HAP and VAP after 2016 y 2017 Pneumonia Guidelines

International Symposium on Immunotherapy of Severe Infections 2024

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DISCLOSURE INTERESTS SPEAKER

(Potential) conflict of interest	See below
Potentially relevant relationships with companies	Company names
• Sponsorship or grant for research • Fee or other (financial) compensation • Shareholder • Other relationship, ……..	• Pfizer • MSD • Menarini • Biotest • Biomerieux • Shionogi

HAP and VAP after Guidelines

- The New Spectrum of the Disease
- Microbial Diagnosis
- MDR/XDR Microorganisms
- New Antibiotics
- Antibiotic Treatment Duration
- Treatment Failure
- Inhaled Antibiotics
- Non Antibiotic Treatments

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

This official statement of the American Thoracic Society and the Infectious Diseases Society of America was approved by the ATS Board of Directors, December 2004 and the IDSA Guideline Committee, October 2004

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

2005 2009 2016 2017

Intensive Care Med (2009) 35:9–29
DOI 10.1007/s00134-008-1336-9

SPECIAL ARTICLE

Antoni Torres
Santiago Ewig
Harmut Lode
Jean Carlet
For The European
HAP working group

Defining, treating and preventing hospital acquired pneumonia: European perspective

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT)

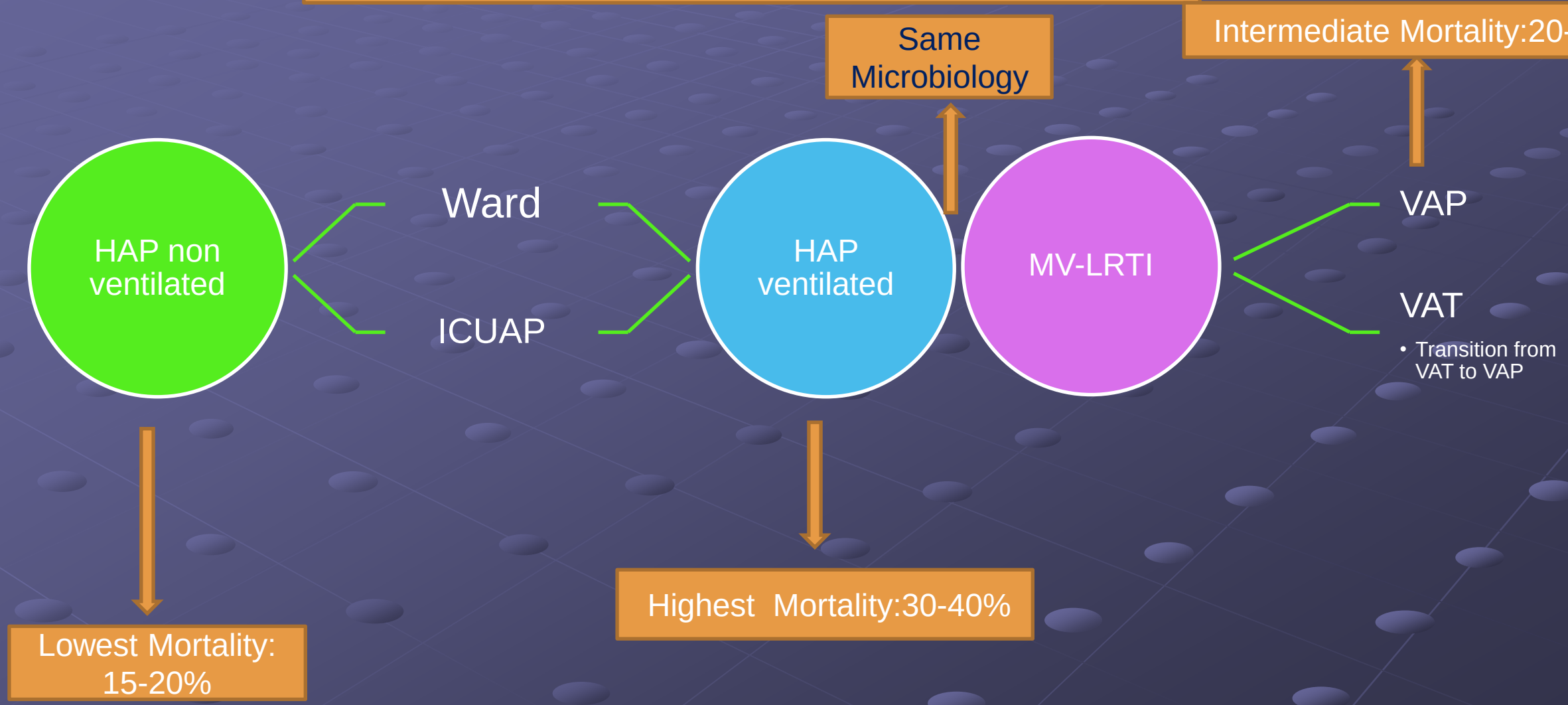
Antoni Torres[1,16], Michael S. Niederman[2,16], Jean Chastre[3], Santiago Ewig[4], Patricia Fernandez-Vandellos[5], Hakan Hanberger[6], Marin Kollef[7], Gianluigi Li Bassi[1], Carlos M. Luna[8], Ignacio Martin-Loeches[9], J. Artur Paiva[10], Robert C. Read[11], David Rigau[12], Jean François Timsit[13], Tobias Welte[14] and Richard Wunderink[15]

DEFINITIONS

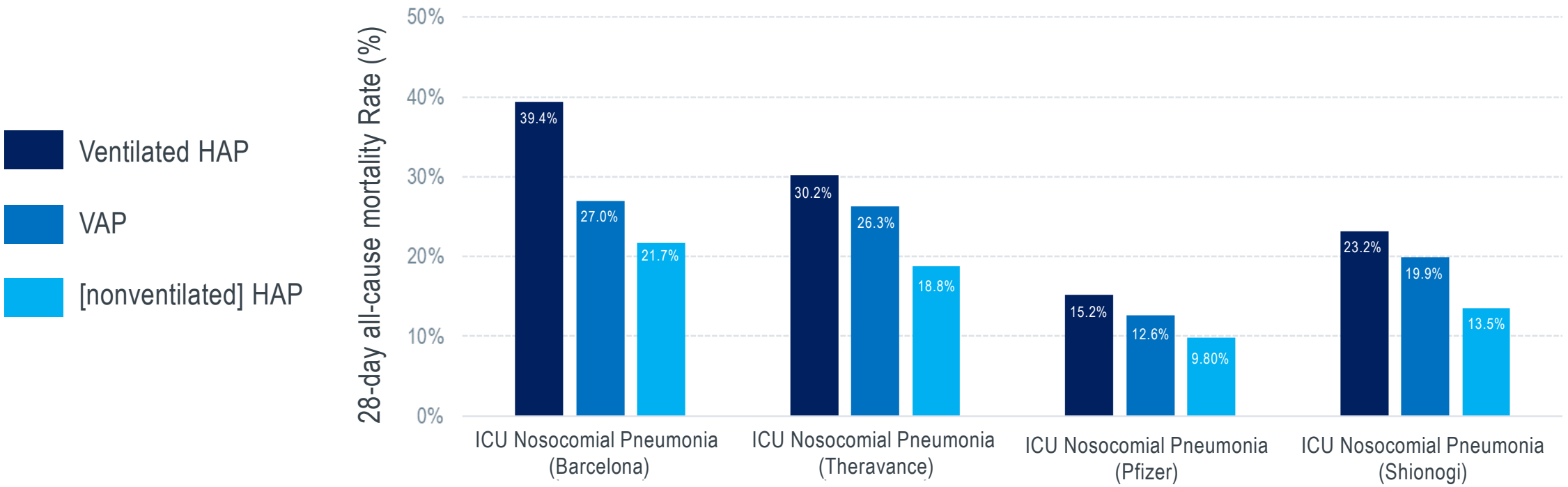
- Hospital Acquired Pneumonia (HAP)
  - A pneumonia that occurs 48 hours or more after admission; which was not incubating at the time of admission; not associated with mechanical ventilation
- Ventilator-Associated Pneumonia (VAP)
  - A pneumonia that arises more than 48 hours after mechanical ventilation
- Ventilated Hospital-Acquired Pneumonia (vHAP)
  - Pneumonia that occurs 48 hours or more after admission; which was not incubating at the time of admission; not associated with mechanical ventilation
  - Patients with severe HAP who require mechanical ventilation
- Non-Ventilated ICU-Acquired Pneumonia (NV-ICUAP)
  - A pneumonia that occurs 48 hours or more after ICU admission

1 Saied et al. Crit Care Med 2018. 2 Torres A et al. Eur Respir J 2017; 50: 1700582;
3 Kalil AC et al. Clin Infect Dis 2016; 63: e61-111; 4 Kollef et al. Up-to-Date 2020, available at
https://www.uptodate.com/contents/clinical-presentation-and-diagnostic-evaluation-of-ventilator-associated-pneumonia

The New Spectrum of Nosocomial Pneumonia



Nosocomial Pneumonia 28-day All-cause Mortality Rates



ICU: intensive care unit; HAP: hospital-acquired pneumonia; VAP: ventilator associated pneumonia
Talbot GH et al. J Infect Dis 2019; advanced access

Rapid Detection of Methicillin-Resistant *Staphylococcus aureus* in BAL: A Pilot Randomized Controlled Trial CHEST 2019: 155: 999-1007
Joseph R.Paonessa *et al.*

1-Ventilated patients with VAP suspicion: RDT vs usual care (22 vs 23 %)

2-Sensitivity of RDT for MRSA in BAL: 95.7%

3-Lower days of linezolid or vancomycin in the intervention arm

4-14 RDT vs 39% ususal care mortality

RDT: Rapid Diagnostic Testing

Table 3 Molecular rapid diagnostics for pathogen identification in hospital-acquired and ventilator-associated pneumonia

Molecular method	ID/AST	Examples	Pathogen/Resistance detection		Turnaround time	Clinical considerations
Antigen test	±	Alere BinaxNOW	S. pneumoniae		<30 min	SENS 86%; SPEC 94%a SPEC lower in children due to nasopharyngeal colonization
	±	Alere BinaxNOW	L. pneumophila (serogroup 1)		<30 min	44% false negatives in a recent study
	±	Sofia SARS Antigen FIA	SARS-CoV-2		<30 min	Symptomatic: SENS 80%; SPEC 99% Asymptomatic: SENS 41%; SPEC 98%
Real-time PCR	±	GeneXpert MRSA/SA	MRSA, MSSA, mec A/C		≤2 h	Prompt differentiation between MRSA and MSSA
	±	BD MAX MRSA XT	MRSA, MSSA, mec A/C		≤2 h	
	±	GeneXpert Carba-R	KPC, NDM, VIM, OXA-48, IMP		≤2 h	Prompt identification of carbapenem resistance genes
Multiplex PCR	±	BioFire Film Array	Viruses: Adenovirus Coronavirus Human metapneumovirus Human rhinovirus Huma enterovirus Influenza A/B Parainfluenza virus Respiratory syncytial virus Antimicrobial Resistance Genes: Methicillin resistance-mec A/C and MREJ Carbapenemases- KPC NDM OXA-48-like VIM IMP ESBL- CTX-M	Bacteria: A. calcoaceticus–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 Atypical bacteria: C. pneumoniae L. pneumophila M. pneumoniae	≤2 h	• Comprehensive number of targets. • Rapid turnaround. • Identify presence of bacterial resistance genes. • Semi-quantitative bacterial analysis. • BAL (SENS 96%; SPEC98%).a • Sputum (SENS 96%; SPEC 97%).a
	±	Curetis Unyvero LRT Panel	Fungi: P. jirovecii Antimicrobial Resistance Genes: Carbapenemases- OXA-48 OXA-58 VIM IMP	Bacteria: Acinetobacter spp. C. pneumoniae C. freundii E. cloacae complex E. coli H. influenzae K. aerogenes K. oxytoca	4–5 h	• Comprehensive number of targets. • Rapid turnaround. • Identify presence of bacterial resistance genes. • Semi-quantitative bacterial analysis.
			KPC NDM OXA-23 OXA-24/40 ESBL- CTX-M Methicillin resistance-mec A/C Penicillin: TEM SHV	K. pneumoniae K. variicola L. pneumophila M. catarrhalis M. morganii M. pneumoniae Proteus spp. P. aeruginosa S. marcescens S. aureus S. maltophilia S. pneumoniae		

