ème
31 CONGRÈS NATIONAL
LA SOCIÉTÉ TUNISIENNE
DE PATHOLOGIE INFECTIEUSE

Comment traiter une infection à BGN multirésistants en 2022 ?

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Hammamet, le 20 mai 2022

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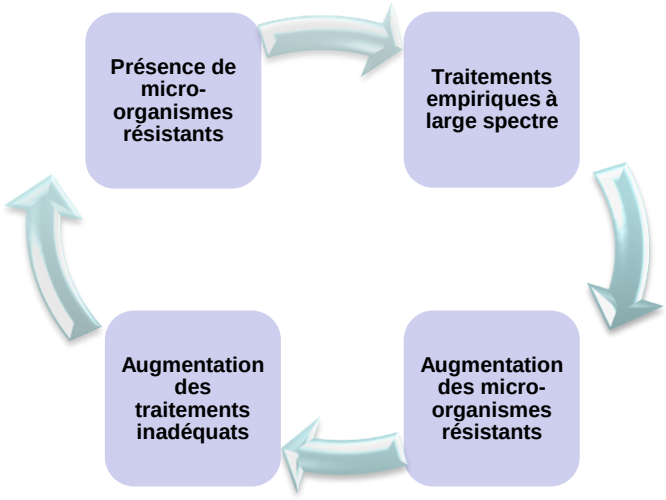
EPS MONASTIR

Introduction

- Antibiorésistance : problème majeur de santé publique
- Augmentation constante de la résistance non contre balancée par la découverte de nouvelles molécules
- Accès aux antibiotiques
- Impasses thérapeutiques



