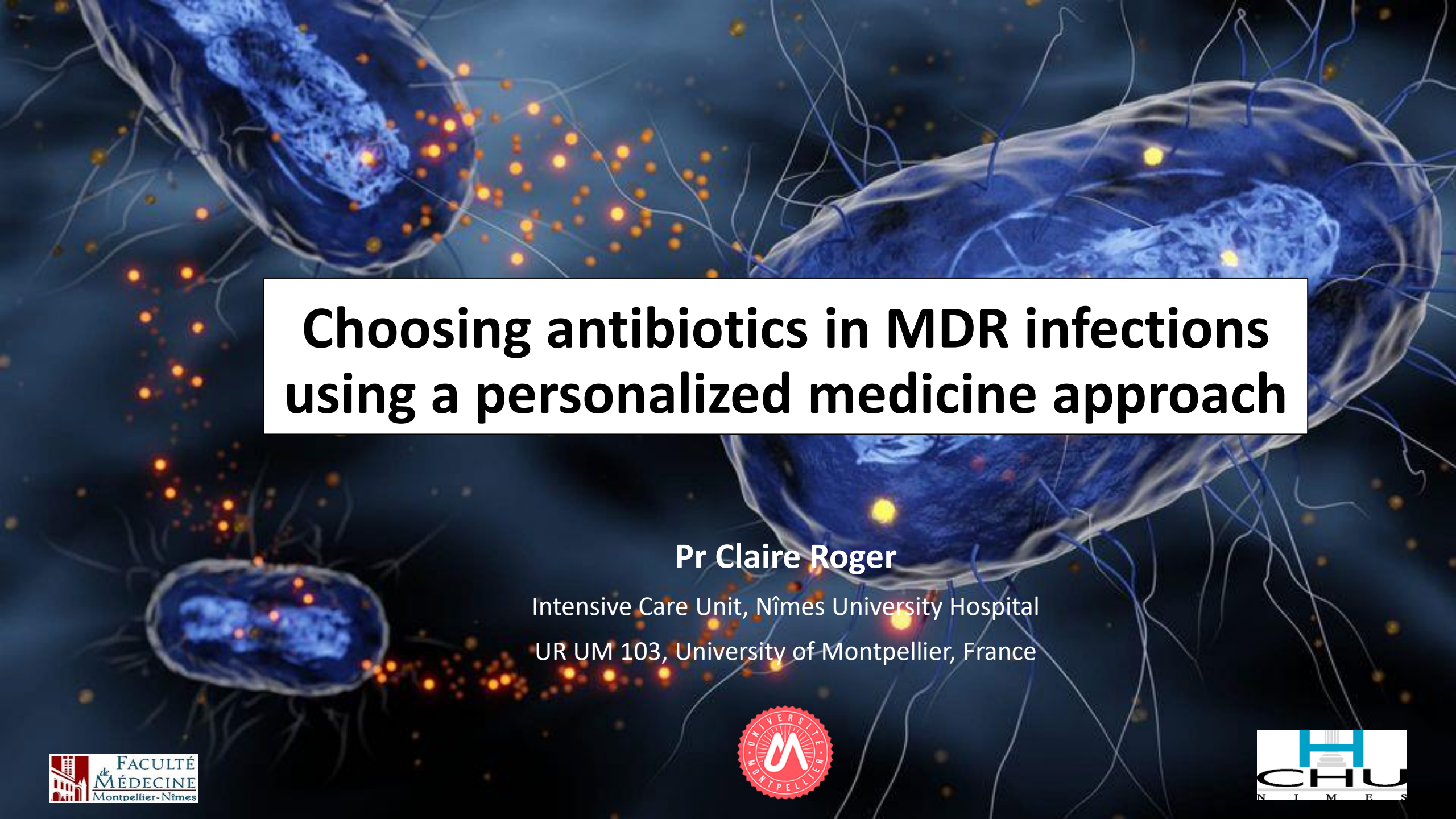

# Choosing antibiotics in MDR infections using a personalized medicine approach

**Pr Claire Roger**

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UR UM 103, University of Montpellier, France

# Disclosures

- Speaker fees:
  - MSD
  - Pfizer
  - Shionogi
  - bioMerieux
  - Advanz pharma
- Scientific advisory board:
  - bioMerieux
  - Viatris

# Risk of inappropriate empirical antimicrobial treatment in immunocompromised patients

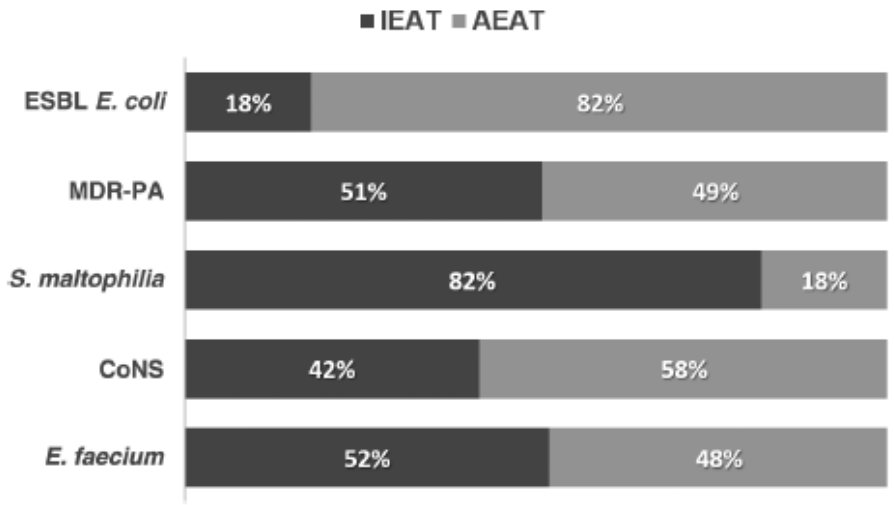
## Inappropriate Empirical Antibiotic Treatment in High-risk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance

Gemma Martinez-Nadal,[1,a] Pedro Puerta-Alcalde,[2,a] Carlota Gudiol,[3,4] Celia Cardozo,[2] Adaia Albasanz-Puig,[3] Francesc Marco,[5,6] Júlia Laporte-Amargós,[3] Estela Moreno-García,[2] Eva Domingo-Doménech,[7] Mariana Chumbita,[2] José Antonio Martínez,[2,8] Alex Soriano,[2,8] Jordi Carratalà,[3,4] and Carolina Garcia-Vidal[2,8]

1615 infectious episodes

14% MDR GNB infections

24% inappropriate empirical antimicrobial therapy




## High Rate of Inappropriate Antibiotics in Patients with Hematologic Malignancies and *Pseudomonas aeruginosa* Bacteremia following International Guideline Recommendations

Mariana Chumbita,[a] Pedro Puerta-Alcalde,[a] Lucrecia Yáñez,[b] Maria Angeles Cuesta,[c] Anabelle Chinea,[d] Ignacio Español-Morales,[e] Pascual Fernandez-Abellán,[f] Carlota Gudiol,[g] Pedro González-Sierra,[h] Rafael Rojas,[i] José María Sánchez-Pina,[j] Irene Sánchez Vadillo,[k] Miguel Sánchez,[k] Rosario Varela,[l] Lourdes Vázquez,[m] Manuel Guerreiro,[n] Patricia Monzo,[a] Carlos Lopera,[a] Tommaso Francesco Aiello,[a] Oliver Peyrony,[a,p] Alex Soriano,[a,o] Carolina Garcia-Vidal[a,o]

**TABLE 2** Resistance profiles among bloodstream infections caused by *Pseudomonas aeruginosa* in hematologic patients with febrile neutropenia[a]

| Antibiotic | N = 280 (%) |
|---|---|
| Quinolones | 82 (29.3) |
| Piperacillin-tazobactam | 61 (21.8) |
| Cefepime | 72 (25.7) |
| Meropenem | 70 (25) |
| Amikacin | 41 (14.6) |
| MDR-*P. aeruginosa* | 59 (21.1) |
| XDR-*P. aeruginosa* | 32 (11.4) |
| Resistance to at least 1 of the β-lactam antibiotics recommended in the international guidelines | 101 (36.1) |

[a]EUCAST MIC breakpoints R> (mg/L): Ciprofloxacin: >0.5; Piperacillin-tazobactam: >16; Cefepime: >8; Meropenem: >8; Amikacin: >16. Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant.

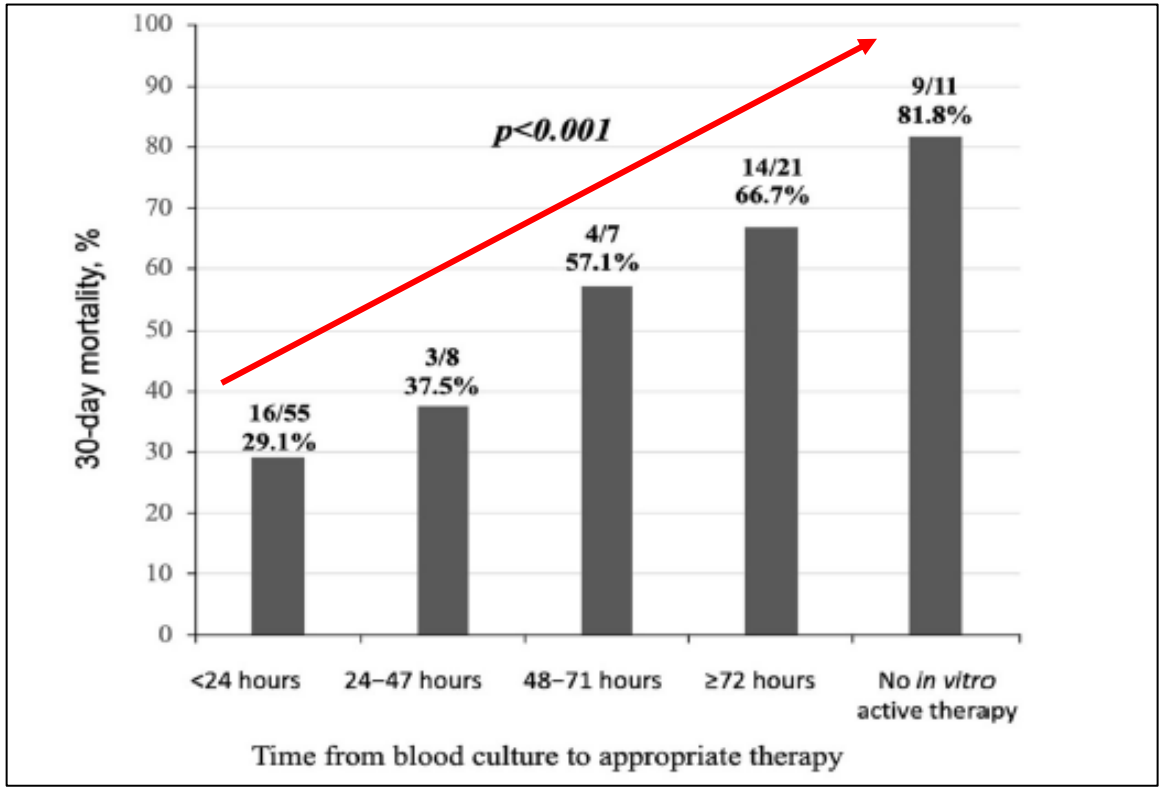
Chumbita et al. Microbiol Spectr 2023

Martinez-Nadal et al. CID 2020; 70: 1068-74.

RESEARCH Open Access

# Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae*

Marco Falcone[1*], Matteo Bassetti[2], Giusy Tiseo[1], Cesira Giordano[3], Elia Nencini[4], Alessandro Russo[1], Elena Graziano[5], Enrico Tagliaferri[1], Alessandro Leonildi[3], Simona Barnini[3], Alessio Farcomeni[6] and Francesco Menichetti[1]




**How to shorten the time to appropriate antimicrobial therapy?**

Falcone et al. Crit Care 2020

Original Investigation | Infectious Diseases

# Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use

Chanu Rhee, MD, MPH; Sameer S. Kadri, MD, MSc; John P. Dekker, MD, PhD; Robert L. Danner, MD; Huai-Chun Chen, PhD; David Fram, BA; Fang Zhang, PhD; Rui Wang, PhD; Michael Klompas, MD, MPH; for the CDC Prevention Epicenters Program

## How to improve antibiotics selection?

**Table 2. Outcomes Associated With Inadequate and Unnecessarily Broad Empiric Antibiotic Therapy[a]**

| | Inadequate vs adequate empiric therapy | | | | | | Unnecessarily broad vs not unnecessarily broad empiric therapy[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No./total No. (%) | | | | | | No./total No. (%) | | | | | |
| Outcome | Inadequate | Adequate empiric therapy | Unadjusted OR (95% CI) | *P* value | Adjusted OR (95% CI) | *P* value | Unnecessarily broad | Not unnecessarily broad | Unadjusted OR (95% CI) | *P* value | Adjusted OR (95% CI) | *P* value |
| In-hospital death | 488/2785 (17.5) | 2011/12 388 (16.3) | 1.10 (0.98-1.22) | .09 | 1.19 (1.03-1.37) | .02 | 1575/8405 (18.7) | 436/3993 (10.9) | 1.88 (1.68-2.11) | <.001 | 1.22 (1.06-1.40) | .007 |
| Hospital-onset acute kidney injury | 486/2785 (17.5) | 2196/12 398 (17.7) | 0.98 (0.88-1.09) | .74 | 1.02 (0.90-1.16) | .72 | 1641/8405 (19.5) | 555/3993 (13.9) | 1.50 (1.35-1.67) | <.001 | 1.12 (1.00-1.26) | .05 |
| *Clostridioides difficile* | 207/2785 (7.4) | 498/12 398 (4.0) | 1.92 (1.63-2.27) | <.001 | 1.19 (0.98-1.45) | .09 | 367/8405 (4.4) | 131/3993 (3.3) | 1.34 (1.10-1.65) | .004 | 1.26 (1.01-1.57) | .04 |

Rhee et al. JAMA Network Open 2020; 3: e202899.

