Terapia di Combinazione:
Come, Quando, Perché e con Che Cosa?

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Francesco G. De Rosa

AOU Città della Salute & Scienza

Fellow, Infectious Diseases Society of America

Consultant/Advisory Board/Speaker fees

- Pfizer, MSD, Angelini, Thermo Fisher, Shionogi, BioTest, Nordic Pharma, InfectoPharma
- Gilead Sciences, GSK, Hikma, Advanz, Basilea
- Tillots, Menarini, Correvio
- **Research grant**
    - Pfizer, MSD, Shionogi

Antibiotic Treatment

- **Combination**
  - Gram-positives
  - Gram-negatives
- **Dose optimization & administration**
- **Drug Penetration at the site of infection**
- **De-escalation**
- **Duration**

Combination Therapy

- **Broader coverage**
  - In the empiric setting
- **Prevent emergence of reduced susceptibility**
  - Theoretical issue
- **Bacterial synergy**
  - Clear examples in enterococcal infections
- **Differential penetration into cells and tissues**
  - Different mechanisms of action

Combination Therapy in Gram-negative Sepsis

MiceK ST et al. AAC 2010; 54: 1742-8

TABLE 5. Appropriateness of various antibiotic combinations against Gram-negative pathogens in the study cohort[a]

Antibiotic	% Susceptible to at least one antibiotic plus:		
	None	Ciprofloxacin	Gentamicin
Cefepime	83.4	86.4	89.9
Imipenem or meropenem	89.7	92.4	94.2
Piperacillin-tazobactam	79.6	87.0	91.4

Epidemiology & Inappropriate Therapy

- **789 patients with Gram-negative bacteremias**
  - Inappropriate empiric treatment → higher risk of 30-day all cause mortality
  - HR 1.68, 95% CI 1.19-2.38
    - Baltas I et al. JAC 2021; 76: 813-9
- **CRE infections**
  - 3-times more likely to be inappropriately treated than non-CRE patients
  - Increased costs, length of stay & mortality
    - Zilderberg MD et al. BMC Infect Dis 2017; 17:279

MDR Gram-negative Bacterial Infections

Yassin A et al. Clin Infect Dis 2023; 77(9):e46-e56

- **82-year-old female was transferred from a nursing home to the emergency department (ED) due to hypotension and fevers**
  - Cough and pleuritic chest pain for 1 week before presentation
  - IV Pip-tazo at the nursing home for 5 days without improvement
  - History of hypertension, diabetes mellitus, and chronic kidney disease
  - Recent hospitalization approximately 2 months prior
    - Embolization for a ruptured cerebral aneurysm
    - ICU admitted for 10 days during a total hospital stay of 18 days
    - Treated for a ceftriaxone-resistant *E. coli* UTIs