Ramos-Castaneda, J Inf, 2018

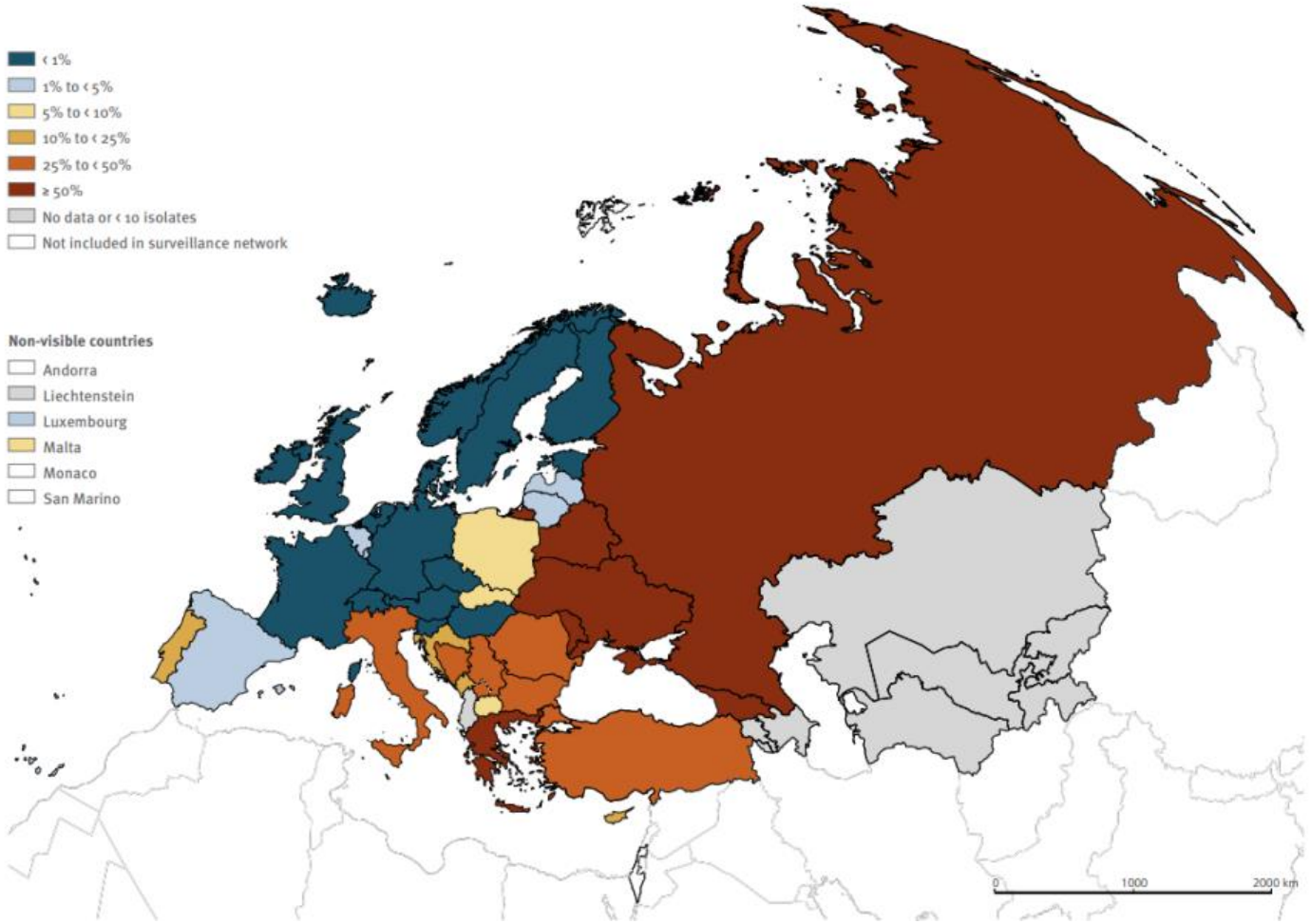
Résistance – mortalité

- Mortalité :
  - Infections causées par KPC-K. pneumoniae : 40%
  - Mortalité des bactériémies à *P. aeruginosa* : 20-40%
  - Mortalité à J30 des infections à entérobactéries OXA-48 : 50%
- Impact économique majeur :
  - Europe : 1,9 billion euros / an
  - USA : 20 billions USD

