CNR RÉSISTANCE AUX ANTIBIOTIQUES

JN 23es Journées Nationales d'Infectiologie

Bordeaux et la région Aquitaine
Palais des Congrès
du mercredi 15 juin 2022
au vendredi 17 juin 2022

## SYMPOSIUM CEFIDEROCOL

# Intérêt du céfidérocol sur les *Acinetobacter*, *Achromobacter* et *Stenotrophomonas* multirésistants

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# Declaration of interest

Shionogi

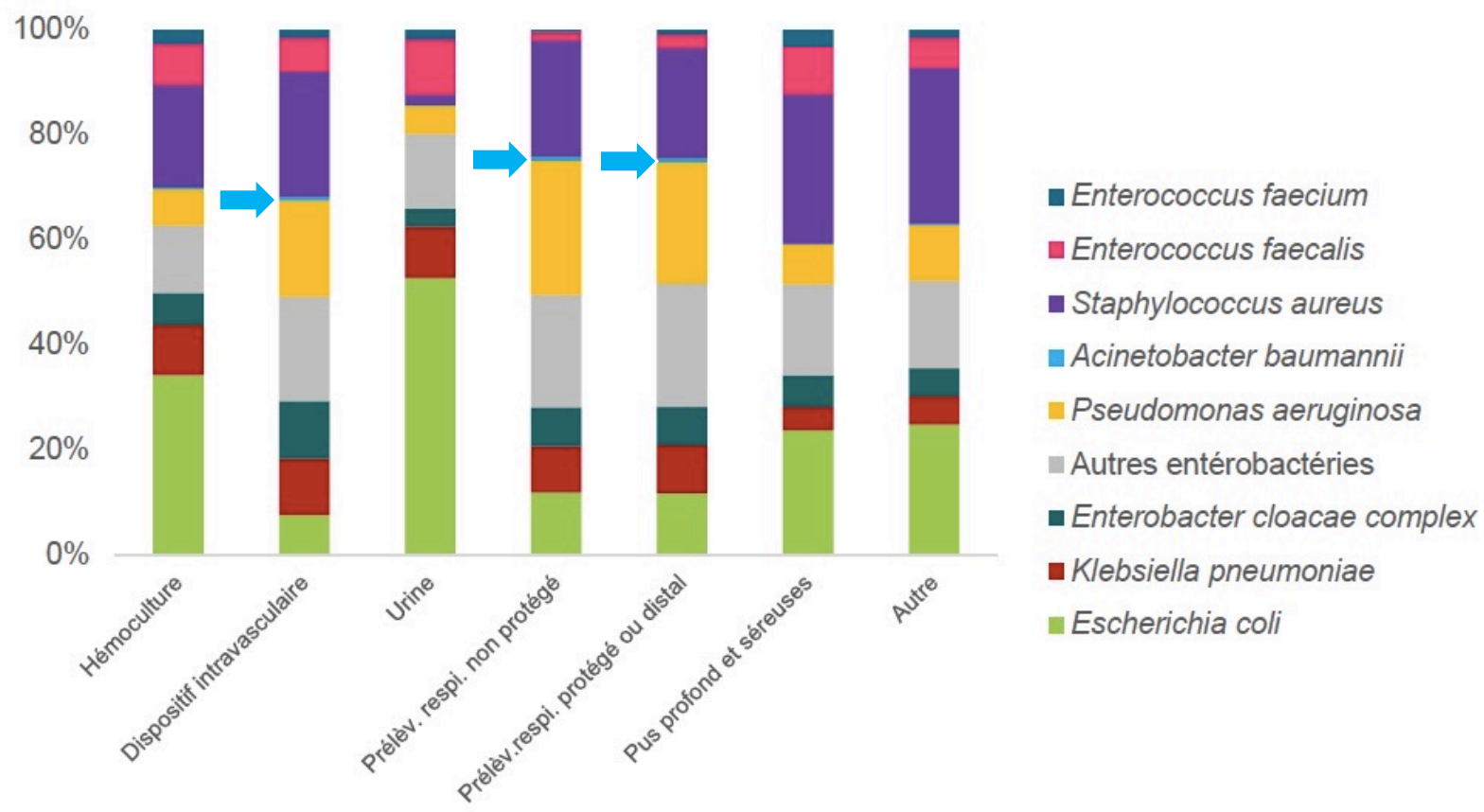
Pfizer

MSD

Specific Dx

# Nosocomial bacterial pathogens in France

(SPARES 2020)






https://www.santepubliquefrance.fr

# Causes of ICU-acquired pneumonia in Europe: ECDC 2017

| Microorganism | Belgium (n=82) | Estonia (n=11) | France (n= 6 216) | Germany (n= 5 069) | Hungary (n=37) | Italy (n=811) | Lithuania (n=23) | Luxembourg (n=25) | Portugal (n=442) | Romania (n=420) | Slovakia (n=30) | Spain (n=546) | United Kingdom (n=111) | Total (n=14 033) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Pseudomonas aeruginosa* | 17.1 | 9.1 | 23.1 | 16.1 | 32.4 | 19.4 | 14.6 | 20.0 | 29.2 | 23.3 | 33.3 | 24 | 7.2 | 19.9 |
| *Staphylococcus aureus* | 12.2 | 0.0 | 18.0 | 19.8 | 8.1 | 20.1 | 13.3 | 24.0 | 13.8 | 8.6 | 3.3 | 18.9 | 30.6 | 18.5 |
| *Klebsiella* spp. | 13.4 | 27.3 | 11.5 | 18.2 | 16.2 | 17.6 | 27 | 20.0 | 19.7 | 21.9 | 36.7 | 13.2 | 9.0 | 15.2 |
| *Escherichia coli* | 20.7 | 18.2 | 12.2 | 16.3 | 13.5 | 9.7 | 6.9 | 16.0 | 5.2 | 6.4 | 3.3 | 11.0 | 18.9 | 13.5 |
| *Enterobacter* spp. | 3.7 | 45.5 | 13.0 | 9.4 | 5.4 | 6.5 | 5.6 | 4.0 | 9.7 | 0.2 | 0.0 | 10.1 | 5.4 | 10.4 |
| *Serratia* spp. | 9.8 | 0.0 | 4.7 | 7.1 | 2.7 | 3.3 | 2.1 | 4.0 | 5.7 | 0.0 | 0.0 | 6.8 | 4.5 | 5.3 |
| *Haemophilus* spp. | 9.8 | 0.0 | 5.6 | 3.4 | 2.7 | 3.3 | 3.9 | 4.0 | 6.3 | 0.0 | 0.0 | 4.2 | 20.7 | 4.5 |
| *Stenotrophomonas maltophilia* | 8.5 | 0.0 | 5.6 | 3.9 | 0.0 | 3.1 | 1.3 | 4.0 | 3.4 | 0.0 | 0.0 | 5.7 | 0.9 | 4.5 |
| *Acinetobacter* spp. | 0.0 | 0.0 | 2.7 | 1.5 | 16.2 | 14.7 | 16.7 | 4.0 | 4.3 | 39.5 | 20.0 | 4.6 | 1.8 | 4.5 |
| *Proteus* spp. | 4.9 | 0.0 | 3.6 | 4.4 | 2.7 | 2.2 | 8.6 | 0.0 | 2.7 | 0.0 | 3.3 | 1.6 | 0.9 | 3.8 |