      7 days of pip-tazo
    - Discharged to the nursing home

General / Specific considerations

Severity of Infection

Colonization by MDR / CRE

Hospital/Ward rate of CRE / MDR *P. aeruginosa*

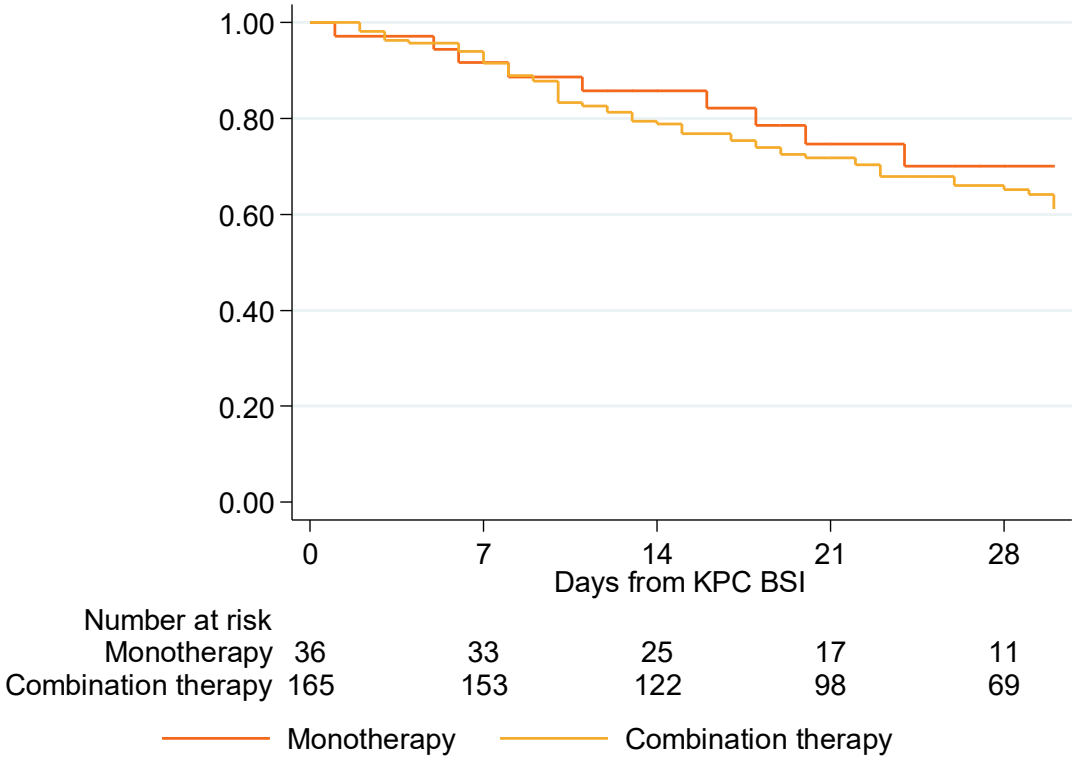
MDR Gram-negative Bacterial Infections

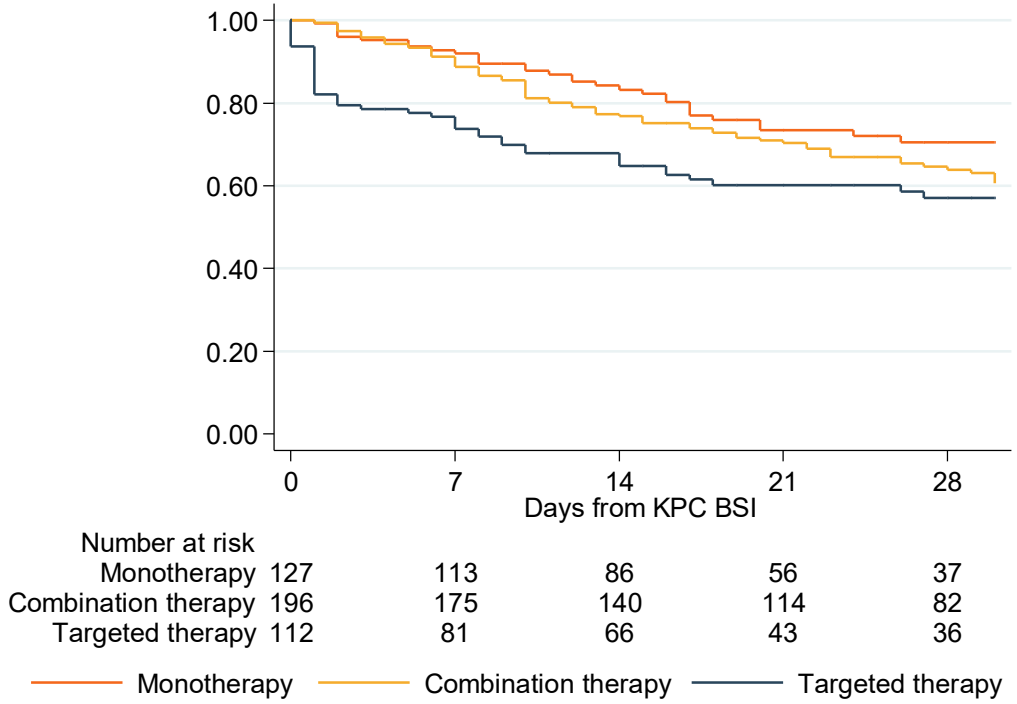
Yassin A et al. Clin Infect Dis 2023; 77(9):e46-e56

