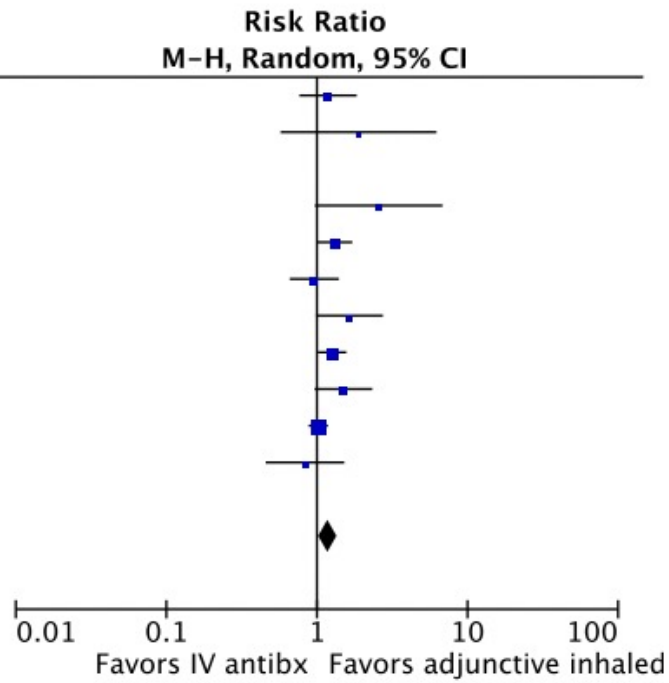
Niederman MS, et al. Lancet Infect Dis. 2020;20(3):330-340.

Εισπνεόμενα αντιβιοτικά και λύση της VAP

Study or Subgroup	Adjunctive inhaled antibx Events	Total	IV antibx alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brown 1990	24	45	18	40	7.7%	1.19 [0.76, 1.84]	1990
LeConte 2000	7	21	3	17	1.2%	1.89 [0.57, 6.22]	2000
Hallal 2007	5	5	3	5		Not estimable	2007
Palmer 2008	8	14	4	18	1.8%	2.57 [0.97, 6.82]	2008
Korbila 2009	62	78	26	43	15.5%	1.31 [1.01, 1.72]	2009
Rattanaumpawan 2010	26	51	26	49	9.7%	0.96 [0.66, 1.40]	2010
Kofteridis 2010	23	43	14	43	5.9%	1.64 [0.98, 2.74]	2010
Tumbarello 2013	72	104	57	104	19.5%	1.26 [1.02, 1.57]	2013
Doshi 2013	24	44	20	55	7.6%	1.50 [0.96, 2.33]	2013
INHALE 1 2017	149	255	145	253	26.5%	1.02 [0.88, 1.18]	2017
IASIS 2017	15	71	18	71	4.5%	0.83 [0.46, 1.52]	2017
Total (95% CI)		**726**		**693**	**100.0%**	**1.20 [1.05, 1.37]**	
Total events	410		331				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 12.75$, df = 9 (P = 0.17); $I^2 = 29\%$

Test for overall effect: Z = 2.60 (P = 0.009)



Sweeney DA, Kalil AC. Clin Microbiol Infect. 2019 Oct;25(10):1195-1199.

Drug	Suggested IV dose for ARDS lung infections (with normal CrCl)	Notes	Suggested inhaled dose
Penicillins			
Ampicillin	2 gm 6 hourly (q6h)		1 g q 12 h [119]
Ampicillin–sulbactam			3 g q 8 h [120]
Cephalosporins			
Ceftazidime	2 gm 6–8 hourly		250 mg q 12 h [121, 122] 15 mg/kg q 3 h [123]
Carbapenems			
Meropenem	1 gm 4–6 hourly		Not recommended (no data)
Imipenem	500–1000 mg 6 hourly		50 mg q 6 h [124]
Quinolones			
Moxifloxacin	400 mg daily		Not recommended (no data)
Ciprofloxacin	400 mg 8 hourly		Not recommended (no data in ventilated patients)
Levofloxacin	750 mg daily up to 500 mg 12 hourly		240 mg q 12 h [125]
Sulfonamide			
Trimethoprim/sulfamethoxazole	8–10 mg trimethoprim/kg/day		Not recommended (no data)
Glycopeptide			
Vancomycin	30 mg/kg loading Same dose per day (divided or continuous infusion)	Keep serum level 20–25 mg/L	120 mg q8 h [126, 127]
Aminoglycosides			
Gentamicin	7 mg/kg loading dose	Used primarily to sterilize blood	80 mg q8h [126, 127]
Tobramycin	7 mg/kg loading dose	Used primarily to sterilize blood	300 mg q12 h [128]
Amikacin	25–30 mg/kg loading dose	Used primarily to sterilize blood	25 mg/kg/day [123] 40 mg/kg/day [129] 400 mg q12h [100]
Polymyxins			
Colistin	4 mg/kg loading, then 500 mg 6 hourly (33.33 mg colistin = 1 million units)		4 MIU q 8 h [129]
Phosphonic acid derivative			
Fosfomycin	4 g 6–8 hourly	Never alone	120 mg fosfomycin q12h [99]
Monobactam			
Aztreonam	1 g 6 hourly		75 mg q 8 h [130]