Kollef M et al, SRCCM 2022,

Original research

Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study

Virve I Enne,[1] Alp Aydin,[1] Rossella Baldan,[2,3] Dewi R Owen,[1] Hollian Richardson,[3] Federico Ricciardi,[4] Charlotte Russell,[3] Brenda O Nomamiukor-Ikeji,[1] Ann-Marie Swart,[5] Juliet High,[5] Antony Colles,[5] Julie Barber,[4] Vanya Gant,[6,7] David M Livermore,[3] Justin O'Grady,[3,8] INHALE WP1 Study Group

Enne VI, *et al*. *Thorax* 2022;**0**:1–9. doi:10.1136/thoraxjnl-2021-216990

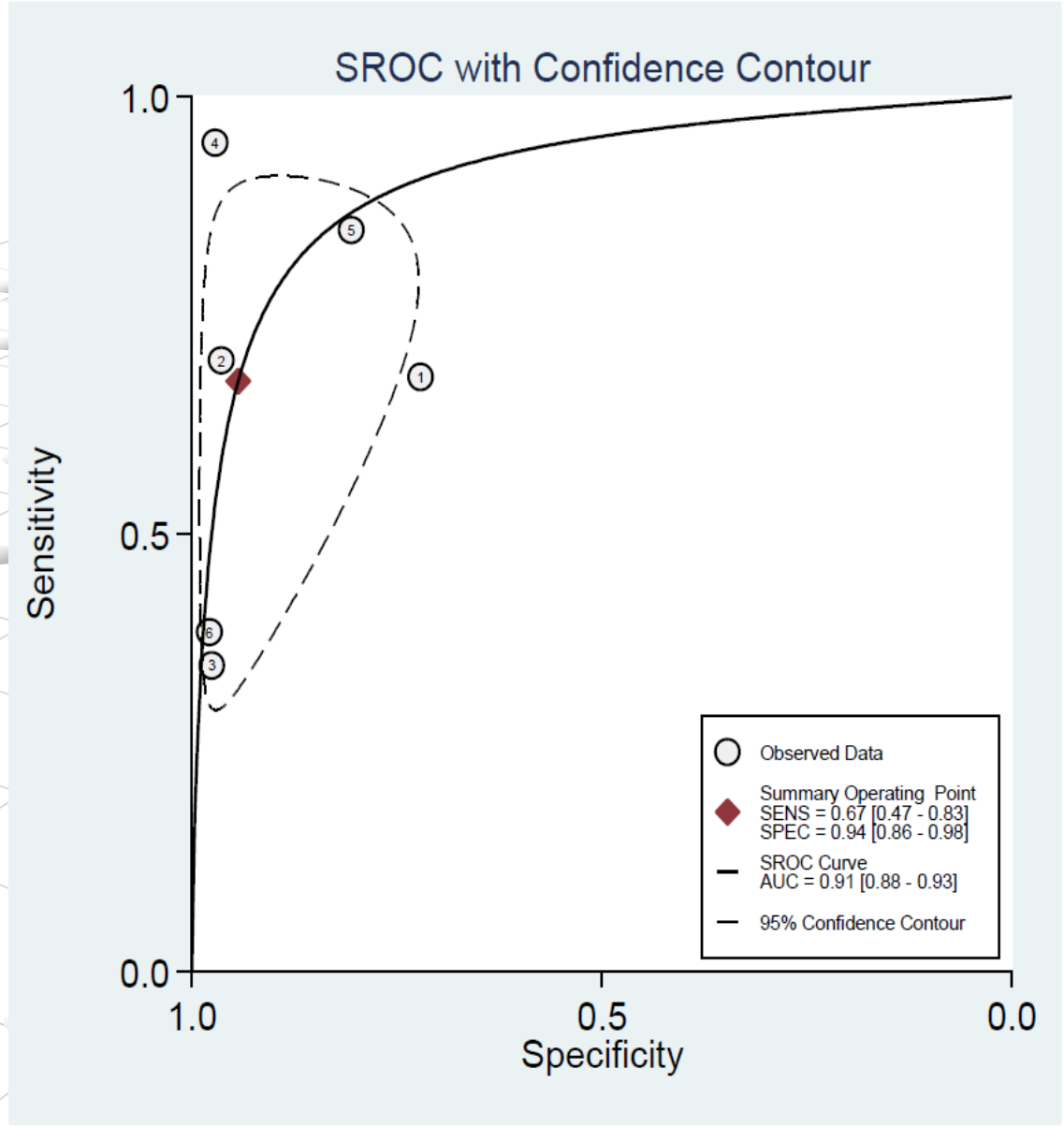
Table 2 Concordance-based performance of PCR tests compared with routine microbiology

		All detections		Detections reported at higher concentrations*	
Category	**Definition**	**Unyvero (%, 95% CI)**	**FilmArray (%, 95% CI)**	**Unyvero (%, 95% CI)**	**FilmArray (%, 95% CI)**
Full positive concordance	Organisms detected were an exact match	19.3 (16.2 to 22.4)	18.2 (15.2 to 21.3)	22.4 (19.1 to 25.8)	21.1 (17.9 to 24.3)
Full negative concordance	No organisms detected by either method	37.3 (33.4 to 41.1)	32.1 (28.4 to 35.8)	42.1 (38.1 to 46.0)	44.5 (40.6 to 48.4)
Partial concordance	PCR detected the same organism as RM plus additional organism(s)	18.2 (15.1 to 21.2)	21.0 (17.8 to 24.2)	11.6 (9.0 to 14.1)	11.8 (9.2 to 14.3)
Minor discordance	RM was negative but machine found ≥1 organism	20.6 (17.4 to 23.8)	26.9 (23.4 to 30.4)	15.8 (12.9 to 18.7)	14.5 (11.7 to 17.3)
Major discordance	RM found ≥1 organism, at least one of which was on the PCR panel, but not detected	4.6 (2.9 to 6.3)	1.8 (0.7 to 2.8)	8.1 (5.9 to 10.3)	8.1 (5.9 to 10.2)

*Calculated based on semi-quantitative detections Reported as ++or +++ by Unyvero or 10^6 or ≥10^7 copies/ml by FilmArray.
RM, routine microbiology.

Gram stain morphological evaluation optimizes the use of empiric anti-staphylococcal therapy in HAP/VAP: a systematic review and meta-analysis

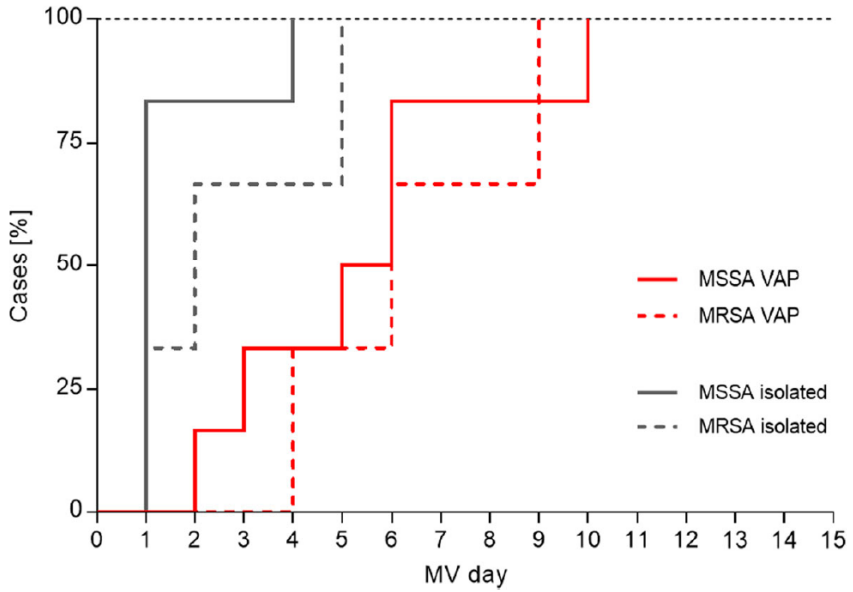
Otavio T. Ranzani, Anna Motos, Chiara Chiurazzi, Adrian Ceccato, Mariano Rinaudo, Gianluigi Li Bassi, Miquel Ferrer, Antoni Torres



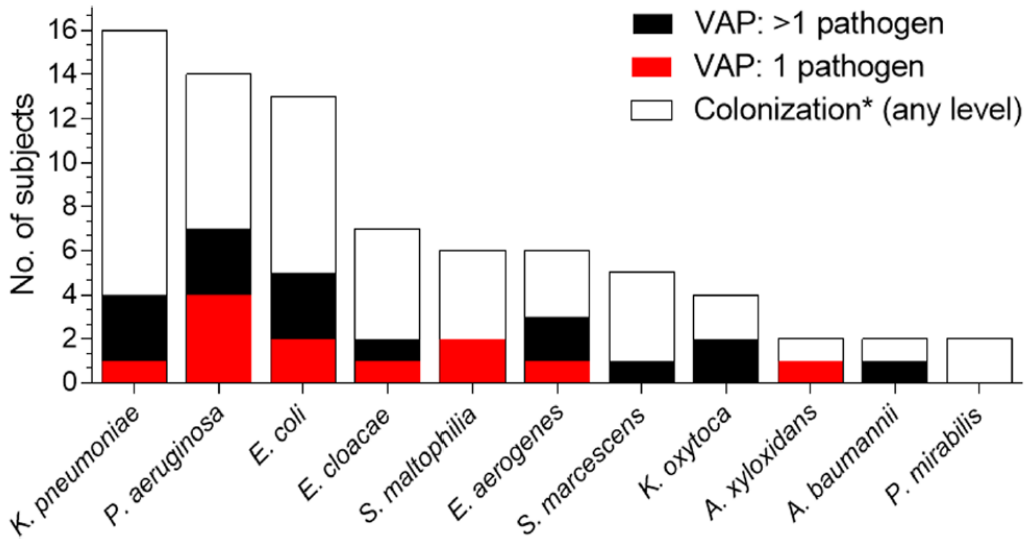
AUC, area under the curve; HAP, hospital-acquired pneumonia; SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating curve; VAP, ventilator-associated pneumonia

Ranzani O, et al. *Clin Microbiol Infect* 2020;1456–63.

Detection of *S. aureus* in the ETA preceded VAP by approximately 4 days, while
Gram-negative organisms were first detected 2.5 days prior to Gram-negative VAP



First detection of *S. aureus* lower airway colonization and progression to *S. aureus* VAP. Cumulative curves of first *S. aureus* ETA colonization detection and first day of *S. aureus* monomicrobial VAP diagnosis shown against MV days. One of 10 *S. aureus* VAP subjects was excluded: no ETA was collected during the first 5 days of MV



Role of Gram-negative organisms in VAP and colonization. *Does not exclude VAP-positive subjects with no pathogens isolated in VAP-relevant period

ETA, endotracheal aspirate; MSSA, methicillin-sensitive *S. aureus;* MV, mechanical ventilation; VAP, ventilator-associated pneumonia
Kabak E, et al. *BMC Infect Dis* 2019;19:756

BMC Infectious Diseases
The Utility of Endotracheal Aspirate Bacteriology in Identifying Mechanically Ventilated Patients at Risk for Ventilator Associated Pneumonia: a Single-Center Prospective Observational Study

Classification of Microorganisms according to Resistances

REVIEW Open Access

What's new in multidrug-resistant pathogens in the ICU?