- **Dyspneic**
  - BP 80/42 mm Hg; HR120/min, T = 101.2 °F, RR = 28/min, $SatO_2$ 86% room air
  - Crackles at the left lung base
  - LABS: WBC of 18 × $10^3/\mu L$ (baseline 6 × $10^3/\mu L$; N = 97%) lactate = 4 mmol/L, creatinine of 3 mg/dL (baseline 1.5 mg/dL)
- **A chest radiograph revealed a dense infiltrate on the left side**
- **Follow-up: quick worsening in ED → intubated → norepinephrin**
  - Two sets of blood cultures and respiratory cultures were obtained
- **Which antimicrobials?**

Impact of Appropriate (Empiric) Therapy on Mortality for KPC-BSI

Corcione S & De Rosa FG Biomedicine 2022





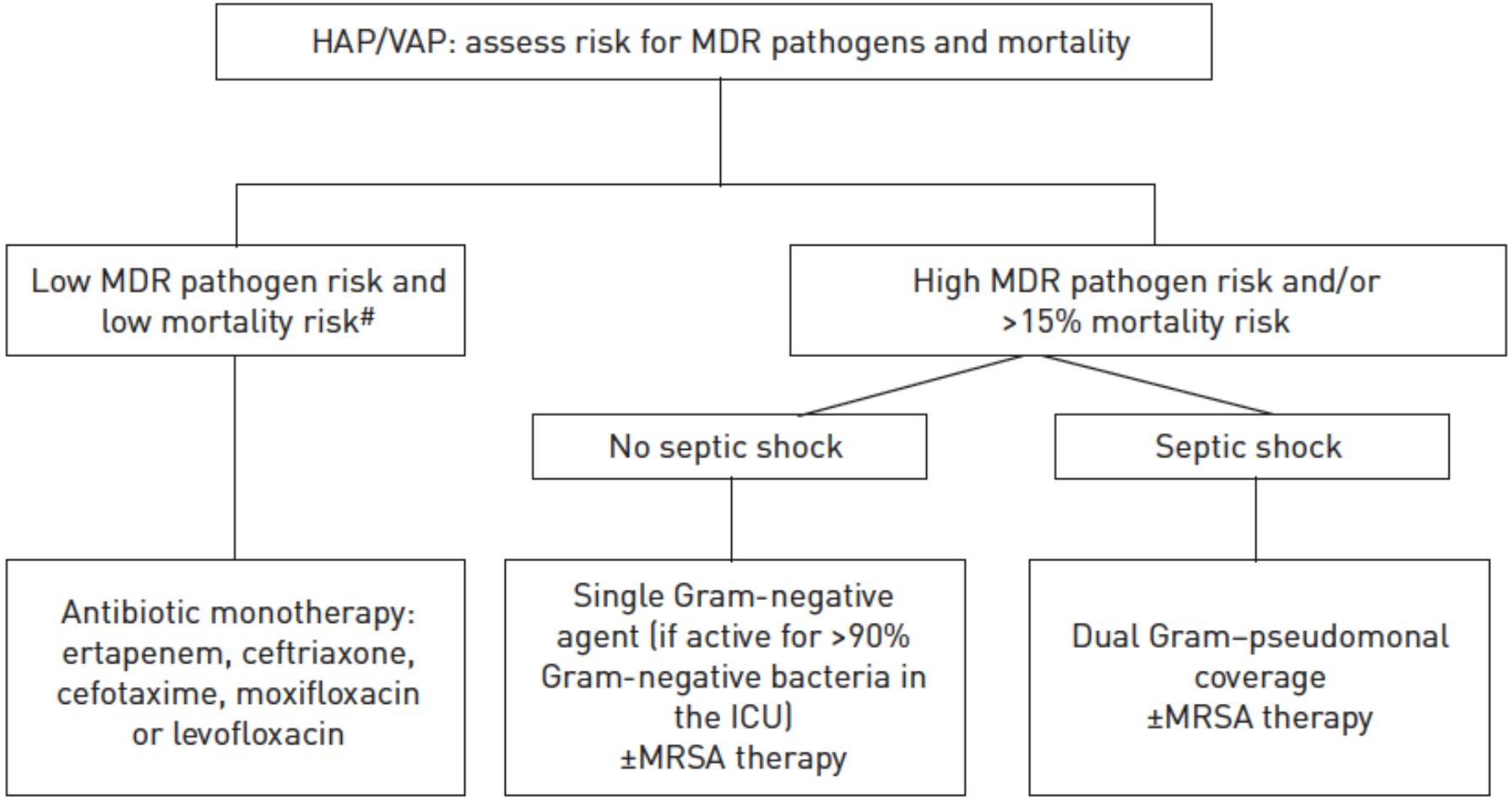
Cefiderocol Use in Gram-negative Infections with Limited Therapeutic Options: Is Combination Therapy the Key