https://www.ecdc.europa.eu/

# Causes of ICU-acquired BSI in Europe: ECDC 2017

| Microorganism | Belgium (n=47) | Estonia (n=15) | France (n=2 467) | Germany (n=2 974) | Hungary (n=28) | Italy (n=743) | Lithuania (n=40) | Luxembourg (n=43) | Malta (n=16) | Portugal (n=380) | Romania(n= 187) | Slovakia (n=21) | Spain (n=865 ) | United Kingdom (n=103) | Total (n=7 929) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Coagulase-negative staphylococci | 19.1 | 0.0 | 19.5 | 30.3 | 10.7 | 17.9 | 45.0 | 11.6 | 0.0 | 10.8 | 0.0 | 9.5 | 29.7 | 19.4 | 23.6 |
| *Enterococcus* spp. | 14.9 | 53.3 | 12.4 | 20.2 | 10.7 | 9.3 | 10.0 | 25.6 | 6.2 | 7.9 | 9.1 | 9.5 | 12.1 | 13.6 | 14.9 |
| *Klebsiella* spp. | 8.5 | 6.7 | 12.8 | 7.5 | 25.0 | 18.0 | 5.0 | 14 | 43.8 | 21.1 | 34.8 | 23.8 | 13.3 | 15.5 | 12.4 |
| *Staphylococcus aureus* | 17.0 | 6.7 | 12.0 | 13.9 | 3.6 | 11.8 | 17.5 | 4.7 | 6.2 | 9.7 | 18.2 | 9.5 | 5.0 | 16.5 | 12.0 |
| *Pseudomonas aeruginosa* | 8.5 | 13.3 | 12.8 | 4.9 | 35.7 | 11.4 | 2.5 | 7.0 | 25 | 19.2 | 13.4 | 19 | 9.2 | 2.9 | 9.5 |
| *Escherichia coli* | 14.9 | 13.3 | 11.6 | 8.5 | 0.0 | 10.2 | 7.5 | 7.0 | 6.2 | 6.3 | 4.3 | 4.8 | 6.4 | 13.6 | 9.2 |
| *Enterobacter* spp. | 4.3 | 6.7 | 14.1 | 4.6 | 7.1 | 5.7 | 2.5 | 14 | 6.2 | 10.0 | 1.1 | 4.8 | 8.1 | 3.9 | 8.3 |
| *Candida* spp. | 6.4 | 0.0 | 0.0 | 6.4 | 0.0 | 5.1 | 7.5 | 9.3 | 0.0 | 6.8 | 0.0 | 4.8 | 9.5 | 10.7 | 4.5 |
| *Serratia* spp. | 6.4 | 0.0 | 3.6 | 3.1 | 0.0 | 2.4 | 0.0 | 7.0 | 6.2 | 5.5 | 0.0 | 0.0 | 4.5 | 2.9 | 3.4 |
| *Acinetobacter* spp. | 0.0 | 0.0 | 1.3 | 0.6 | 7.1 | 8.1 | 2.5 | 0.0 | 0.0 | 2.6 | 19.3 | 14.3 | 2.2 | 1.0 | 2.3 |



https://www.ecdc.europa.eu/

# Drug resistance of invasive *Acinetobacter* in Europe 2020

***Acinetobacter* spp.: total number of invasive isolates tested (N = 7162)[a] and AMR percentage (%) per phenotype, EU/EEA, 2020**

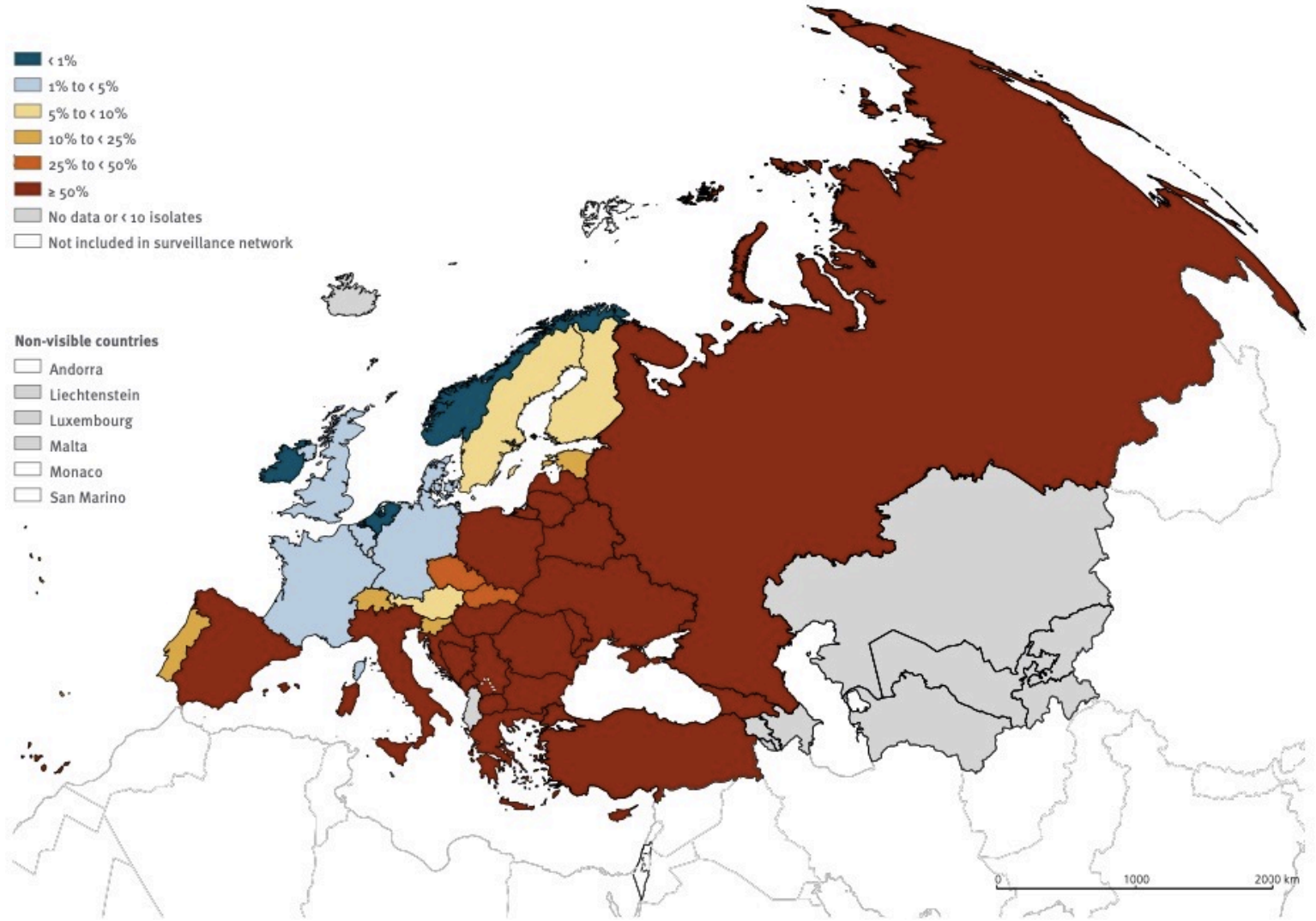
| AMR pattern[b] | Number of isolates | Percentage of total[c] |
|---|---|---|
| Fully susceptible (to included antimicrobial groups) | 2 461 | 34.4 |
| **Single resistance (to indicated antimicrobial group)** | | |
| Total (any single resistance) | 238 | 3.3 |
| Fluoroquinolones | 146 | 2.0 |
| Other antimicrobial groups | 92 | 1.3 |
| **Resistance to two antimicrobial groups** | | |
| Total (any two-group combinations) | 358 | 5.0 |
| Fluoroquinolones + carbapenems | 242 | 3.4 |
| Fluoroquinolones + aminoglycosides | 103 | 1.4 |
| Other antimicrobial group combinations | 13 | 0.2 |
| **Resistance to three antimicrobial groups** | | |
| Fluoroquinolones + aminoglycosides + carbapenems | 4 105 | 57.3 |

Population weighted mean of **carbapenem resistance in Europe : 38% in 2020** (36.9% in 2016)
Population weighted mean of **fluoroquinolone + aminoglycoside + carbapenem resistance : 34.1% in 2020** (32.3% in 2016)