Gabor Zilahi[1], Antonio Artigas[2,3] and Ignacio Martin-Loeches[1,3,4,5*]

Annals of Intensive Care 2017

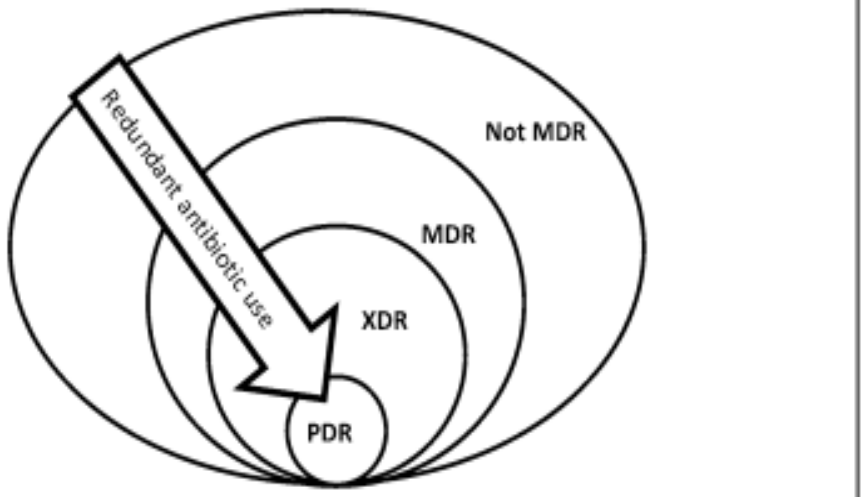
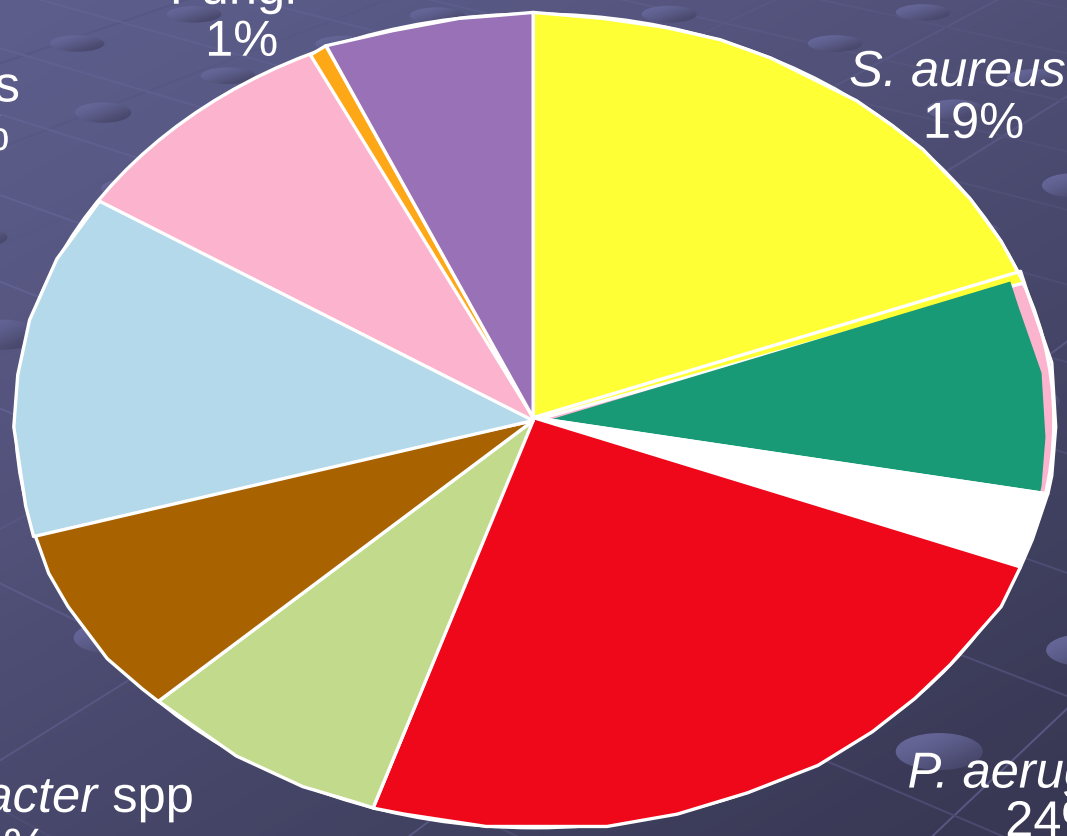


Fig. 1 Multidrug-resistant organisms (MDR) have been divided into three categories depending on their resistance profile: 1. MDR—non-susceptible to at least 1 agent in 3 antimicrobial categories; 2. extensively drug-resistant (XDR)—non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories and 3. pan-drug-resistant (PDR)—non-susceptible to all agents in all antimicrobial categories

Magiorakos et al. Clin Miicrobiol Infect 2012

Microbial Etiology of ICU-acquired HAP/VAP in Hospital Clinic (30% MDR/XDR)



A.Torres Personal Communication

Main Therapeutic Principles in HAP/VAP

- MDR/XDR pathogens are associated to a higher rates of initial inadequate antibiotics
- Initial non-adequate antibiotic treatment is associated with higher mortality
- Microbes and resistances present a very high variability
- Mortality of MDR/XDR/PDR HAP/VAP is increased

Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis

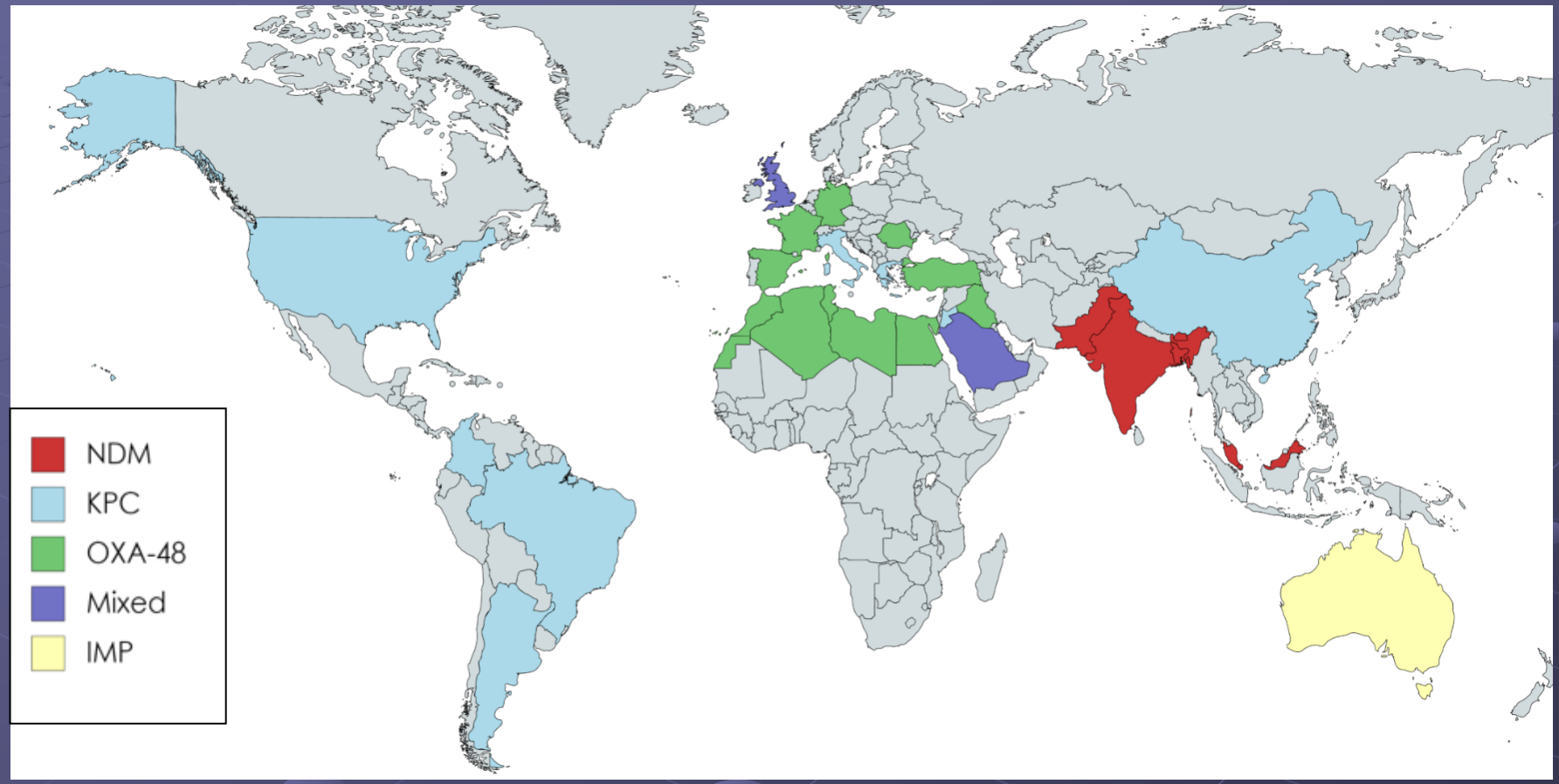
Evelina Tacconelli, Elena Carrara*, Alessia Savoldi*, Stephan Harbarth, Marc Mendelson, Dominique L Monnet, Céline Pulcini, Gunnar Kahlmeter, Jan Kluytmans, Yehuda Carmeli, Marc Ouellette, Kevin Outterson, Jean Patel, Marco Cavaleri, Edward M Cox, Chris R Houchens, M Lindsay Grayson, Paul Hansen, Nalini Singh, Ursula Theuretzbacher, Nicola Magrini, and the WHO Pathogens Priority List Working Group†

MDR and extensively resistant *Mycobacterium tuberculosis*
Other priority bacteria

Priority 1: critical	Priority 2: high	Priority 3: medium
• *Acinetobacter baumannii*, carbapenem resistant • *Pseudomonas aeruginosa*, carbapenem resistant • Enterobacterales, carbapenem resistant, third-generation cephalosporin resistant	• *Enterococcus faecium,* vancomycin resistant • *Staphylococcus aureus*, methicillin resistant, vancomycin resistant • *Helicobacter pylori,* clarithromycin resistant • *Campylobacter* spp., fluoroquinolone resistant • *Salmonella* spp., fluoroquinolone resistant • *Neisseria gonorrhoeae,* third-generation cephalosporin resistant, fluoroquinolone resistant	• *Streptococcus pneumoniae*, penicillin non-susceptible • *Haemophilus influenzae*, ampicillin resistant • *Shigella* spp., fluoroquinolone resistant

Tacconelli E, et al. *Lancet Infect Dis* 2018;18(3):318–27.

WORLDWIDE ENTEROBACTERALES MECHANISMS OF ANTIBIOTIC RESISTANCE



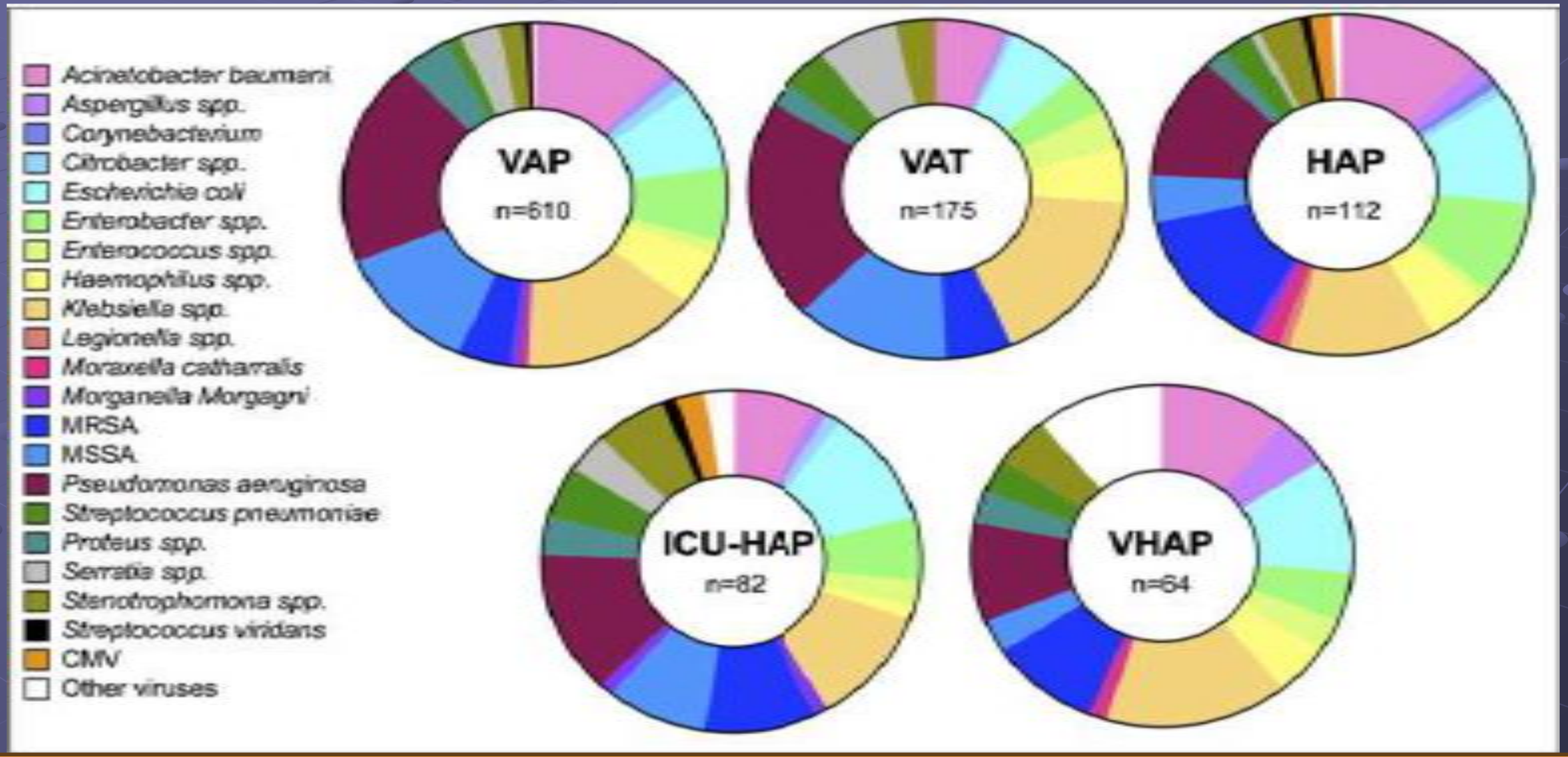
IMP imipenemase-type carbapenemase; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.