# Agenda

- MDR risk factors assessment
- Resistance mechanisms identification
- New therapeutic options
- Dosing optimization

# Identify patients at risk of MDR infections

*Article*

## Risk Factors and Outcomes for Multidrug Resistant *Pseudomonas aeruginosa* Infection in Immunocompromised Patients

Pilar Hernández-Jiménez [1,2,*], Francisco López-Medrano [1,2,3], Mario Fernández-Ruiz [1,2,3], J. Tiago Silva [1,2], Laura Corbella [1,2], Rafael San-Juan [1,2,3], Manuel Lizasoain [1,2], Jazmín Díaz-Regañón [4], Esther Viedma [5] and José María Aguado [1,2,3]

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* | aOR | 95% CI | *p* |
| Diabetes mellitus with no target organ damage | 2.45 | 1.08–5.59 | 0.033 | 4.74 | 1.63–13.79 | 0.004 |
| Previous receipt of antibiotics | 5.81 | 2.53–13.33 | <0.001 | 5.32 | 1.93–14.73 | 0.001 |
| Previous surveillance for MDR colonization | 2.06 | 1.02–4.16 | 0.043 | 1.29 | 0.48–3.43 | 0.616 |
| Previous MDR colonization | 4.2 | 1.81–9.74 | <0.001 | 0.29 | 0.05–1.64 | 0.161 |
| Previous MDR *P. aeruginosa* colonization | 23.5 | 5.12–107.8 | <0.001 | 42.1 | 4.49–394.8 | 0.001 |
| Septic shock at diagnosis | 3.28 | 1.49–7.21 | 0.003 | 3.73 | 1.36–10.21 | 0.010 |

Hernandez-Jimenez et al. Antibiotics 2022; 11: 1459.

# Role of previous carbapenem exposure in neutropenic patients

## Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis

Elda Righi[1,2]*, Anna Maria Peri[2,3], Patrick N. A. Harris[2], Alexander M. Wailan[2], Mariana Liborio[4], Steven W. Lane[5-7] and David L. Paterson[2]

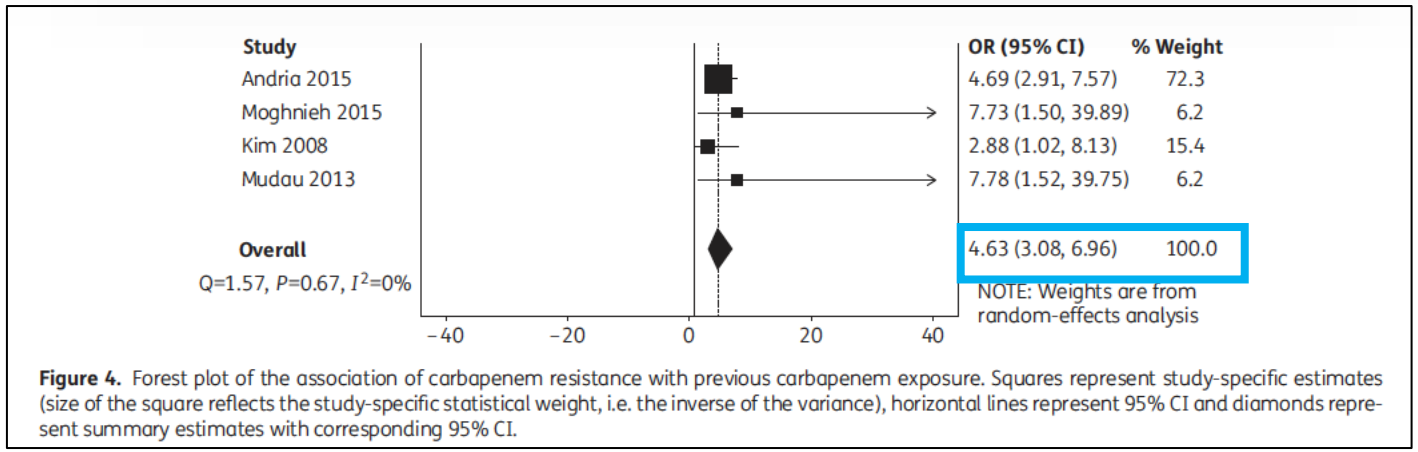



**Figure 4.** Forest plot of the association of carbapenem resistance with previous carbapenem exposure. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance), horizontal lines represent 95% CI and diamonds represent summary estimates with corresponding 95% CI.

Righi et al. JAC 2017; 72:668-677.

# Prior colonization as risk factor for MDR infections

**Risk factors for carbapenem-resistant *Acinetobacter baumannii* (CRAB) bloodstream infections and related mortality in critically ill patients with CRAB colonization**

Francesco Cogliati Dezza[1], Sara Covino[1], Flavia Petrucci[1], Federica Sacco[2], Agnese Viscido[2], Francesca Gavaruzzi[1], Giancarlo Ceccarelli [1], Gianmarco Raponi[2], Cristian Borrazzo [3], Francesco Alessandri[4], Claudio Maria Mastroianni[1], Mario Venditti[1] and Alessandra Oliva [1*]

| Risk factors | OR (95% CI) | *P* value |
|---|---|---|
| **Risk factors for BSI onset in patients with CRAB colonization** | | |
| CCI | 1.34 (1.02–15.2) | **0.026** |
| COVID-19 | 2.32 (1.72–15.8) | **<0.001** |
| Hypertension | 1.87 (0.91–3.87) | 0.089 |
| SAPS II | 2.5 (0.88–11.5) | 0.091 |
| Timing of ICU to colonization | 1.2 (0.84–9.9) | 0.122 |
| Multisite >1 | 2.4 (1.2–4.90) | **0.016** |
| Mechanical ventilation | 2.34 (1.1–5.02) | **0.024** |

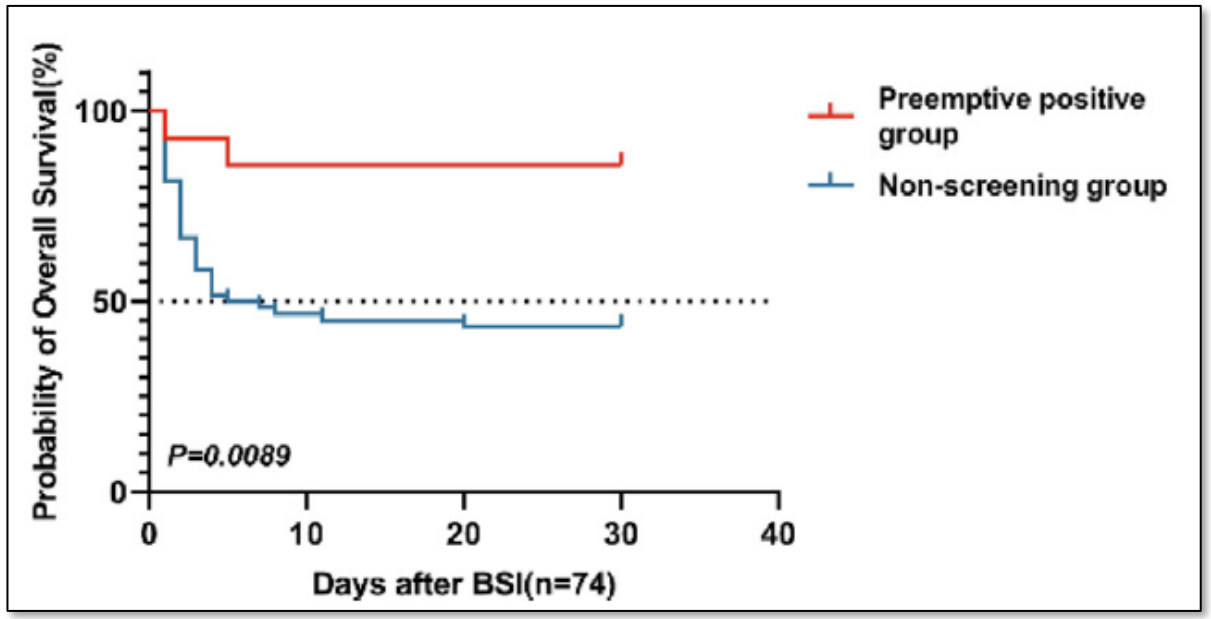
129 patients with CRAB colonization
44% developed BSI

JAC Antimicrob Resist 2023

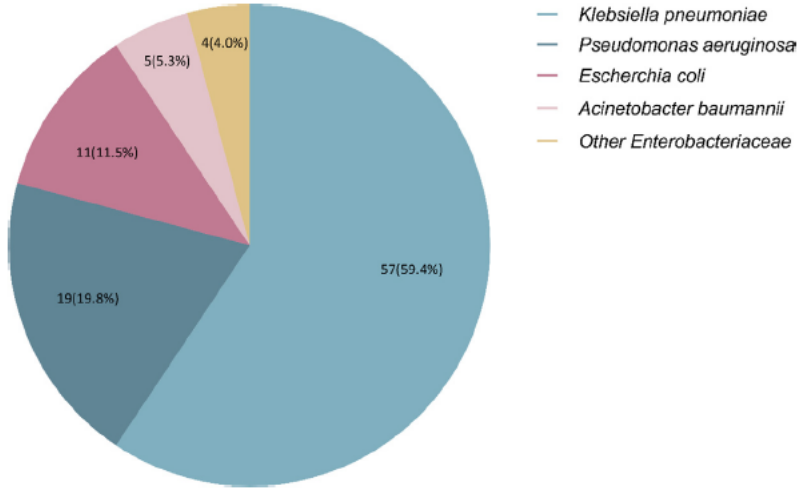
# Rectal culture could predict carbapenem-resistant organism bloodstream infection and reduce the mortality in haematological patients: A retrospective cohort study

Siyu Gao[#], Ran Yan[#], Suping Zhang, Li Li, Ran Zhang, Jinpeng Fan, Jing Qin, Yingnan Peng, Dingming Wan[*], Weijie Cao, Zhilei Bian[*]

*Department of Hematology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou University, Zhengzhou, People's Republic of China*




434 hematological patients with BSI
98 with CRO BSI
75% with positive rectal swab




Gao et al. J Glob Antimicrob Resist 2024; 36:96-104.

# MDR colonisation guides empirical antimicrobial therapy

Treatment of Community-Acquired Pneumonia in Immunocompromised Adults

A Consensus Statement Regarding Initial Strategies

Check for updates

CHEST

In which immunocompromised patients should the initial empirical therapy be extended to cover MDR pathogens?