ECDC report 2020: https://www.ecdc.europa.eu

# Rates of invasive CRAB in Europe 2020






ECDC report: https://www.ecdc.europa.eu

# Drug resistance of *A. baumannii* in France

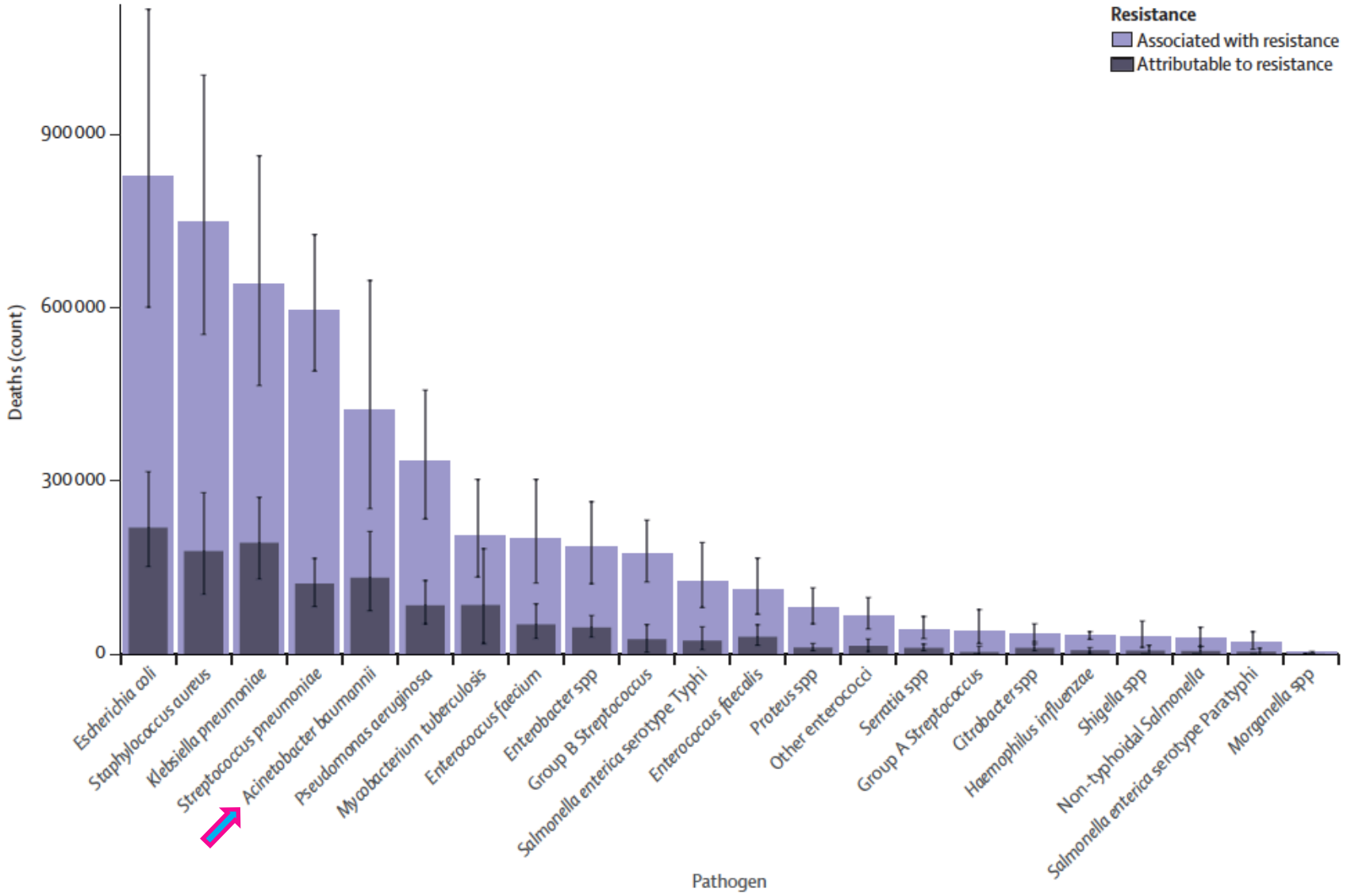
(SPARES 2020)

| Antibiotique | Tous prélèvements confondus | | Hémocultures | |
|---|---|---|---|---|
| | Nb total de souches | % (R+I) | Nb total de souches | % (R+I) |
| Ticarcilline | 1 245 | 20,1% | 226 | 21,2% |
| Pipéracilline - tazobactam | 834 | 21,8% | 138 | 21,0% |
| Ceftazidime | 863 | 22,0% | 151 | 19,9% |
| Céfépime | 1 239 | 17,4% | 222 | 15,3% |
| Imipénème | 1 322 | 8,9% | 237 | 8,9% |
| Méropénème | 1 023 | 11,4% | 170 | 10,6% |
| Amikacine | 868 | 10,4% | 141 | 12,8% |
| Ciprofloxacine | 1 220 | 66,2% | 209 | 62,2% |



https://www.santepubliquefrance.fr

# Antibioresistance associated Deaths in 2019

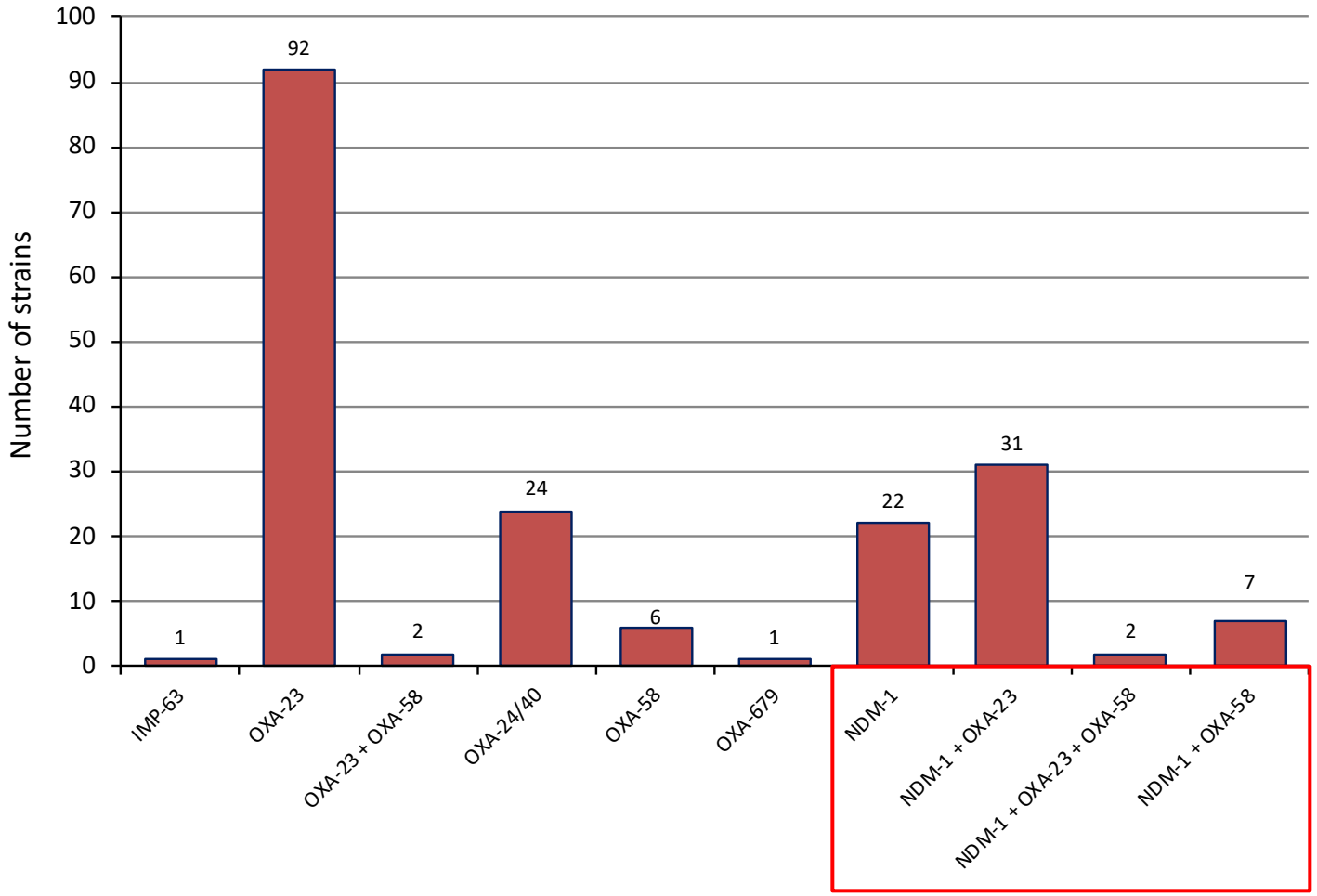


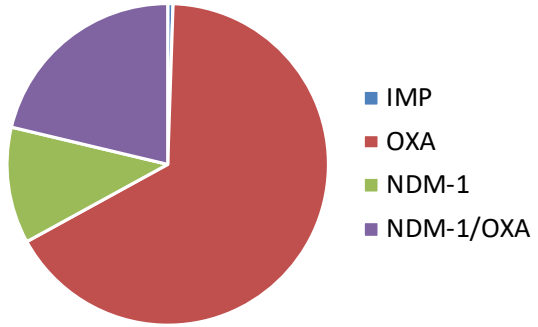



The Lancet 2022: doi.org/10.1016/S0140-6736(21)02724-0

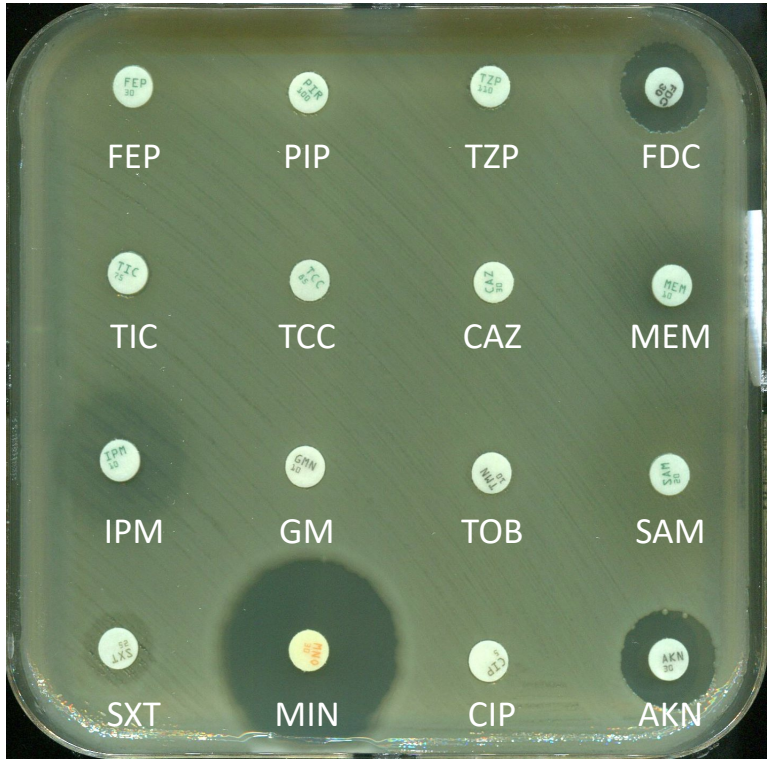
# Carbapenemase positive *A. baumannii* in France