1. Munoz-Price LS, et al. Lancet Infect Dis 2013;13:9:785–96; 2. Johnson AP and Woodford N. J Med Microbiol 2013;62(Pt 4):499–513; 3. Glasner C, et al. Euro Surveill 2013;18:28:pii:20525;
4. Poirel L, et al. J Antimicrob Chemother 2012;67:7:1597–606; 5. Espedido BA, et al. Antimicrob Agents Chemother 2008;52:8:2984–7; 6. Grundmann H, et al. Lancet Infect Dis 2017;17:153–63; 7. Cui X, et al. Front Micro 2019;10:1823.

Considerations in the selection of antibiotic treatment

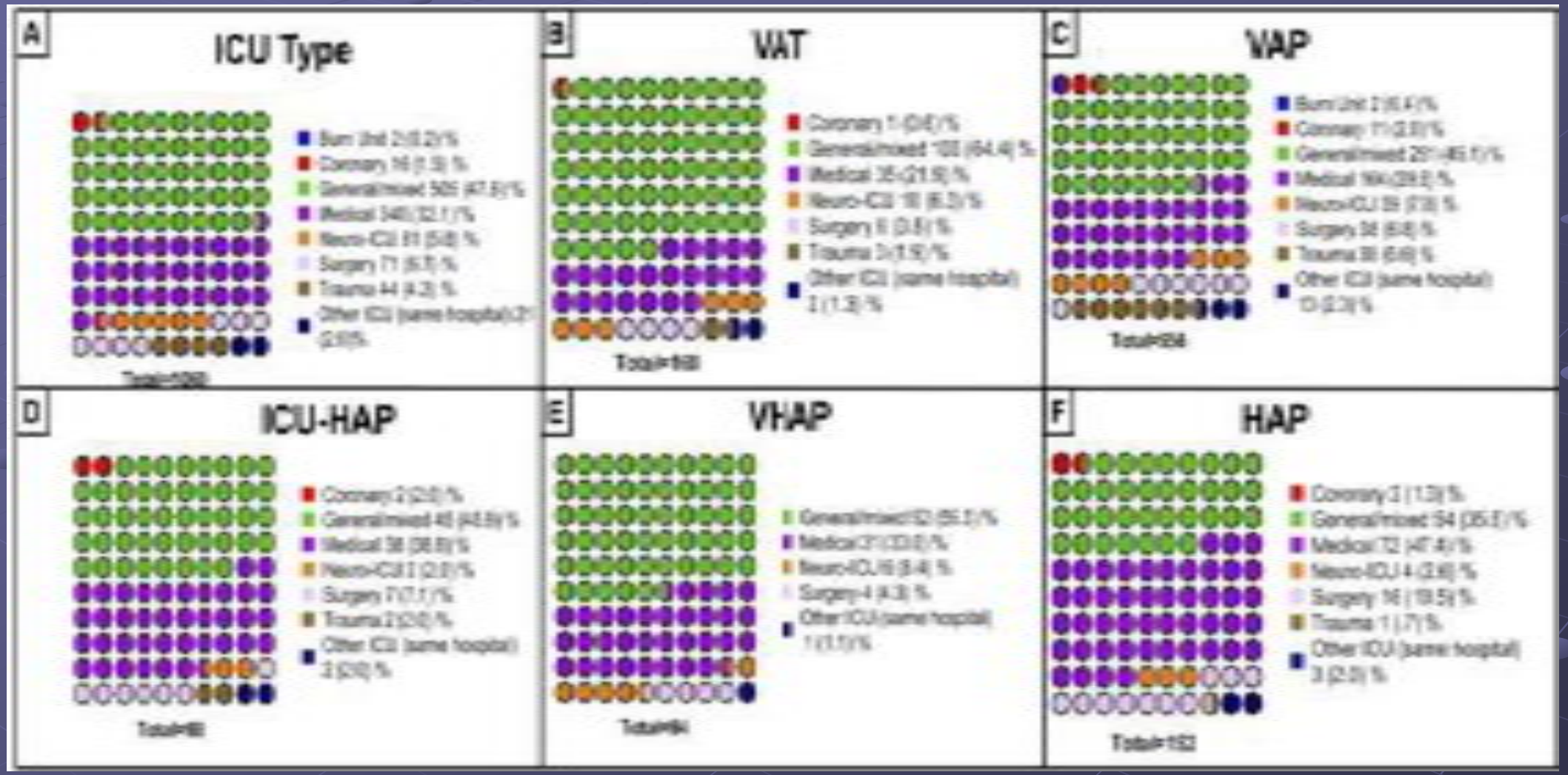
- 1-Do HABP, VABP , and vHABP have the same microbial etiology?
- 2-How can we improve our microbiological prediction?
- 3- Can rapid microbial tests help?
- 4- Which algorithms and antibiotics do you have to use?
- 5-Specific considerations

The European Network for ICU-Related Respiratory Infections (ENIRRIs): A Multinational, Prospective, Cohort Study of Nosocomial LRTI (2016-2019).



Martin-Loeches I, Reyes F, Torres A. Intensive Care Med 2023 . Acepted

The European Network for ICU-Related Respiratory Infections (ENIRRIs): A Multinational, Prospective, Cohort Study of Nosocomial LRTI.



Martin-Loeches I, Reyes F, Torres A. Intensive Care Med 2023 . Acepted

Anke Kohlenberg
Frank Schwab
Michael Behnke
Christine Geffers
Petra Gastmeier

Intensive Care Med (2010) 36:971–978
DOI 10.1007/s00134-010-1863-z

Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database

Aetiology of VAP and NV-ICUAP

Miquel Ferrer
Antoni Torres

Intensive Care Med (2011) 37:1041–1042
DOI 10.1007/s00134-011-2181-9

Comment on "Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database"

A. Kohlenberg
F. Schwab
P. Gastmeier

Intensive Care Med (2011) 37:1043–1044
DOI 10.1007/s00134-011-2185-5

A close look at proportions of pathogens associated with pneumonia

According to patients with etiologic diagnosis only

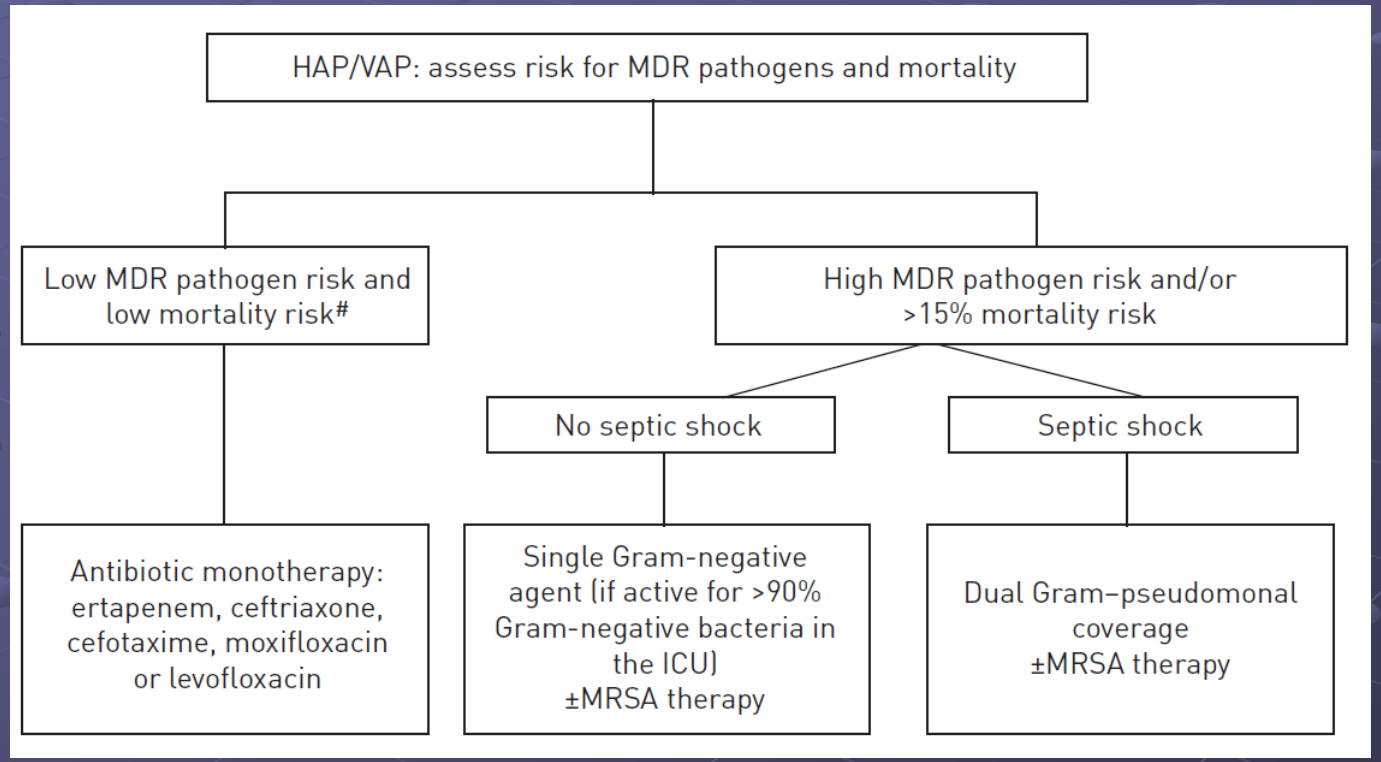
	HAP-noMV N=583	**HAP-IMV N=4667**	P value
Enterobacteriaceae	218 (37%)	1774 (38%)	0.81
Non-fermenting GNB	139 (24%)	1302 (28%)	0.045
Staphylococcus aureus	157 (27%)	1222 (26%)	0.74
Streptococcus sp	27 (5%)	102 (2%)	<0.001

International ERS/ESICM/ESCMID/ALA guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Antoni Torres[1,16], Michael S. Niederman[2,16], Jean Chastre[3], Santiago Ewig[4], Patricia Fernandez-Vandellos[5], Hakan Hanberger[6], Marin Kollef[7], Gianluigi Li Bassi[1], Carlos M. Luna[8], Ignacio Martin-Loeches[9], J. Artur Paiva[10], Robert C. Read[11], David Rigau[12], Jean François Timsit[13], Tobias Welte[14] and Richard Wunderink[15]

Eur Respir J 2017; 50: 1700582

Algorithm for the empiric antibiotic treatment in HAP/VAP



- High rates of MDR
- Previous ATBs
- Recent hospitalisation
- Previous colonisation by MDR