Corcione S & De Rosa FG Int J of Inf and Public Health 2022

- **18 pazienti** (83.3% M, età 57); ICU **83.3**%, medicina 11.1%, chirurgia 5.6%
- Durata degenza media: **40 giorni** (IQR 29.75-99.5)
- SOFA score mediano all'inizio del cefiderocol 6 (IQR 4-11.5), APACHE III score 14.5 (IQR 7.75-19.5)
- **33.4%** in CRRT; 16.7% in vv-ECMO
- CR *A. baumannii* 83.3%, ***E. coli*** **NDM 5.6%, *K. pneumoniae* NDM 5.6%;** *S. malthophilia* 5.6%
- 100% pregressa/concomitante **colonizzazione** gastroenterica o respiratoria
- **Durata** mediana del trattamento: 9.5 giorni (IQR 7-13)
- Uso in **combinazione** nel 77.8% (57.1% *colistin-sparing*)
- **Mortalità** ospedaliera: 27.8% (pari a quella a 30 giorni); mortalità in ICU a 30 giorni dal ricovero: 22.2%

	Overall (n = 18) Median (IQR) or N (%)	**Monotherapy (n = 4) Median (IQR) or N (%)**	**Combination therapy (n = 14) Median (IQR) or N (%)**	**p**
30-days outcomes	4 (22.2)	2 (50)	2 (14.29)	0.355
admitted to ICU	1 (5.6)	1 (25)	0 (0)	
admitted to medicine ward	5 (27.8)	0 (0)	5 (35.71)	
discharge to low/no care need				