*We suggest that in patients with a recent history of colonization or infection with MDR gram-negative bacilli, the initial empirical therapy should cover the possibility of infection due to the colonizing MDR gram-negative bacilli.*

*We suggest that initial empirical therapy to cover for MRSA should be started in patients with a history of colonization or infection with MRSA in the previous 12 months.*

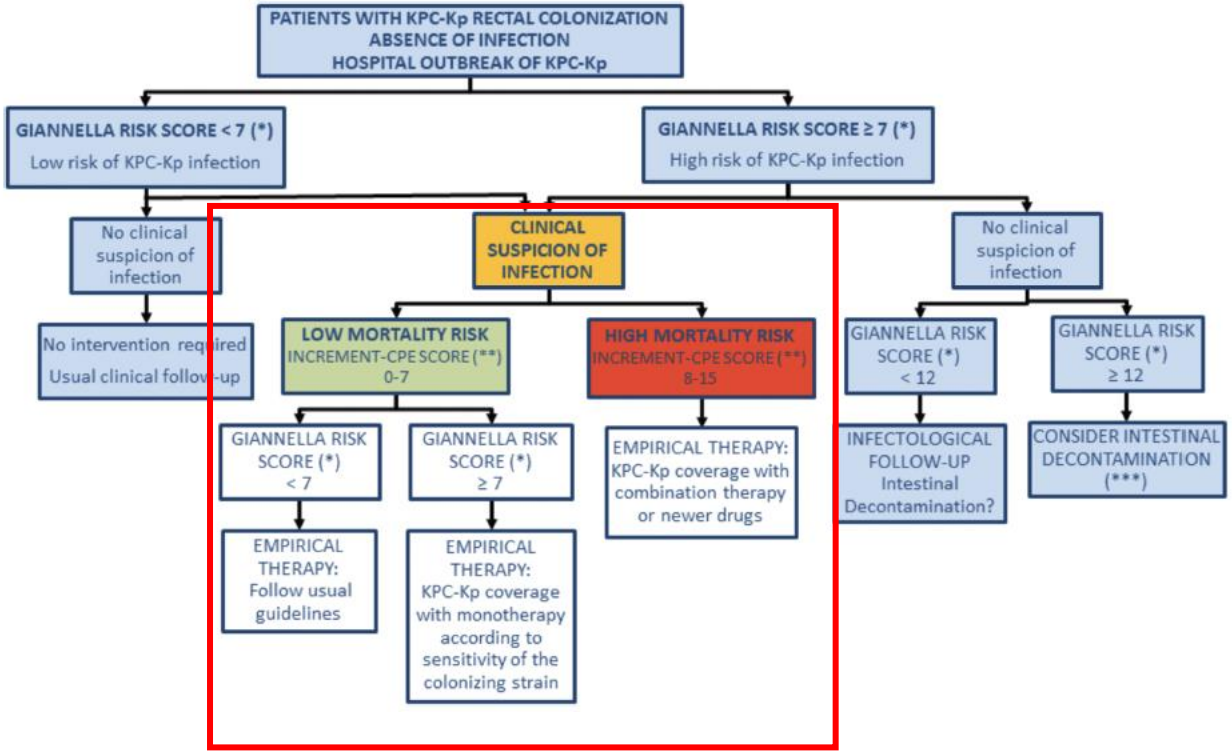
Ramirez et al. Chest 2020; 158: 1896-1911.

# MDR risk score may guide empirical KPC-Kp coverage

Giannella risk score

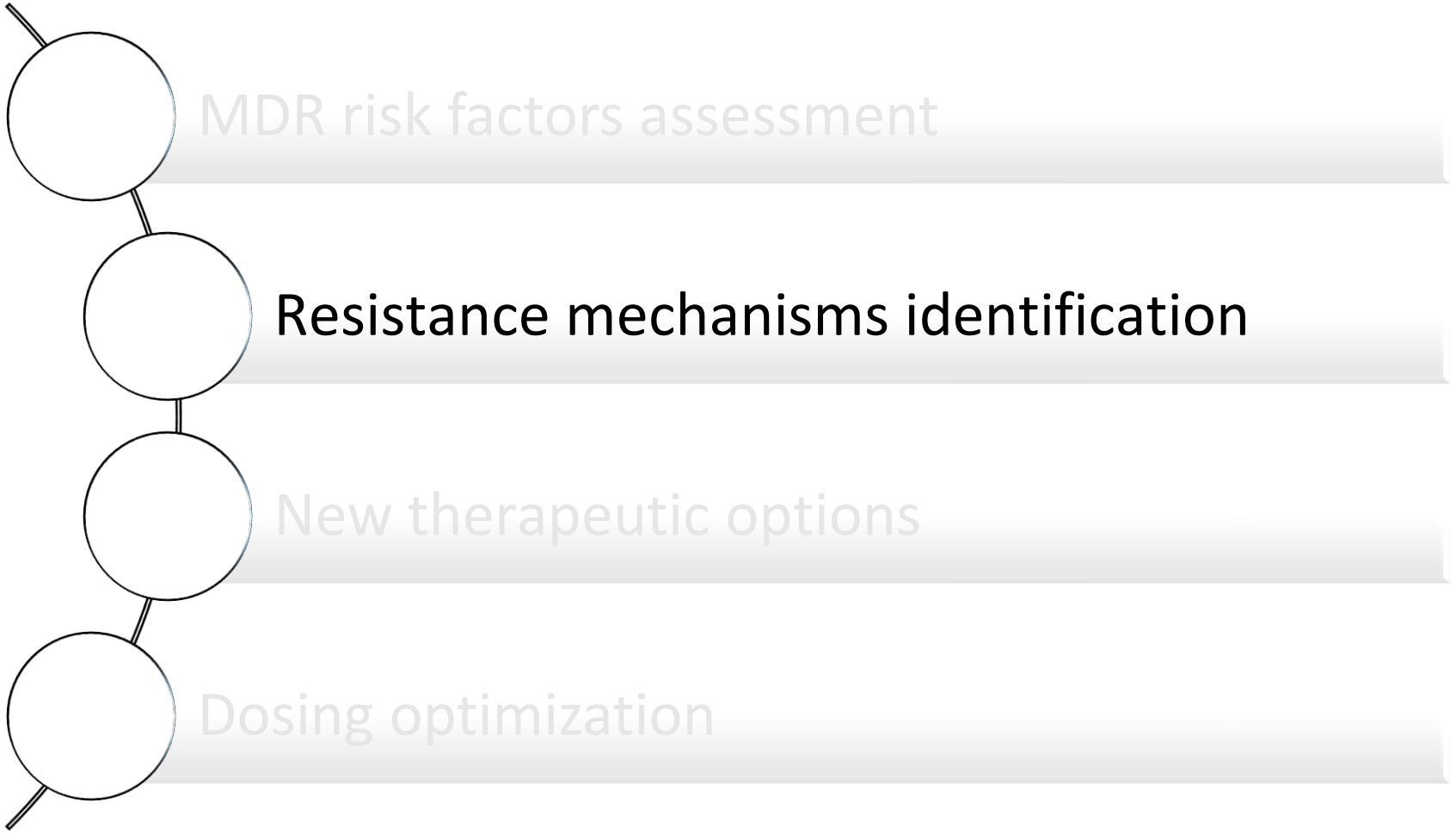
**Table 3.** Giannella risk score. Risk factors for CR-KP BSI development in rectal carriers.[7]

| Risk factors | Risk score point |
|---|---|
| Admission to ICU | 2 |
| Invasive abdominal procedures | 3 |
| Chemotherapy/radiation therapy | 4 |
| Colonization at site besides stool (risk per each additional site) | 5 per site |

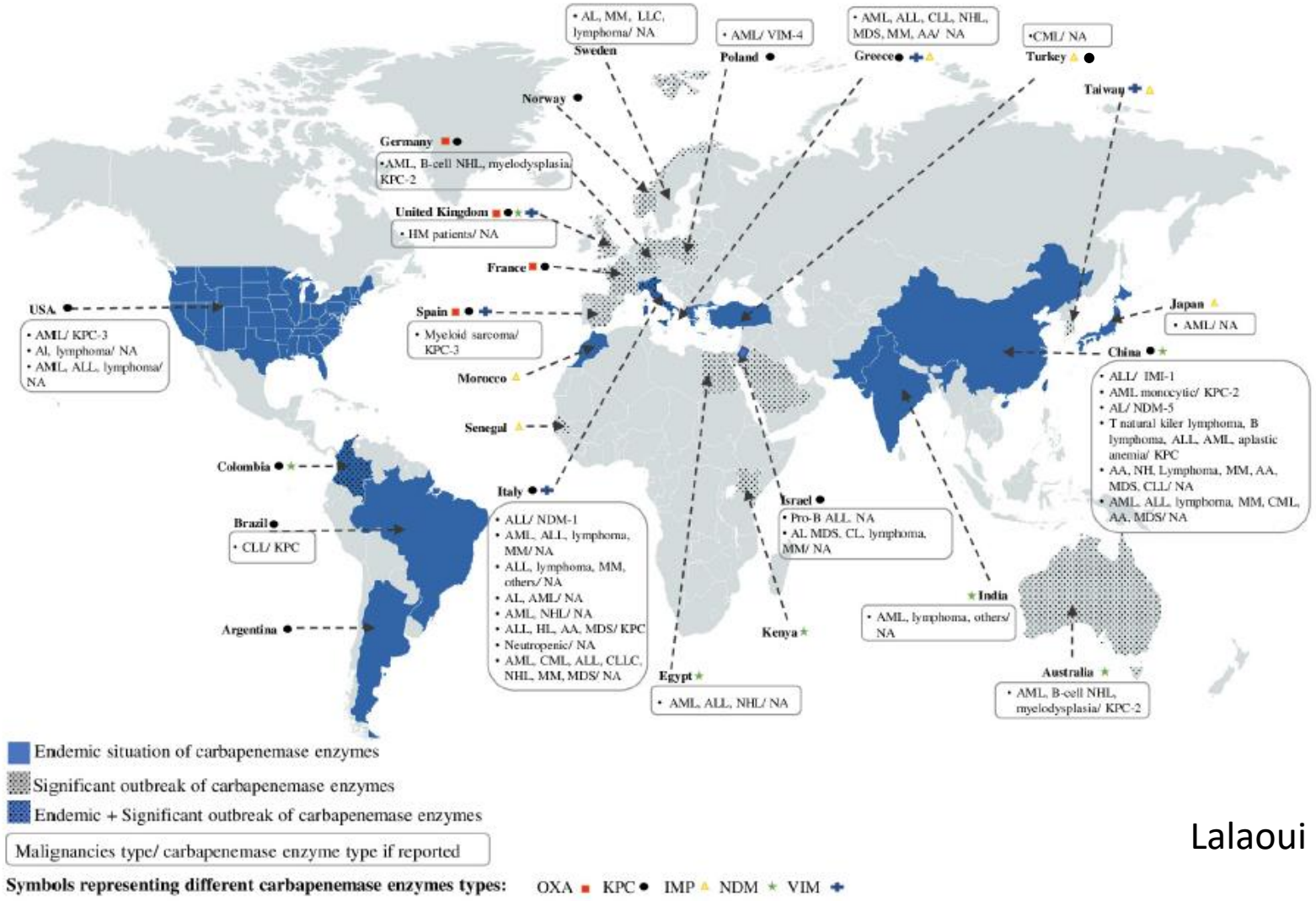



Giannella et al. CMI 2014
Cano et al. CID 2018

# Agenda


MDR risk factors assessment
Resistance mechanisms identification
New therapeutic options
Dosing optimization

# Consider the local epidemiology



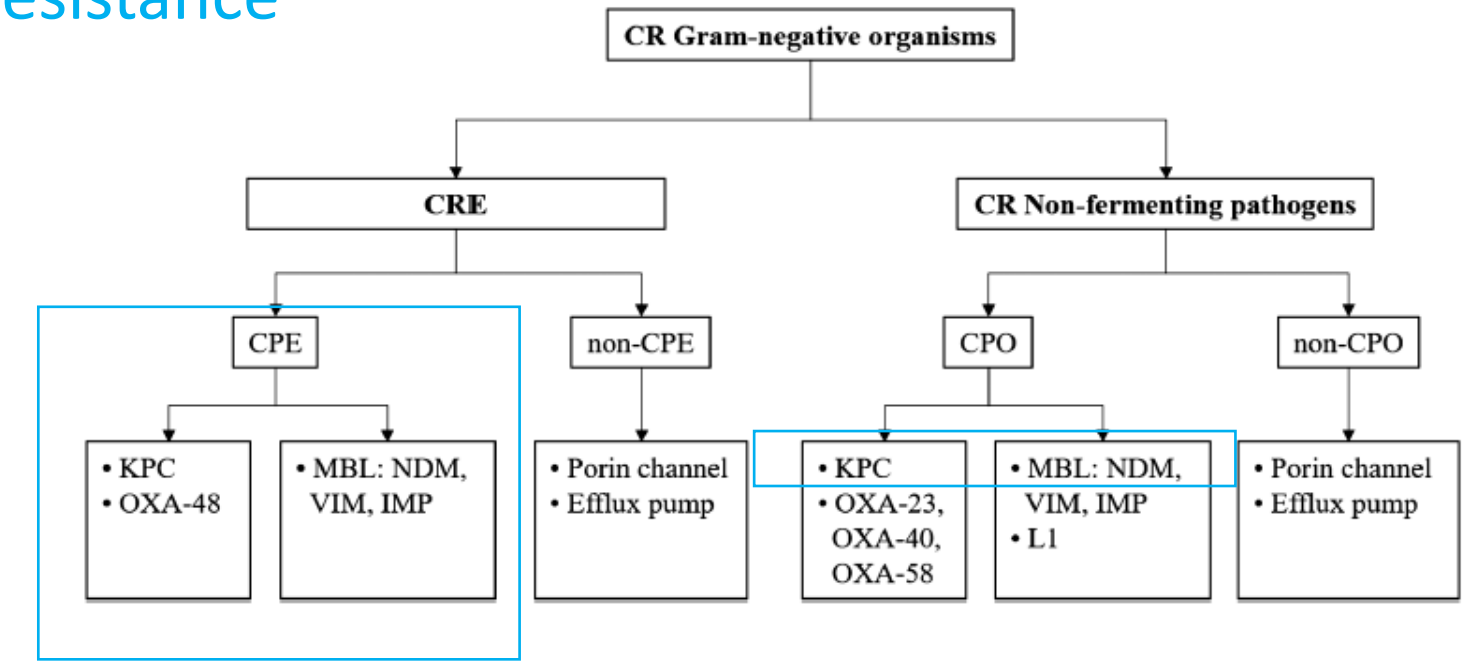

**Worldwide distribution of carbapenemase enzymes in hematological patients.**

OXA-48
KPC
NDM
IMP
VIM

Lalaoui et al. Front Microbiol 2020; 11: 1422.