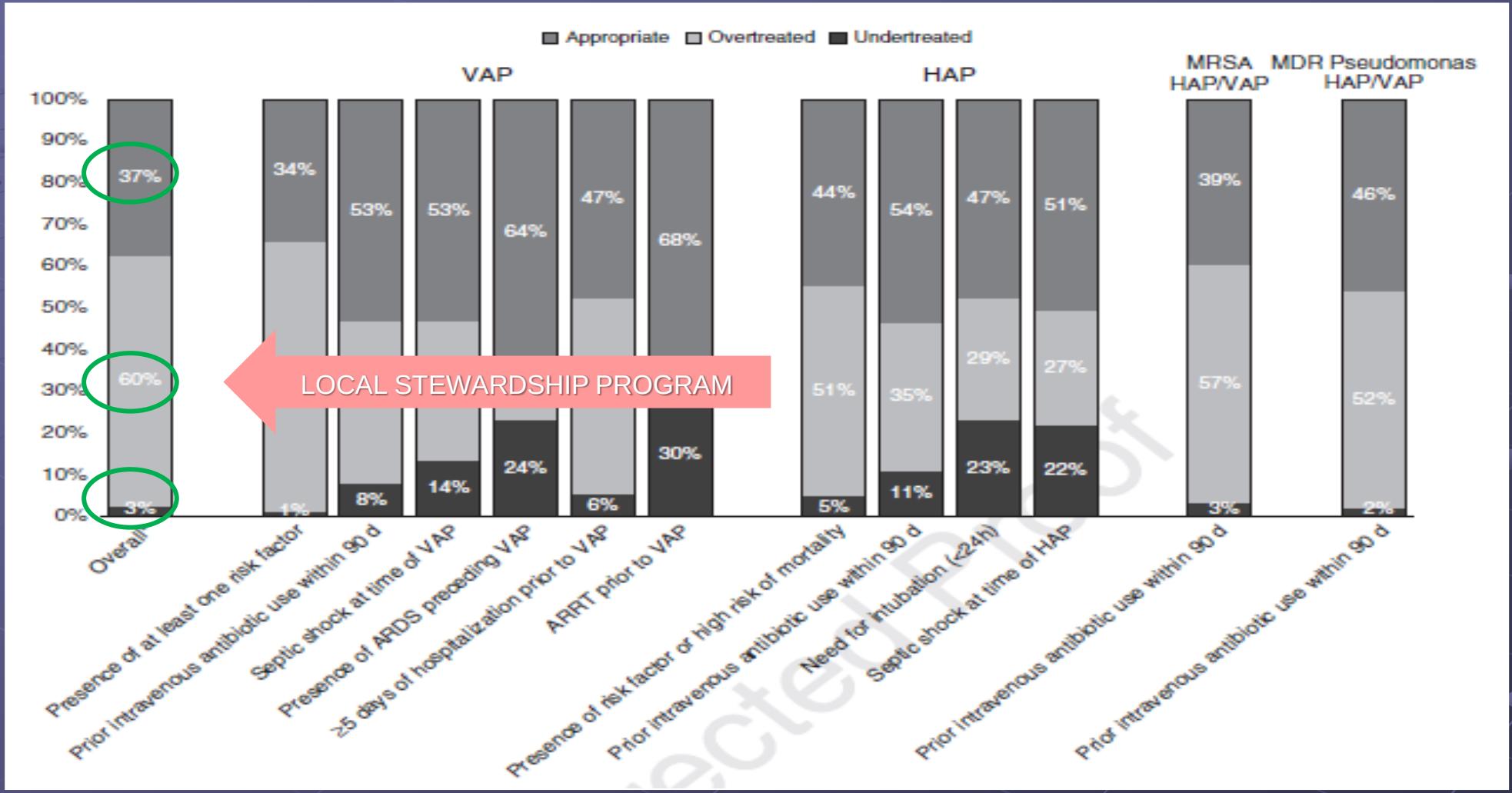
Expected mortality <15%

POTENTIAL PATIENTS AT RISK FOR POOR HAP/VAP OUTCOMESSUMMARY OF EUROPEAN AND AMERICAN GUIDELINES

EUROPEAN GUIDELINES (HIGH-RISK PATIENTS) International ERS/ESICM/ESCMID/ALAT Guidelines	AMERICAN GUIDELINES (RISK FOR MDR) ATS/IDSA Guidelines
• Septic shock • Previous antibiotic use • Recent prolonged hospital stay (>5 days of hospitalization) • Previous colonization with MDR pathogen • Prevalence of resistant pathogens in local microbiological data >25%	For all types: HAP, VAP, MRSA and *Pa:* • Prior IV antibiotic use within 90 days Additional risks for VAP: • Septic shock at time of VAP • ARDS preceding VAP • ≥5 days hospitalization prior to occurrence of VAP • Acute renal replacement therapy prior to VAP onset

MDR: multidrug resistant; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; MRSA: methicillin-resistant S. aureus; Pa: P. aeruginosa; IV: intravenous; ARDS: acute respiratory distress syndrome

Bassetti M, et al. Curr Opin Crit Care 2018; 24: 385-93; Torres A, et al. Eur Respir J 2017; 50: 1700582; Kalil, et al. 2016; CID: 1-51



Kormaz P et al . Am J Respir Crit Care Med 2018

Performance of MDR/XDR Risk Factors of European Guidelines

Criteria	Presence at diagnosis	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	AUC (95% CI)
Previous antibiotic use	401/507 (79%)	85% (77% to 92%)	22% (18% to 27%)	35% (31% to 40%)	85% (78% to 92%)	1.09 (0.99 to 1.20)	0.68 (0.42 to 1.11)	0.54 (0.48 to 0.60)
>5 days of hospitalization	355/507 (70%)	78% (70% to 86%)	32% (27% to 37%)	23% (19% to 28%)	85% (79% to 91%)	1.15 (1.02 to 1.30)	0.68 (0.46 to 1.01)	0.55 (0.49 to 0.61)
Hospital settings with high rates of MDR pathogens	423/507 (83%)	92% (87% to 98%)	19% (15% to 23%)	23% (19% to 27%)	90% (84% to 97%)	1.14 (1.06 to 1.22)	0.40 (0.20 to 0.81)	0.56 (0.50 to 0.62)
Previous respiratory MDR pathogen isolation	17/507 (3%)	16% (9% to 24%)	100% (100% to 100%)	100% (97% to 100%)	82% (79% to 86%)	-	0.84 (0.77 to 0.91)	0.58 (0.52 to 0.65)

•Dominedo & Ceccato, Torres A. Annals of ATS 2020

Clinical Infectious Diseases

IDSA GUIDELINE

Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Clinical Infectious Diseases® 2016;63(5):575–82

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

Suggested empiric treatment options where empiric MRSA coverage and double anti-pseudomonal/gram-negative coverage are appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

New Antibiotics for GNB HAP/VAP

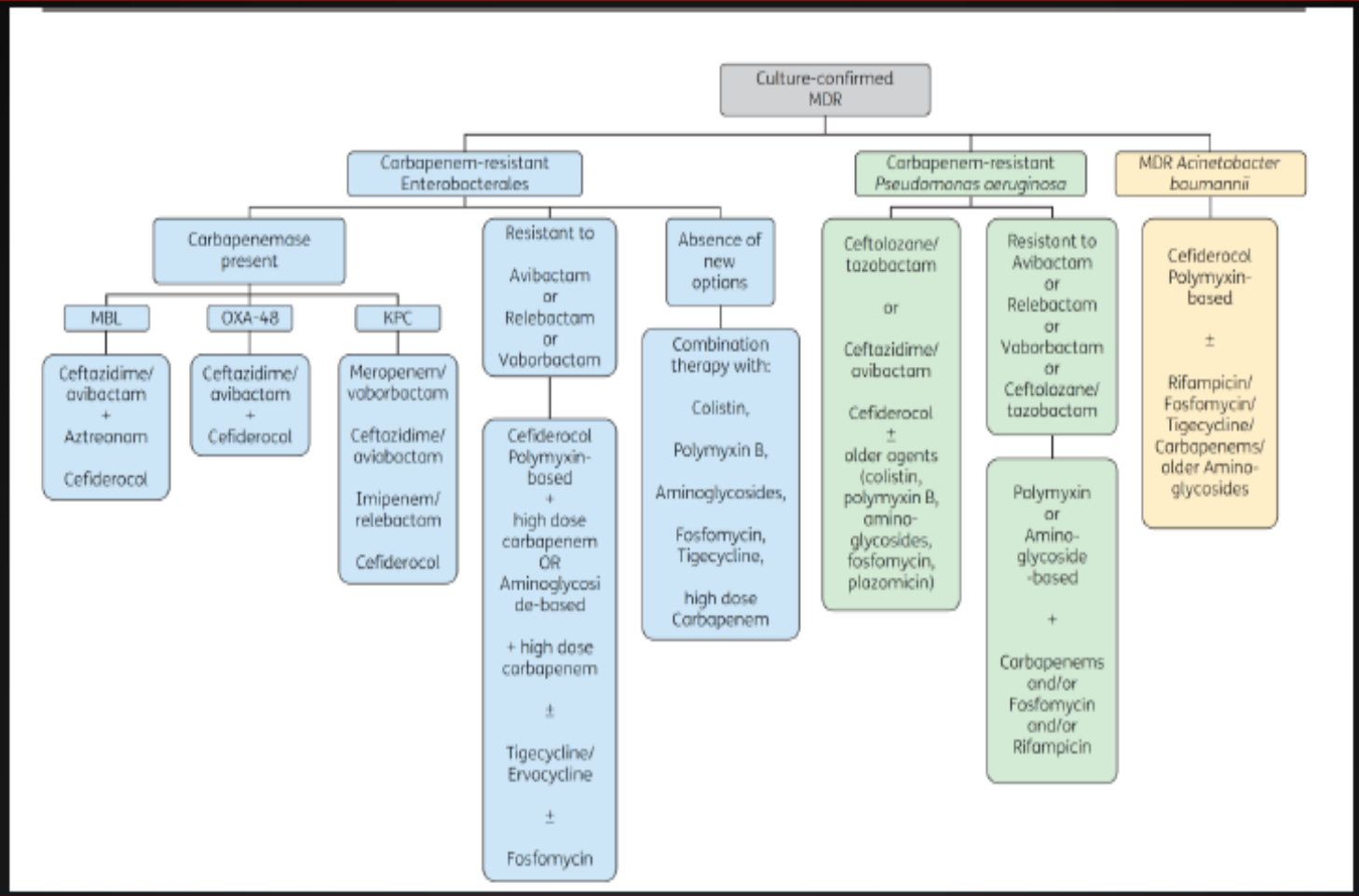
Table 1 New molecules FDA and EMA approved for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia

Drug	Spectrum	Labeled indications	Approved dosage for the treatment of HAP/VAP
Ceftobiprole	Nonextended spectrum β-lactamase, non-AmpC and non-carbapenemases-producing *Enterobacterales*, *P. aeruginosa*, MRSA	EMA: HAP excluding VAP, CAP, ABSSSI	500 mg every 8 h by IV infusion over 2 h
Ceftazidime-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 g of ceftazidime and 0.5 g of avibactam every 8 h by IV infusion over 2 h
Ceftolozane-tazobactam	ESBL-producing *Enterobacterales*, MDR *P. aeruginosa*, some anaerobes, *Streptococcus* spp., MSSA	FDA: HAP/VAP, cUTIs, cIAIs EMA: HAP/VAP, cUTIs, cIAIs	2 g of ceftolozane and 1 g of tazobactam every 8 h by IV infusion over 1 h
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	2 g of meropenem and 2 g of vaborbactam every 8 h by IV infusion over 3 h
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	500 mg of imipenem; 500 mg of cilastatin, and 250 mg of relebactam administered by IV infusion every 6 h over 30 min
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 g every 8 h by IV infusion over 3 h

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant *Enterobacterales*; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; ESBLs, extended-spectrum β-lactamases; FDA, Food And Drug Administration; GNB, gram-negative bacteria; HAP, hospital-acquired pneumonia; IV, intravenous; MBL, metallo-β lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; OXA, oxacillinase; VAP, ventilator-associated pneumonia.