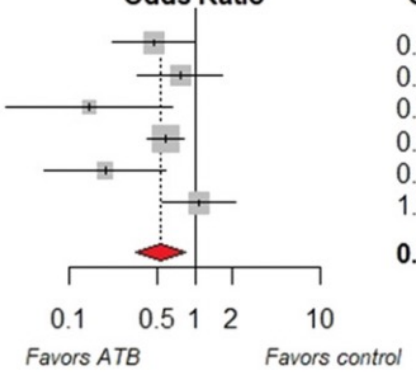
Luyt CE, et al. Intensive Care Med. 2020; 46(12):2168-83.

Εισπνεόμενα αντιβιοτικά για πρόληψη και θεραπεία της VAP

Καταληκτικό σημείο: εμφάνιση VAP

Author	ATB VAP (n)	ATB Patients (N)	Control VAP (n)	Control Patients (N)	OR	95%-CI	Weight
Karvouniaris et al. 2015	14	84	25	84	0.47	[0.23; 0.99]	17.6%
Claridge et al. 2007	21	53	24	52	0.77	[0.35; 1.66]	16.8%
Wood et al. 2002	3	20	11	20	0.14	[0.03; 0.65]	7.1%
Rouby et al. 1994	97	347	100	251	0.59	[0.42; 0.83]	27.9%
Klastersky et al. 1974	5	43	17	42	0.19	[0.06; 0.59]	11.0%
Lode et al. 1992	29	85	25	77	1.08	[0.56; 2.07]	19.6%
Total (95% CI)	**169**	**632**	**202**	**526**	**0.53**	**[0.34; 0.84]**	**100.0%**

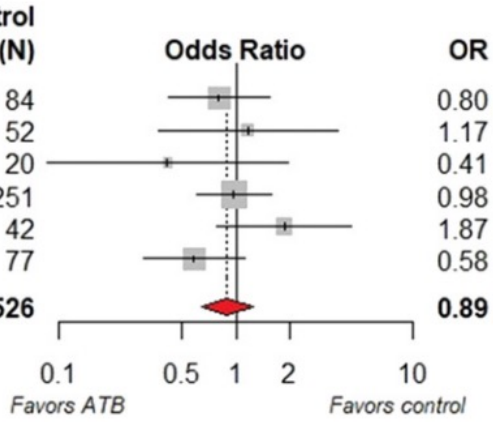
Heterogeneity: $I^2 = 55\%$, $\tau^2 = 0.1596$, $p = 0.05$



Καταληκτικό σημείο: θνητότητα

Author	ATB Death (n)	ATB Patients (N)	Control Death (n)	Control Patients (N)	OR	95%-CI	Weight
Karvouniaris et al. 2015	25	84	29	84	0.80	[0.42; 1.54]	21.5%
Claridge et al. 2007	7	53	6	52	1.17	[0.36; 3.74]	7.6%
Wood et al. 2002	3	20	6	20	0.41	[0.09; 1.95]	4.4%
Rouby et al. 1994	42	347	31	251	0.98	[0.60; 1.60]	32.6%
Klastersky et al. 1974	23	43	16	42	1.87	[0.79; 4.43]	13.2%
Lode et al. 1992	23	85	30	77	0.58	[0.30; 1.13]	20.8%
Total (95% CI)	**123**	**632**	**118**	**526**	**0.89**	**[0.64; 1.25]**	**100.0%**

Heterogeneity: $I^2 = 14\%$, $\tau^2 = 0.0244$, $p = 0.33$



Póvoa FCC, et al. J Crit Care. 2018;43:240-245.