# Early determination of underlying multidrug resistance mechanisms


1. Rapid identification of the pathogen
2. Rapid identification of resistance mechanisms
   - Genotypic tests
   - Phenotypic tests




Nordmann et al. CID 2019

# The Evolving Role of the Clinical Microbiology Laboratory in Identifying Resistance

BCs' MALDI-TOF direct ID


NG-Test Carba 5

FILMARRAY system (ME,BC, pneumonia, GI)


T2Dx Instrument (Bacteria, candida, AMR)

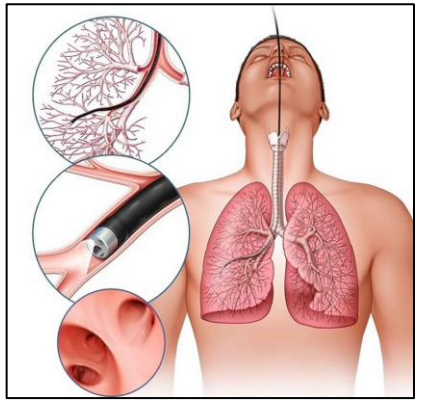
NG-Test CTX-M Multi


Eazyplex MRSAplus

Unyvero System (tissue, fluids, urine)

WGS

# Role of molecular rapid diagnostic testing to inform optimal treatment decisions ?



**Recherche de pathogènes respiratoires par amplification génique**

**Nature du prélèvement: LBA**

| | |
|---|---|
| Chlamydia pneumoniae | Négative |
| Mycoplasma pneumoniae | Négative |
| Legionella pneumophila | Négative |
| Staphylococcus aureus | Négative |
| Recherche de méticillino-résistance (mecA/C et MREJ) | Non applicable |
| Streptococcus pneumoniae | Négative |
| Streptococcus agalactiae | Négative |
| Streptococcus pyogenes | Négative |
| Haemophilus influenzae | Négative |
| Moraxella catarrhalis | Négative |
| Escherichia coli | Négative |
| Klebsiella pneumoniae group | POSITIVE: ADN détecté à 10^6 copies/mL (quantification non équivalente à CFU/mL) |
| Klebsiella oxytoca | Négative |
| Klebsiella aerogenes | Négative |
| Enterobacter cloacae complex | Négative |
| Proteus spp. | Négative |
| Serratia marcescens | Négative |
| Pseudomonas aeruginosa | Négative |
| Acinetobacter calcoaceticus-baumannii complex | Négative |

Rapid identification of the pathogen

Multiplex PCR

Rapid identification of resistance mechanisms

| | |
|---|---|
| Recherche de bétalactamase à spectre étendu (BLSE) de type CTX-M | Négative |
| Recherche de carbapénémase de type IMP | Négative |
| Recherche de carbapénémase de type KPC | Négative |
| Recherche de carbapénémase de type NDM | Négative |
| Recherche de carbapénémase de type OXA48 | POSITIVE |
| Recherche de carbapénémase de type VIM | Négative |
| Adénovirus | Négative |
| Enterovirus/Rhinovirus | Négative |
| MERS CoV | Négative |
| Coronavirus (autres que SARS-CoV1/2) | Négative |
| Virus de la grippe A | Négative |
| Virus de la grippe B | Négative |
| Virus parainfluenza | Négative |
| Metapneumovirus | Négative |
| Virus respiratoire syncitial | Négative |

*FilmArray Pneumonia Panel plus, Biomérieux*

# Diagnosis and Treatment of Bacterial Pneumonia in Critically Ill Patients with COVID-19 Using a Multiplex PCR Assay: A Large Italian Hospital's Five-Month Experience

Brunella Posteraro,[a,b] Venere Cortazzo,[a] Flora Marzia Liotti,[a,c] Giulia Menchinelli,[a,c] Chiara Ippoliti,[a] Giulia De Angelis,[a,c] Marilena La Sorda,[c] Gennaro Capalbo,[d] Joel Vargas,[a] Massimo Antonelli,[a,e] Maurizio Sanguinetti,[a,c] Gennaro De Pascale,[a,e] Teresa Spanu[a,c]

| Microbial target | No. positive by FA-PP and SoC/no. positive by SoC | PPA (%) (95% CI) | No. negative by FA-PP and SoC/no. negative by SoC | NPA (%) (95% CI) | No. positive only by FA-PP for samples from patients who were[b]: | |
|---|---|---|---|---|---|---|
| | | | | | Under antimicrobial therapy | Not under antimicrobial therapy |
| Bacterial species | | | | | | |
| *Acinetobacter calcoaceticus-baumannii* complex | 53/53 | 100 (93.2–100) | 159/159 | 100 (97.7–100) | | |
| *Enterobacter cloacae* complex | 4/4 | 100 (39.8–100) | 206/207 | 99.5 (97.4–100) | 1 | |
| *Escherichia coli* | 15/15 | 100 (78.2–100) | 195/196 | 99.5 (97.2–100) | 1 | |
| *Haemophilus influenzae* | 2/2 | 100 (15.9–100) | 208/209 | 99.5 (97.4–100) | | 1 |
| *Klebsiella aerogenes* | 5/5 | 100 (47.8–100) | 207/207 | 100 (98.2–100) | | |
| *Klebsiella oxytoca* | 2/2 | 100 (15.8–100) | 204/207 | 98.6 (95.9–99.7) | 1 | 2 |
| *Klebsiella pneumoniae* group | 23/23 | 100 (85.2–100) | 189/189 | 100 (98.1–100) | | |
| *Proteus* spp. | 2/2 | 100 (15.9–100) | 210/210 | 100 (98.3–100) | | |
| *Pseudomonas aeruginosa* | 19/19 | 100 (82.4–100) | 185/189 | 97.9 (94.8–99.4) | 4 | |
| *Serratia marcescens* | 6/6 | 100 (54.1–100) | 200/203 | 98.5 (95.8–99.7) | 2 | 1 |
| *Staphylococcus aureus* | 45/45 | 100 (92.1–100) | 155/161 | 96.4 (92.3–98.7) | 5 | 1 |
| *Streptococcus agalactiae* | 0/0 | NC | 208/210 | 99.1 (96.6–99.9) | | 2 |
| *Streptococcus pneumoniae* | 4/4 | 100 (39.8–100) | 206/207 | 99.5 (97.4–100) | | 1 |
| Total species | 180/180 | 100 (98.0–100) | 2,532/2,554 | 99.2 (98.7–99.5) | 14 | 8 |
| Antimicrobial resistance genes | | | | | | |
| CTX-M | 12/12 | 100 (73.5–100) | 200/200 | 100 (98.2–100) | | |
| KPC | 10/10 | 100 (69.2–100) | 202/202 | 100 (98.2–100) | | |
| *mecA*/-C and MREJ[c] | 23/23 | 100 (85.2–100) | 185/187 | 98.9 (96.2–99.9) | 2 | |
| Total genes | 45/45 | 100 (92.1–100) | 587/589 | 99.7 (98.8–100) | 2 | |

150 ICU patients
SARS Cov-2
pneumonia

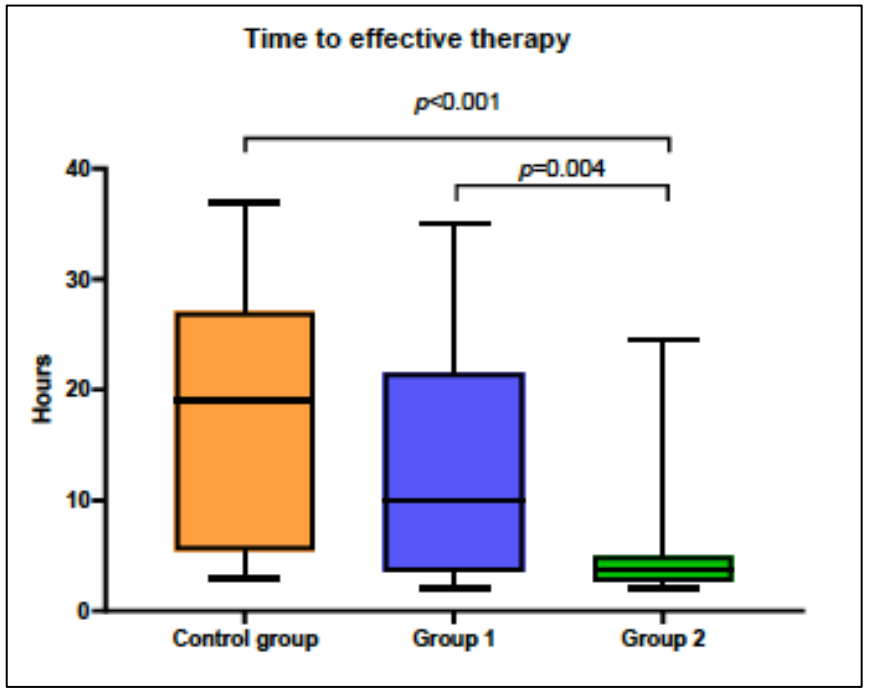
Posteraro et al. Microbiol Spectr 2021

# Rapid PCR-based blood culture reduces time to effective therapy in neutropenic patients

*Article*

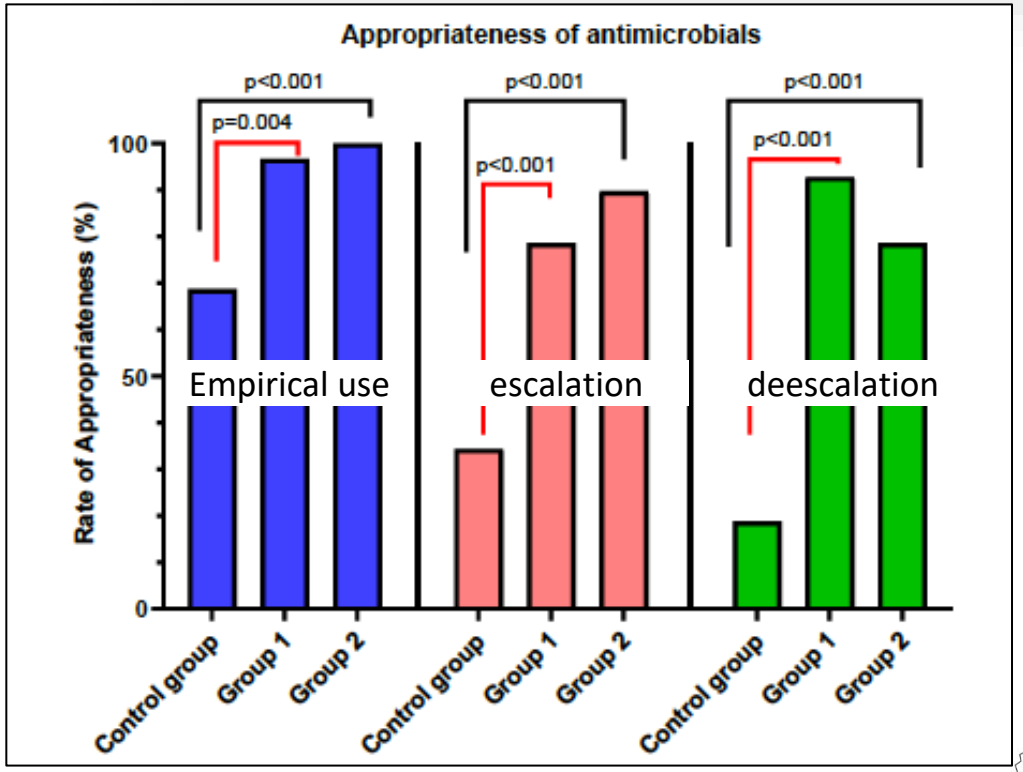
**Impact of Adding a Rapid PCR-Based Blood Culture Identification Panel to the Antimicrobial Stewardship Program of Patients with Febrile Neutropenia in a Peruvian Referral Hospital**

Reduce time to effective therapy




**Group 1: ASP**

**Group 2: mPCR+ ASP**




Perez-Lazo et al. Antibiotics 2023; 12:648.