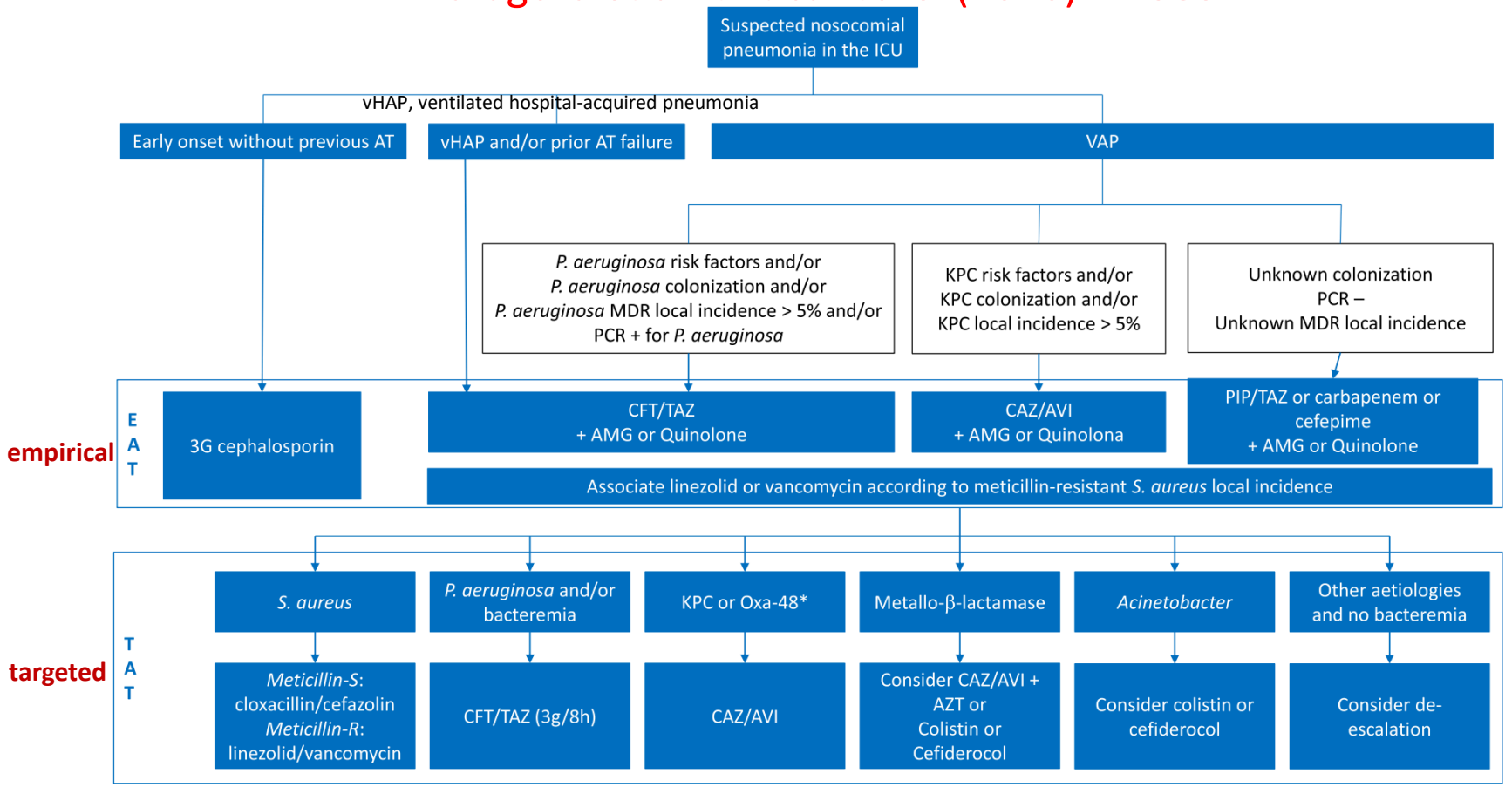
ERS Guidelines 2017



Torres et al. Eur Respir J 2017; 50: 1-26

Treatment Algorithm

Zaragoza et al. Critical Care (2020) 24:383



Readiness: Fosfomycin

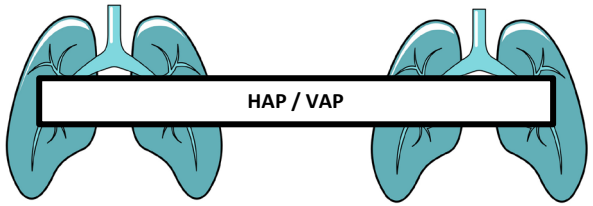
- **MDR & ESBL Enterobacterales**
  - Falagas ME et al Lancet Infect Dis 2010
- **Published evidence on MDR**
  - Karageorgopoulos DE et al. JAC 2011
- **IV Fosfo for CR *K. pneumoniae* in ICU**
  - Michalopoulos A et al. CMI 2010
- **Population PK in critically ill patients**
  - Parker SL et al. AAC 2015
- **Efficacy in ICU patients with PDR, XDR and CRE**
  - Pontikis K et al. Int J Antimicrob Ag 2014
- **MDR Gram-negative Infections & synergy**
  - Reffert JL et al. Pharmacotherapy 2014

Our Treatment Strategies

Fosfomycin: Place in therapy

CNS

Bone



UTI

BSI

High Risk for MRSA and/or PA

Safety

Alternative "Sparing":

Glycopeptides-sparing
Oxazolidinones-sparing
«Old» BL/BLIs-sparing
Carbapenem-sparing
AG-sparing

Stewardship

City of Health & Sciences, Turin, Italy

KPC

Paul et al., CMI, 2021 (ESCMID)

- For patients with CRE infections susceptible to and treated with ceftazidime-avibactam, meropenem-vaborbactam, or cefiderocol, the guidelines do not recommend combination therapy
  Strong recommendation with low level of evidence