Ramos-Castaneda, J Inf, 2018 / ECDC 2009 / Kaye, Pharmacotherapy 2015

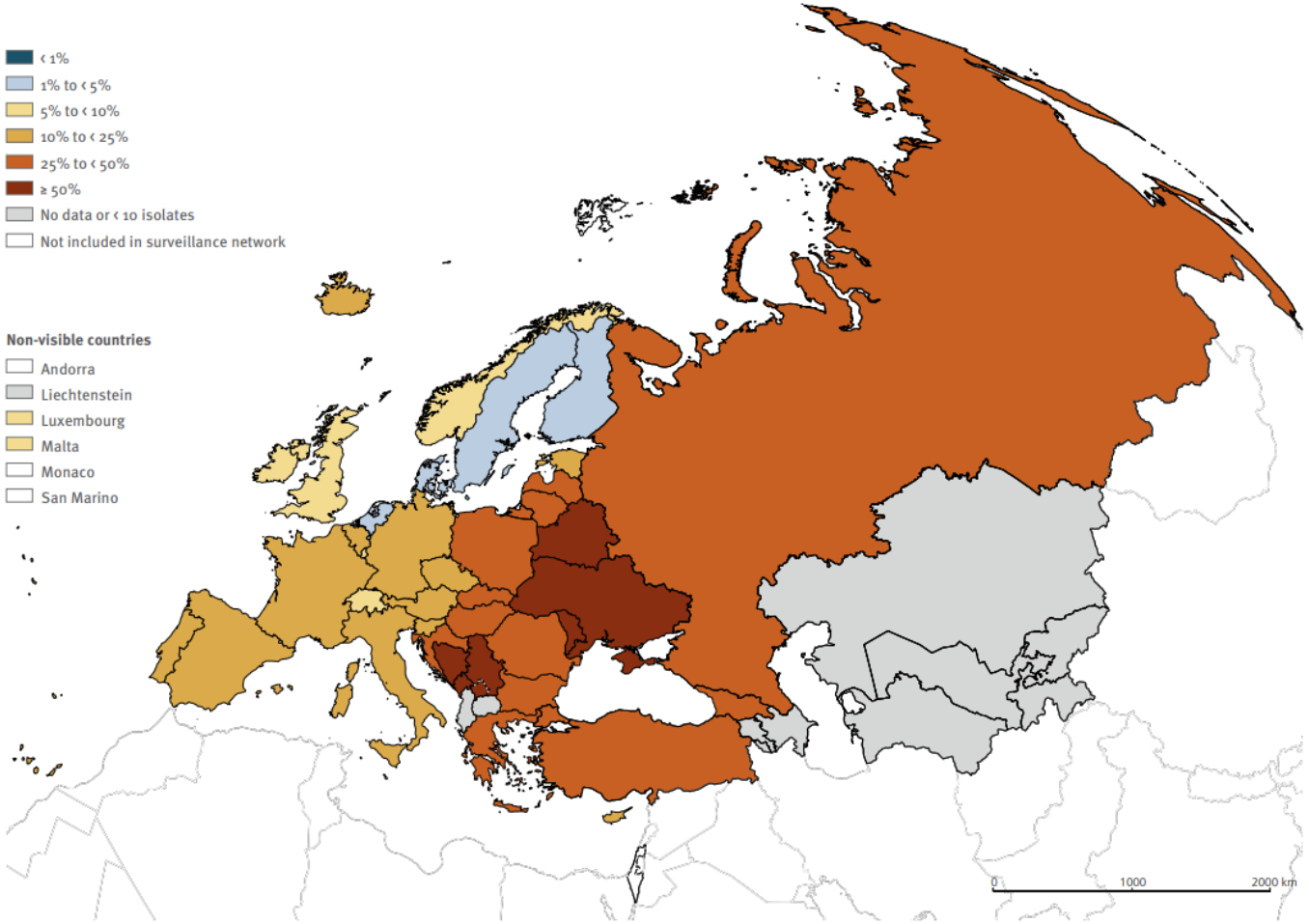
Résistance = état des lieux

K. pneumoniae : souches invasives résistantes aux carbapénèmes



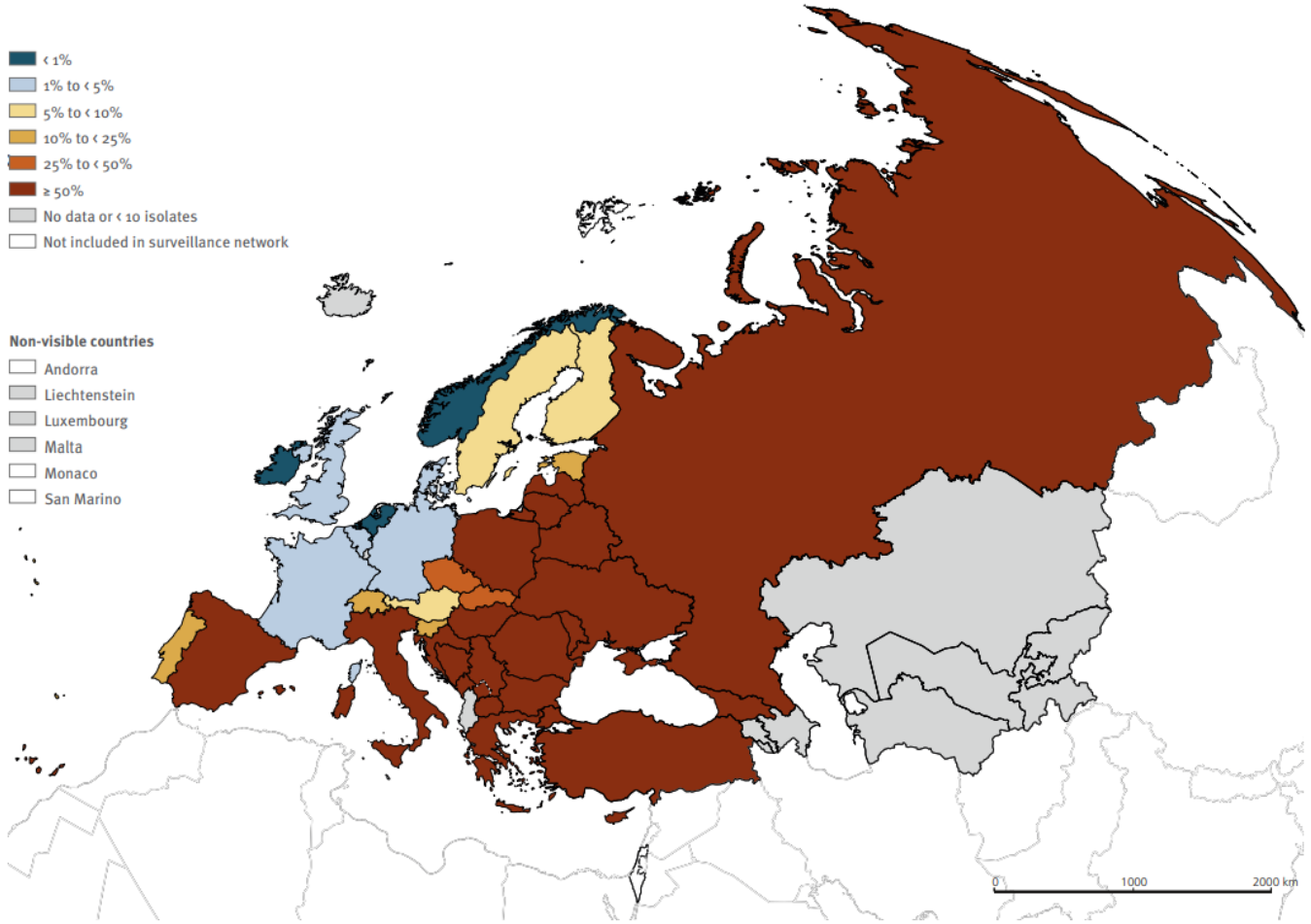
Données ECDC 2020

P. aeruginosa : souches invasives résistantes aux carbapénèmes



Données ECDC 2020

A. baumannii : souches invasives résistantes aux carbapénèmes



Données ECDC 2020

En Tunisie : données de LART (2019)

P. aeruginosa

		Total			Hémocultures			Poumon	
Nombre	**Nb de souches testées**	**2243**		**Nb de souches testées**	**143**		**Nb de souches testées**	**934**	
		R	**R+I**		**R**	**R+I**		**R**	**R+I**
Ticarcilline	1743	31,8	31,8	100	41	41	698	28,1	28,1
Pipéracilline	1687	31,8	31,8	105	32,4	32,4	672	28,1	28,1
Pipéracilline+Tazobactam	1990	25,8	26	115	29,6	29,6	805	23,4	23,4
Ceftazidime	2036	22	22,3	105	26,7	27,6	866	18,8	18,9
Céfépime	1923	22,1	22,5	113	24,8	26,6	737	18,9	19,1
Aztréonam	1607	9,6	55,6	100	13	55	613	9,8	64,1
Imipénème	**2066**	**22,8**	**25,8**	**111**	**27**	**28,8**	**850**	**23,1**	**26,7**
Méropénème	982	19,3	25,8	53	20,8	28,3	498	23,1	25,9
Gentamicine	1712	26,8	26,8	96	27,1	27,1	711	21,9	21,9
Tobramycine	1461	19,2	19,2	86	26,7	26,7	543	16	16
Amikacine	1926	17,1	22,2	113	21,2	26,6	714	14	19,9
Ciprofloxacine	1793	25,7	26	101	27,7	28,7	687	18,8	19,1