(CNR data 2021, *n*=188 CRAB)

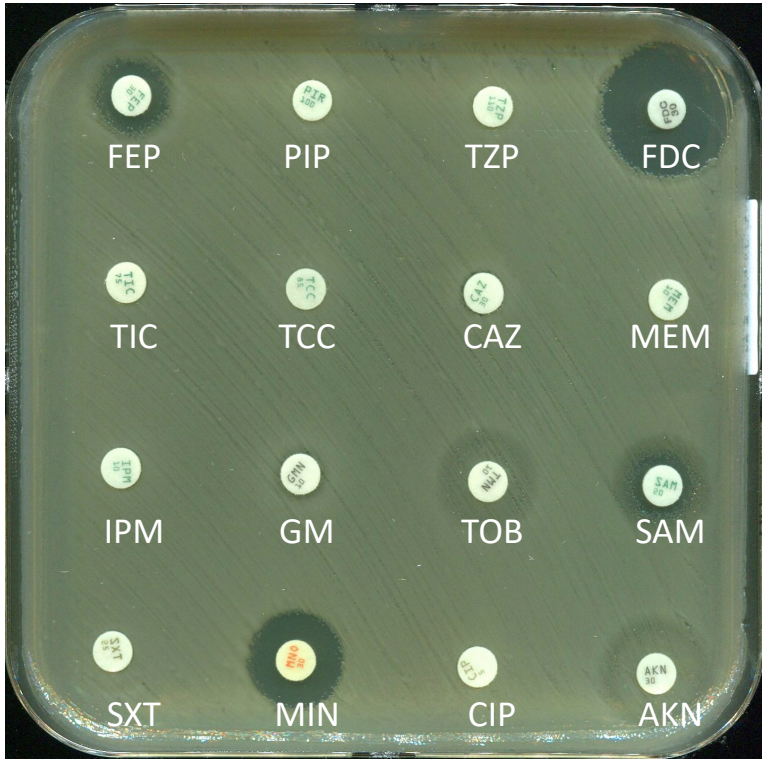


# CRAB XDR profiles



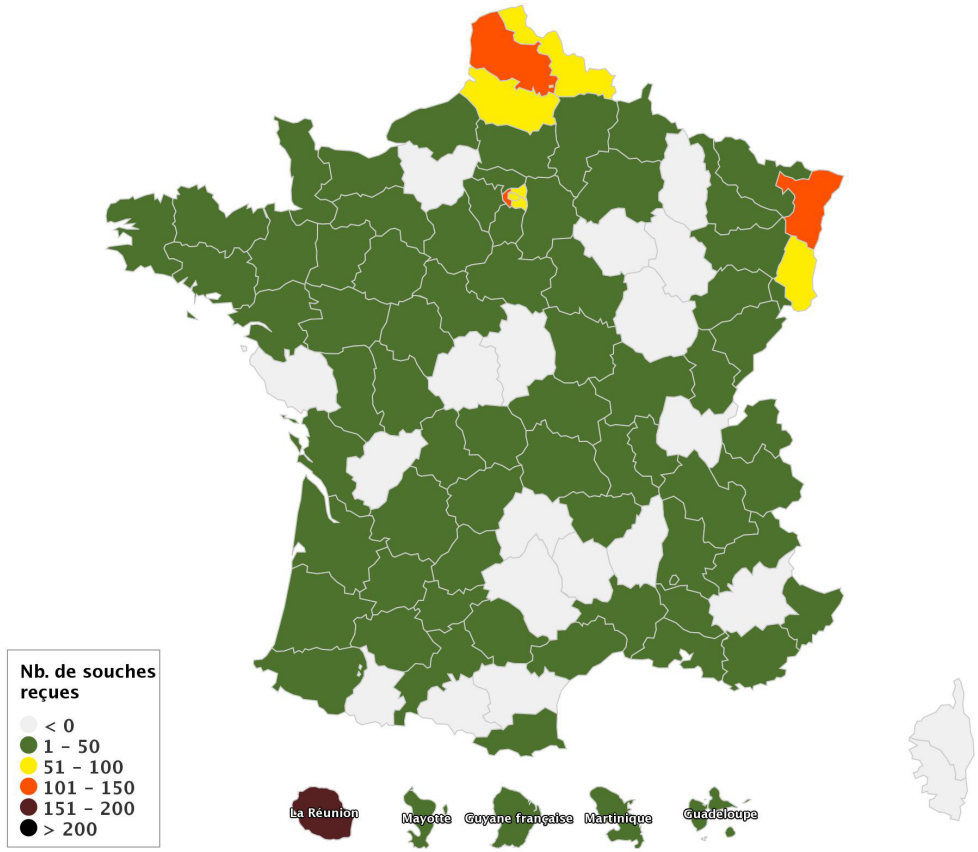

**NDM-1**



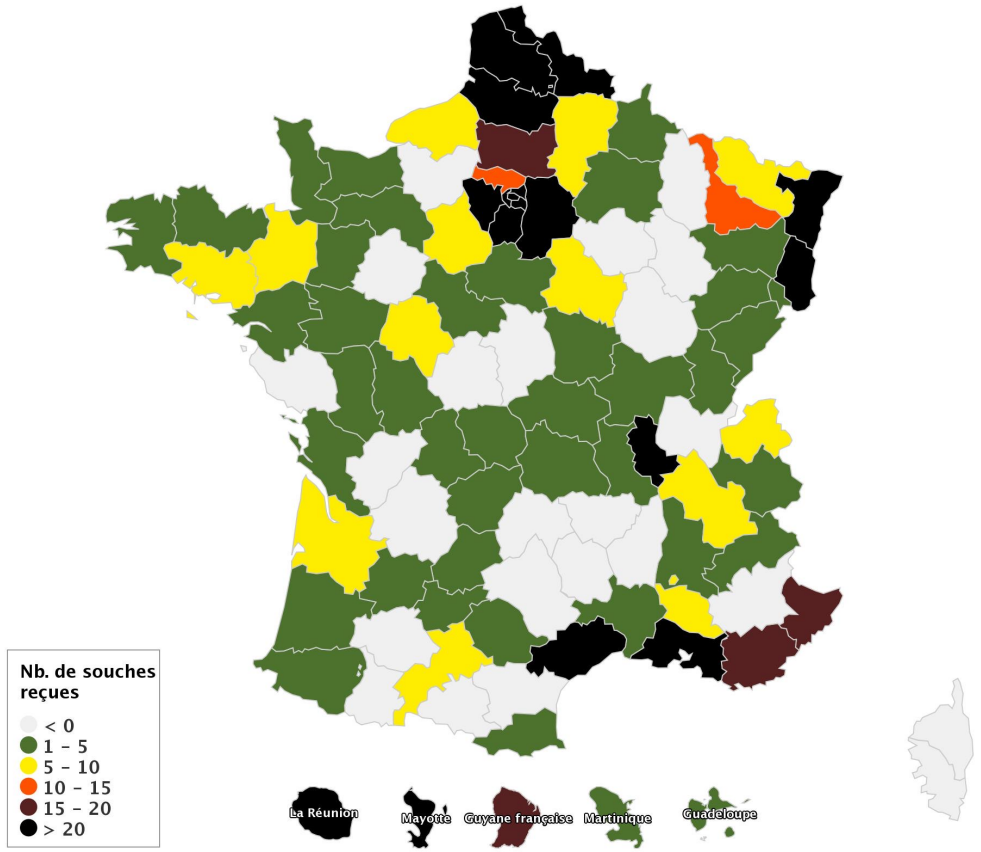

**NDM-1/OXA-23**

# Epidemiology of CRAB in France

(CNR data 2017-2021)




