Prise en charge des infections à germes pan-résistants

Pr Hatem KALLEL

Service de Réanimation Polyvalente - CH de Cayenne

Equipe de recherche « Tropical Biome and immunopathology
CNRS UMR-9017, Inserm U 1019, Université de Guyane »

26ème Congrès National de l'Association Tunisienne de Réanimation; 17-19/11/2022 à Hammamet.

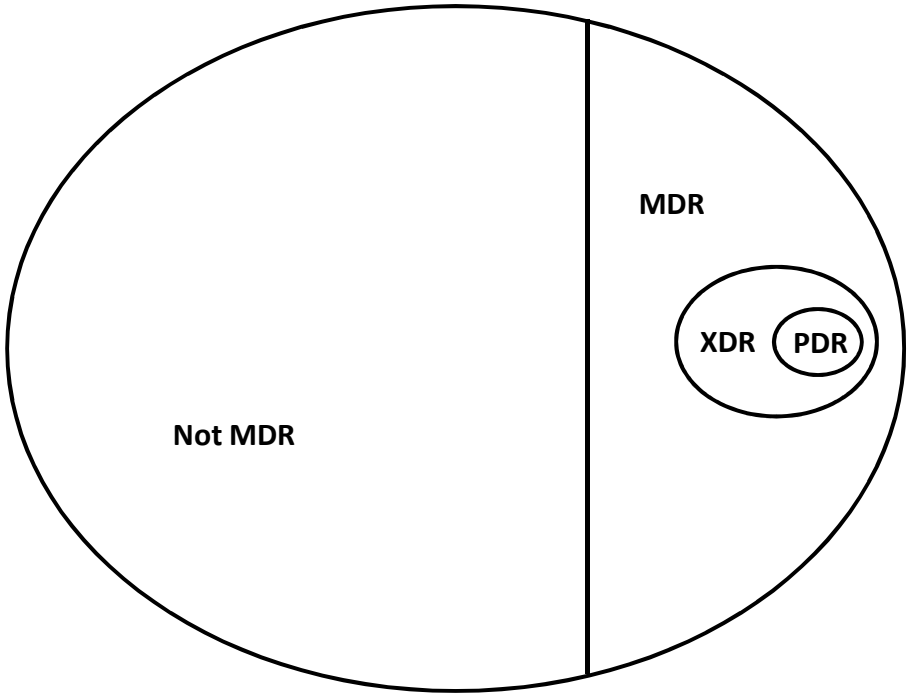
Pas de conflit d’intérêt

Assistance graphique Taha KALLEL

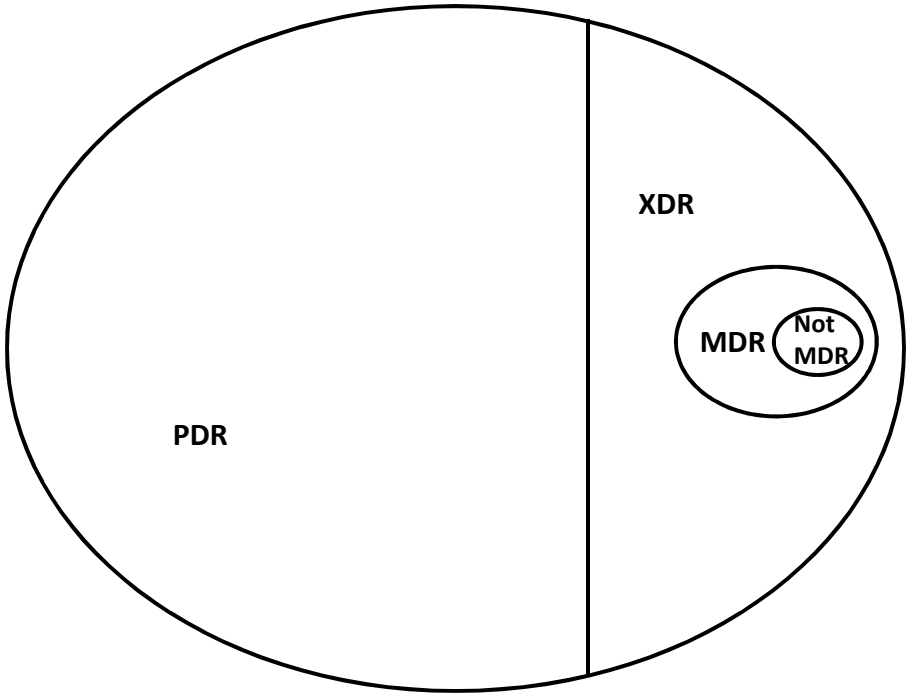
ORIGINAL ARTICLE BACTERIOLOGY

Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

Epidemiology

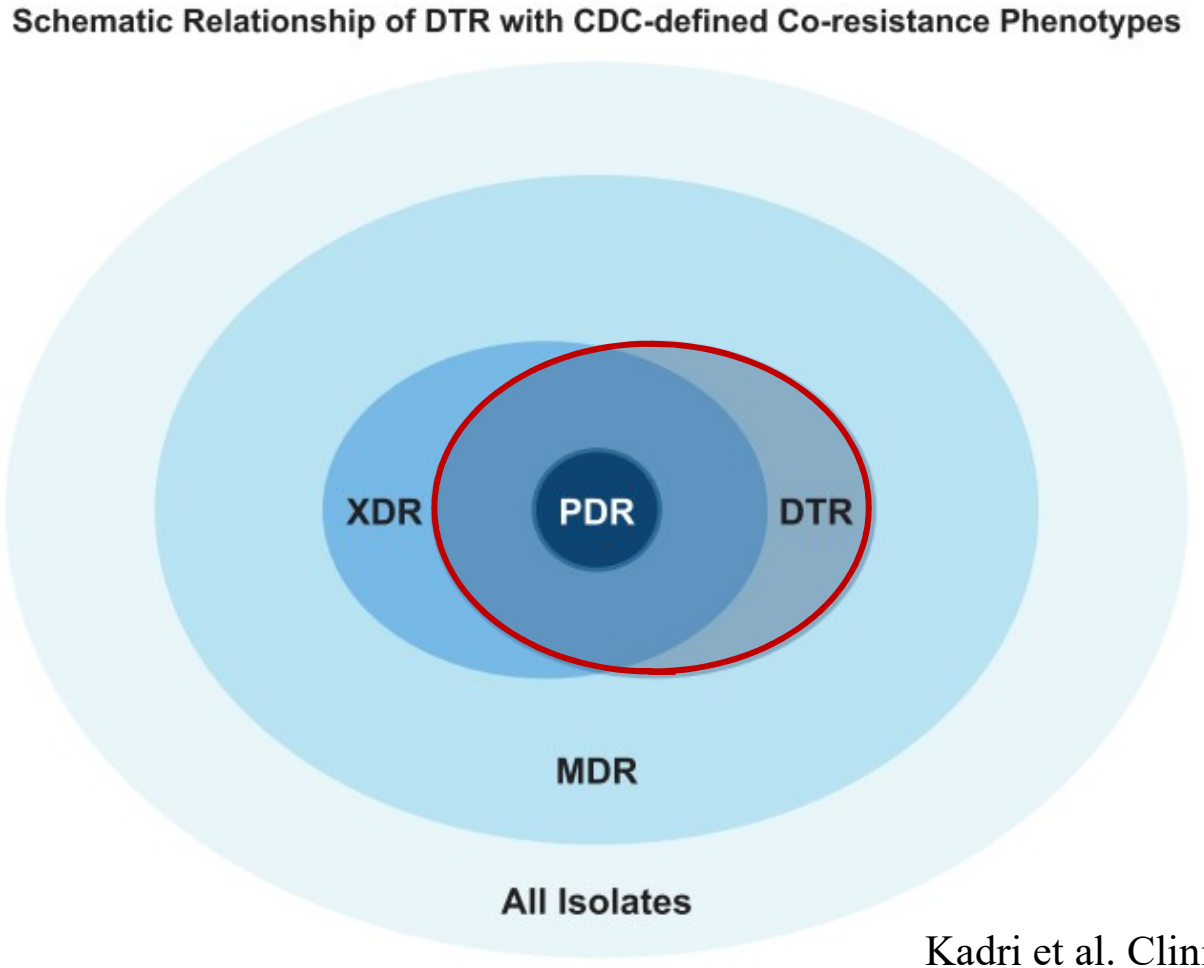


Burden and difficulty to treat



Magiorakos et al. Clinical Microbiology and Infection (2012

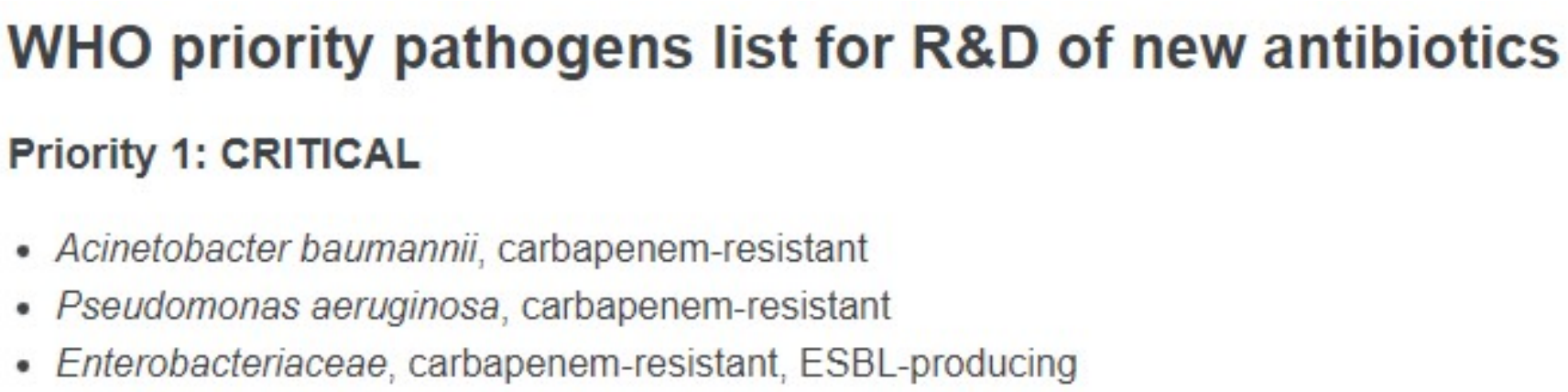
Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents



Kadri et al. Clinical Infectious Diseases (2018)

WHO publishes list of bacteria for which new antibiotics are urgently needed

27 February 2017 | News release | GENEVA | Reading time: 3 min (784 words)



World Health Organization

REVIEW Open Access

Mechanisms of antimicrobial resistance in Gram-negative bacilli

tienne Ruppé[1], Paul-Louis Woerther[2] and François Barbier[3*]

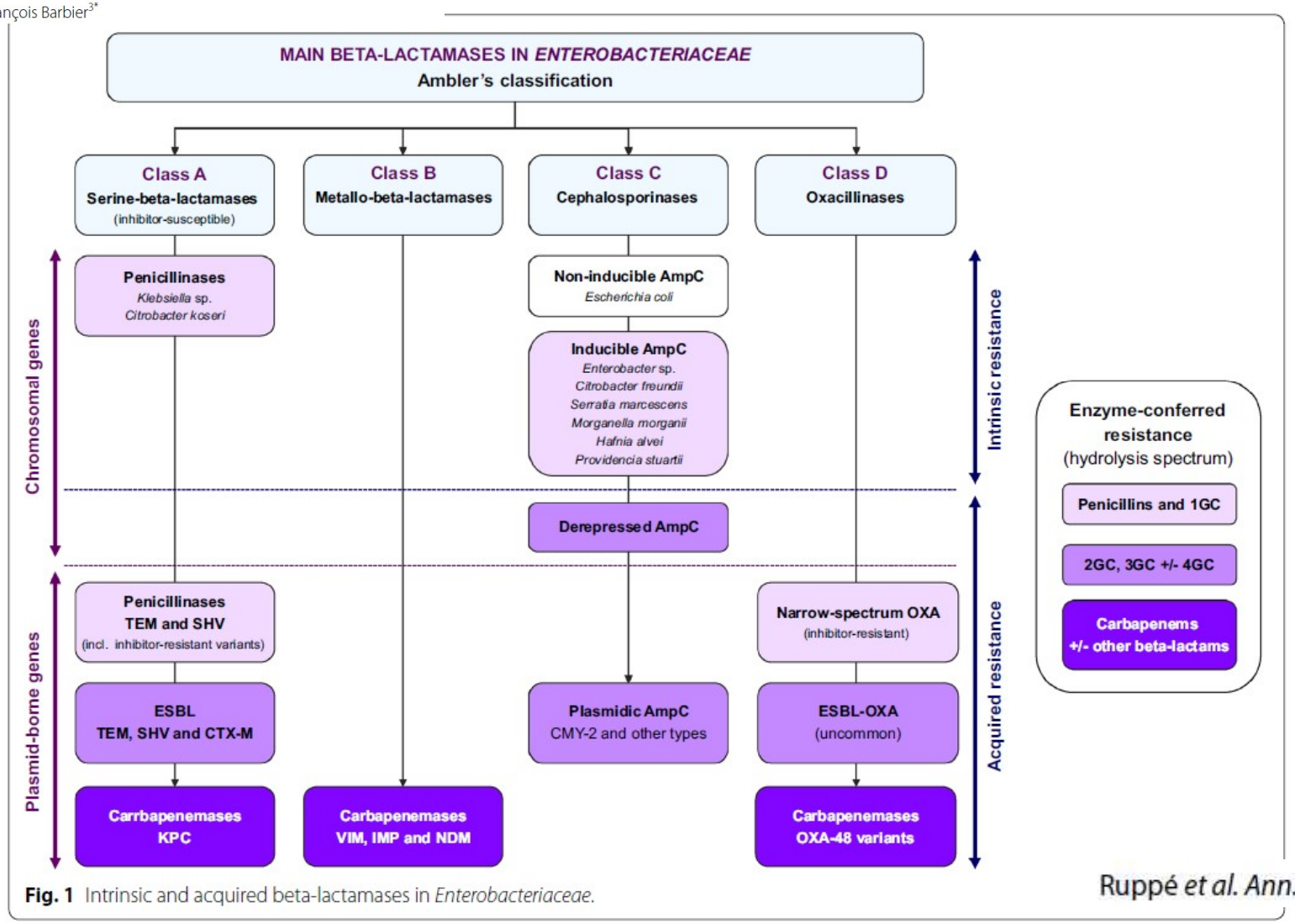
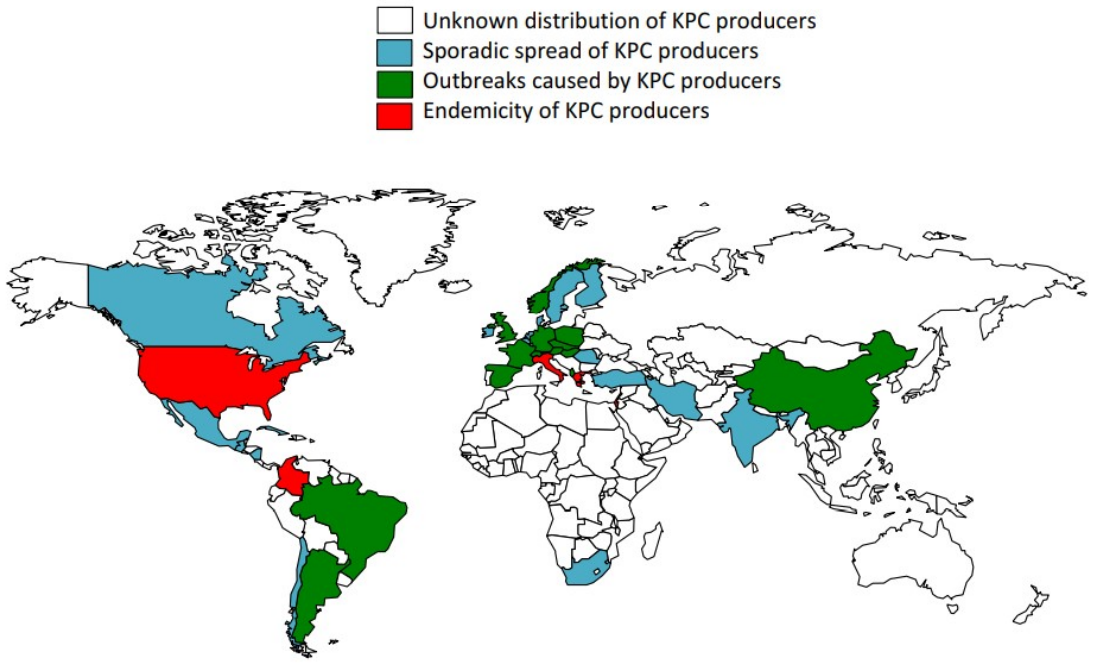
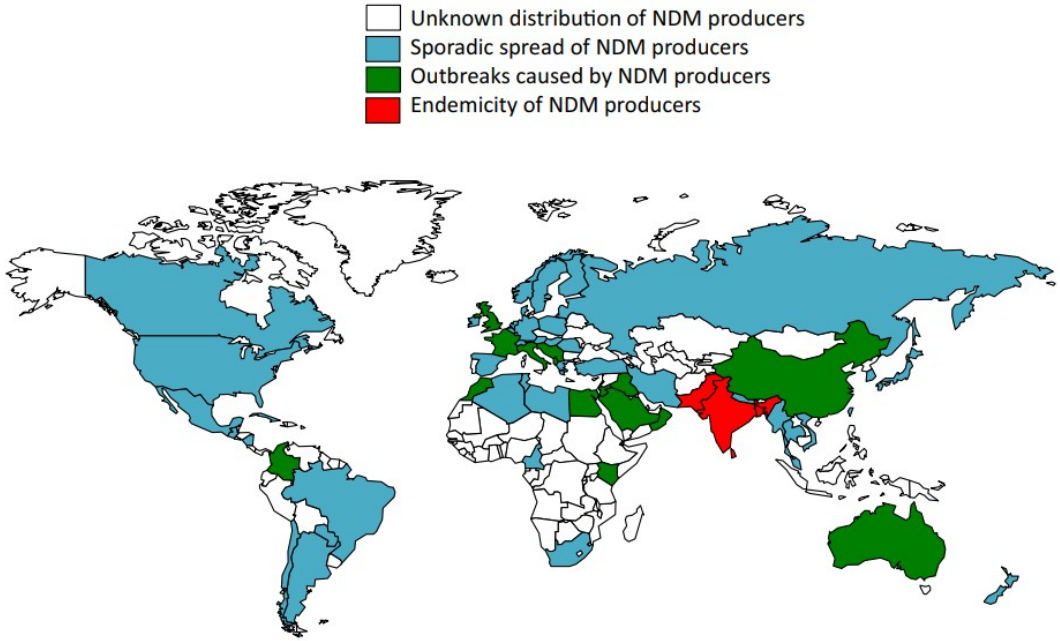


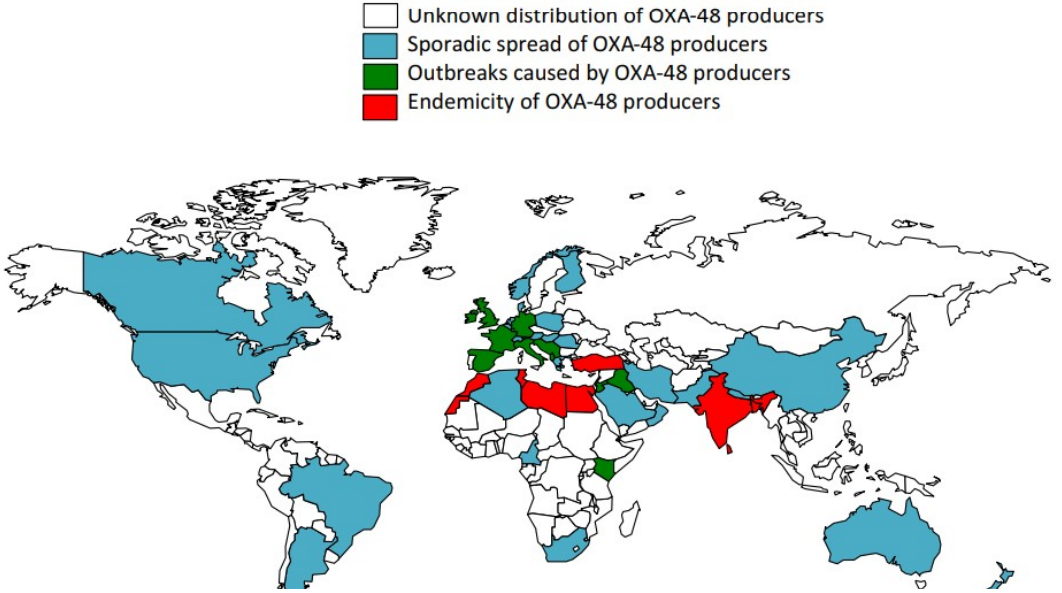
Fig. 1 Intrinsic and acquired beta-lactamases in *Enterobacteriaceae*.