Basetti M , et al Seminars RCCM 2022

Suggested treatments for carbapenem-resistant Enterobacterales, multidrug-resistant *Pseudomonas aeruginosa*, and multidrug-resistant *Acinetobacter baumannii*



Bassetti M, Garau X. . *J Antimicrob Chemother* 2021; 76 : iv23–iv37

Treatment Failure

- Treatment failure can be divided in early (4-5 days) and late (10 to 14 days)
- To detect early failure is important in order to modify antibiotic treatment or to search for complications
- Late failure (clinical and microbiological) is used to investigate the eficacy of antibiotics

Early Treatment Failure

- There is not a clear-cut definition
- Early clinical failure includes day 3 to 5 period
- Microbiological early failure includes peristence of bacterial burden comparing two microbiological samples (day 1-day 4-5)
- Early treatment failure is associated to higher 28 day mortality

Esperatti M, et al. Crit Care Med 2013,. Ceccato A.Eur Respir J 2023

Follow-up Cultures

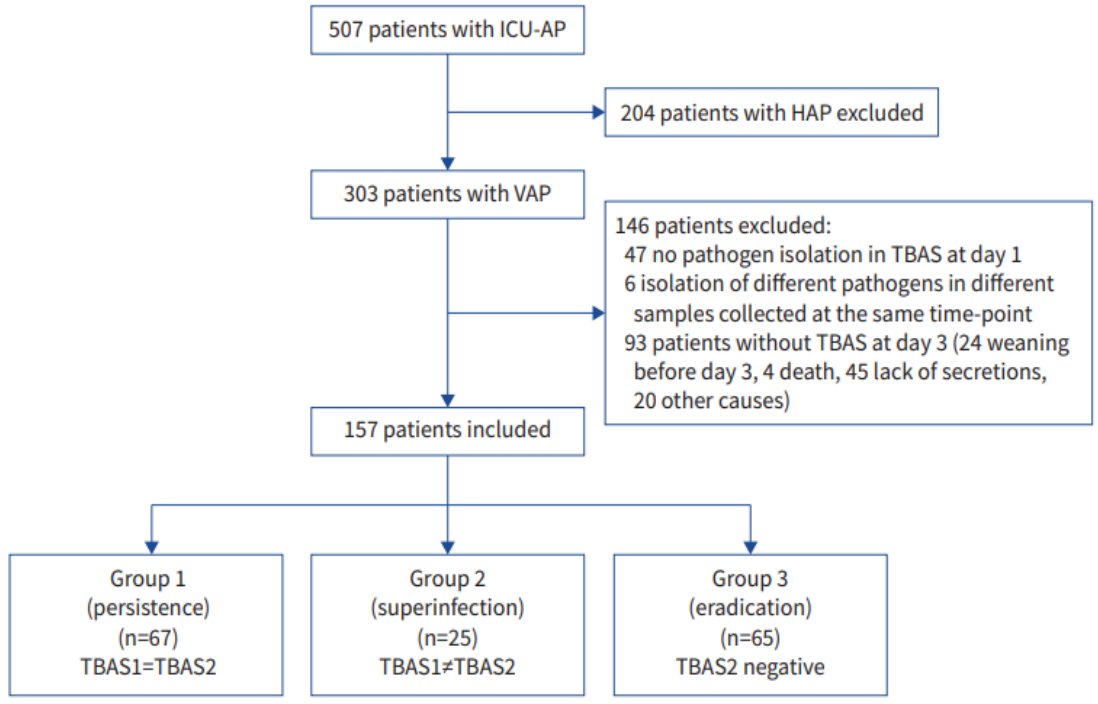


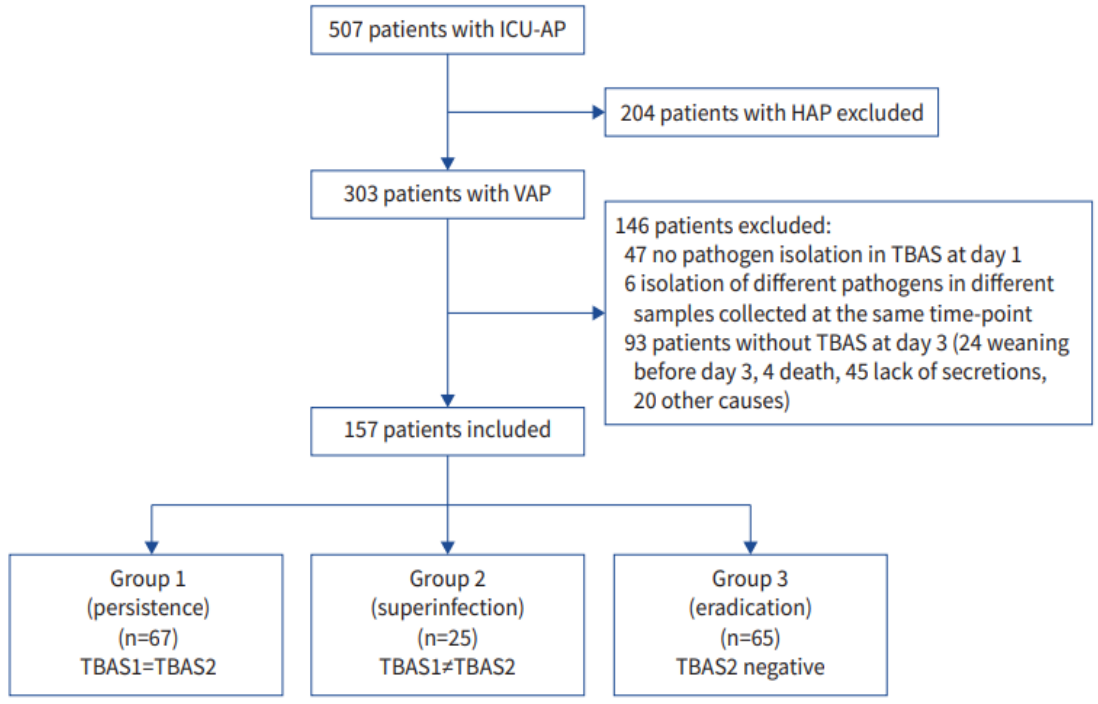
FIGURE 1 Participant flowchart. ICU-AP: intensive care unit-acquired pneumonia; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; TBAS: tracheobronchial aspirate (TBAS1=at admission, TBAS2=at 3–5 days).

Shareable abstract (@ERSpublications)

Follow-up cultures on day 3 after a VAP diagnosis can help the clinician stratify patients. Those patients who present early with superinfection have worse ICU mortality, worse 90-day mortality and require more days of mechanical ventilation. https://bit.ly/2W5wFLk

Cite this article as: Ceccato A, Dominedò C, Ferrer M, *et al*. Prediction of ventilator-associated pneumonia outcomes according to the early microbiological response: a retrospective observational study. *Eur Respir J* 2022; 59: 2100620 [DOI: 10.1183/13993003.00620-2021].

Follow-up Cultures



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Early Predictors of 28 day Mortality

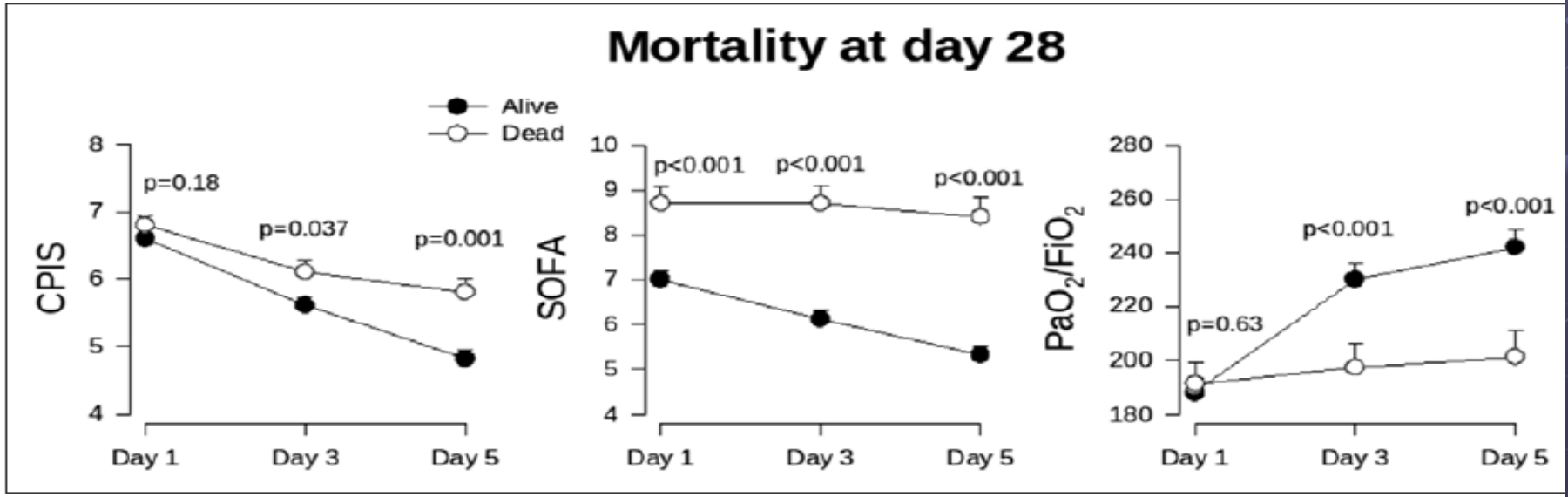


Figure 1. Evolution from day 1 to day 5 of the Clinical Pulmonary Infection Score (CPIS), Sequential Organ Failure Assessment (SOFA) score, and the ratio of arterial oxygen tension to Pao_2/Fio_2 accordingly to mortality at day 28 in patients with ICU-acquired pneumonia. The results are expressed as mean ± SEM. *Closed circle* = alive; *open circle* = dead.

Esperatti M, et al Crit Care Med 2013

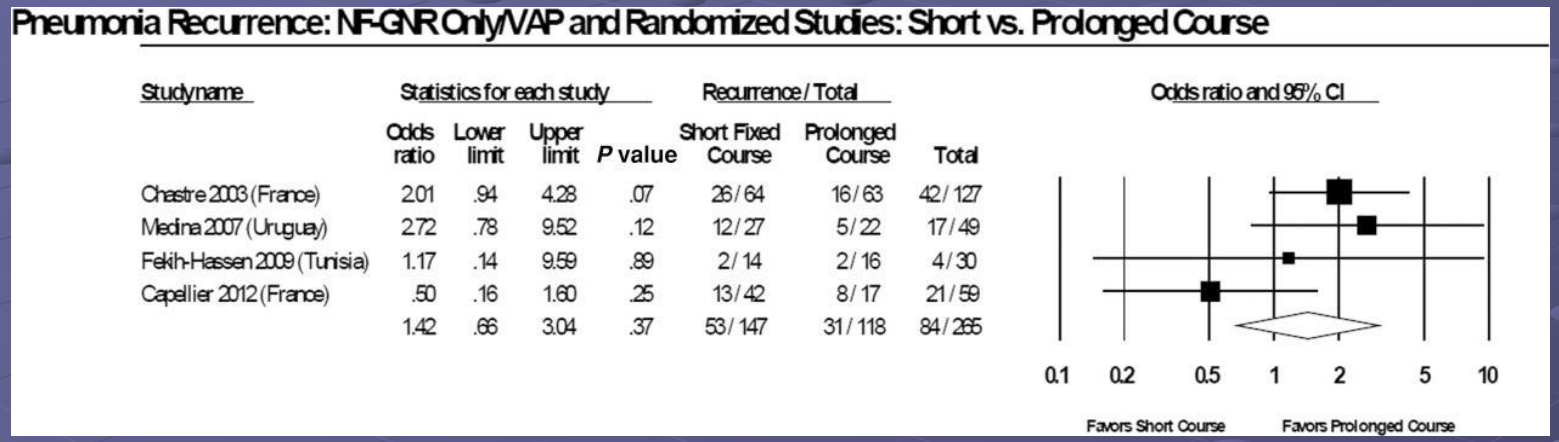
MDR pathogen (mechanism)		Ceftazidime–avibactam	Ceftolozane–tazobactam	Meropenem–vaborbactam	Imipenem–relebactam	Cefiderocol
ESBL	SHV / TEM	✓	✓	✓	✓	✓
	CTX-M	✓	✓	✓	✓	✓
Enterobacterales	AmpC	✓	✗	✓	✓	✓
P. aeruginosa	AmpC	✓	✓	✓	✓	✓
CRE	KPC	✓	✗	✓	✓	✓
	MBL	✗	✗	✗	✗	✓
	OXA-48	✓	✗	✗	✗	✓
P. aeruginosa	Carbapenem-resistant	✓	✓	✗	✓	✓
	MDR	✓	✓	✗	✓	✓
Acinetobacter spp.	Carbapenem-resistant	✗	✗	✗	✗	✓

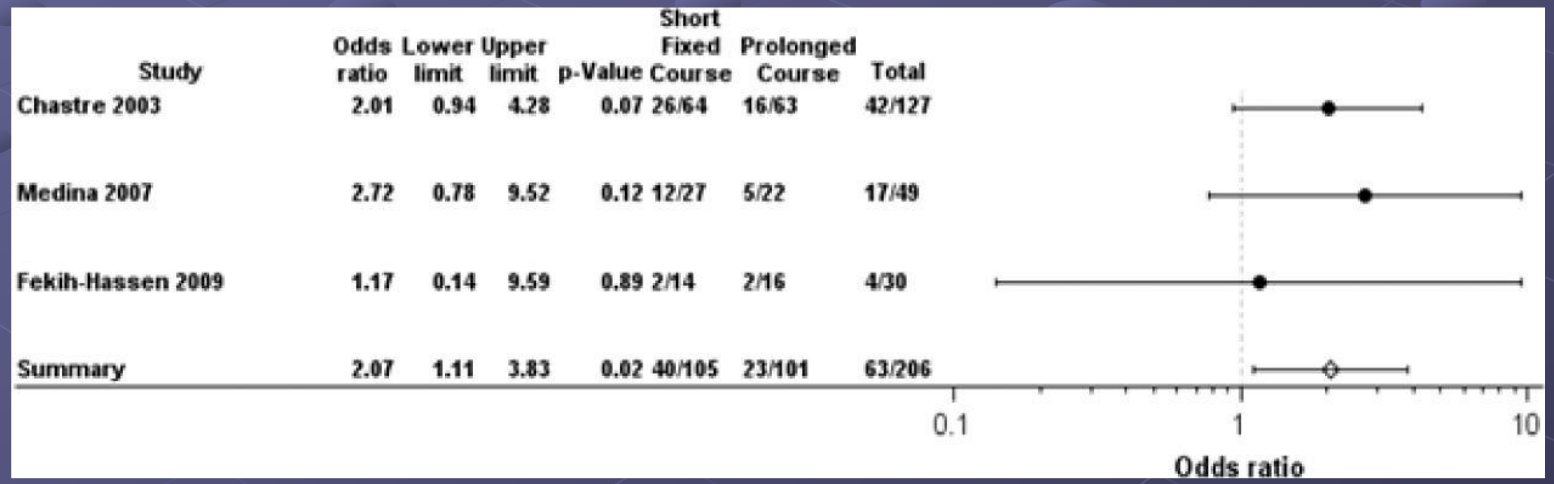
✗ = Resistant; ✓ Susceptible

AmpC, ampicillin class C β-lactamase; BL, β lactam; BLI, β-lactamase inhibitor; CRE, carbapenem-resistant Enterobacterales; CTX-M, cefotaximase; ESBL, extended-spectrum β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MDR, multidrug-resistant; OXA, oxacillinase; SHV, sulfhydryl variable β-lactamase; TEM, Temoneira β-lactamase.