- For targeted treatment of severe infections caused by CRE resistant to novel agents and susceptible *in vitro* only to polymyxins, aminoglycosides, tigecycline and/or fosfomycin, the guidelines suggest treatment with more than one drug active *in vitro,* with no recommendation for or against specific combinations
  Conditional recommendation with moderate level of evidence

Tamma et al., CID, 2022 (IDSA)

- Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/relebactam are preferred treatment options for severe infections caused by KPC-Kp resistant to both ertapenem and meropenem
  No recommendations or Levels of Evidence reported
- Combination of a novel b-lactam agent with an aminoglycoside, fluoroquinolone, or polymyxin is not routinely recommended for the treatment of infections caused by CRE
  No recommendations or Levels of Evidence reported
- Polymyxin B and colistin should be avoided for the treatment of severe infections caused by CRE

Agreement:
Monotherapy > Combo

CR-PA

Paul et al., CMI, 2021 (ESCMID)

Tamma et al., CID, 2022 (IDSA)

- Lacking evidence, **we cannot recommend for or against the use of combination therapy with the new BLBLI** (ceftazidime-avibactam and ceftolozane-tazobactam) or cefiderocol for CRPA infections

- When treating severe infections caused by CRPA with polymyxins, aminoglycosides, or fosfomycin, we suggest treatment with two in vitro active drugs
  Conditional recommendation for use, very low certainty of evidence

- No recommendation for or against specific combinations can be provided

- **Monotherapy** with Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, is preferred for infections outside of the urinary tract by DTR-*P. aeruginosa*

- **Combination antibiotic therapy is not routinely recommended** for infections caused by DTR-*P. aeruginosa* if *in vitro* susceptibility to a first-line antibiotic (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed

Different View:
Monotherapy vs. Combo

CR-AB

Paul et al., CMI, 2021 (ESCMID)

- Severe and high-risk CRAB infections, we suggest combination therapy including two *in vitro* active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations)

  Conditional recommendation for use, very low certainty of evidence
- CRAB infections with a meropenem MIC <8 mg/L, we consider carbapenem **combination therapy,** using high-dose extended-infusion carbapenem dosing, as good clinical practice **(good practice statement)**
- Conditional recommendation against cefiderocol for infections by CRAB

  Conditional recommendations against use, low certainty of evidence
- No recommendation for polymyxin-meropenem combination / polymyxin-rifampin combination therapy

  Strong recommendation against use, high/moderate certainty of evidence

Tamma et al., CID, 2022 (IDSA)

- High-dose ampicillin-sulbactam is a preferred therapy for CRAB infections when susceptibility has been demonstrated. High-dose ampicillin-sulbactam remains a treatment consideration as a component of combination therapy even when susceptibility has not been demonstrated (at least two agents)
- Polymyxin B can be considered as monotherapy for mild CRAB infections and in combination with at least one other agent for the treatment of moderate to severe CRAB infections. Colistin is suggested rather than polymyxin B for urinary CRAB infections
- Cefiderocol should be limited to the treatment of CRAB infections refractory to other antibiotics or in cases where intolerance to other agents precludes their use. When cefiderocol is used to treat CRAB infections, the panel suggests prescribing the agent as part of a combination regimen

Agreement:
Combination

Enterococcal Infective Endocarditis

- **NVE due to non-HLAR *Enterococcus* spp.**
  - Ampi / Amoxi + ceftriaxone for 6 weeks or with gentamicin for 2 weeks
- **PVE and complicated PVE or >3 months of symptoms due to non-HLAR *Enterococcus* spp.**
  - Ampi / Amoxi + ceftriaxone for 6 weeks or with gentamicin for 2 weeks
- **NVE / PVE due to HLAR *Enterococcus* spp.**
  - Ampi / Amoxi + ceftriaxone for 6 weeks
- **IE due to resistant *Enterococcus* spp. (*E.faecium*)**
  - Vanco for 6 weeks combined with genta for 2 weeks
- **IE due to Vanco-resistant *Enterococcus* spp.**
  - Dapto combined with beta-lactams (ampi, erta, ceftaroline) or fosfo

Conclusioni

- Come?
- Quando?
- Perchè?
- Con che cosa?

- Cosa?
- > In terapia empirica
- Prudenza in fase diagnostica
- Fosfo > AG