# Rapid diagnostic tools allow rapid selection of appropriate antibiotics

Retrospective study
5 centres in US

N=854
Bacteremia

Rapid AST vs
conventional technique

**Table 4. Antimicrobial Modifications and Clinical Outcomes**

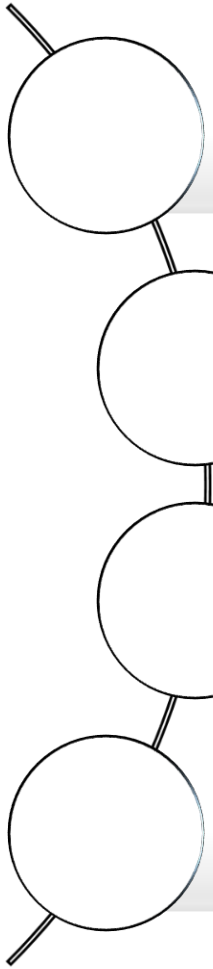
| | All[a] | | | Gram-Negative[b] | | |
|---|---|---|---|---|---|---|
| Endpoint | Pre-AXDX | Post-AXDX | *P* Value | Pre-AXDX | Post-AXDX | *P* Value |
| Antimicrobial modification[c] | | | | | | |
| Time to first antimicrobial modification[d] | 24.2 (7.3–46.2) | 13.9 (5.0–31.1) | **<.0001** | 22.8 (7.0–45.3) | 13.6 (5.8–30.9) | **.01** |
| Time to first gram-positive antimicrobial modification[e] | 30.1 (11.2–52.8) | 18.3 (6.7–41.8) | **.0013** | 28.1 (10.5–51.7) | 18.6 (9.4–42.1) | .11 |
| Time to first gram-negative antimicrobial modification[f] | 34.6 (9.2–53.4) | 18.6 (8.2–36.8) | **<.0001** | 30.2 (7.6–52.8) | 16.7 (8.6–35.2) | **.003** |
| Time to first antimicrobial escalation[g] | 9.5 (3.4–28.9) | 9.0 (3.7–18.4) | .22 | 9.5 (3.7–31.6) | 9.6 (3.9–18.4) | .44 |
| Time to first antimicrobial deescalation[h] | 36.0 (17.1–54.5) | 27.2 (13.5–43.6) | **.0004** | 34.5 (16.6–52.8) | 25.4 (12.0–42.5) | **.003** |
| Time to effective therapy[i] | 13.3 (3.1–35.9) | 6.7 (3.1–16.2) | **.02** | 13.7 (3.3–38.1) | 10.0 (3.6–18.6) | .10 |

Median time to ID: 2.5h vs 24.8h
Median time to AST: 7.9h vs 39.5h

MDR pathogens: 16%
Pathogens identified: ESBL-E, MDR P. aeruginosa, MDR A. baumannii, MRSA, VRE

Balhodi et al. CID 2022; 75:269-77.

# Agenda



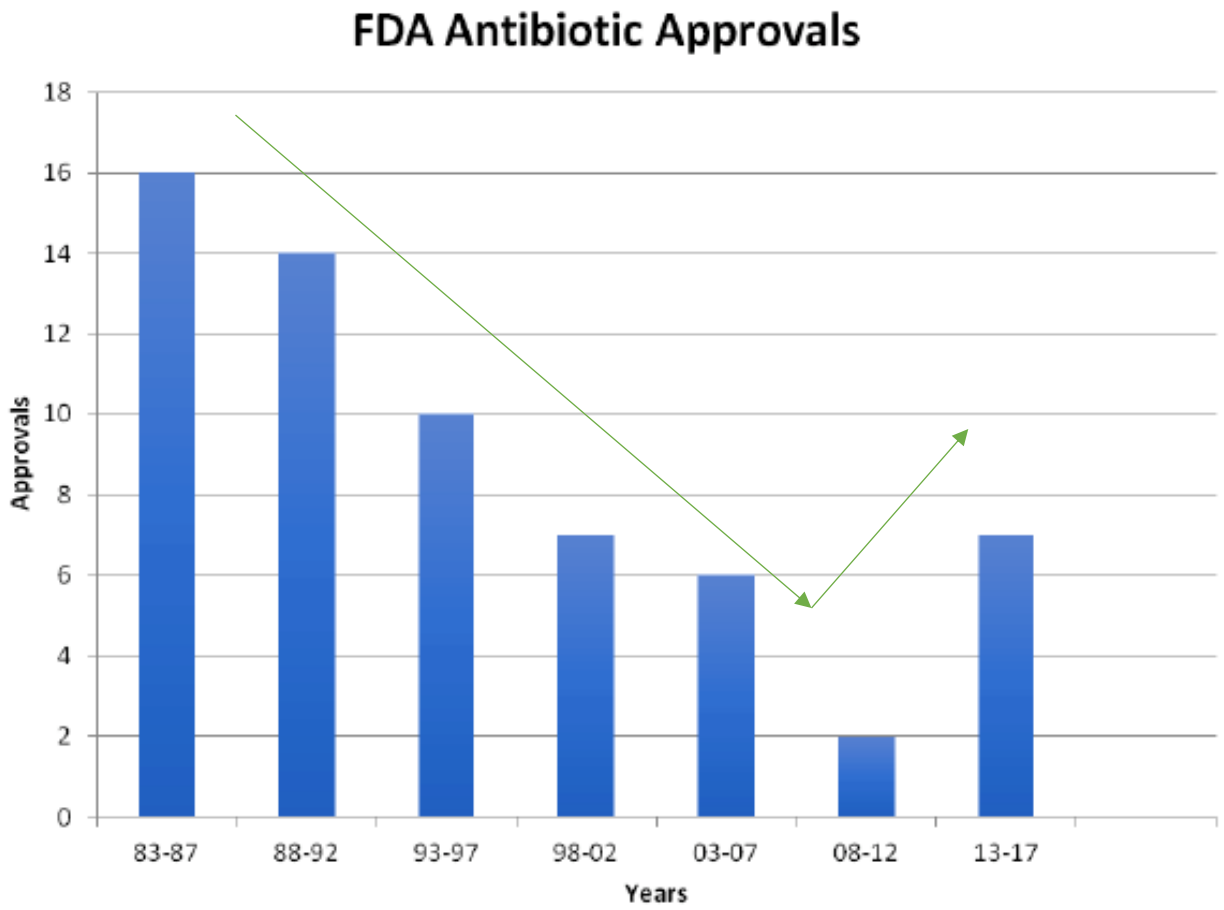
MDR risk factors assessment

Resistance mechanisms identification

New therapeutic options

Dosing optimization

# New antimicrobial drugs have been developped to tackle different mechanisms of resistance




1. synthesis of new β-lactam compounds refractory to hydrolysis by these enzymes (eg, cefiderocol)
2. Development of new beta-lactam inhibitors

Talbot CID 2019; doi 10.1093/cid/ciz089

# New treatment options based on resistance mechanisms

| | *Enterobacterales* | | | | | | *P. aeruginosa* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Resistance mechanisms** | **AmpC** | **ESBL** | **CRE Non-CPE** | **KPC** | **NDM VIM** | **OXA-48** | **AmpC** | **Efflux** | **AmpC Efflux OprD-** | **NDM VIM** | **CRAB** | ***Steno*** | ***E. faec*** | **MRSA** | ***Anas*** |
| **Ceftobiprole** | | | | | | | | | | | | | | | |
| **Ceftazidime-avibactam** | | | | | | | | | | | | | | | |
| **Ceftolozane-tazobactam** | | | | | | | | | | | | | | | |
| **Imipenem-relebactam** | | | | | | | | | | | | | | | |
| **Meropenem-vaborbactam** | | | | | | | | | | | | | | | |
| **Aztreonam-avibactam** | | | | | | | | | | | | | | | |
| **Cefiderocol** | | | | | | | | | | | ⚠ | | | | |

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

IDSA Infectious Diseases Society of America

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

# Carbapenem Resistant ENTEROBACTERALES

| | IDSA | | ESCMID |
|---|---|---|---|
| | 1st line | Alternative | |
| KPC | Ceftazidime avibactam<br>Meropenem vaborbactam<br>Imipenem relebactam | Cefiderocol | Ceftazidime avibactam<br>Meropenem vaborbactam<br>Imipenem relebactam |
| Metallo β lactamases | Aztreonam avibactam | Cefiderocol | Cefiderocol<br>Aztreonam avibactam |
| OXA 48 like carbapenemase | Ceftazidime avibactam | Cefiderocol | Ceftazidime avibactam |

*CID 2021; 72:169-83. Updated 7th March 2022*
*CMI 2021; 10.1016/j.cmi.2021.11.025*

# DTR *Pseudomonas aeruginosa*

IDSA
Infectious Diseases Society of America

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

| | First line | 2nd line |
|---|---|---|
| cUTI | Ceftolozane-tazobactam<br>Ceftazidime-avibactam<br>Imipenem-relebactam<br>Cefiderocol | Aminoglycoside |
| Infections outside cUTI | Ceftolozane-tazobactam<br>Ceftazidime-avibactam<br>Imipenem-relebactam | Cefiderocol |

ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

ELSEVIER

CMI CLINICAL MICROBIOLOGY AND INFECTION

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

| | |
|---|---|
| Severe infections | Ceftolozane-tazobactam |

*Tamma et al. CID* 2022;75(2):187–212.
*Paul et al. CMI 2022; 28: 521-547.*

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

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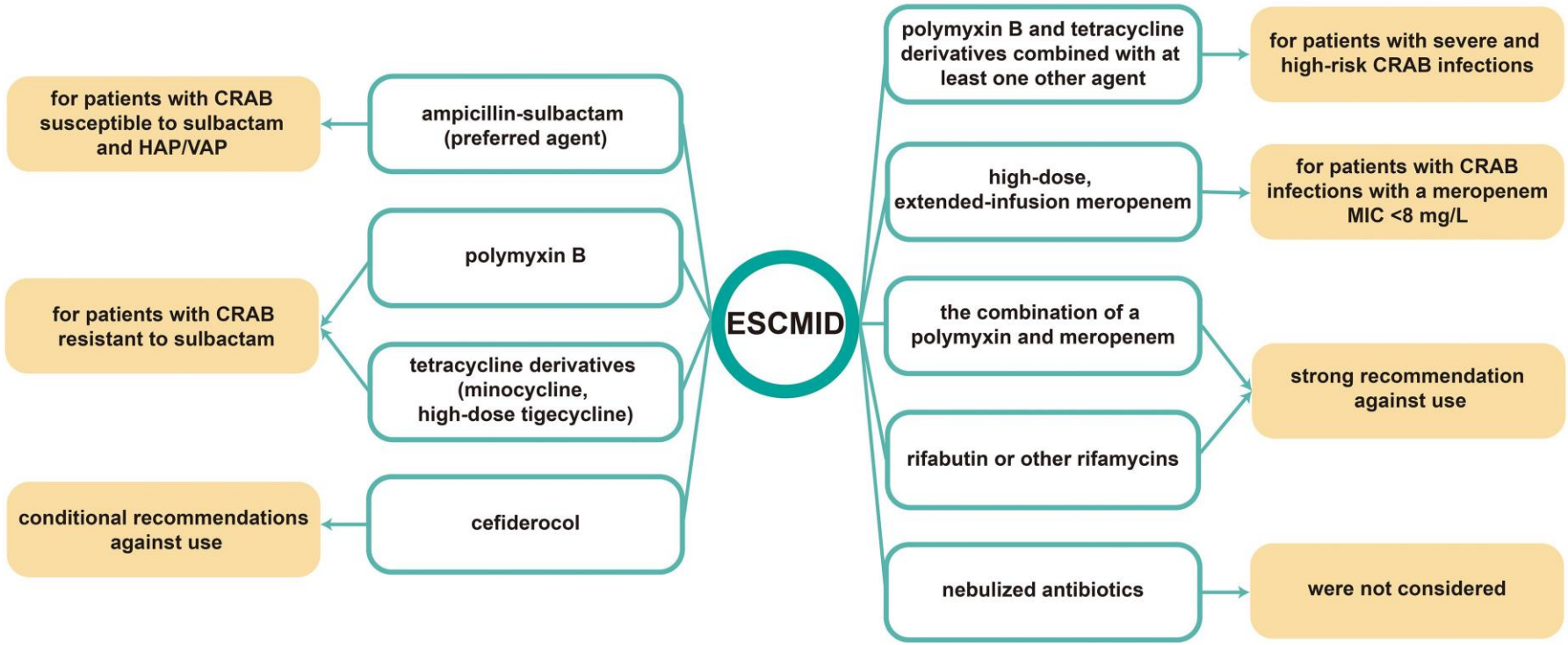
ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