REVIEW 10.1111/1469-0691.12719

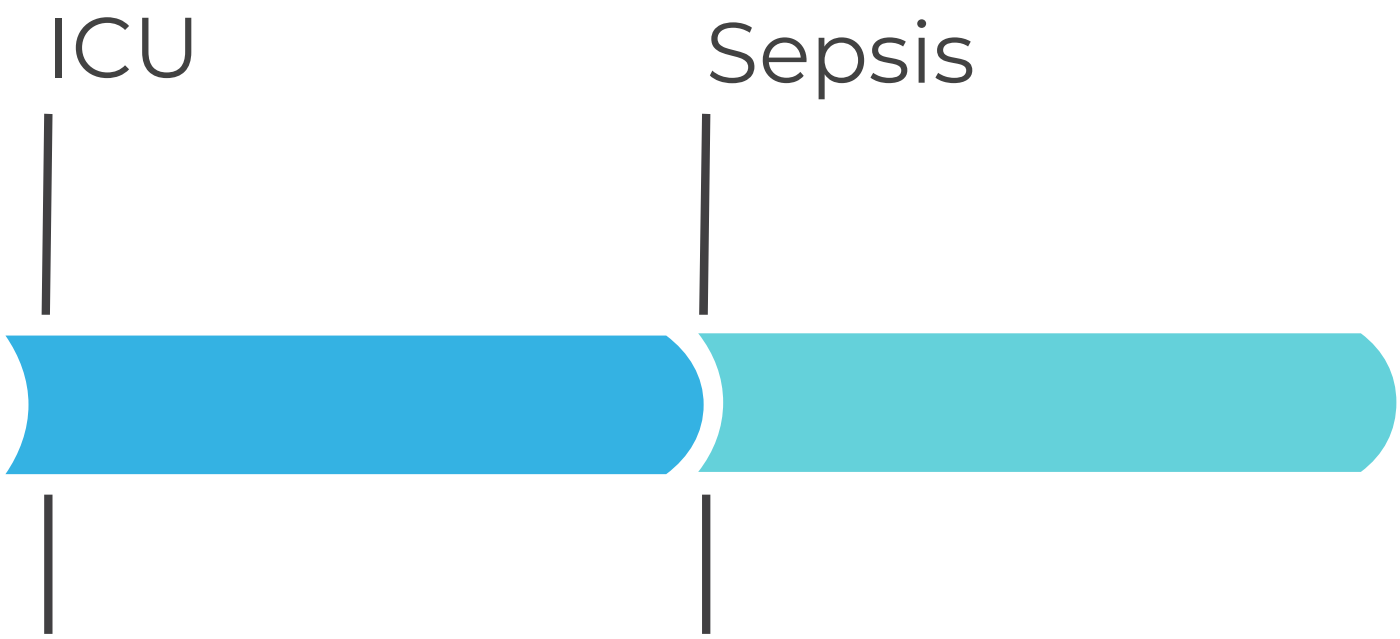
The difficult-to-control spread of carbapenemase producers among *Enterobacteriaceae* worldwide