**Total CRAB (*n*=1605)**

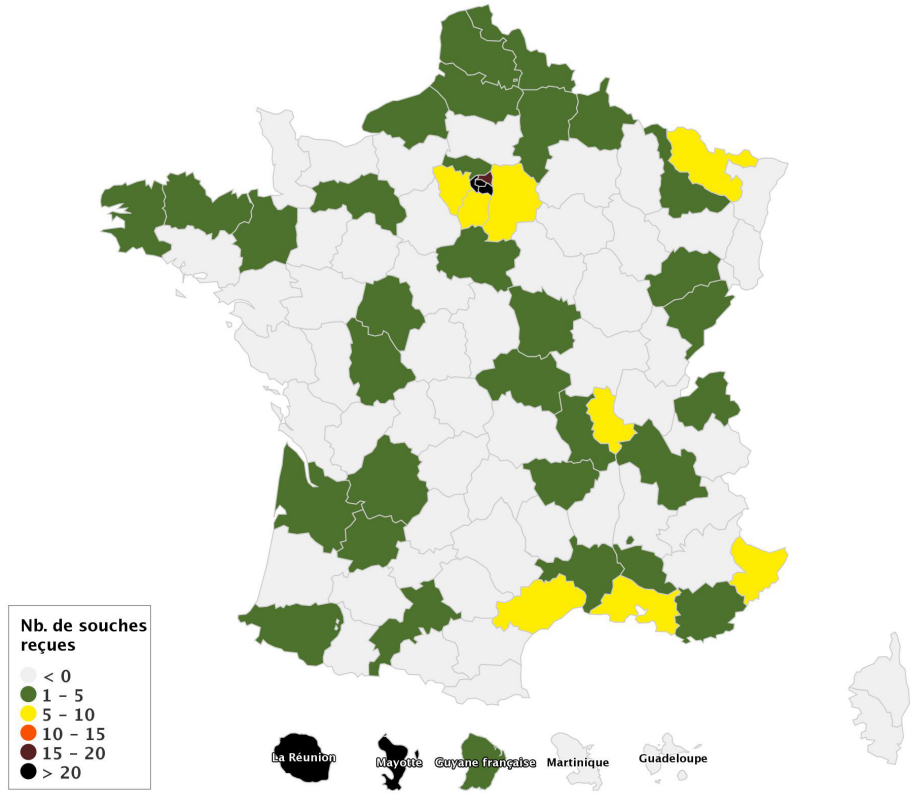



**OXA-23 producing CRAB**

± OXA-51,-72, PER, NDM **(*n*=1191)**

# NDM-1 producing CRAB in France

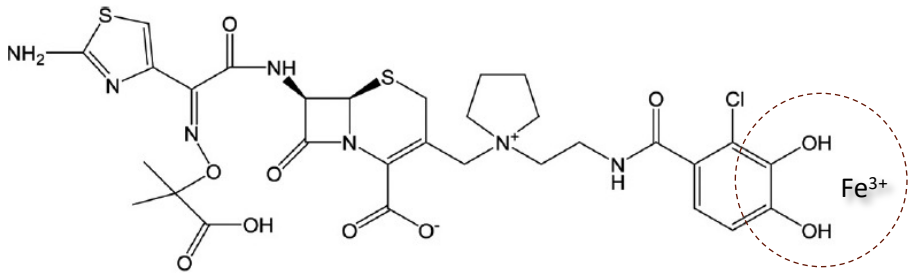
(CNR data 2017-2021)




**NDM-1 producing CRAB**

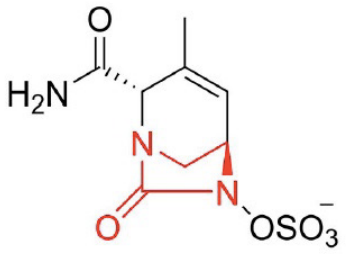
± OXA-23, -24, -58, -420 **(*n*=275)**

# Novel anti-CRAB solutions




**Cefiderocol**

- **Active intracellular penetration through siderophores uptake pathways**
- **Stability to many β-lactamases**
- **Poor substrate of efflux pumps**



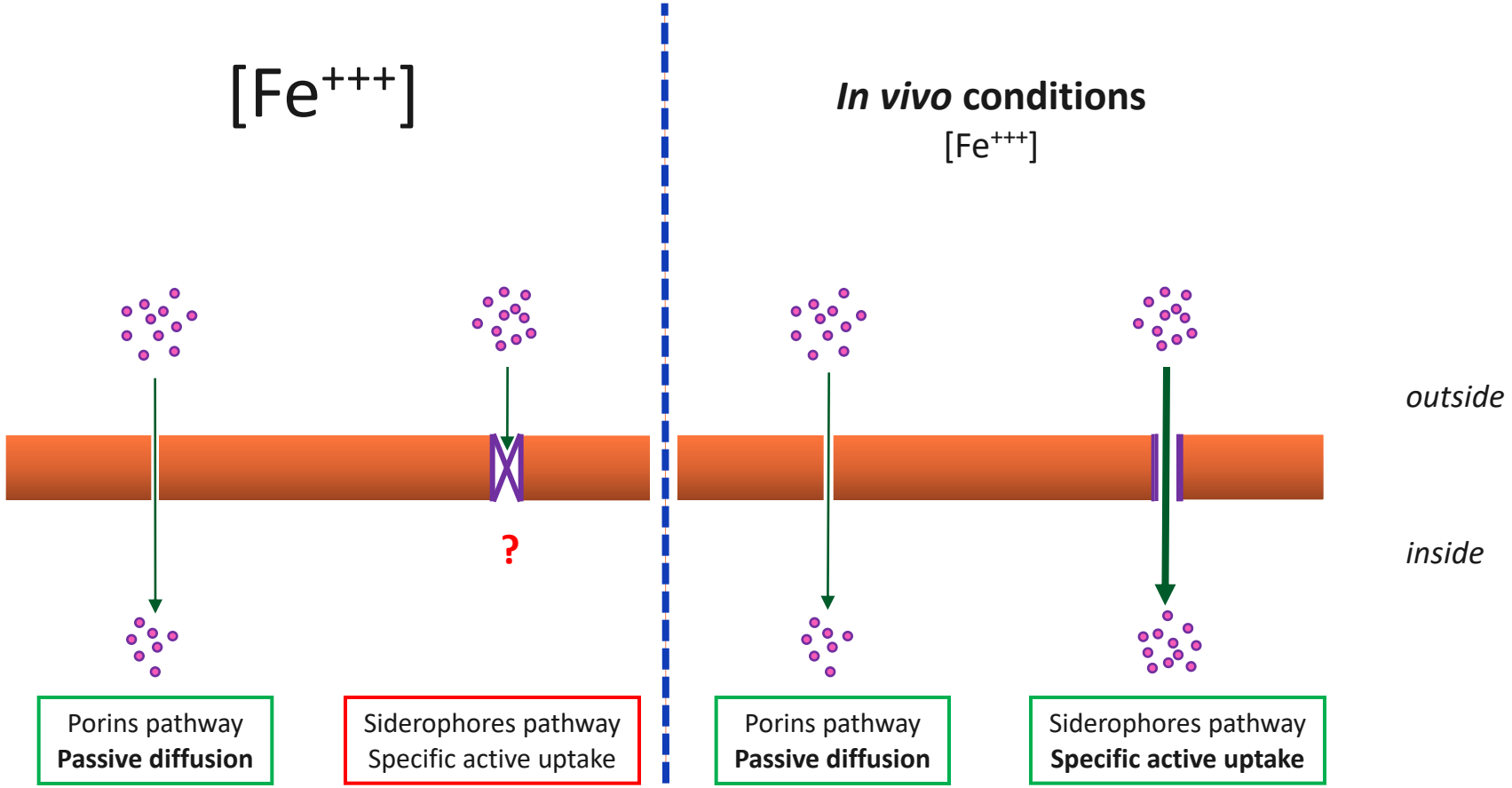

**Durlobactam (DBO)**

- **Broad inhibitor of serine β-lactamases (A-, C-, and D-types)**
- **Restores sulbactam activity against CRAB by β-lactamase inhibition**
- **Activity impaired by PBP3 mutations or MBL production**