E. coli

	Total			Urine			Hémoculture		
	Nombre	% R	% R+I	Nombre	% R	% R+I	Nombre	% R	% R+I
Amoxicilline	7874	73,3	73,4	6862	72,9	72,9	195	77,9	77,9
Ticarcilline	7262	72,3	72,4	6302	72,2	72,2	186	75,8	75,8
Amoxicilline – Acide clavulanique	7860	36,1	35,8	6835	36,1	36,1	199	46,7	46,7
Pipéracilline - Tazobactam	7464	7,5	16,5	6449	7,2	16,5	186	10,2	25,8
Céfoxitine	4875	3,0	4,2	4174	2,3	3,4	112	13,4	14,3
Céfotaxime	7260	18,3	18,8	6320	17,3	17,8	186	32,8	34,4
Ceftazidime	7151	15,4	18,0	6205	14,7	15,5	190	29,5	34,7
Imipénème	6936	0,2	0,3	6006	0,1	0,2	186	0,5	1,1
Ertapénème	8202	0,6	1,0	7132	0,5	0,7	209	1,4	1,9
Gentamicine	5828	11,3	13,3	5033	11,2	13,3	139	8,6	11,5
Tobramycine	5200	12,5	16,2	4639	11,8	15,6	140	15,0	16,4
Amikacine	7503	0,6	1,8	6535	0,4	1,7	187	3,2	4,3
Tigécycline	5134	0,2	1,0	4392	0,2	1,0	130	0,8	1,5
Acide nalidixique	7244	31,2	32,8	6310	31,2	32,7	168	31,5	35,1
Ciprofloxacine	6355	23,2	24,3	5498	24,4	25,6	175	25,7	28
Cotrimoxazole	6010	38,8	39,2	5227	38,7	39,1	137	40,1	41,6
Mecillinam	-	-	-	4424	23	23	-	-	-
Nitrofuranes	-	-	-	4720	2,1	2,1	-	-	-
Fosfomycine	-	-	-	4050	1	1	-	-	-

K. pneumoniae (n = 3678)

	Total			Hémocultures			Urines		
	Nombre	%R	%R+I	Nombre	%R	%R+I	Nombre	%R	%R+I
Amoxicilline – Acide clavulanique	3355	49,0	49,1	382	69,1	64,2	1903	43,7	43,7
Pipéeacilline - Tazobactam	3199	30,6	41,4	354	46,2	58,8	1835	26,7	36,4
Céfoxitine	2050	33,2	34,6	257	42,9	44,2	1051	28,2	30,1
Céfotaxime	3113	45,3	48,2	337	69,6	72,6	1797	38,7	41,0
Ceftazidine	3116	45,9	49,6	332	69,0	75,7	1758	38,5	41,7
Imipénème	**3097**	**13,1**	**18,7**	**355**	**17,5**	**25,7**	**1707**	**11,4**	**15,5**
Ertapénème	3594	20,3	22,4	401	29,1	32,5	2030	16,2	17,9
Gentamicine	2449	32,5	39,7	273	50,8	54,8	1342	26,3	28,6
Tobramycine	2266	34,2	38,1	256	50,9	56,2	1331	27,6	31,2
Amikacine	3230	12,6	18,3	369	19,9	27,0	1834	9,7	13,4
Acide nalidixique	2882	36,5	45,5	347	42,9	52,4	1657	34,7	42,3
Ciprofloxacine	3037	34,9	37,6	332	43,9	46,9	1763	31,3	34,0
Cotrimoxazole	2442	39,7	41,5	256	47,2	50,2	1381	38,9	40,3

Entérobactéries résistantes aux carbapénèmes (ERC)

ANTIBIOGRAMME

Germe : ***Escherichia coli***

Numération culture :