# Carbapenem Resistant Acinetobacter baumannii



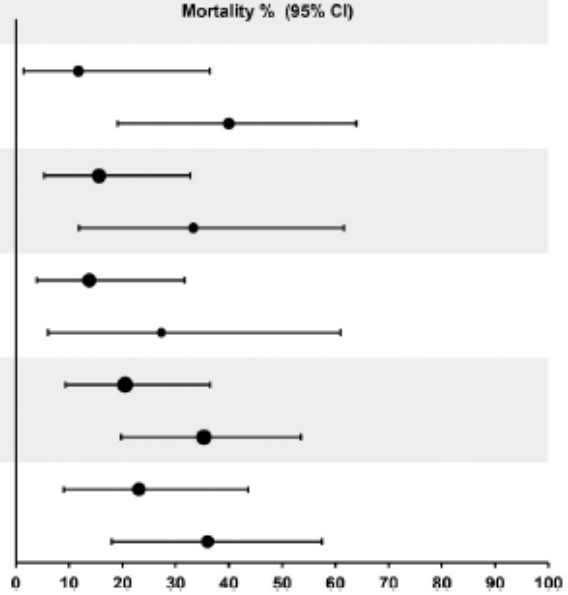

*CMI 2021; 10.1016/j.cmi.2021.11.025*

# All-cause mortality rates in adults with carbapenem-resistant Gram-negative bacterial infections: a comprehensive review of pathogen-focused, prospective, randomized, interventional clinical studies

Thomas P. Lodise[a], Matteo Bassetti[b], Ricard Ferrer[c], Thierry Naas[d], Yoshihito Niki[e], David L. Paterson[f], Markus Zeitlinger[g] and Roger Echols[h]

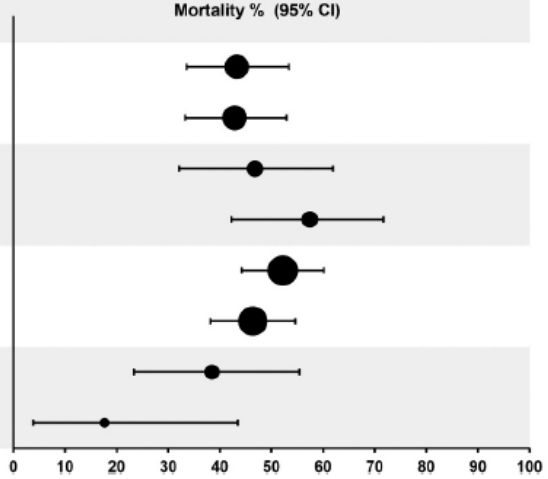
## Carbapenem-resistant Enterobacterales

| Clinical Trial | Antibiotic | Day 28 ACM % (n/N) |
|---|---|---|
| CARE (NCT01970371)[29] | plazomicin | 11.8% (2/17) |
| | colistin | 40.0% (8/20) |
| TANGO II (NCT02168946)[30] | meropenem/vaborbactam | 15.6% (5/32) |
| | BAT | 33.3% (5/15) |
| CREDIBLE-CR (NCT02714595)[31] | cefiderocol | 13.8% (4/29) |
| | BAT | 27.3% (3/11) |
| AIDA (NCT01732250)[32] | colistin + meropenem | 20.5% (8/39) |
| | colistin | 35.3% (12/34) |
| Ji et al.[35] | cefepime + amoxicillin/clavulanic acid | 23.1% (6/26) |
| | tigecycline-based antibiotic therapy | 36.0% (9/25) |




## Carbapenem-resistant Acinetobacter baumannii

| Clinical Trial | Antibiotic | Day 28 ACM % (n/N) |
|---|---|---|
| Durante-Mangoni (NCT01577862)[33] | colistin + rifampicin | 43.3% (45/104) |
| | colistin | 42.9% (45/105) |
| Sirijatuphat (NCT01297894)[34] | colistin + fosfomycin | 46.8% (22/47) |
| | colistin | 57.4% (27/47) |
| AIDA (NCT01732250)[32] | colistin + meropenem | 52.2% (84/161) |
| | colistin | 46.4% (70/151) |
| CREDIBLE-CR* (NCT02714595)[31] | cefiderocol | 38.5% (15/39) |
| | BAT | 17.7% (3/17) |




Lodise et al. Exp Rev Infect Ther 2022

# Available data of ceftazidime-avibactam in SOT recipients

Efficacy of ceftazidime-avibactam in the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections: Focus on solid organ transplantation recipients

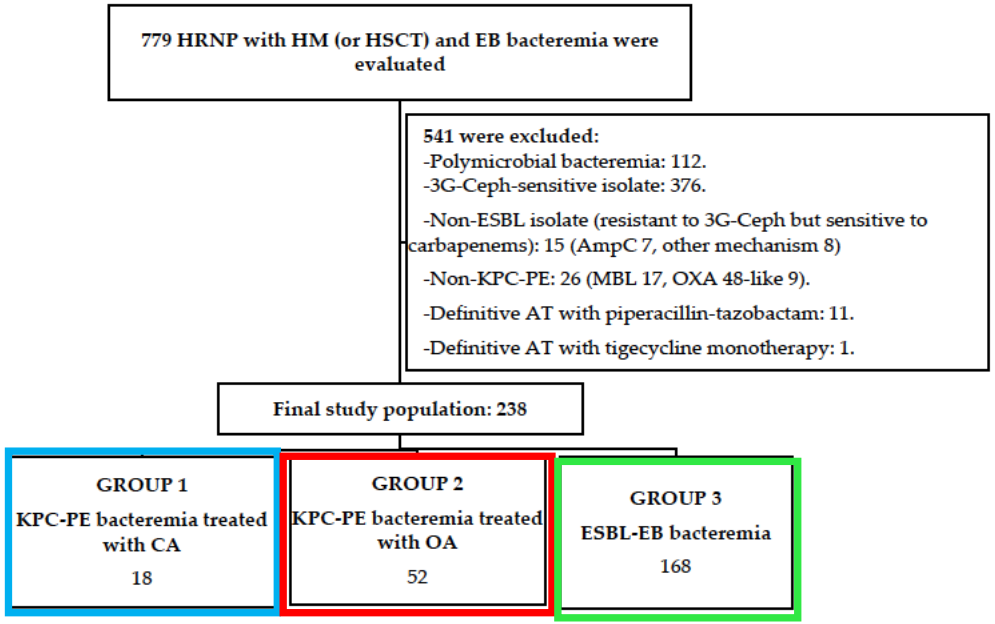
Juan Hu[a,#], Lei Zha[b,#], Yong-Wei Yu[a], Qun Su[a], Xue-Ling Fang[a], Jin-Ru Ji[c], Ping Shen[c], Yun-Bo Chen[c], Xia Zheng[a,*], Yong-Hong Xiao[c,**]

| | Patients included in analysis | | Adjusted ORs (95% CI) | *P* |
|---|---|---|---|---|
| | CAZ-AVI | Other regimens | | |
| **Solid organ transplantation recipients** | | | | |
| 30-day mortality n (%) | 7 (23.3) | 12 (60.0) | 0.19 (0.05,0.69) | 0.014 |
| Clinical cure n (%) | 27 (90.0) | 8 (40.0) | 20.2 (4.10,26.7) | < 0.001 |
| 90-day mortality n (%) | 10 (35.7) | 13 (86.7) | 0.06 (0.01,0.32) | 0.003 |
| Length of ICU stay (median [IQR]) | 43 (23, 71) | 34.5 (22.5, 66.25) | 1.25 (-19.6,22.1) | 0.905 |
| LOS (median [IQR]) | 63 (48, 99.5) | 45.5 (33.5, 77.25) | 22.1 (-9.30,53,5) | 0.163 |
| **Microbiological clearance*** | | | | |
| Respiratory infection n (%) | 9 (56.2) | 0 (0.0) | NA | 0.012 |
| Intra-abdominal infection n (%) | 6 (54.5) | 0 (0.0) | NA | 0.017 |
| Bacteraemia n (%) | 11 (91.7) | 5 (38.5) | NA | 0.019 |
| Polymicrobial infection | | | 1.22 (0.36-4.06) | 0.74 |

Other regimens:
Polymyxin B combination therapy (45%), Tigecyclin + Polymyxin B (30%)

Hu et al. IJAA 2024; 63: 107152.

# Available data of ceftazidime-avibactam in neutropenic patients

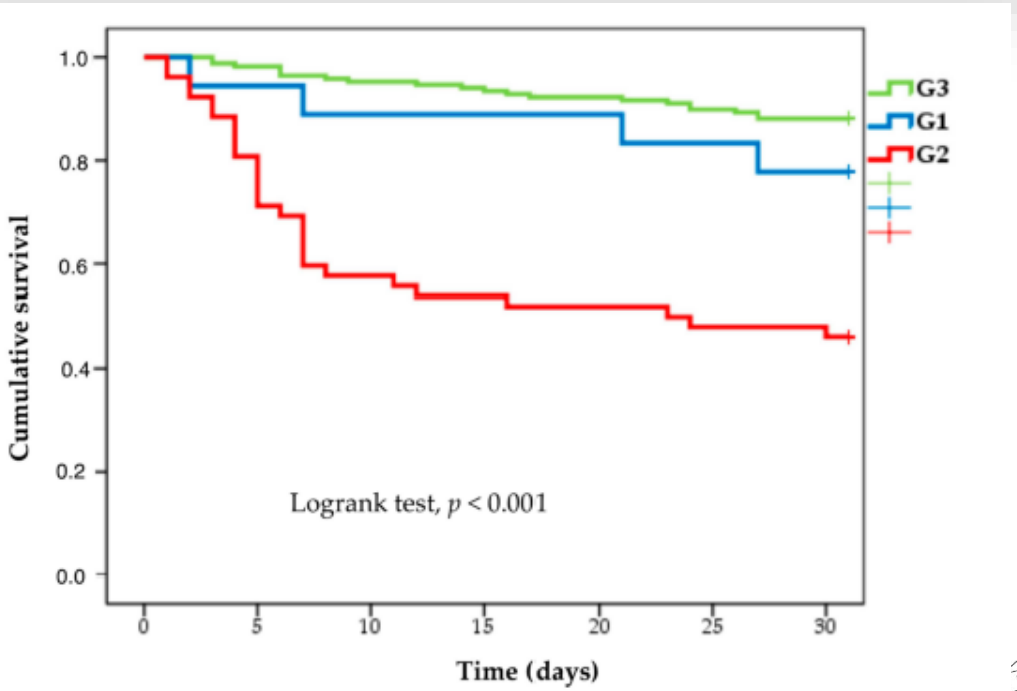



Other antibiotics: carbapenem, tigecyclin, colistin, amikacin

*Article*

**Ceftazidime–Avibactam Improves Outcomes in High-Risk Neutropenic Patients with *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacterales Bacteremia**

Fabián Herrera [1,*], Diego Torres [1], Ana Laborde [2], Rosana Jordán [3], Noelia Mañez [4], Lorena Berruezo [5], Sandra Lambert [6], Nadia Suchowiercha [7], Patricia Costantini [8], Andrea Nenna [9], María Laura Pereyra [10], José Benso [11], María Luz González Ibañez [2], María José Eusebio [3], Laura Barcán [4], Nadia Baldoni [5], Lucas Tula [6], Inés Roccia Rossi [7], Martín Luck [8], Vanesa Soto [9], Verónica Fernández [11] and Alberto Ángel Carena [1,†] on behalf of the Argentine Group for the Study of Bacteremia in Cancer and Stem Cell Transplant (ROCAS) Study




Herrera et al. Microorganisms 2024; 12,95.