Adapted from: 1. Lagacé-Wiens P, et al. *Core Evid* 2014;9:13–25; 2. ZAVICEFTA® (ceftazidime–avibactam) Summary of Product Characteristics. Pfizer, 2021; 3. Liscio JL, et al. *Int J Antimicrob Agents* 2015;46:266–71; 4. Bush K. *Int J Antimicrob Agents* 2015;46:483–93; 5. Zhanel GG, et al. *Drugs* 2013;73:159–77; 6. Wright H, et al. *Clin Microbiol Infect* 2017;23:704–12; 7. Munita JH, et al. *Clin Infect Dis* 2017;65:158–61; 8. ZERBAXA® (ceftolozane–tazobactam) Summary of Product Characteristics. Merck, 2019; 9. Sader HS, et al. *Diagn Microbiol Infect Dis* 2015;83:389–94; 10. Walkty A, et al. *Antimicrob Agents Chemother* 2011;55:2992–4; 11. Lomovskaya O, et al. *Antimicrob Agents Chemother* 2017;61:e01443-17; 12. RECARBRIO® (imipenem+cilastatin/relebactam) Summary of Product Characteristics. Merck, 2019; 13. Bush K, et al. *Antimicrob Agents Chemother* 2010;54:969–76; 14. VABOREM® (meropenem–vaborbactam) Summary of Product Characteristics. Menarini, 2021; 15. Noval M, et al. *Curr Infect Dis Rep* 2020;22:1; 16. FETROJA® (cefiderocol) US Prescribing Information. Shionogi, 2021.

Short vs Prolonged Course of Antibiotics

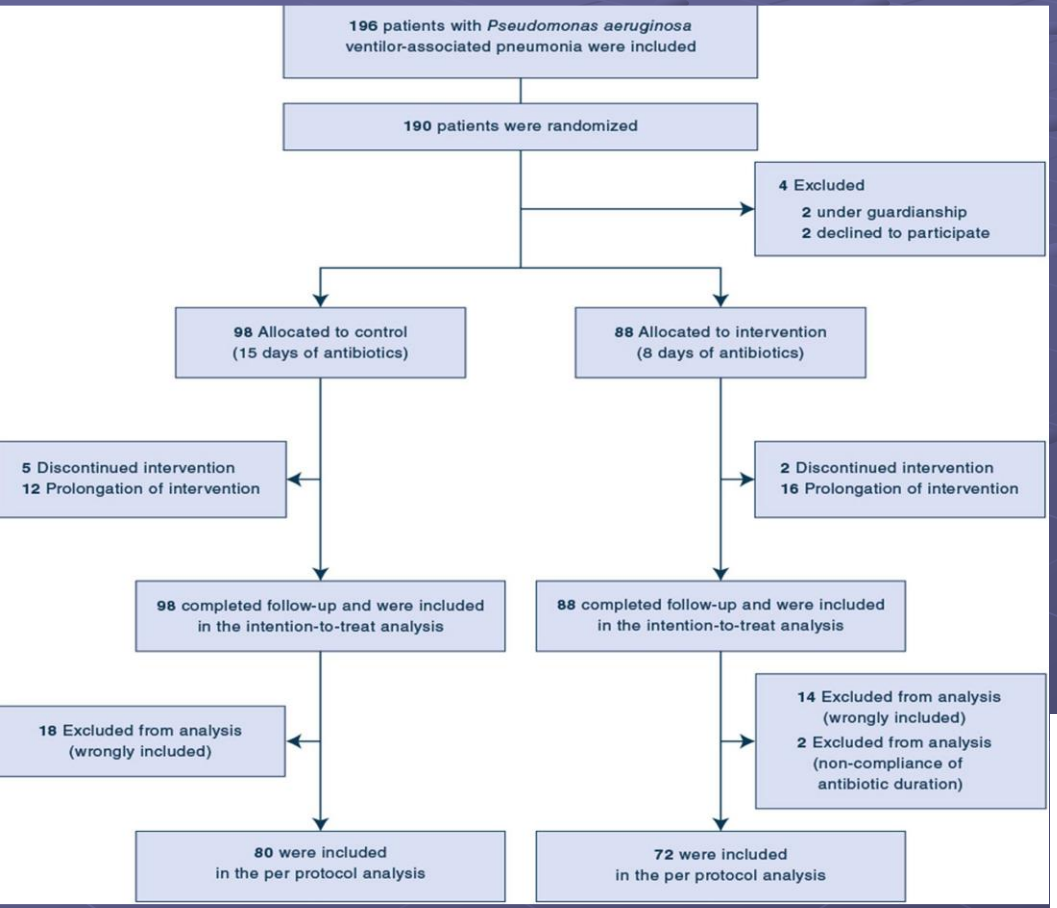




The fourth and final study included by the panel in the meta-analysis was a prospective, open-label trial by Capellier et al of 225 patients with early-onset VAP randomized to 8 versus 15 days of antibiotic treatment [9]. This study contributed significantly to the panel's meta-analysis (59 patients, 22%); however, no patients in this trial had VAP due to non-fermenting gram-negative bacilli at the time of enrollment. Of the 143 baseline gram-negative pathogens identified, 30% were Enterobacterales and 66% were Haemophilus spp. For this reason, the findings of this study are immaterial to an analysis of NF-GNB VAP treatment durations, and they should not have been included in the panel's meta-analysis.

Owen R. Albin, et al CID 2023

Comparison of 8 versus 15 days of antibiotic therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia in adults: arandomized, controlled, open-label trial



Results: The study was stopped after 24 months due to slow inclusion rate. In intention-to-treat population (*n* = 186), the percentage of patients who reached the composite endpoint was 25.5% (*N* = 25/98) in the 15-day group versus 35.2% (*N* = 31/88) in the 8-day group (difference 9.7%, 90% confidence interval (CI) −1.9%–21.2%). The percentage of recurrence of PA-VAP during the ICU stay was 9.2% in the 15-day group versus 17% in the 8-day group. The two groups had similar median days of mechanical ventilation, of ICU stay, number of extra pulmonary infections and acquisition of multidrug-resistant (MDR) pathogens during ICU stay

Despite randomization, there were notable differences in some clinically relevant markers of illness at baseline between the two arms. Therefore, post hoc adjusted analyses were performed on these 2 populations and the differences between arms became slightly more pronounced (ITT 12.5%, 90% CI: 1.3–23.6; PP 16.3% 90% CI: 3.9–28.8%). When assessed individually 90-day survival was 81.4% in the 15-day group and 75.6% in the 8-day group (HR=1.37, 90% CI: 0.81–2.33) and recurrence rates were 9.2% and

Bougle A et al ICM 2023

Nebulized Antibiotics

- Nebulized adjuntive antibiotics were promising in animal and human (SC) studies to treat or prevent VAP
- However, the two most important RCT´s resulted negative (Cardeas and Bayer) in part due to a bad selection of the target population
- In animal models NB antibiotics act mainly in upper airways but not in lower airways
- The role of NB antibiotics needs to be reconsidered both in treatment and in the prevention of VAP

Piglet Animal Model of VAP

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia

Ehrmann S et al. DOI: 10.1056/NEJMoa2310307

CLINICAL PROBLEM

Ventilator-associated pneumonia is the most frequent presentation of hospital-acquired infection of the lower respiratory tract. Microaspirations around the tracheal-tube cuff and the formation of biofilm can lead to progressive bacterial spread in the tracheobronchial tree, ultimately leading to pneumonia. Inhaled antibiotic therapy enables delivery of very high antibiotic concentrations to the tracheobronchial tree, lung parenchyma, and tracheal-tube biofilm. Whether preventive inhaled antibiotics may reduce the incidence of ventilator-associated pneumonia is unclear.

CLINICAL TRIAL

Design: A multicenter, double-blind, randomized, placebo-controlled trial in France examined the efficacy and safety of inhaled amikacin in critically ill adults who had undergone invasive mechanical ventilation for ≥72 hours.

Intervention: 847 patients were randomly assigned to receive inhaled amikacin at a dose of 20 mg per kilogram of ideal body weight or placebo once daily for 3 days. The primary outcome was a first episode of ventilator-associated pneumonia through day 28.

RESULTS

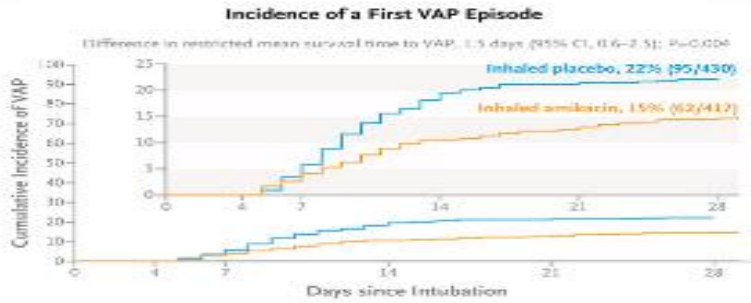
Efficacy: At 28 days, ventilator-associated pneumonia had developed in fewer patients in the amikacin group than in the placebo group.

Safety: Trial-related serious adverse effects were seen in 7 patients in the amikacin group and 4 patients in the placebo group.

LIMITATIONS AND REMAINING QUESTIONS

- The trial was not powered to investigate other patient-centered outcomes, such as death or length of stay in the ICU and hospital.
- The trial was also not powered to detect whether preventive inhaled antibiotics could reduce the use of systemic antibiotics to limit antibiotic-resistance selection pressure.

Links: Full Article | NEJM Quick Take



CONCLUSIONS

Among critically ill patients who had undergone mechanical ventilation for more than 3 days, a subsequent 3-day course of inhaled amikacin reduced the burden of ventilator-associated pneumonia during 28 days of follow-up.

Previous RCTs for corticosteroids in severe CAP , and in ARDS

- Hydrocortisone and glucocorticosteroids have been tested in patients with severe CAP .Some of these studies used CRP base line levels to enrich populations
- Steroid efficacy has also been widely tested for the treatment of ARDS.
- No studies reported adverse events defined as leading to discontinuation of study medication in RCTs realized in ARDS patients
- It did not appear as any signal for increase in superinfection in COVID-19 patients treated with steroids

1. Torres, A. *et al.*. *Jama* **313**, 677–686 (2015).
2. Dequin, P.-F. *et al.* Hydrocortisone in Severe Community-Acquired Pneumonia. *New Engl J Med* **388**, 1931–1941 (2023).
3. Villar, J. *et al.* Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Medicine* **8**, 267–276 (2020).
4. Lewis, S. R., Pritchard, M. W., Thomas, C. M. & Smith, A. F. Pharmacological agents for adults with acute respiratory distress syndrome. Cochrane Database Syst. Rev. 7, CD004477 (2019
5. Chaudhuri, D. et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intens Care Med 1–17 (2021) doi:10.1007/s00134-021-06394-2.