Nordmann et al. Clinical Microbiology and Infection (201

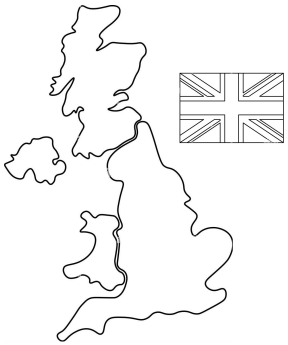


Epidémiologie locale

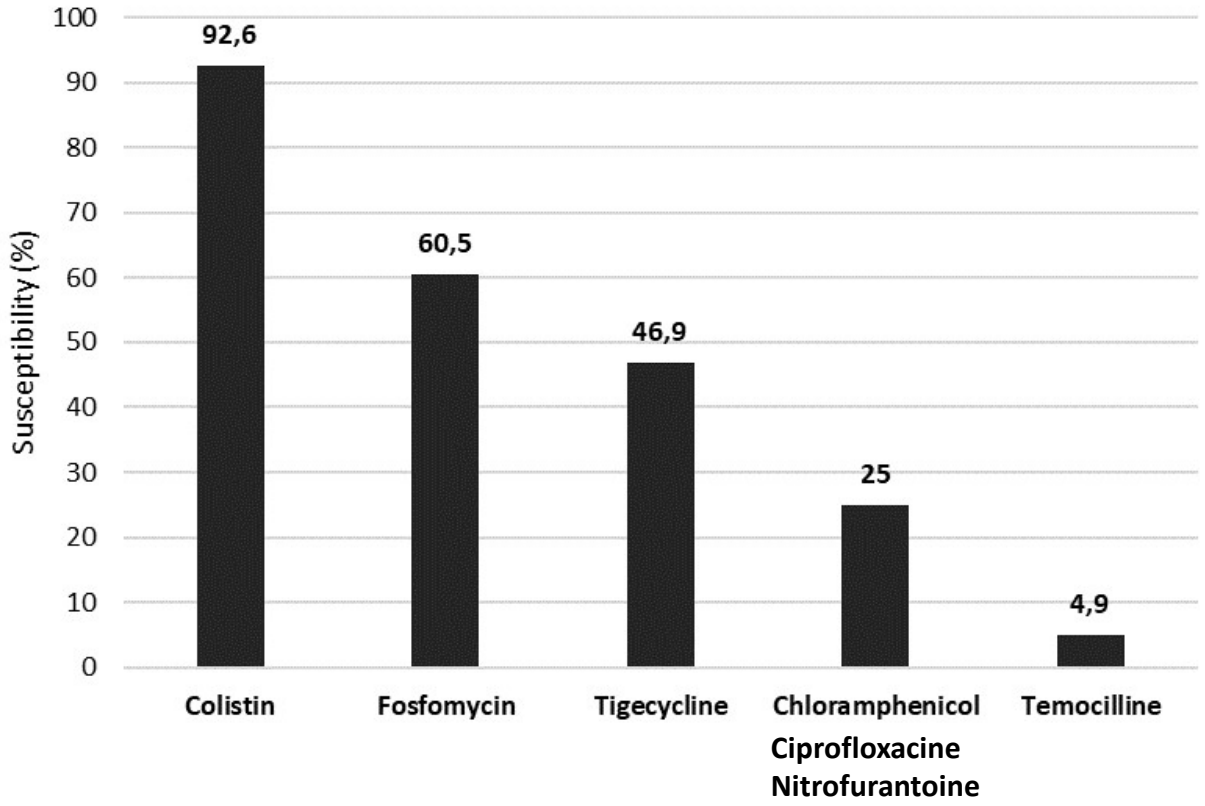
ATB probabiliste

Molécule ?
Principes de prescription

What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline

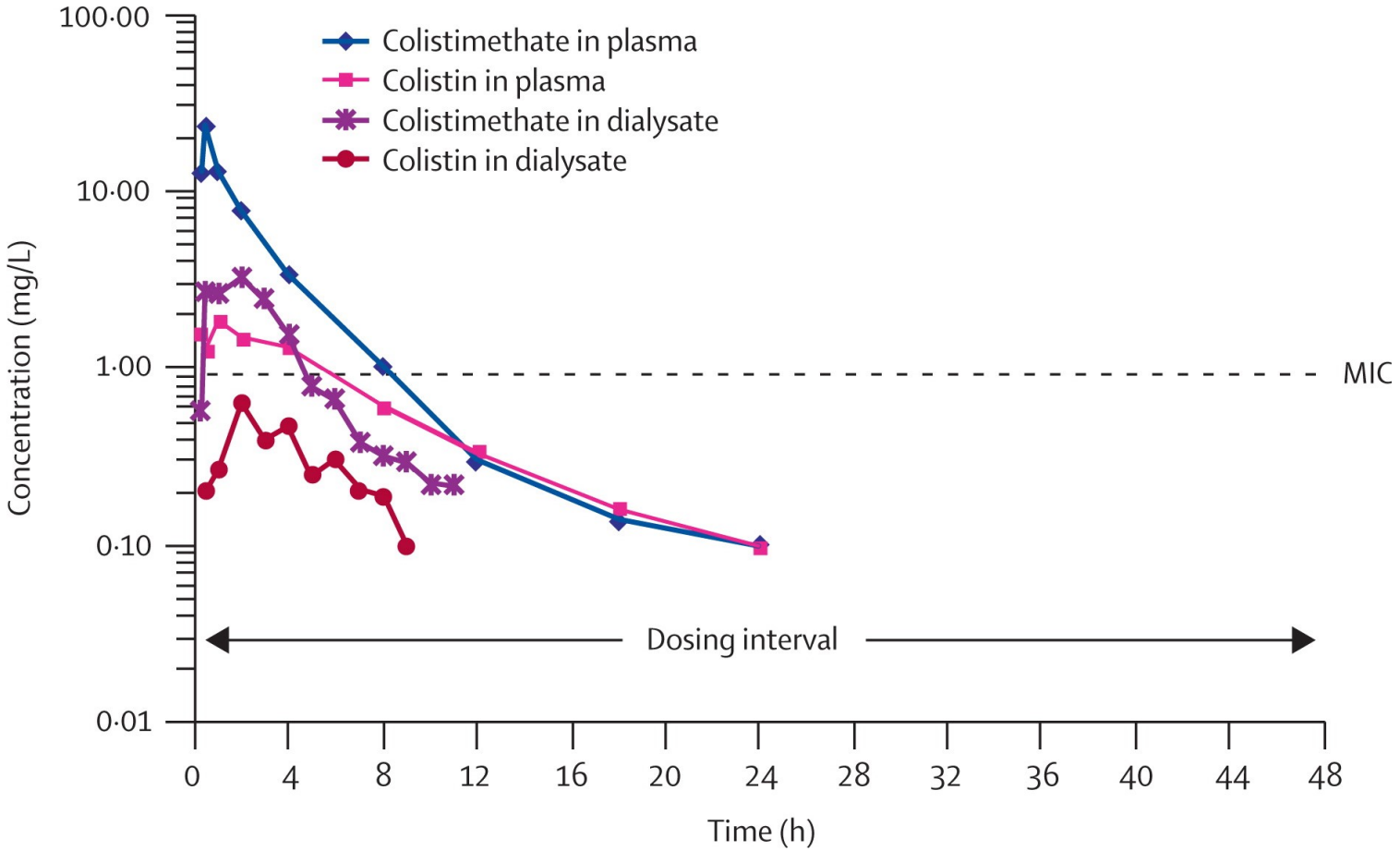


81 Carba-R Enterobacteriaceae isolates

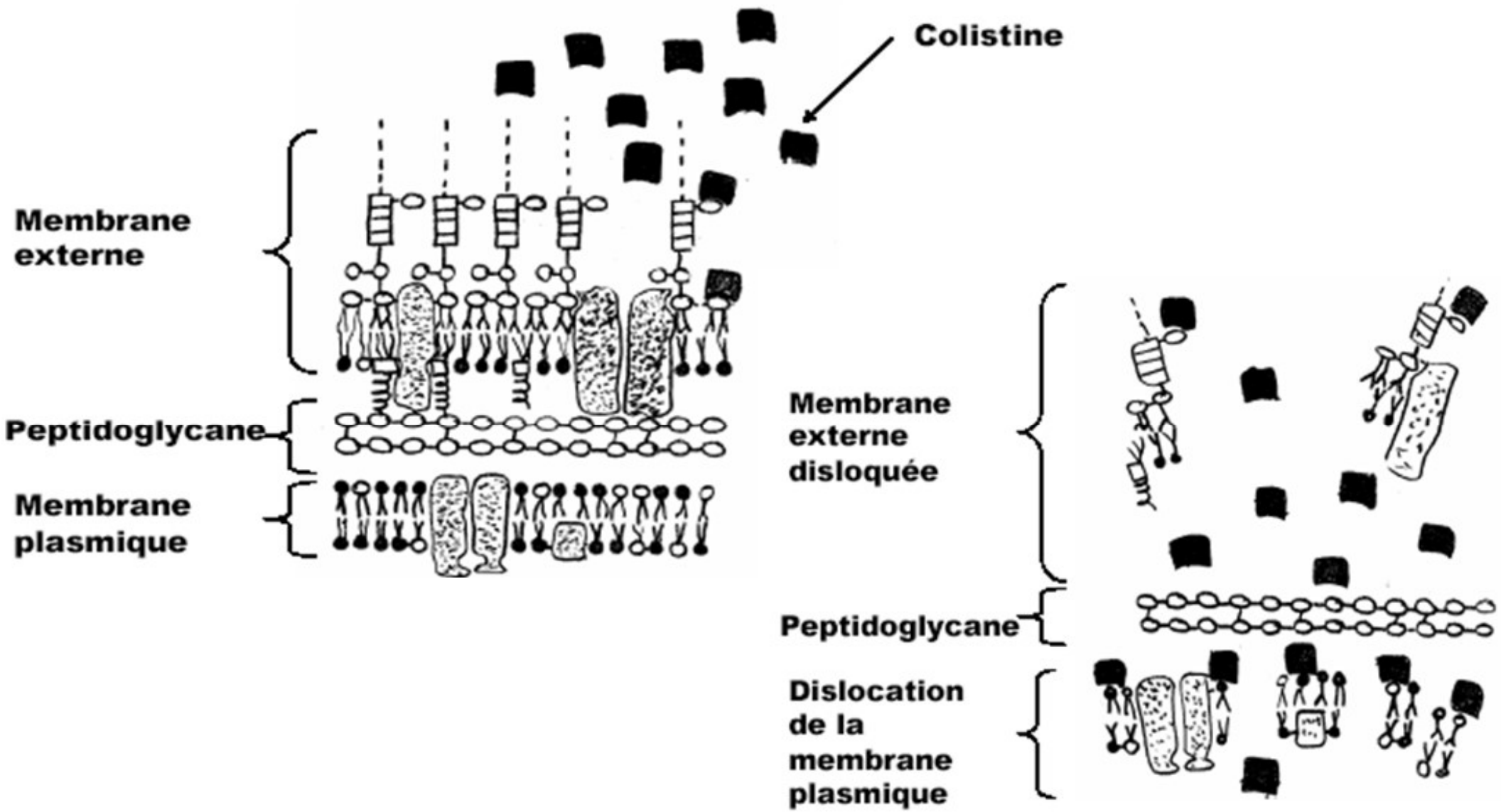


Livermore et al. International Journal of Antimicrobial Agents (2011)

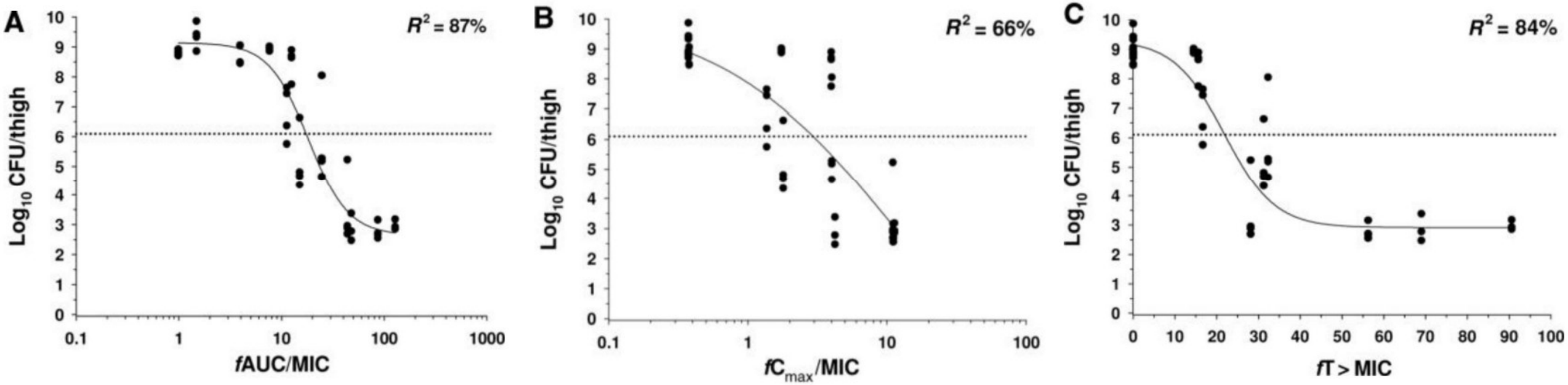
Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections



Li et al. The Lancet (2006)


Colistine
Membrane externe
Peptidoglycane
Membrane plasmique
Membrane externe disloquée
Peptidoglycane
Dislocation de la membrane plasmique

Dosing of colistin – back to basic PK/PD



Berjen et al. Curr Opin Pharmacol. (2011)

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria[▽]†

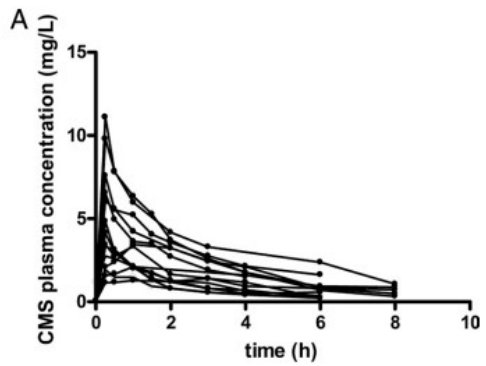


FIG. 1. Observed individual concentrations of CMS (A) and colistin (B) in plasma after the administration of the first dose of CMS. Data for patients 14, 15, 17, and 18 (Table 1) were not available after the first dose.