Antibiotique	Résultat interprété	CMI	Seuils CMI	Spécilaité
AMOXICILLINE 20µg	Résistant		8 - 8	CLAMOXYL
AMOXICILLINE + AC.CLAVULANIQUE 20-10µg	Résistant	>8	8 - 8	AUGMENTIN
TICARCILLINE 75µg	Résistant	>16	8 - 16	TICARPEN
TICARCILLINE + AC.CLAVULANIQUE 75-10µg	Résistant	>16	8 - 16	CLAVENTIN
PIPERACILLINE 30µg	Résistant		8 - 16	PIPERILLIN
PIPERACILLINE + TAZOBACTAM 30-6µg	Résistant	>128	8 - 16	TAZOCILLIN
CEFALEXINE 30µg	Résistant		16 - 16	
CEFUROXIME IV 30µg	Résistant		8 - 8	CUROXIME
CEFOXITINE 30µg	Résistant	>64	8 - 16	MEFOXIN
CEFIXIME 5µg	Résistant	>1	1 - 1	OROKEN
CEFOTAXIME 5µg	Résistant	>16	1 - 2	CLAFORAN
CEFEPIME 30µg	En cours		1 - 4	AXEPIM
AZTREONAM 30µg	Résistant	256	1 - 4	AZACTAM
ERTAPENEME 10µg	Résistant	>32	0,5 - 1	INVANZ
TOBRAMYCINE 10µg	Résistant	>16	2 - 4	NEBCINE
NETILMICINE 10µg	Résistant	16	2 - 4	NETROMICIN
AMIKACINE 30µg	Résistant	>64	8 - 16	AMIKLINCIN
ACIDE NALIDIXIQUE 30µg	Résistant	>16	16 - 16	NEGRAM
NORFLOXACINE 10µg	Résistant	>16	0,5 - 1	NOROXINE
OFLOXACINE 5µg	Résistant	128	0,25 - 0,5	OFLOCET
CIPROFLOXACINE 5µg	Résistant	256	0,25 - 0,5	CIFLOX
LEVOFLOXACINE 5µg	Résistant	>8	0,5 - 1	
FOSFOMYCINE 200µg	SENSIBLE	<=32	32 - 32	FOSFOCINE
CHLORAMPHENICOL 30µg	Résistant	>8	8 - 8	
NITROFURANTOINE 100µg	Résistant	>64	64 - 64	ERCEFURYL
TRIMETHOPRIME + SULFAMIDES 1.25-23.75µg	Intermédiaire	>2	2 - 4	BACTRIM
TIGECYCLINE 15µg	SENSIBLE	<1	1 - 2	

Que choisir ?

Les études ?

- Patients très graves :
  - Impact de l'antibiothérapie sur le pronostic ?
- Endpoint : mortalité ?
- Protocoles en double aveugle ?
- Randomiser les malades ?
- Études avec faibles effectifs …

ERC : Molécules

- Ceftazidime-avibactam
- Méropénème-vaborbactam
- Céfidérocol
- Imipénème-relebactam
- Tigécycline
- Aminosides
- Colistine
- Fosfomycine

Paul, CMI, 2022

ERC : Molécules

- Ceftazidime-avibactam
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Paul, CMI, 2022

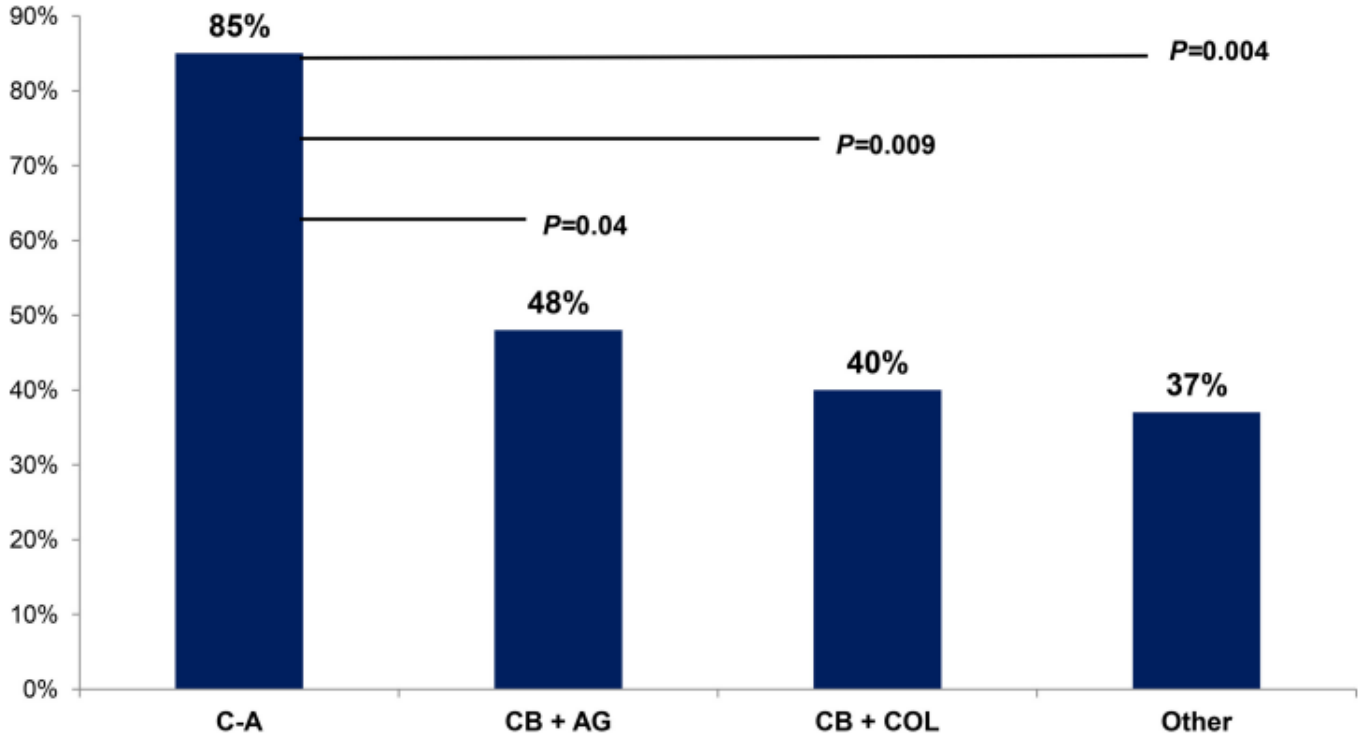
Ceftazidime – avibactam

- Nouvelle BL/IBL
- Activité sur :
  - BLSE
  - Enzymes de classes A (KPC) et C (Amp C)
  - Certaines de classe D (OXA-48)