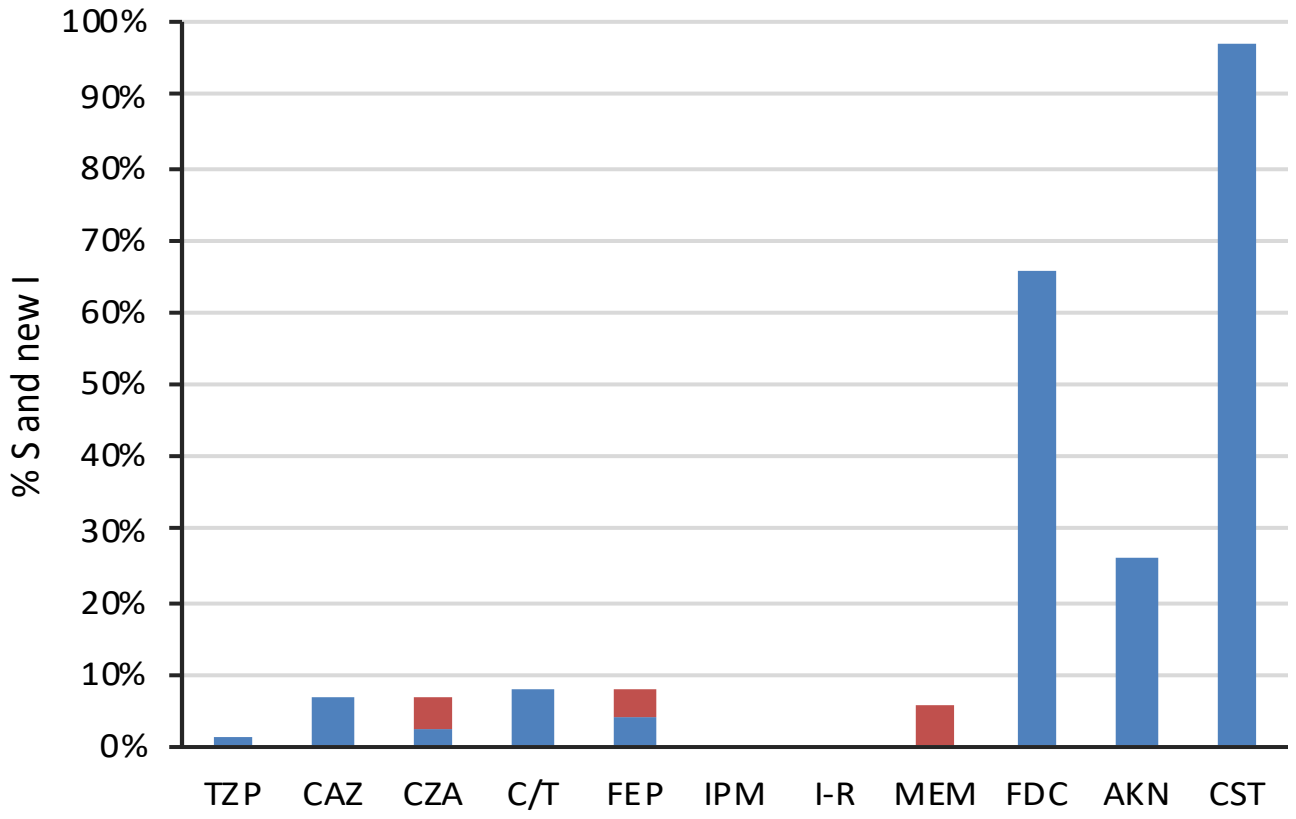
Shapiro A.B. *et al.* Front, Microbiol. 2021, 12: 709974

# Principle of action of siderophore-antibiotics



# CRAB drug susceptibility to cefiderocol

(CNR data, *n*=73 strains, CA-SFM 2022 or PK/PD breakpoints)

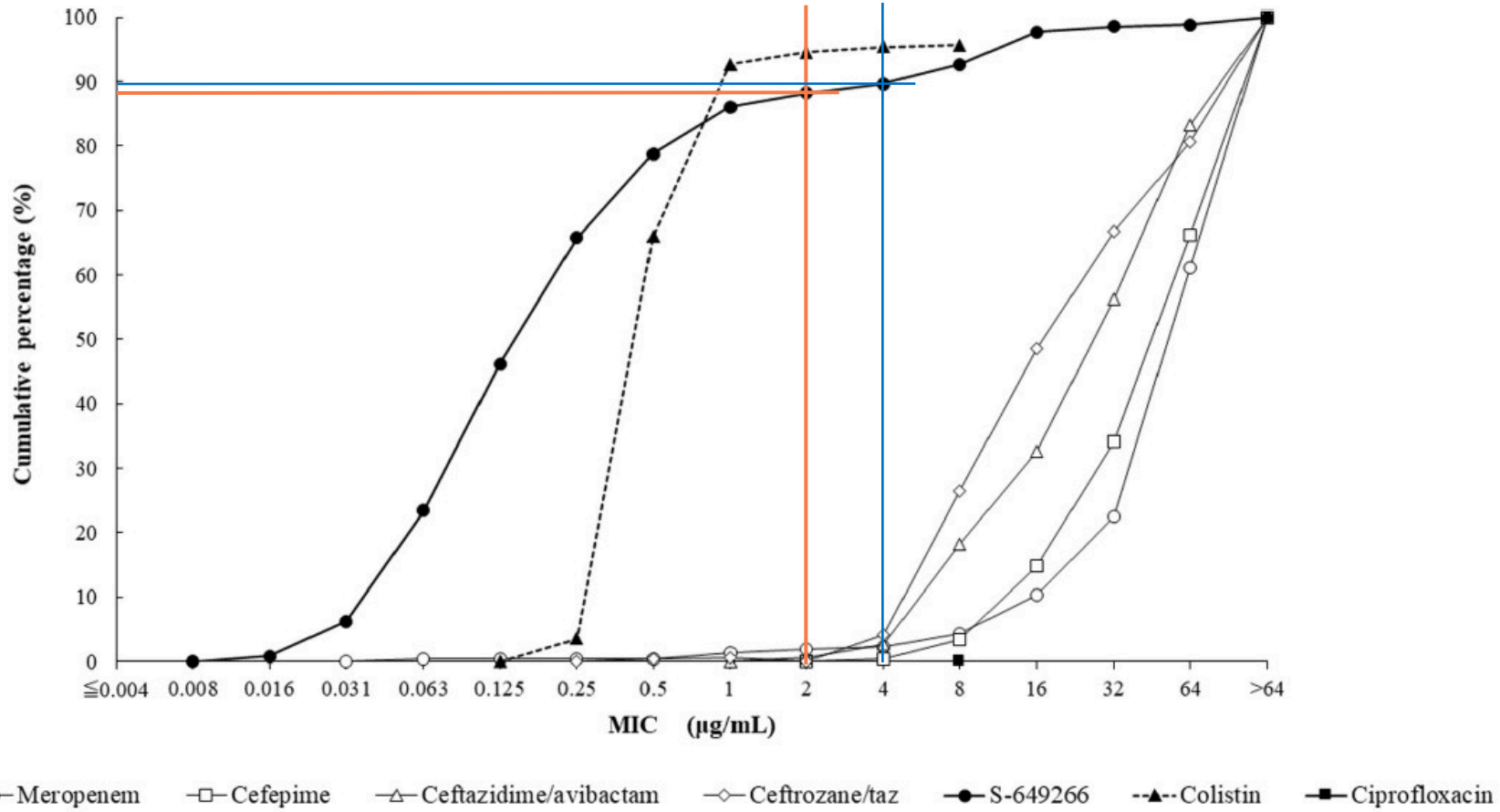



TZP: piperacillin/tazobactam (16/4-64/4 mg/L)
CAZ: ceftazidime (8-16)
CZA: ceftazidime/avibactam (8-16)
C/T: ceftolozane/tazobactam (4/4)
FEP: cefepime (8-16)
IPM: imipenem (2-4)
I-R: imipenem/relebactam (2-4)
MEM: meropenem (2-8)
FDC: cefiderocol (2)
AKN: amikacin (8)
CST: colistin (2)

**65.8% (48/73) CRAB exhibited FDC MICs of ≤ 2 mg/L** (ThermoFisher microdilution technique)

# International studies

(*n*=368 strains from 52 countries)




**89.7% (330/368) CRAB exhibited FDC MICs of ≤ 4 mg/L** (CLSI microdilution technique)



Hackel M.A. *et al.* AAC 2018, 62:e01968-17

# International studies (2)

(*n*=652 *Acinetobacter* sp. from the USA and Europe)