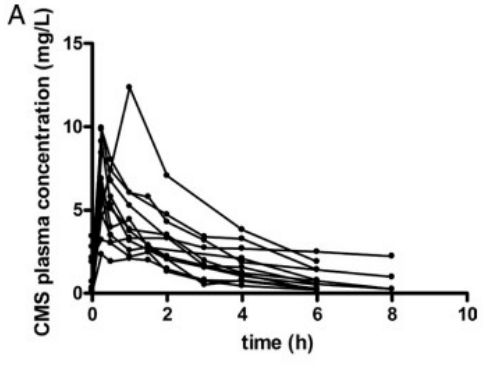
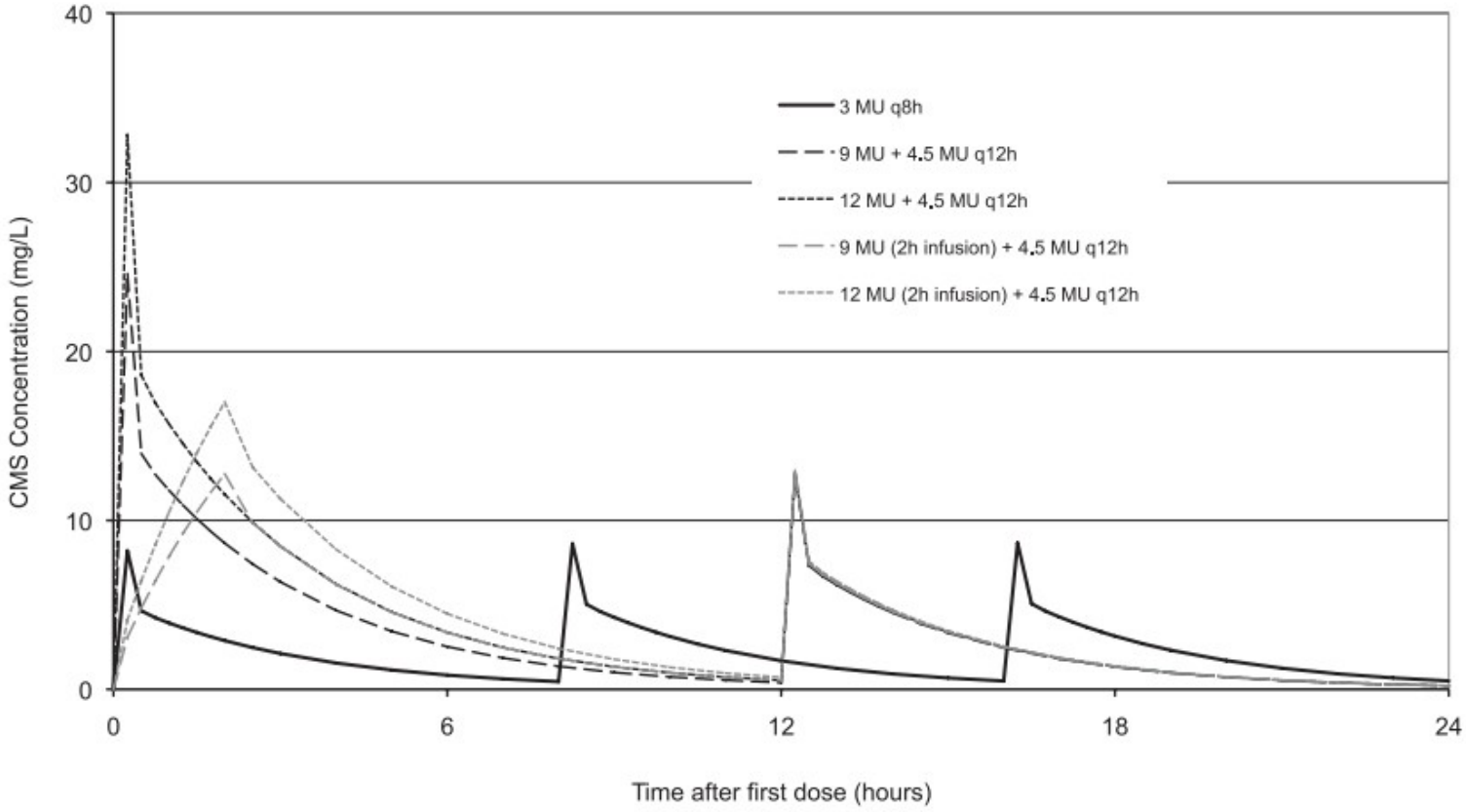


FIG. 2. Observed individual concentrations of CMS (A) and colistin (B) in plasma after the administration of the fourth dose of CMS. Data for patients 4, 14, 15, 16, 17, and 18 (Table 1) were not available after the fourth dose.

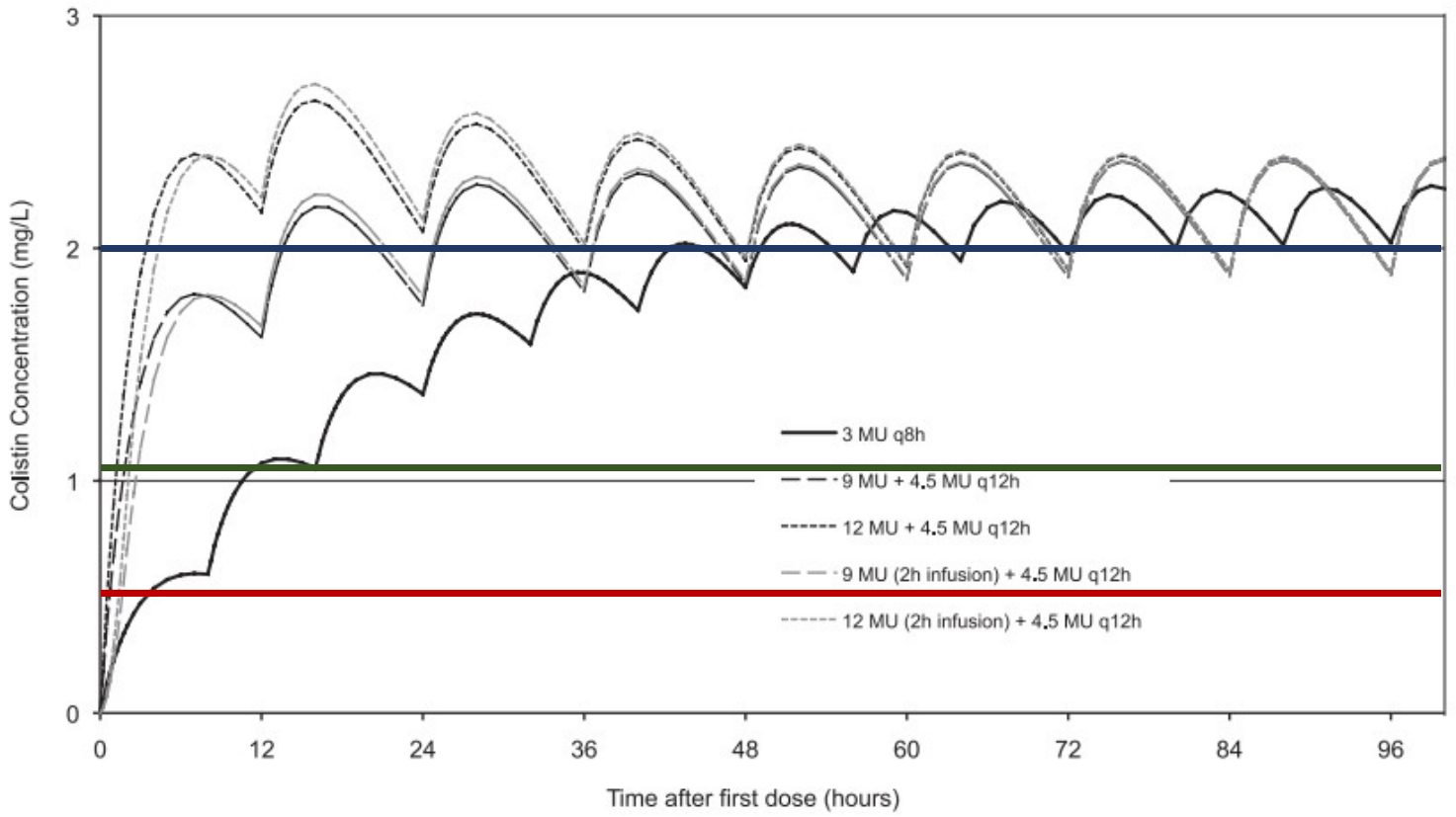
Plachouras et al. Antimicrobial Agents and Chemotherapy (2009)

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria[▽]†



Plachouras et al. Antimicrobial Agents and Chemotherapy (2009)

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria[▽]†



CMI 50

PYO

ABB

KP

Plachouras et al. Antimicrobial Agents and Chemotherapy (2009)

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

CMS dosage:

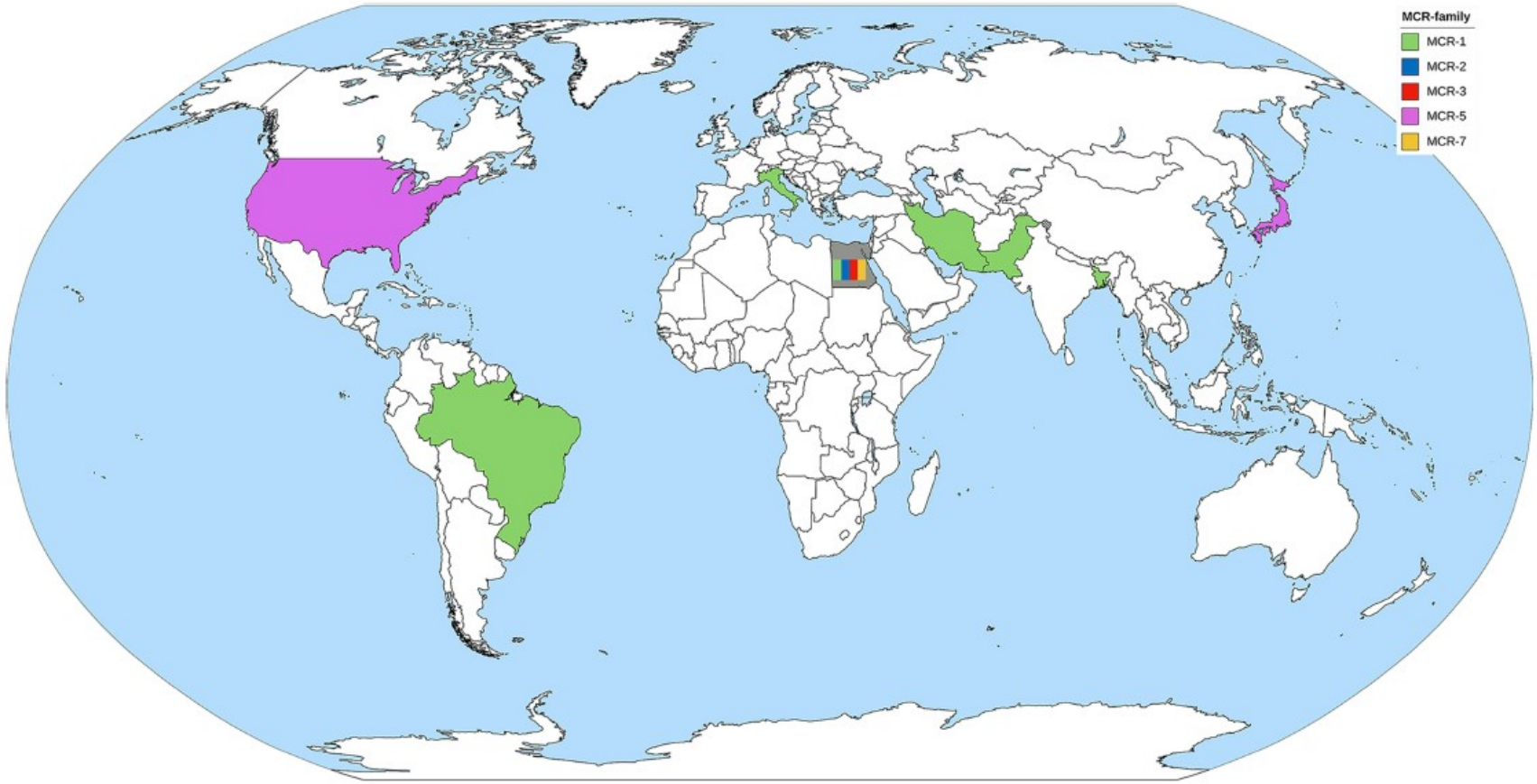
- ✓ **Loading dose** of 300 mg CBA (≈ 9 million IU) infused over 0.5–1 hour
- ✓ The first maintenance dose 12–24 hours later.
- ✓ **A daily dose** of 300–360 mg CBA (≈ 9–11 million IU), divided into two and infused over 0.5–1 hour at 12-hour intervals.

Polymiyxin B dosage:

- ✓ **Loading dose** of 2.0–2.5 mg/kg (≈ 20–25,000 IU/kg) over 1 hour.
- ✓ **Daily dose**: 1.25–1.5 mg/kg (≈ 12,500–15,000 IU/kg) / 12h over 1 hour infusion

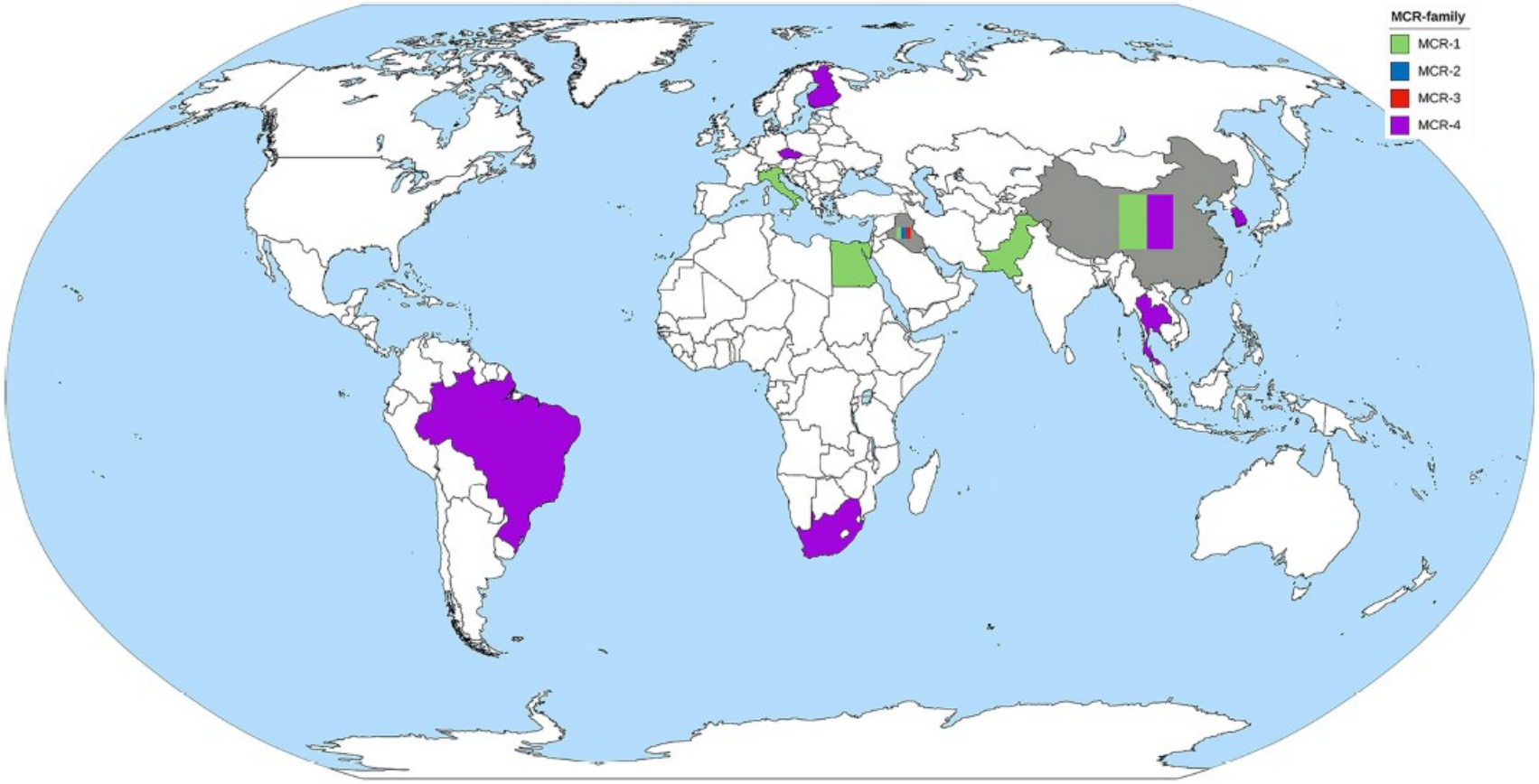
Tsuji et al. Pharmacotherapy (2019)

The worldwide dissemination of the mcr gene in Pseudomonas spp



Khuntayaporn et al. Frontiers (2022)

The worldwide dissemination of the mcr gene in Acinetobacter spp



Khuntayaporn et al. Frontiers (2022)

Predictors of outcome in ICU patients with septic shock caused by *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*

Retrospective analysis

Nov 2010 to Dec 2014

Teaching hospital (Rome-Italy)

111 ICU patients

KPC-Kp infection and septic shock

Antibiotic therapy[a]	Surviving patients (n = 67)	Nonsurviving patients (n = 44)	p
Colistin + meropenem	5 (7.4)	0	0.15
Colistin + tigecycline	6 (8.9)	0	0.08
Tigecycline + gentamicin	5 (7.4)	7 (15.9)	0.2
Meropenem + tigecycline	10 (14.9)	6 (13.6)	1.0
Colistin + tigecycline + meropenem	17 (25.3)	4 (9)	0.04*
Tigecycline + meropenem + fosfomycin	3 (4.4)	9 (20.4)	0.01*
Colistin + tigecycline + imipenem	3 (4.4)	2 (4.5)	1.0
Colistin + tigecycline + rifampicin	1 (1.5)	0	1.0
Meropenem + ertapenem + colistin	4 (5.9)	1 (2.2)	0.6
Colistin + tigecycline + meropenem + gentamicin	12 (17.9)	7 (15.9)	1.0
No use of *in vitro* active antibiotics	9 (13.4)	16 (36.3)	0.009*
Only one *in vitro* active antibiotic used within 24 hours	30 (44.7)	20 (45.4)	1.0
Two or more *in vitro* active antibiotics used within 24 hours	28 (41.8)	8 (18.1)	0.01*
Definitive therapy with fewer than two antibiotics displaying *in vitro* activity	10 (14.9)	34 (77.2)	<0.001*
Definitive therapy with two or more antibiotics displaying *in vitro* activity	57 (85.1)	7 (15.9)	<0.001*

Falcone et al. Clin Mirobiol Infect (2016)

Predictors of outcome in ICU patients with septic shock caused by *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*

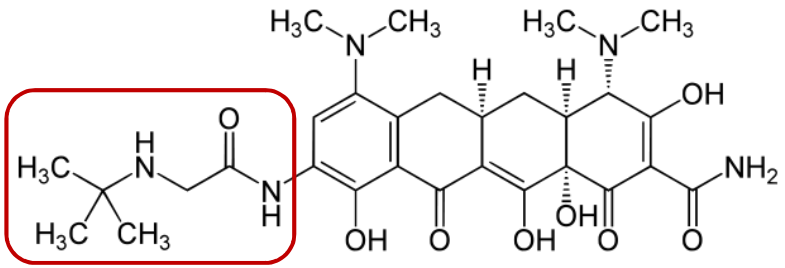
Cox regression analysis of factors associated with death

Factor	HR	95% CI	p
Colistin-containing antibiotic regimen	0.21	0.05–0.72	<0.001
Two or more *in vitro* active antibiotics as definitive therapy	0.08	0.02–0.21	<0.001
Control of removable source of infection	0.14	0.04–0.25	<0.001
Colistin-resistant strain	8.09	3.14–11.23	0.001
Intra-abdominal source of infection	2.92	2.11–4.12	0.002

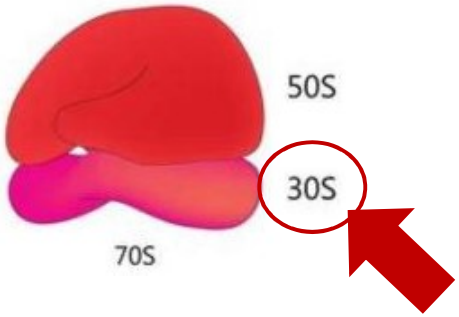
CI, confidence interval; HR, hazard ratio.