Van Duin, CID, 2018

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia

- Étude rétrospective, 109 patients
- Succès clinique à J30



Shields, AAC, 2017

Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase–Producing *K. pneumoniae* Infections: A Retrospective Observational Multicenter Study

- The cohort comprised 577 adults with bloodstream infections (n = 391) or nonbacteremic infections involving mainly the urinary tract, lower respiratory tract, and intra-abdominal structures. All received treatment with CAZ-AVI alone (n = 165) or with ≥1 other active antimicrobials (n = 412). The all-cause mortality rate 30 days after infection onset was 25% (146/577). There was no significant difference in mortality between patients managed with CAZ-AVI alone and those treated with combination regimens (26.1% vs 25.0%, *P* = .79). In multivariate analysis, mortality was positively associated with presence at infection onset of septic shock (*P* = .002), neutropenia (*P* < .001), or an INCREMENT score ≥8 (*P* = .01); with lower respiratory tract infection (LRTI) (*P* = .04); and with CAZ-AVI dose adjustment for renal function (*P* = .01). Mortality was negatively associated with CAZ-AVI administration by prolonged infusion (*P* = .006). All associations remained significant after propensity score adjustment.

Tumbarello, CID, 2021

Ceftazidime-Avibactam

Ceftazidime-avibactam actif sur la plupart des KPC et OXA-48 selon seuils définis (≤8/4 mg/L)

Revue des séries et cas cliniques des infections à EPC traités par Ceftazidime-avibactam

no. of sites; inclusion Reference criteria	*n*	Types of infections and pathogens	Mortality definition (no. of deaths/no. of patients treated [%] [CAZ-AVI vs other regimens])	Clinical cure (no. of patients with cure/no. of patients treated [%] [CAZ-AVI vs other regimens])
Retrospective cohort, hematological,	31	4 sites; BSI due to CRE, 85% *K. pneumoniae*; 60% OXA-48 producers and 40% KPC producers; sources: 14 (45.1%) primary, 6 (19.3%) HAP	Day 30; 2/8 (25) vs 12/23 (52.2); *P* = 0.24	Day 14; 6/8 (75) vs 8/23 (34.8); *P* = 0.03
Retrospective cohort, 1 site; BSI due to CR *K. pneumoniae*, ≤3 days of therapy	109	All *K. pneumoniae*;97% KPC; 50% in ICU; Source: 50 (45.8%) IAI, 28 (25.6%) primary BSI	30-day; 1/13 (7.6) vs 30/96 (31.2)	Day 30; 11/13 (85) vs 30/96 (40.6); *P* 0.006; adjusted OR 8.64 (95% CI 1.61–43.39)
Retrospective, 1 site; CRE infections treated with CAZ-AVI	37	84% *K. pneumoniae*; 78.3% KPC	30-day; 9/37 (24.3)	23/37 (62); for monotherapy, 58%; for combination therapy, 64%; 10 (27%) recurrences, with 3 isolates developing resistance
Retrospective, 1 site; CRE infections treated with CAZ-AVI	6	All *K. pneumoniae*, KPC; all susceptible to CAZ-AVI	In-hospital; 3/6 (50)	4/6 (66.6); 2 relapses, no development of resistance
Retrospective cohort, 15 sites; CRE infections treated with CAZ-AVI, salvage therapy	38	34 *K. pneumoniae*;23 KPC, 13 OXA-48; type of infection: 15 (39.4%) IAI, 7 (18.4%) HAP	In-hospital; overall, 15/38 (39.5); for IAI, 6/15 (40); for HAP, 5/7 (71.4)	28 (73.7); for monotherapy, 69.2%; for combination therapy, 76%; 2 relapses, no resistance detected
Retrospective cohort, 9 health care systems in USA; CRE infections treated with CAZ-AVI for ≤24 h	60	83% *K. pneumoniae*; type of infection: 38% BSI, 28% UTI, 27% HAP	In-hospital; overall, 19/60 (32); for monotherapy, 30%; for combination therapy, 33%; for BSI, 39%; for UTI, 12%; for pneumonia, 56%	39/60 (65); for monotherapy, 67%; for combination therapy, 63%
Prospective cohort, 18 hospitals in USA; CRE infections	137	97% *K. pneumoniae*, 96% KPC-producers; type of infection: 46% BSI, 22% HAP, 14% UTI	30-day, adjusted; 8% vs 32% (difference, 23%; 95% CI, 9–35%)	30-day adjusted probability of better outcome (using desirable outcome ranking), 64% (95% CI, 57–71%) with ceftazidime-avibactam

- Absence d'activité sur classe B (NDM)
- Intérêt d'associer aztreonam

Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems?