**TABLE 4** Antimicrobial activity of cefiderocol and comparator agents tested against 650 *Acinetobacter* isolates

| | MIC (mg/L) | | | CLSI (%)[a] | | |
|---|---|---|---|---|---|---|
| Organism (no.)/antimicrobial agent | $MIC_{50}$ | $MIC_{90}$ | MIC range | S | I | R |
| *Acinetobacter* spp. (650)[d] | | | | | | |
| Cefiderocol | 0.25 | 1 | ≤0.004 to >64 | 97.7 | 0.9 | 1.4 |
| Imipenem-relebactam | 0.5 | >8 | ≤0.03 to >8 | 53.1[b] | 0.2 | 46.8 |
| Ceftazidime | 8 | >32 | 0.25 to >32 | 50.8 | 4.5 | 44.8 |
| Piperacillin-tazobactam | 128 | >128 | ≤0.06 to >128 | 45.8 | 2.2 | 52 |
| Meropenem | 1 | >32 | 0.03 to >32 | 52.6 | 0.3 | 47.1 |
| Ciprofloxacin | 2 | >4 | ≤0.008 to >4 | 49.1 | 1.1 | 49.8 |
| Colistin | 0.5 | 8 | ≤0.06 to >8 | —[c] | 86.3 | 13.7 |
| Meropenem resistant (306) | | | | | | |
| Cefiderocol | 0.5 | 2 | 0.015 to >64 | 95.8 | 1.3 | 2.9 |
| Imipenem-relebactam | >8 | >8 | 0.25 to >8 | 0.3[b] | 0.3 | 99.3 |
| Ceftazidime | >32 | >32 | 2 to >32 | 8.8 | 2.9 | 88.2 |
| Piperacillin-tazobactam | >128 | >128 | ≤0.06 to >128 | 1.0 | 0.3 | 98.7 |
| Meropenem | >32 | >32 | 8 to >32 | 0.0 | 0.0 | 100.0 |
| Ciprofloxacin | >4 | >4 | 1 to >4 | 0.7 | 0.3 | 99.0 |
| Colistin | 0.5 | >8 | 0.12 to >8 | —[c] | 76.4 | 23.6 |

[a]Criteria as published by CLSI (2021).
[b]FDA criteria are shown, no CLSI breakpoints.
[c]As CLSI removed the susceptible breakpoint for colistin, all wild-type isolates are considered intermediate.

S ≤ 4 mg/L

S ≤ 4 mg/L



Shortridge D. *et al.* Microbiol. Spectrum 2022, 10:e0271221

# Cefiderocol is not a good substrate for β-lactamases

- Acquired β-lactamases
  - Relative stability to most carbapenemases (IMP-, VIM-, CHDL OXA-types)
  - Low hydrolysis by **carbapenemases of KPC-, NDM- and SPM-types**
  - Low hydrolysis by **ESBL of PER-, BEL- and SHV-types** (GES ?)
- Intrinsic class C cephalosporinases (AmpC)
  - Good stability to overexpressed cephalosporinases from *P. aeruginosa, E. cloacae*, and *A. baumannii*
  - Partially hydrolized by AmpC variants (PDC E221K)
  - Not inducer of AmpC production
- Cefiderocol therapeutic targets
  - **XDR strains including carbapenemase positives**


Ito T. *et al.* AAC 2016, 60: 4384
Ito A. *et al.* AAC 2018, 73: 3049
Ito A. AAC 2018, 62: e01454-17
Poirel L. *et al.* AAC 2021, 76: doi:10.1128/AAC.00877-21
Poirel L. *et al.* IJAA 2018, 52: 866
Mushtaq S. *et al.* AAC 2020, 64: 12 e01582-20
Simner P. *et al.* Open Forum Infect Dis. 2021, 8(7):ofab311

# Role of β-lactamases in CRAB resistance to cefiderocol ?

(CNR data, *n*=73 strains)

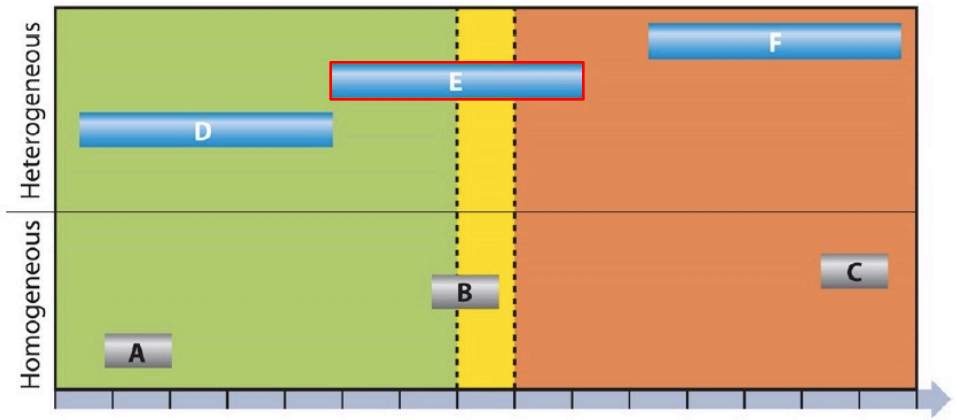
| FDC MIC | Total | OXA-23 | OXA-24 | OXA-58 | OXA-72 | OXA-420 | IMP-63 | NDM-1 | PER-1 | PER-7 | GES-11 | CTX-M-115 | OXA-35 | CARB-14 | CARB-16 | TEM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **≤ 0.5** | **32** | 23 | 1 | 3 | 5 | | | | | | | 4 | | | 2 | 6 |
| **1** | **4** | 4 | | | | | | | | | | | | | | 4 |
| **2** | **12** | 6 | | | 2 | 3 | 1 | 4 | | | 1 | | 1 | | 3 | 1 |
| **4** | **10** | 4 | | 1 | 4 | | | 5 | | | | 1 | | 1 | | 1 |
| **8** | **8** | 5 | | | | 1 | | 7 | | | | | | | | 1 |
| **> 8** | **7** | 1 | | | | | 1 | 6 | 1 | 1 | | | | | | |

**Other mechanisms ?** ADC structural variants, alteration of iron uptake and metabolism, PBP mutations, active efflux…



Karakonstantis C. *et al.* Antibiotics 2022, 11: 723

# What about the heteroresistance of *A. baumannii* ?




Antibiotic concentrations at twofold increments

Discrepancies between clinical outcomes (mortality) and AST data in CREDIBLE-CR trial

A problem of *in vitro* testing method ?

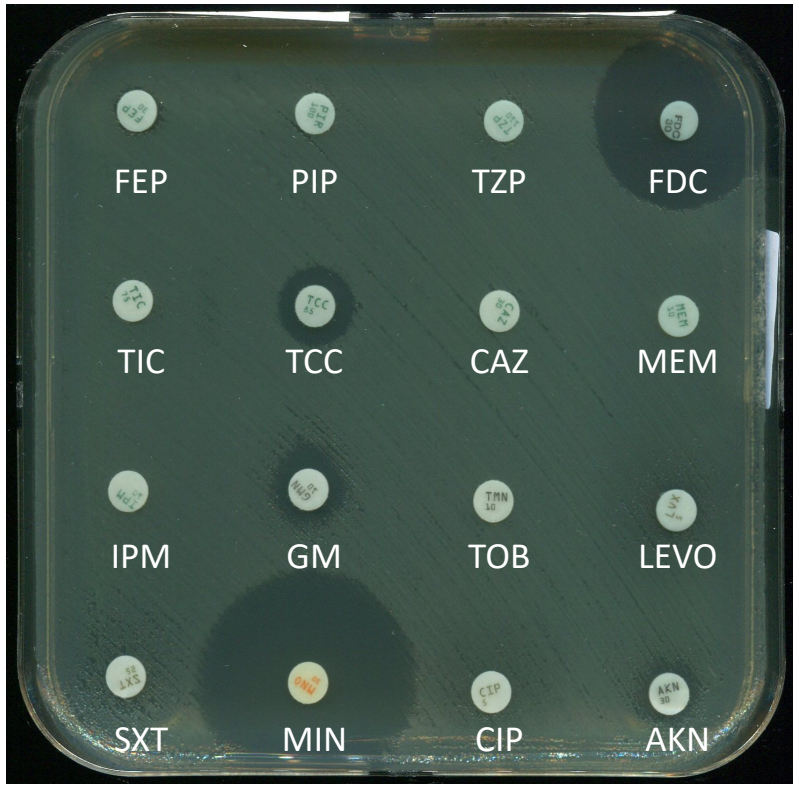
| | *Acinetobacter* | *Klebsiella* | *Pseudomonas* | *Stenotrophomonas* |
|---|---|---|---|---|
| **CREDIBLE-CR trial**[1] | | | | |
| All-cause mortality* | 49% (19/39) | 21% (6/28) | 18% (2/11) | 67% (2/3) |
| Detected resistance† | 3% (1/36) | 0% (0/27) | 0% (0/12) | 0% (0/5) |
| **SIDERO-CR study**[5] | | | | |
| Detected resistance | 10% (38/368) | 2% (12/720) | 1% (2/262) | 0% (0/217) |
| **GA, USA, surveillance** | | | | |
| Detected resistance | 8% (9/108) | 6% (5/89) | 0% (0/69) | 0% (0/29) |
| Heteroresistance | 59% (64/108) | 30% (27/89) | 9% (6/69) | 48% (14/29) |

All-cause mortality data are from the CREDIBLE-CR trial.[1] Detected resistance data (minimum inhibitory concentration >4 µg/mL) are from the CREDIBLE-CR trial[1] or SIDERO-CR study,[5] or were generated by disk diffusion assay on carbapenem-resistant isolates from GA, USA, according to Clinical and Laboratory Standards Institute guidance. Heteroresistance data were established by population analysis profile to identify minority resistant subpopulations within an isolate. *All-cause mortality data for *Klebsiella*, *Pseudomonas*, and *Stenotrophomonas* spp are for patients who did not have *Acinetobacter* spp coinfection. †Data not available for all isolates in the CREDIBLE-CR trial.