Backup slides

Cross-Resistance Among Newer β-Lactamase Inhibitor Combinations

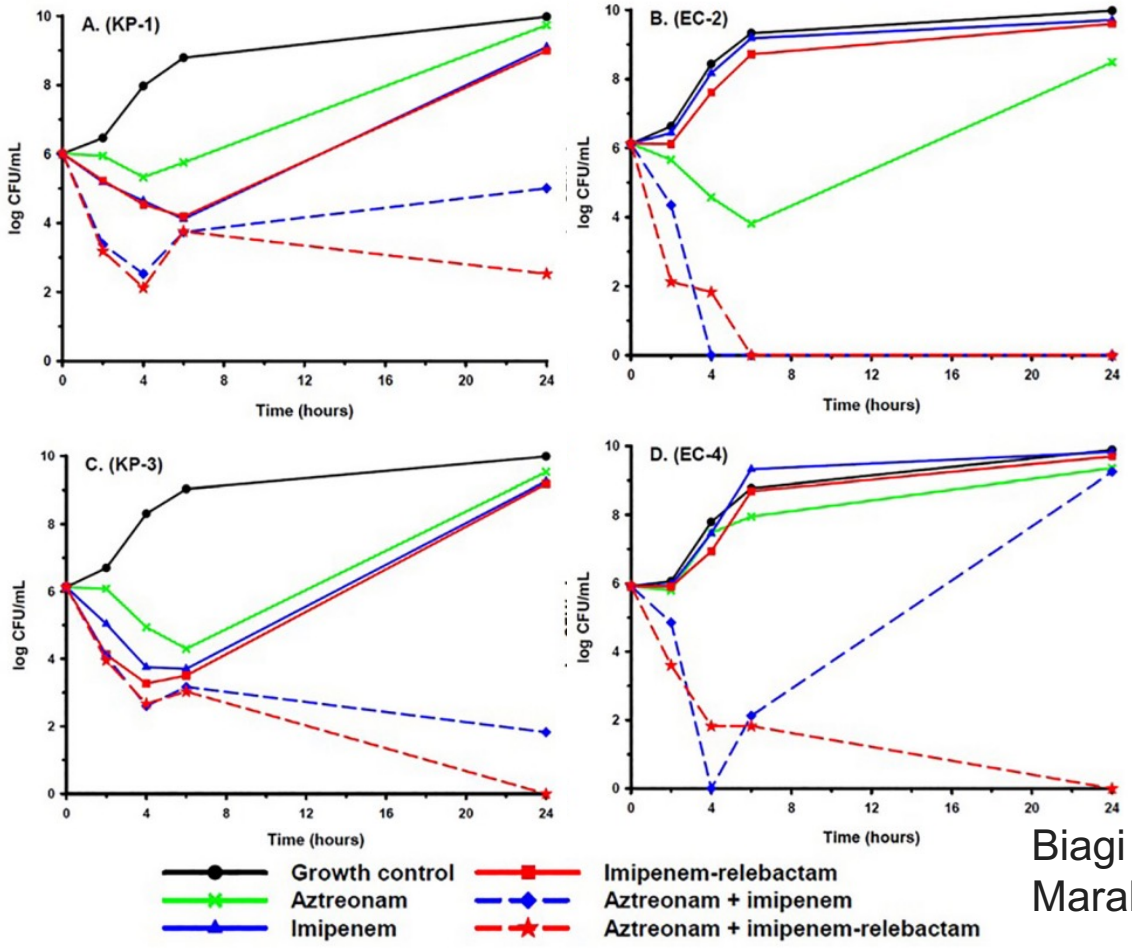
C/T remained active against 54.7% of CZA non-susceptible (NS) isolates and against 68.9% of IMI/REL NS isolates
IMI/REL remained active against 64.2% of CZA NS isolates to CZA and 64.8% of C/T NS isolates

Resistance phenotype (n)	% Susceptibility		
	CZA	C/T	IMI/REL
CZA NS (95)	-	54.7	64.2
C/T NS (63)	31.7	-	64.8
IMI/REL NS (61)	52.5	68.9	-

Sader HS, et al. Int J Antimicrob Agents. 2023 Apr;61(4):106744

Synergy with Aztreonam (*in vitro*)