Corticosteroids in Critically Ill Patients With Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia Focused Update 2024. *Chaudhuri et al Crit Care Med 2024*

TABLE 1.
Summary of Recommendations

Recommendations	Recommendation Strength, Quality of Evidence
Septic shock	
1A. We "suggest" administering corticosteroids to adult patients with septic shock	Conditional recommendation, low certainty evidence
1B. We "recommend against" administration of high dose/short duration corticosteroids (> 400 mg/d hydrocortisone equivalent for less than 3 d) for adult patients with septic shock (strong recommendation, low certainty)	Strong recommendation, moderate certainty evidence
Acute respiratory distress syndrome	
2A. We "suggest" administering corticosteroids to adult hospitalized patients with acute respiratory distress syndrome	Conditional recommendation, moderate certainty evidence
Community-acquired bacterial pneumonia	
3A. We "recommend" administering corticosteroids to adult patients hospitalized with severe bacterial community acquired pneumonia	Strong recommendation, moderate certainty evidence

THE HAP-DEX STUDY

- **Phase III double blind placebo-controlled multicenter study in Europe**
- **Adult** patients (18yr to 85yr)
- **Hospital-acquired pneumonia (HAP)** according to European guidelines (Torres et al. Eur Respir J 2017):
- HAP severity defined as a **PaO2/FiO2 ratio < 200.**
- Biological systemic inflammatory response defined as **CRP ≥ 150 mg/L (15 mg/dL**)
- Receiving **curative antimicrobial therapy for the current episode of HAP pneumonia for less than 48 hours.**
- **Severe Septic shock patients excluded**
- Dexamethasone 0.2 $mg.kg^{-1}.day^{-1}$ iv. for 5-7 days vs Placebo. Six hour window to start dexamethasone or placebo.
- Primary end points: Clinical cure at test of cure and 28 day all cause mortality

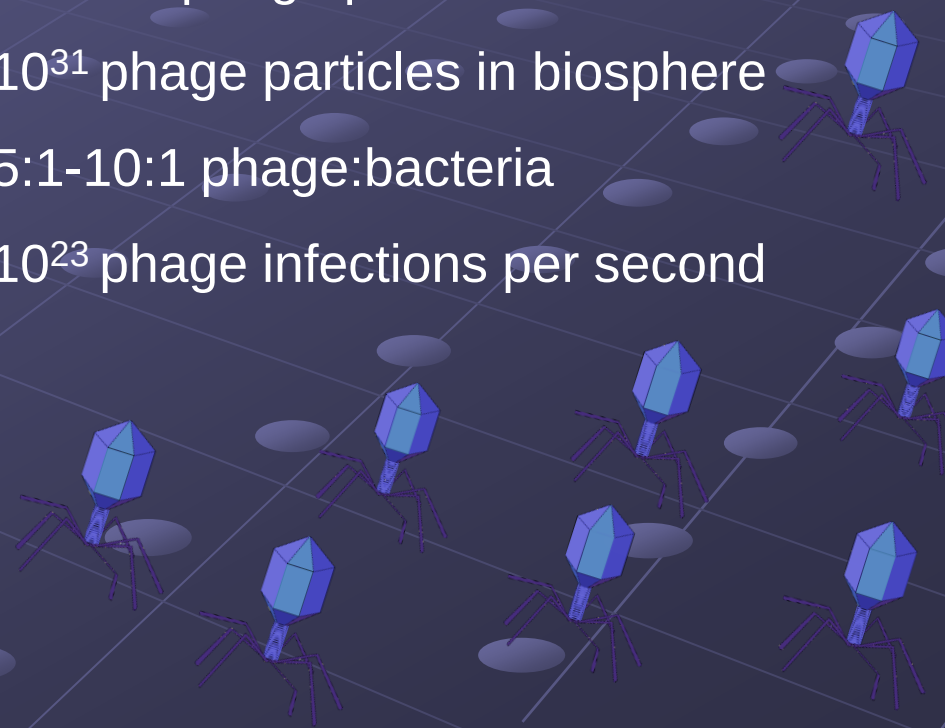
NON-ANTIBIOTIC TREATMENTS: PHAGES

What are bacteriophages?

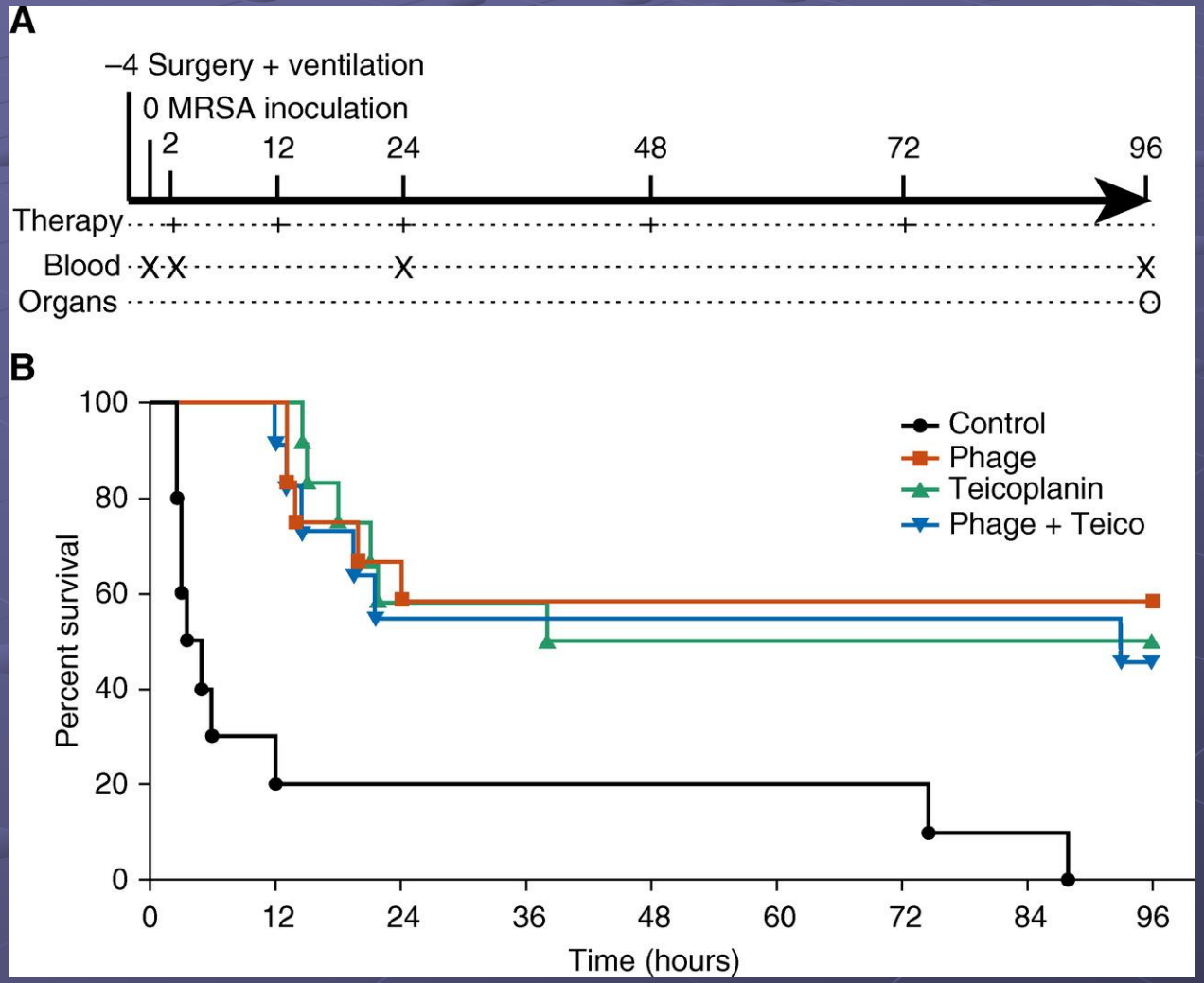
- **Phages are viruses that infect/kill bacteria**
- **Host-dependent replication**
- **Lytic or temperate**
- **Population is vast, dynamic, old and highly diverse**
- **Source: nature, engineered and synthetic**

The phage population is vast

- 10^{6}-10^{7} phage particles/ml
- 10^{31} phage particles in biosphere
- 5:1-10:1 phage:bacteria
- 10^{23} phage infections per second



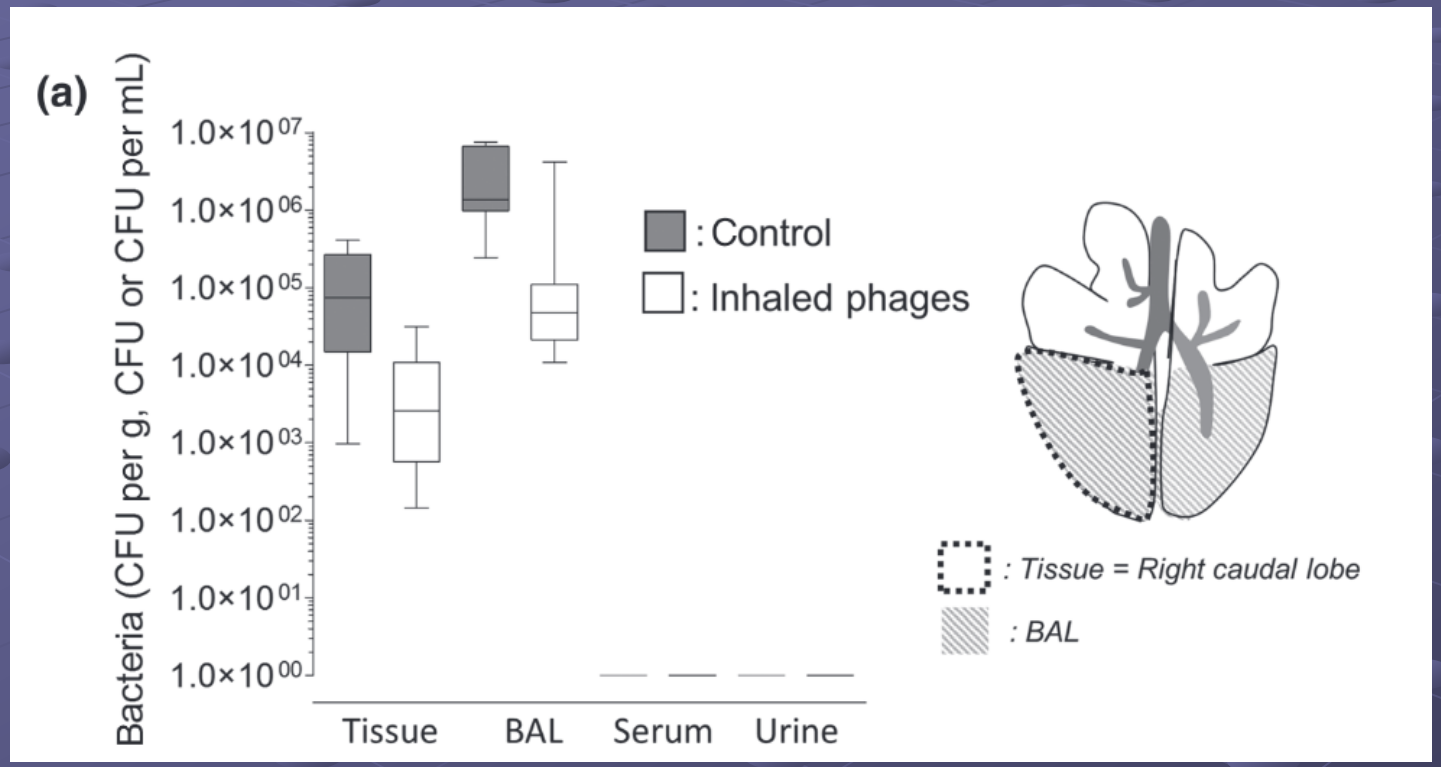
Bacteriophages Improve Outcomes in Experimental MRSA VAP



- Phage cocktail (n=4 phages), intravenous
- Similar survival rates between Phage (58%), Teicoplanin (50%) or Phage+Teico (45%)

Josef Prazak, Am J Respir Crit Care Med 2019

Inhaled bacteriophage therapy in a porcine model of pneumonia caused by *Pseudomonas aeruginosa* during mechanical ventilation



Phage cocktail (n=5 phages) 2 and 11 h after bacterial challenge, by inhalation

After 21 hours of MV phage treated animals: 1.5 log CFU/mL in lung tissue and BAL

Large amounts of phages into the lungs and in areas of pneumonia with loss of aeration

Guillon A, Br J Pharmacol. 2021

Conclusions

- HABP, VABP, and VHABP are different categories of HAP with similar microbial etiology
- Rapid molecular tests are a major step forward in diagnosis and adequate treatment of HAP
- Treatment failure is not well defined and it is crucial for new studies
- New algorithms including the new antibiotics are developed and need to be validated
- Longer antibiotic duration is probably needed in NFGNB
- Nebulized antibiotics need to be reconsidered
- There is need to investigate non-antibiotic treatments