Dalkos GL et al, CMI, 2011

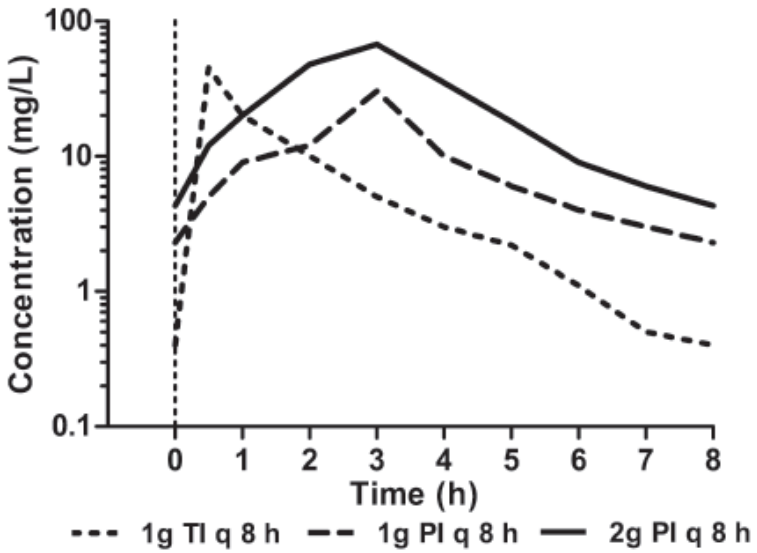


FIG. 1. Simulated concentration–time profiles of three different dosing regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [35,45,47].

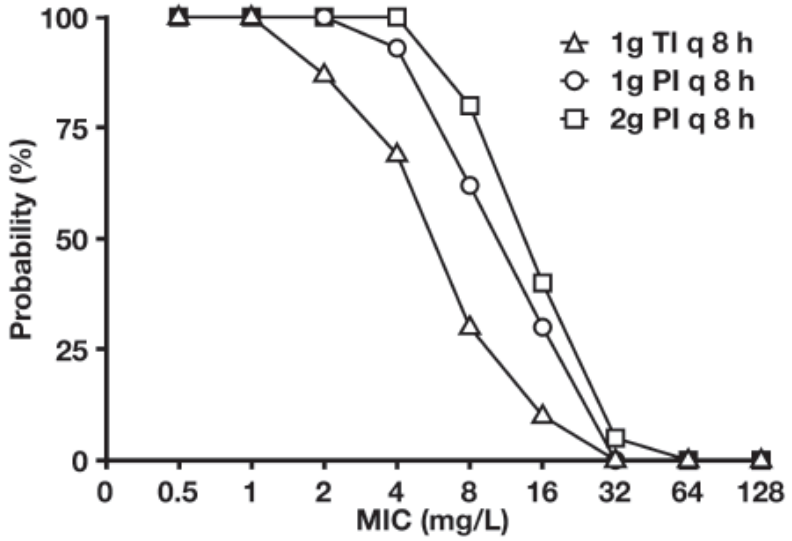


FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% *T* > MIC) of three different regiments of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

Double carbapenem as a rescue strategy for the treatment of severe carbapenemase-producing *Klebsiella pneumoniae* infections: a two-center, matched case-control study

- Étude cas témoins observationnelles
- Infections documentées KPC
- Comparaison double carbapénèmes vs traitement au choix
- Certaines souches résistantes à la colistine