# Available data of ceftolozane/tazobactam in neutropenic patients

## Real-Life Use of Ceftolozane/Tazobactam for the Treatment of Bloodstream Infection Due to *Pseudomonas aeruginosa* in Neutropenic Hematologic Patients: a Matched Control Study (ZENITH Study)

Alba Bergas,[a] Adaia Albasanz-Puig,[a,w] Ana Fernández-Cruz,[b,c] Marina Machado,[b] Andrés Novo,[d] David van Duin,[e] Carolina Garcia-Vidal,[f] Morgan Hakki,[g] Isabel Ruiz-Camps,[h] José Luis del Pozo,[i] Chiara Oltolini,[j] Catherine DeVoe,[k] Lubos Drgona,[l] Oriol Gasch,[m] Malgorzata Mikulska,[n] Pilar Martín-Dávila,[o] Maddalena Peghin,[p] Lourdes Vázquez,[q] Júlia Laporte-Amargós,[a] Xavier Durà-Miralles,[a] Natàlia Pallarès,[r] Eva González-Barca,[s] Ana Álvarez-Uría,[b] Pedro Puerta-Alcalde,[f] Juan Aguilar-Company,[h,t] Francisco Carmona-Torre,[i] Teresa Daniela Clerici,[u] Sarah B. Doernberg,[k] Lucía Petrikova,[l] Silvia Capilla,[v] Laura Magnasco,[n] Jesús Fortún,[o] Nadia Castaldo,[p] Jordi Carratalà,[a,w] Carlota Gudiol[a,w,x]

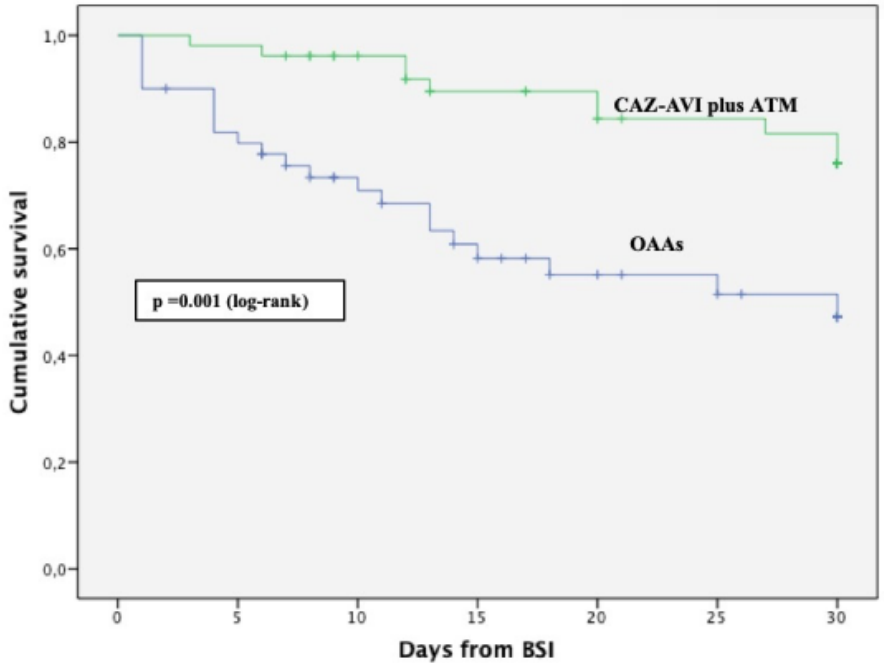
**TABLE 6** Univariate and multivariate analysis of factors associated with 30-day case fatality rate

| Characteristics[a] | Dead *n* = 53 (%) | Alive *n* = 98 (%) | *P* value | Adjusted OR (95% CI)[a] | *P* value[b] |
|---|---|---|---|---|---|
| Female gender | 19 (40.4) | 28 (59.6) | 0.96 | 0.97 (0.38–2.45) | 0.958 |
| Age (yrs) (median, IQR) | 53 (18–90) | 54.5 (18–79) | 0.79 | 0.98 (0.95–1.00) | 0.133 |
| Pneumonia | 20 (58.8) | 14 (41.2) | 0.014 | 5.45 (1.84–16.13) | **0.002** |
| Therapy with ceftolozane-tazobactam | 10 (22.7) | 34 (77.3) | 0.004 | 0.19 (0.07–0.55) | **0.002** |
| Persistent bloodstream infection | 14 (63.6) | 8 (36.4) | 0.009 | 5.44 (1.61–18.31) | **0.006** |
| Infection due to XDR PA | 23 (52.3) | 21 (47.7) | 0.045 | 1.76 (0.68–4.54) | 0.240 |
| Profound neutropenia (<100 cells/mm$^3$) | 41 (48.8) | 43 (51.2) | 0.009 | 5.49 (1.96–0.15.36) | **0.001** |

Bergas et al. Microbiol Spectr 2022; 10: e0229221.

# Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

Marco Falcone,[1] George L. Daikos,[2] Giusy Tiseo,[1] Dimitrios Bassoulis,[2] Cesira Giordano,[3] Valentina Galfo,[1] Alessandro Leonildi,[3] Enrico Tagliaferri,[1] Simona Barnini,[3] Spartaco Sani,[4] Alessio Farcomeni,[5] Lorenzo Ghiadoni,[6] and Francesco Menichetti[1]




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CAZ-AVI *plus* ATM | 52 | 51 | 50 | 47 | 45 | 45 | 42 |
| OAAs | 50 | 40 | 36 | 31 | 30 | 29 | 28 |

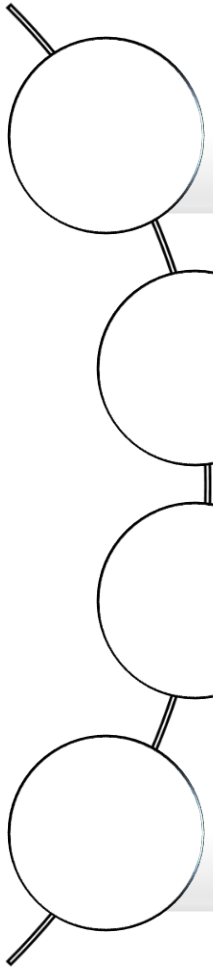
- 102 patients with BSI, 30% immunocompromised
- 80% NDM-producing GNB, 20% VIM-producing GNB
- CAZ-AVI + AZT compared to other antibiotics (COL, FOS, TGC, AZT+FOS)

**Table 5. Propensity Score–Adjusted Analysis for Secondary Study Endpoints**

| CAZ-AVI + ATM | HR (95% CI) | sHR[a] (95% CI) | *P* Value |
|---|---|---|---|
| Clinical failure at day 14 | 0.30 (.14–.65) | … | .002 |
| Length of hospital stay from BSI onset[a] | … | 0.49 (.30–.82) | .007 |

Falcone et al. CID 2021; 72: 1871-8.