- 13 MBL-enterobacteriacae: 9 E. coli, 4 K. pneumoniae
  - All NDM-producing
  - All resistant to IMI/REL, 11 resistant to aztreonam



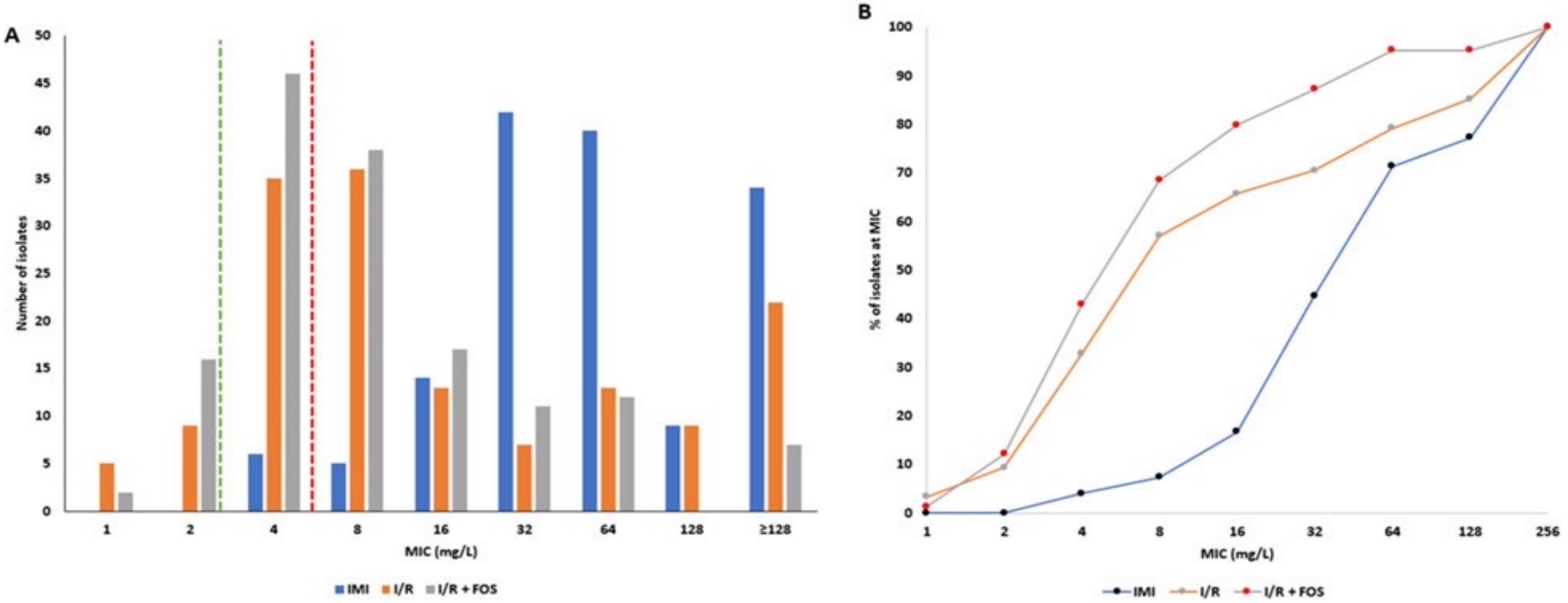
- 40 MBL-Kp isolates:
  - 34 NDM, 3 NDM +VIM, 1 NDM+KPC, 1 VIM+KPC
  - All resistant to aztreonam, CAZ/AVI, and IMI/REL, 95% resistant to M/V

Combination	Synergy % (n/N)	Additivity	Indifference
IMI/REL+ Aztreonam	97.5% (39/40)	0	0
CAZ/AVI + Aztreonam	97.5% (39/40)	0	0
M/V + Aztreonam	72.5% (29/40)	25.0% (10/40)	2.5% (1/40)

Biagi M, et al. Diagn Microbiol Infect Dis. 2022 Jun;103(2):115674.
Maraki S, et al. Eur J Clin Microbiol Infect Dis. 2021 Aug;40(8):1755-1759.

Synergy with fosfomycin

- 149 clinical P. aeruginosa isolates
  - Including OXA-, VIM-2, OprD*, PBP3*



Becka SA, et al. Open Forum Infect Dis. 2025; 12 (Supp_1);ofae631.1681