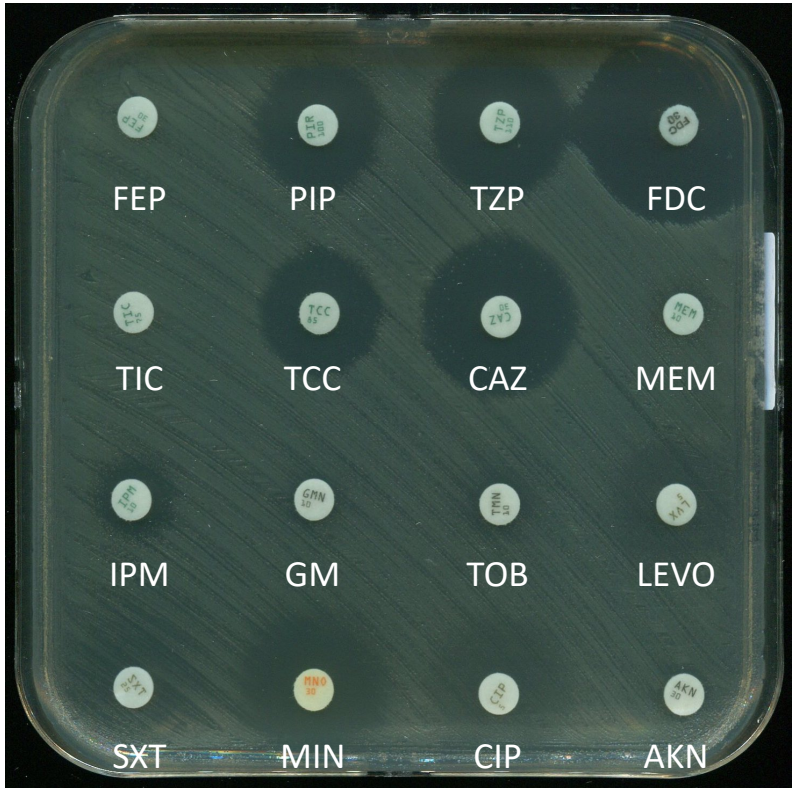
***Table*: All-cause mortality and cefiderocol non-susceptibility among carbapenem-resistant pathogens**

El-Halfawi O. *et al.* Clin. Microbiol. Rev. 2015, 28: 191
Choby J.E. *et al.* The Lancet, 2021, 21:597
Choby J.E. *et al.* The Lancet, 2021, 2:e648
Bassetti M. *et al.* The Lancet, 2021, 21:908

# Other problematic non-fermenting bacilli




**XDR *S. maltophilia***




**MDR *Achromobacter* sp.**



Gibb J. *et al.* Antibiotics 2021, 10: 1226
Isler B. *et al.* AAC 2020, 64: e01025-20

# Cefiderocol *vs S. maltophilia*

(*n*=338 *S. maltophilia* from the USA and Europe)

**TABLE 5** Antimicrobial activity of cefiderocol and comparator agents tested against 338 *Stenotrophomonas maltophilia* isolates

| Antimicrobial agent against *S. maltophilia* (*n* = 338) | MIC (mg/L) | | | CLSI (%)[a] | | |
|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | MIC range | S | I | R |
| Cefiderocol | 0.12 | 0.5 | 0.015 to 4 | 100.0, 97.9[b] | 0.0 | 0.0 |
| Ceftazidime | >32 | >32 | 1 to >32 | 16.6 | 11.6 | 71.8 |
| Levofloxacin | 1 | 8 | 0.12 to 32 | 82.5 | 7.4 | 10.1 |
| Trimethoprim-sulfamethoxazole | ≤0.12 | 0.5 | ≤0.12 to >4 | 97.9 | | 2.1 |
| Minocycline | 0.5 | 1 | 0.12 to 8 | 99.4 | 0.6 | 0.0 |
| Colistin | 8 | >8 | 0.12 to >8 | | | |

[a]Criteria as published by CLSI (2021).
[b]CLSI 2021 (≤4/8/≥16 mg/L) and 2022 (≤1/−/− mg/L) breakpoints shown.

## SIDERO-WT Surveillance Studies 2014 to 2019

(*n*=2,030 strains) : **98.6%** of strains inhibited at ≤ 1 mg/L (CZA $MIC_{50}$ = 16 mg/L)



Shortridge D. *et al.* Microbiol. Spectrum 2022, 10.1128/spectrum.02712-21
Karlowsky J.A. *et al.* AAC 2022, 66:e1990-21

# Cefiderocol *vs Achromobacter* sp.

(*n*=23 *Achromobacter* sp. CF patients, France)

| | MIC (mg/L) 50%/90% | | Percentage of Susceptibility According to the Following Breakpoints | | | |
|---|---|---|---|---|---|---|
| | | | EUCAST [c] | | CLSI [d] | |
| Antimicrobial agent | Merlin [a] | Sensititre [b] | Merlin [a] | Sensititre [b] | Merlin [a] | Sensititre [b] |
| Piperacillin | ≤4/>32 | - | 57 | - | 61 | - |
| Piperacillin—tazobactam | 4/>128 | ≤4/>32 | 57 | 57 | 65 | 65 |
| Aztreonam | >16/>16 | >32/>32 | 0 | 0 | 0 | 0 |
| Cefepime | >8/>8 | >16/>16 | 4 | 9 | 13 | 22 |
| Ceftazidime | >32/>32 | - | 17 | - | 30 | - |
| Ceftazidime—avibactam | >8/>8 | 16/>16 | 26 | 39 | 26 | 39 |
| Ceftolozane—tazobactam | >8/>8 | >8/>8 | 0 | 9 | 0 | 9 |
| Cefiderocol | - | 0.25/1 | - | 91 | - | 91 |
| Imipenem | ≤1/>8 | ≤1/2 | 70 | 91 | 70 | 91 |
| Imipenem—relebactam | - | 1/2 | - | 91 | - | 91 |
| Meropenem | 2/>16 | 2/>16 | 48 | 43 | 70 | 57 |
| Meropenem—vaborbactam | - | 1/16 | - | 87 | - | NA |
| Ciprofloxacin | 4/8 | - | 0 | - | 4 | - |
| Levofloxacin | 4/8 | - | 4 | - | 48 | - |
| Colistin | 8/>8 | 16/>16 | 39 | 30 | 39 | 30 |
| Fosfomycin | >128/>128 | >64/>64 | 0 | 0 | NA | NA |
| Gentamicin | >32/>32 | - | 0 | - | 9 | - |
| Amikacin | >32/>32 | >32/>32 | 0 | 0 | 22 | 13 |
| Tobramycin | 32/>32 | >4/>4 | 0 | 0 | 9 | 13 |
| SXT [e] | ≤1/>8 | - | 65 | - | 65 | - |
| Tigecycline | - | ≤0.5/1 | - | 52 | - | NA |
| Eravacycline | - | 0.5/>0.5 | - | 65 | - | NA |



Beauruelle C. *et al.* Microorg. 2021, 9:2473

# Conclusions

- Cefiderocol shows a good *in vitro* activity against OXA- or IMP/VIM-producing CRAB isolates, as well as against XDR *S. maltophilia* and *Achromobacter* sp.
- Cefiderocol is a last-resort option to consider for the treatment of patients with severe nosocomial CRAB infections, as an alternative to colistin
- Co-expression in some CRAB strains of still not fully characterized mechanisms (β-lactamases, PBP alterations, loss of siderophore receptors, upregulation of active efflux systems…) is able to confer moderate levels of cefiderocol resistance or heteroresistance, of which the clinical relevance needs to be addressed by further studies
- The *in vitro* activity of cefiderocol can be assessed with commercial microdilution tests along with that of last-resort antibiotic molecules such as colistin
- Bacterial population analyses have not been validated yet to predict the effectiveness of cefiderocol *in vivo*.

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

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