# Agenda

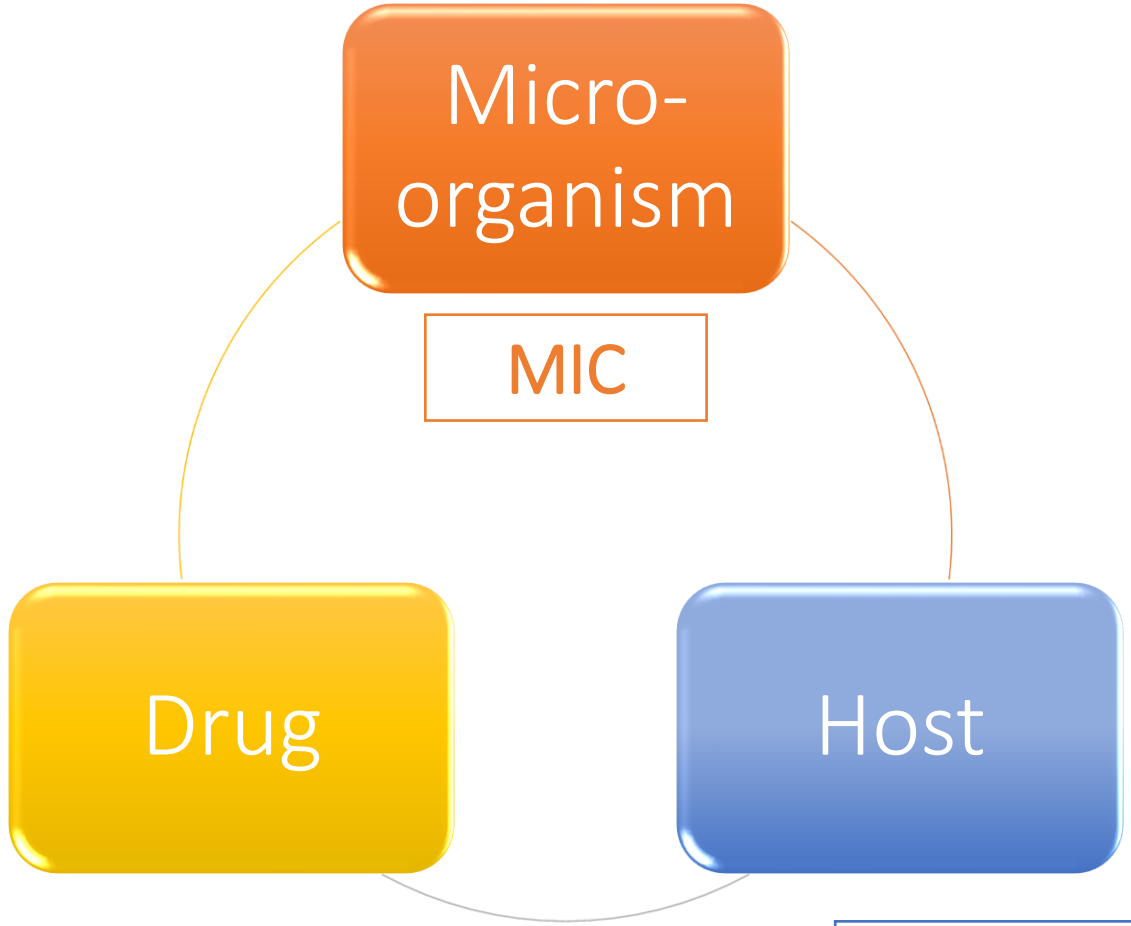


MDR risk factors assessment

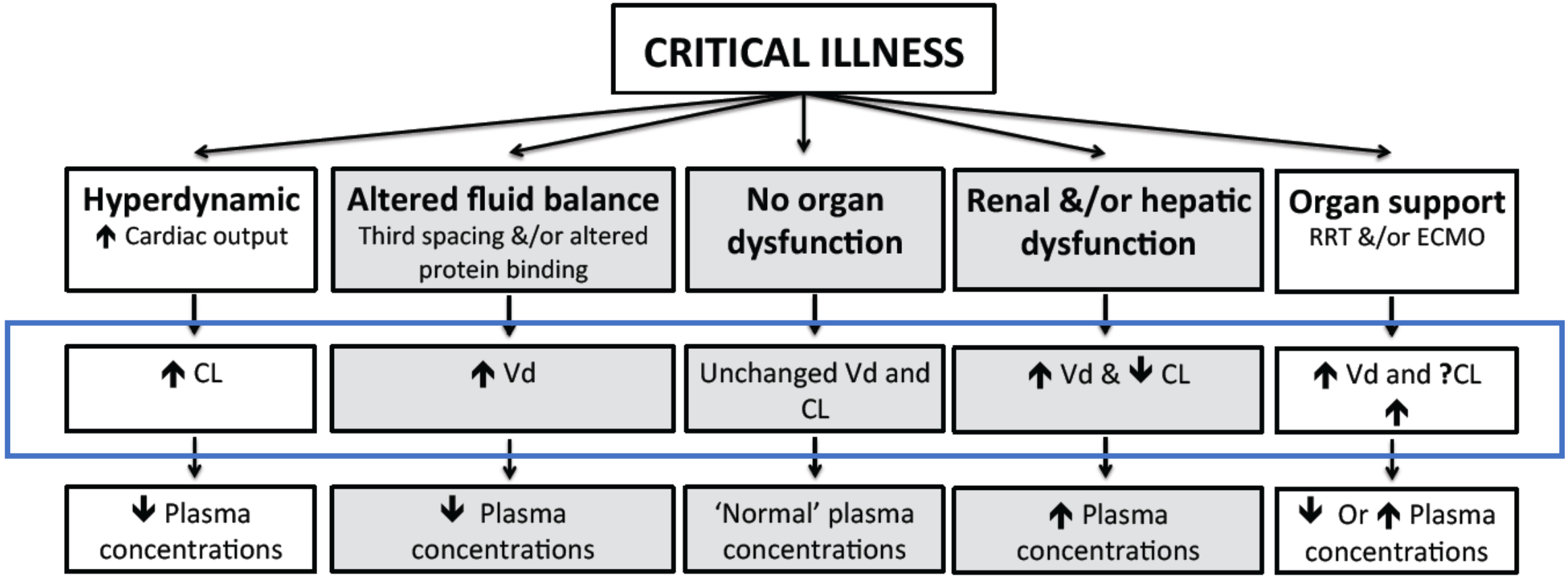
Resistance mechanisms identification

New therapeutic options

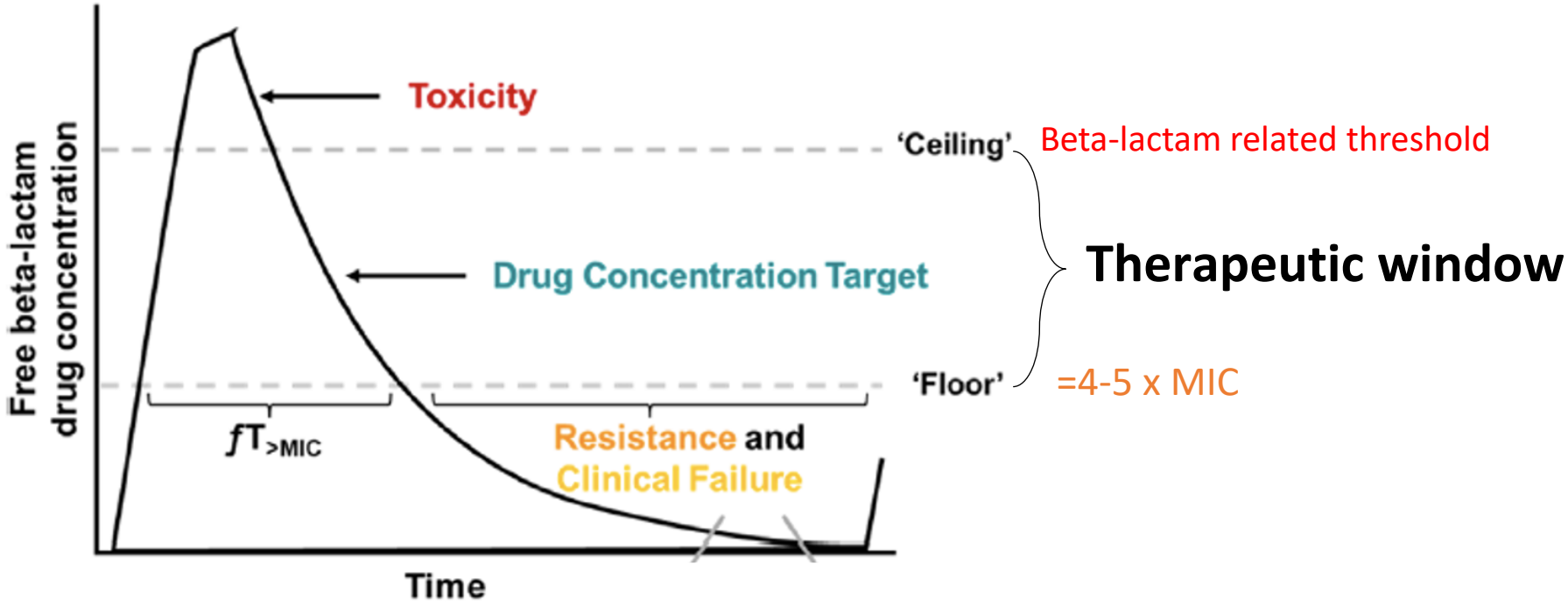
Dosing optimization


Micro-organism
MIC
Drug
Host
Dosing
Mode of administration
Tissue penetration
Immuno compromised

# Pathophysiological alterations in sepsis impact antimicrobial pharmacokinetics



# β –lactams PK/PD target: the challenge of high MICs

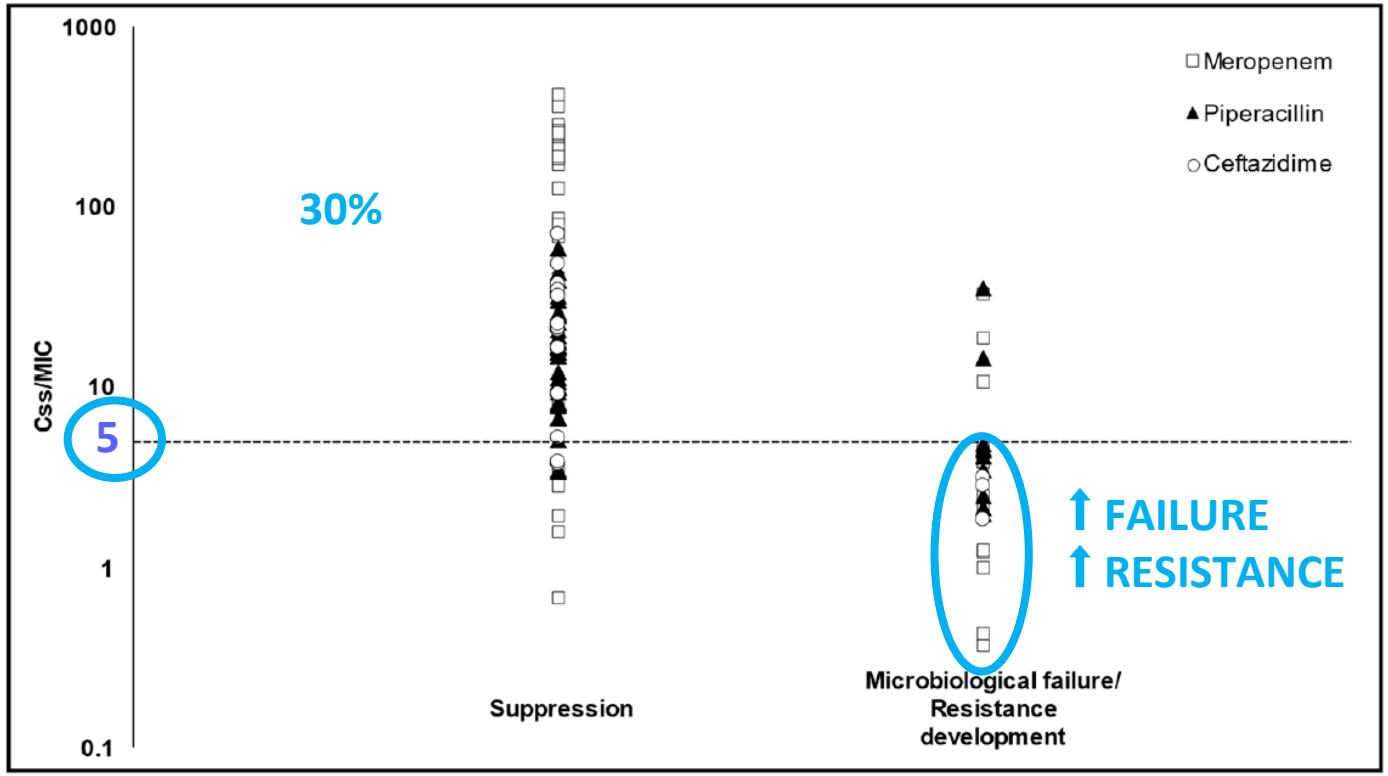



**Therapeutic drug monitoring**

Crit Care 2019; 23(1):104.
Bergen et al. J Antimicrob Chemother 2016; 71:2509-20.

# Css/MIC<5:
# ↑ risk of treatment failure and emergence of resistance

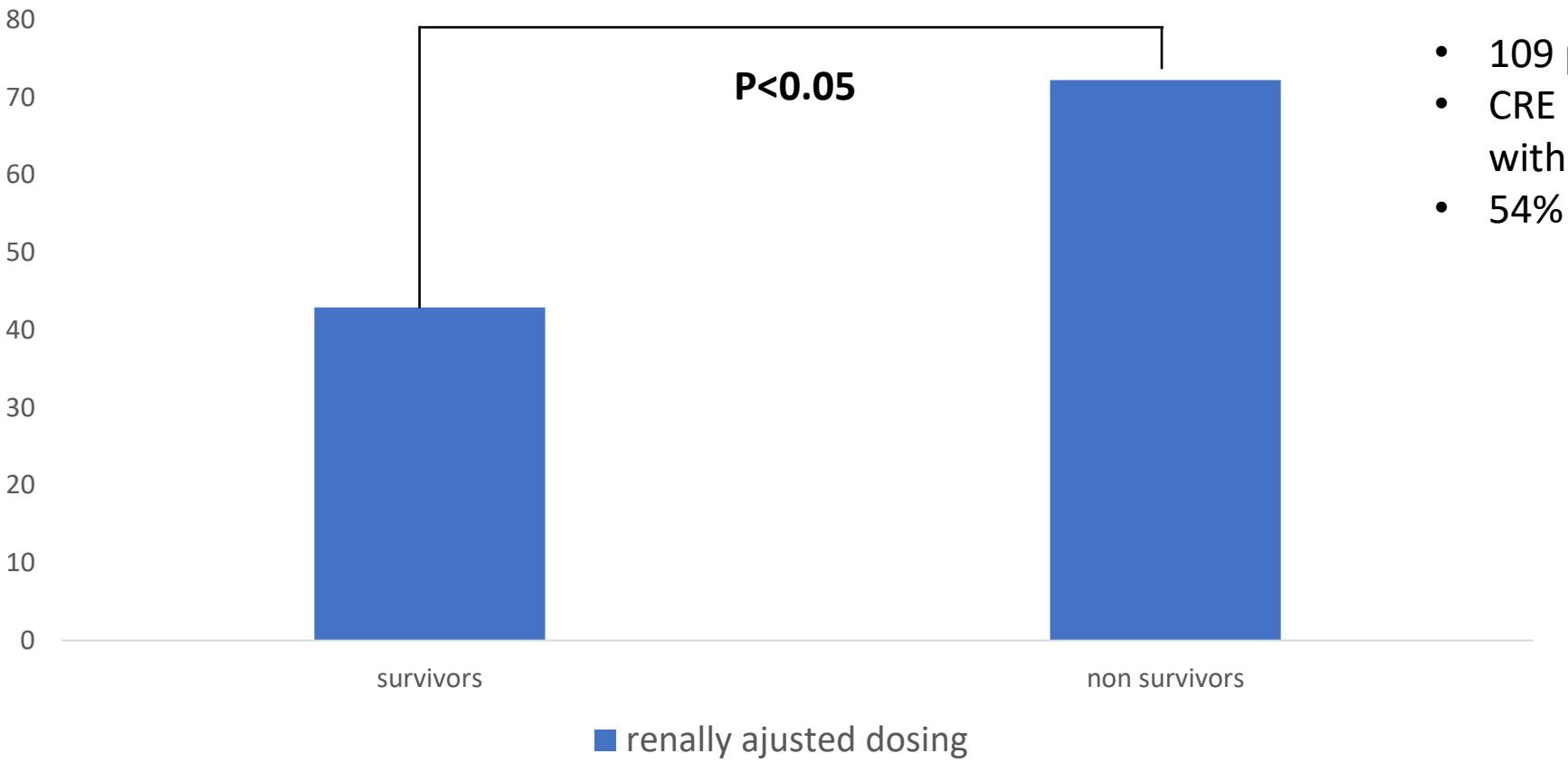
- 116 ICU patients
- GNB infections (50% VAP)
- Beta-lactam concentrations:
  - -Meropenem
  - -Piperacillin
  - -Ceftazidime




**Microbiological failure and/or emergence of resistance**
**x 35**
**if $C_{ss}$ < 5 X CMI**

Gatti et al. Antibiotics 2021; 10:1311.

# Risk of underdosing in renally impaired patients with DTR GNB

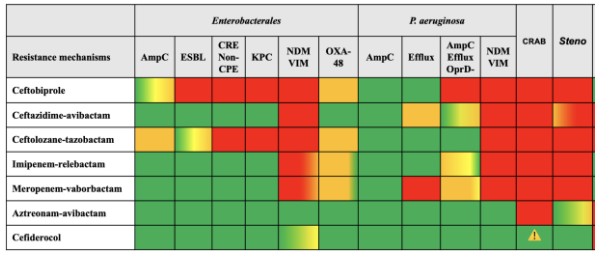



- 109 patients
- CRE infections treated with cefta/avi
- 54% ICU patients

Joregensen et al. Infect Dis Ther 2020; 9:291-304

# Personalized approach for choosing antibiotics in MDR infections
# Take home messages

OXA-48
MBL
KPC
Non CPE



| | *Enterobacterales* | | | | | | *P. aeruginosa* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Resistance mechanisms | AmpC | ESBL | CRE Non-CPE | KPC | NDM VIM | OXA-48 | AmpC | Efflux | AmpC Efflux OprD- | NDM VIM | CRAB | *Steno* |
| Ceftobiprole | | | | | | | | | | | | |
| Ceftazidime-avibactam | | | | | | | | | | | | |
| Ceftolozane-tazobactam | | | | | | | | | | | | |
| Imipenem-relebactam | | | | | | | | | | | | |
| Meropenem-vaborbactam | | | | | | | | | | | | |
| Aztreonam-avibactam | | | | | | | | | | | | |
| Cefiderocol | | | | | | | | | | | | |

Risk factors score
Prior colonization

**Identify patients at high risk of MDR infections** → **Rapid ID of pathogens and resistance mechanisms** → **Selection of appropriate ABx based on resistance mechanisms** → **Dosing optimization**

Genotypic tests
Phenotypic tests





Therapeutic drug monitoring
Prolonged/continuous infusion


THANK YOU
Дякую
Akeva
Köszönöm
Tak
Aitäh
ďakujem
Gracias
Welálin
Cảm ơn anh
Rahmat
Спасибі
Trugéré
Ahéhee
Tualumba
Дзякуй
Takk
Mahalo
Ngiyabonga
Na gode
Falemínderit
Grazzi
Dhanyawaadh
Kiitos
Mulţumesc
Asante
Hvala
Merci
Matur nuwun
Благодаря
Daalụ
Diolch
Grazias
Grazie
Þakka þér
Paldies
Manana
Dank je
Danke
Ačiū
გმადლობ
תודה
Спасибо
Хвала
谢谢
متشكرم
Zikomo
Dankon
Gràcies
Баярлалаа
Misaotra
Tapadh leat
Miigwetch
Dankie
Terima kasih
Tack
Dèkuji
Благодарам
Salamat
Sağ ol
Dziękuję
Grazas
Barka
ευχαριστώ