Falcone et al. Clin Mirobiol Infect (2016)

Str Commune aux cyclines



Groupe t-butylglycyclamide



Affinité 5 X
Supérieure à celle
Des tétracyclines

Tigecycline

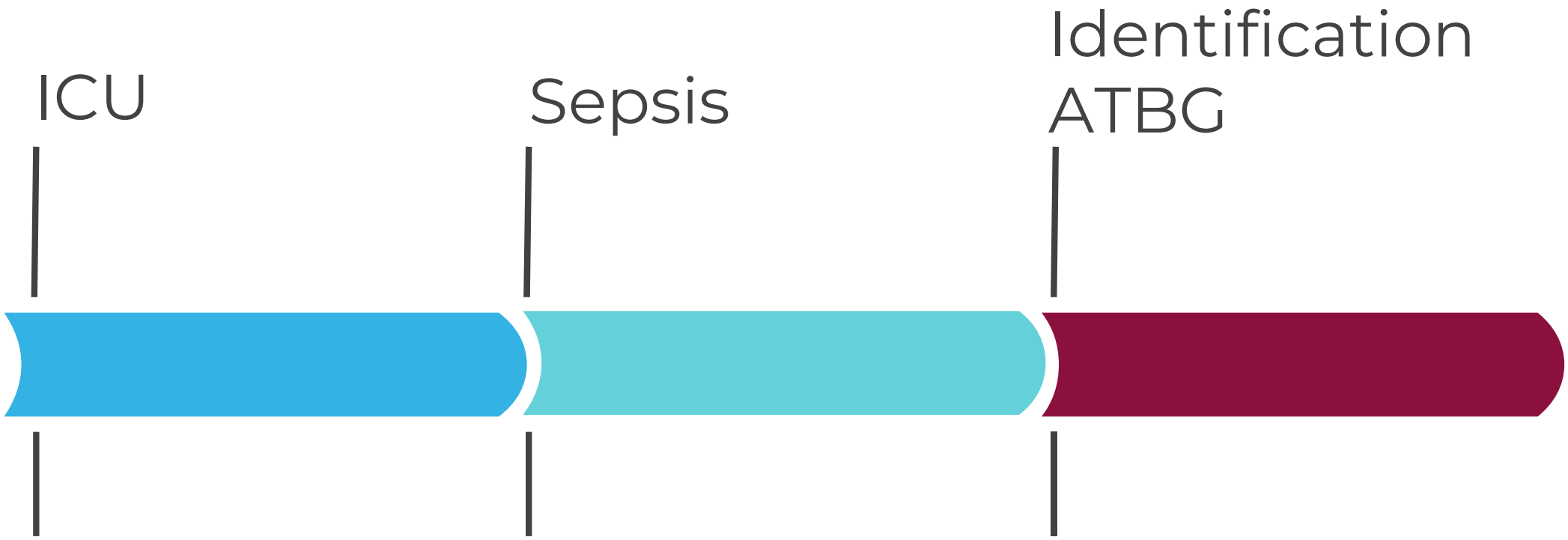
Chopra et al. Curr Opin in Pharmacology (2001)
Bauer et al. J Antimicrob Chemother (2004)

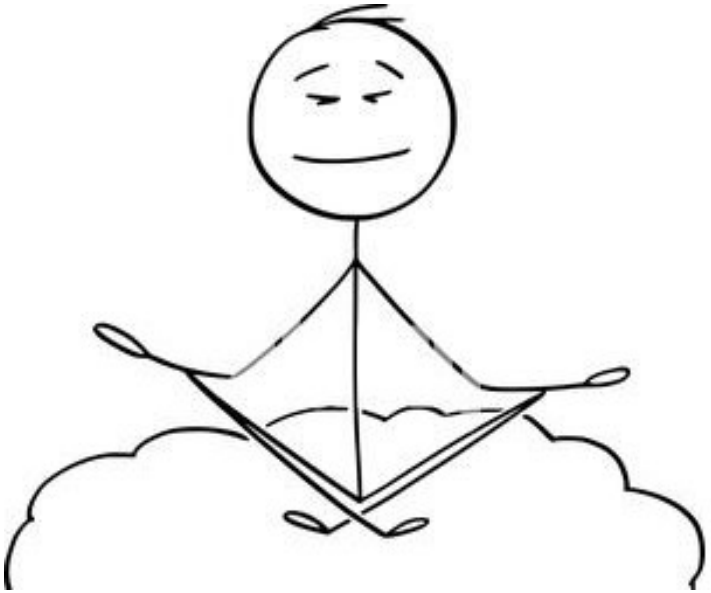
Quelle place pour la tigécycline aujourd'hui ?

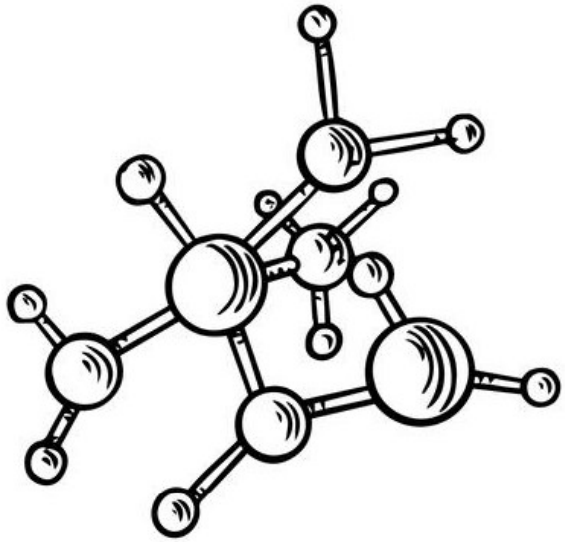
What Role for Tigecycline Today?

- **Spectre d'activité** large :
  - ✓Quasi-totalité des CG+
  - ✓Grande majorité des BGN dont 88 % des EPC / ABB
- Pseudomonas aeruginosa : **résistance naturelle**
- **Pas d'utilisation** si existence d'une alternative efficace
- **Pas de traitement probabiliste** (CMI nécessaire)
- **Dans le cadre des EPC**, prescription :
  - ✓en association (colistine et/ou carbapénèmes)
  - ✓à forte posologie (200 mg puis 100 mg/12 h

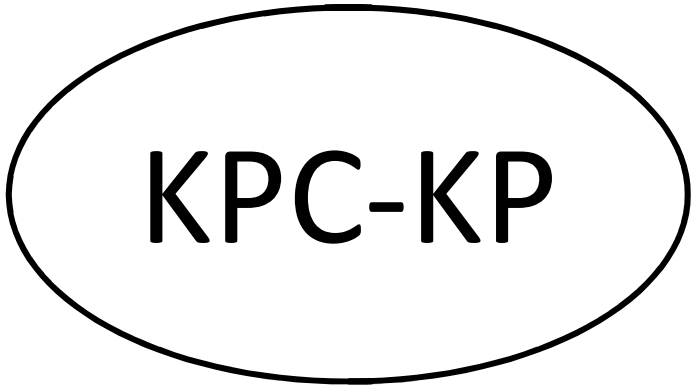
Gauzit et al. Med Intensive Réa (2017)

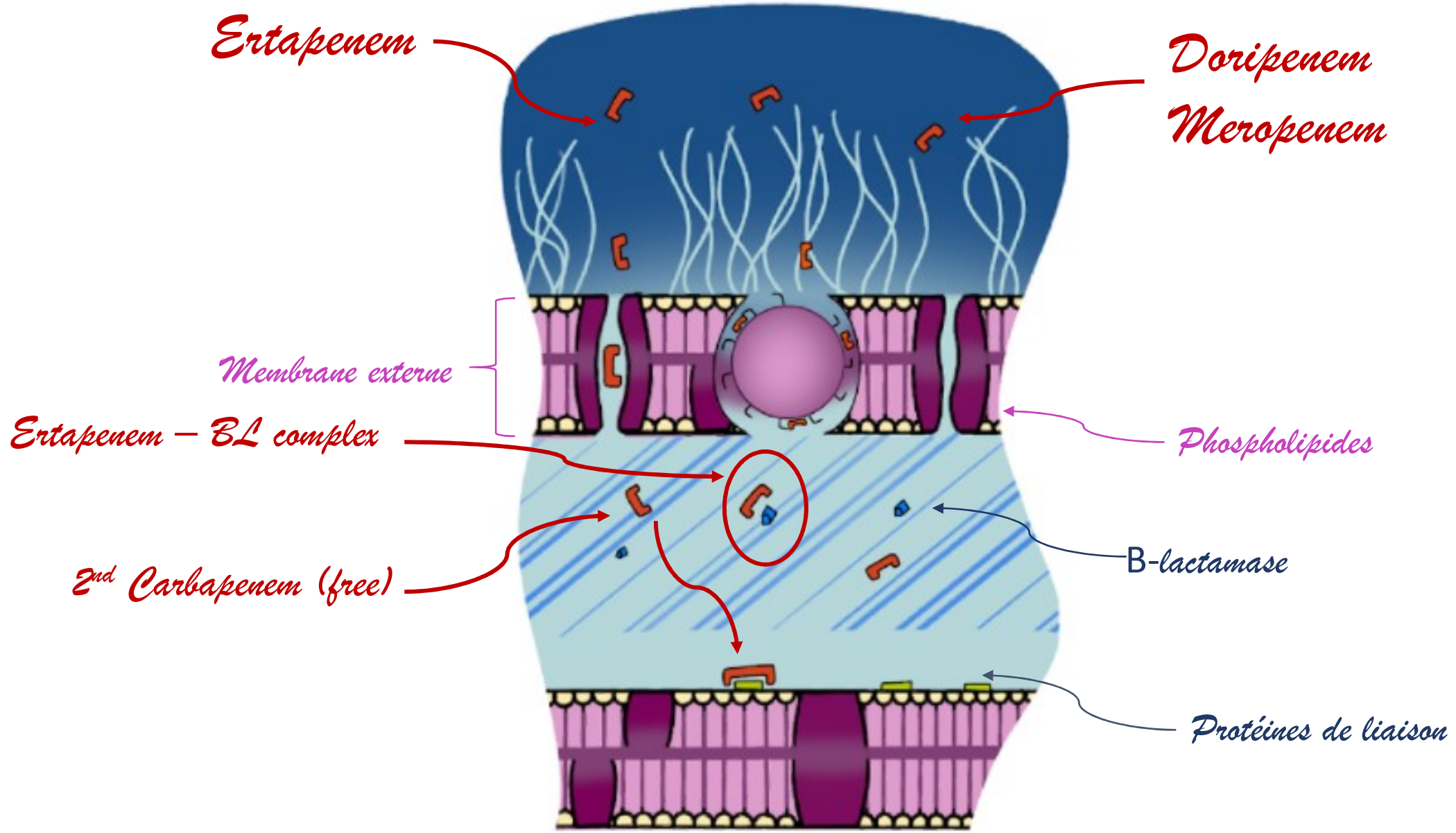

ICU
Sepsis
Identification
ATBG
Connaissance de l’épidémiologie locale
ATB probabiliste
Molécule ?
Principes de prescription
ATB définitive
Molécule ?
Principes de prescription
Stratégie





Double Carbapenem Combination
- DCC -




Ertapenem
Doripenem
Meropenem
Membrane externe
Ertapenem – BL complex
Phospholipides
2nd Carbapenem (free)
B-lactamase
Protéines de liaison

Double-Carbapenem Therapy for Carbapenemase-Producing *Klebsiella pneumoniae*

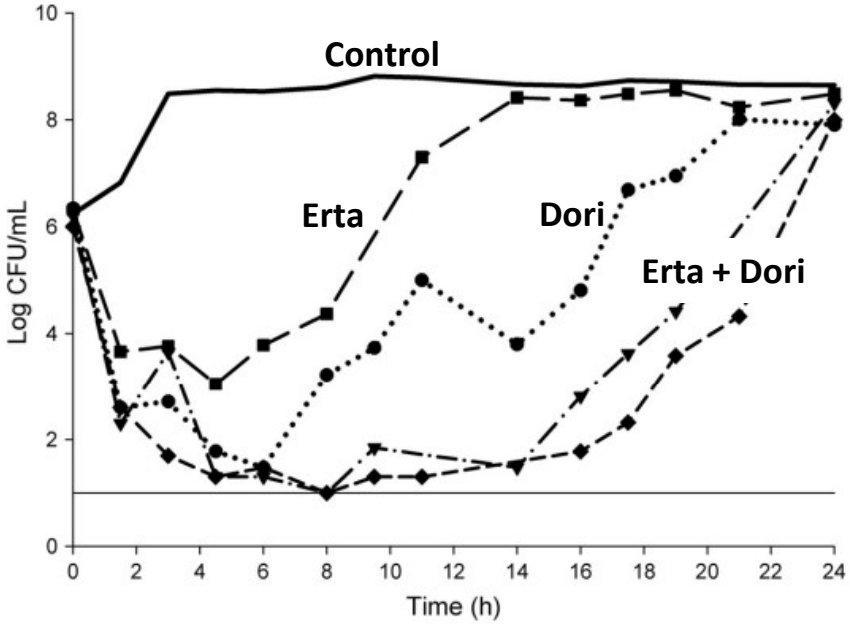


FIG. 1. Bacterial densities of KPC 354 over 24 h in the *in vitro* chemostat model (doripenem MIC, 4 μg/ml). The heavy black solid line represents the control group, the dashed line with squares represents the ertapenem control model (ertapenem alone), the dotted line with circles represents the doripenem control model (doripenem alone), and the dashed lines with either triangles or diamonds represent the doripenem-plus-ertapenem treatment model. The lower limit of detection is set at 10^1 CFU/ml.

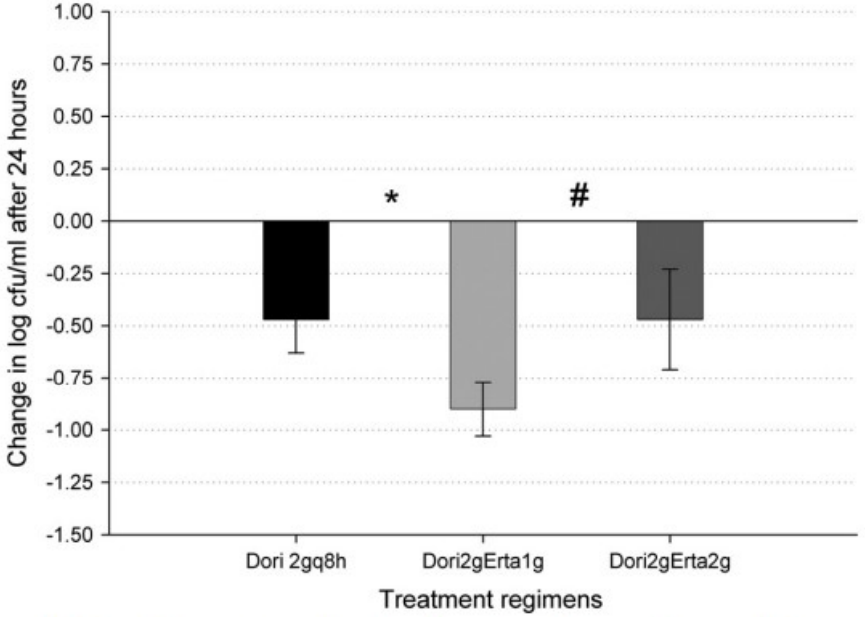


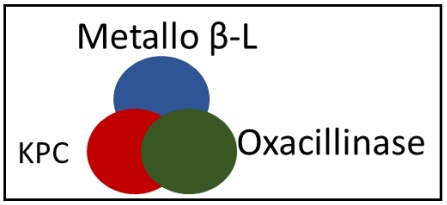
FIG. 2. Comparative efficacies of various dosing regimens of doripenem with or without ertapenem against KPC 354 in the *in vivo* murine thigh infection model (doripenem MIC, 4 μg/ml). The statistical significance of the difference between doripenem alone and doripenem at 2 g plus ertapenem at 1 g is indicated with an asterisk (*), while the statistical significance of the difference between the combination therapies is indicated with a number symbol (#).

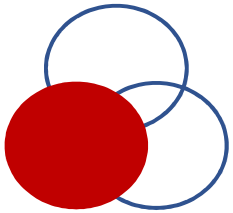
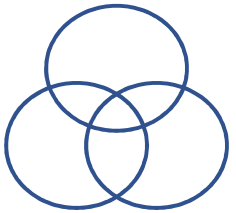
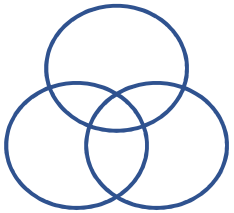
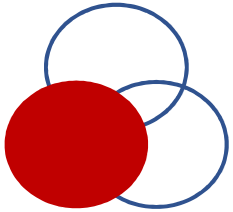
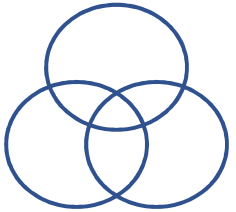
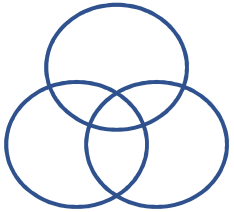
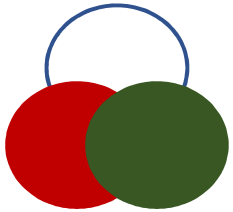
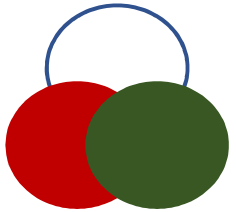
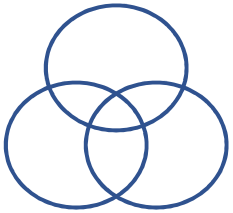
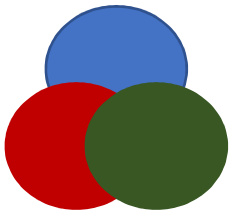
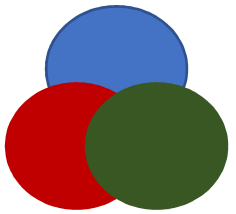
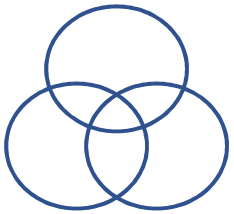
Catharine et al. Antimicrobial Agents and Chemotherapy (2011)

Double-carbapenem therapy in the treatment of multidrug resistant Gram-negative bacterial infections: a systematic review and meta-analysis

- ✓ 90 patients with CRE infection
- ✓ DCT vs. other regimens
- ✓ Clinical improvement: 65,6%
- ✓ Microbiological improvement: 70%
- ✓ Clinical and microbiological responses : idem
- ✓ DCT: lower mortality (OR = 0.44, 95% CI = 0.24–0.82, P = 0.009)
- ✓ Ertapenem: the most reported ATB in DCT regimens

Li et al. BMC Infectious Diseases (2020)



	K pneumoniae	P aeruginosa	A baumanii
Imipénème/cilastatine/relebactam			
Méropénème/vaborbactam			
Ceftazidime/avibactam			
Céfidérocol			

Conclusion

- TTT of DTT bacteria:
  - ✓Knowledge of the unit / hospital epidemiolgy
  - ✓Knowledge of the resistance enzyme / CMI of the causal bacteria
  - ✓Combination based therapy containing colistin
  - ✓Loading dose colistin
  - ✓New molecules !
- Prevention strategy
- Inoculum reduction
- PK/PD