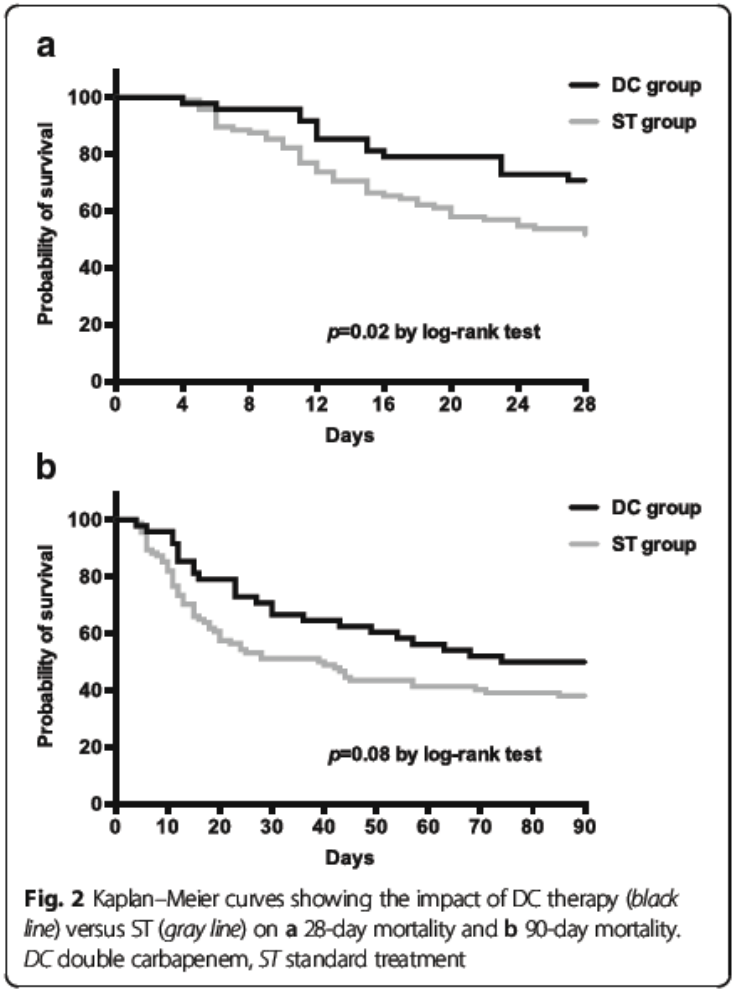


Fig. 2 Kaplan–Meier curves showing the impact of DC therapy (*black line*) versus ST (*gray line*) on **a** 28-day mortality and **b** 90-day mortality. *DC* double carbapenem, *ST* standard treatment

Di pasquale, Crit Care, 2017

Effect of combination therapy containing a high-dose carbapenem on mortality in patients with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection

Maddalena Giannella [a,*], Enrico Maria Trecarichi [b], Daniele Roberto Giacobbe [c], Francesco Giuseppe De Rosa [d], Matteo Bassetti [e], Alessandro Bartoloni [f], Michele Bartoletti [a], Angela Raffaella Losito [b], Valerio del Bono [c], Silvia Corcione [d], Sara Tedeschi [a], Francesca Raffaelli [b], Carolina Saffioti [c], Teresa Spanu [g], Gian Maria Rossolini [h], Anna Marchese [i], Simone Ambretti [j], Roberto Cauda [b], Claudio Viscoli [c], Russell Edward Lewis [a], Pierluigi Viale [a], Mario Tumbarello [b] on behalf of Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva (ISGRI-SITA)

- Analyse post hoc cohorte italienne (6 ans)
- Patients BSI EPC (Kl pn)
- Traités en association
- Evaluation impact forte dose de carbapénèmes (mortalité à J14)

- **Facteurs protecteurs** :
  - Admission en chirurgie (HR 0.44, P = 0.005)
  - Forte dose de carbapénèmes (HR 0.69, P = 0.05)
- Méropénem à forte dose indépendamment associée à moindre mortalité, même chez patients avec **CMI ≥ 16 mg/L**

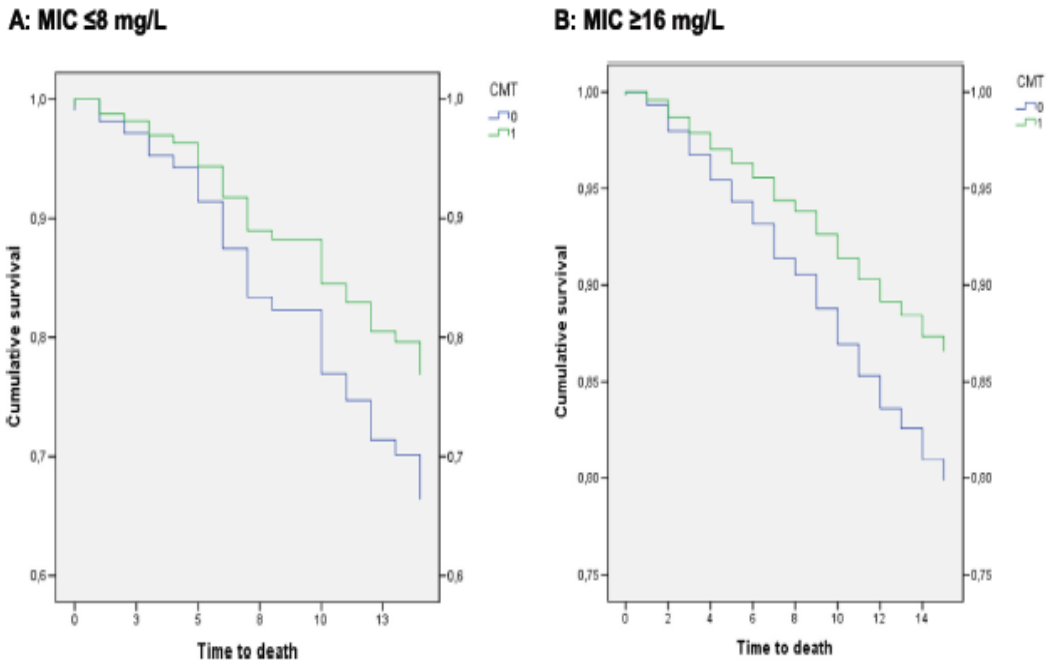


Fig. 1. Cox regression analysis of survival stratified for carbapenem MIC. CMT: combination with meropenem treatment; 0 no, 1 yes. Panel A and Panel B show cumulative survival at 14 days from CR-KP BSI onset for patients who did or did not receive carbapenem combination therapy, it was adjusted for all the covariates included in the Cox regression model and the propensity score. The model was further stratified according to the meropenem MIC ≤8 mg/L (Panel A), MIC ≥16 mg/L (Panel B), the overall aHR for the variable carbapenem combination therapy (CMT) was: 0.63, 95%CI 0.41–0.96, *P*= 0.03.

IJAA 2018

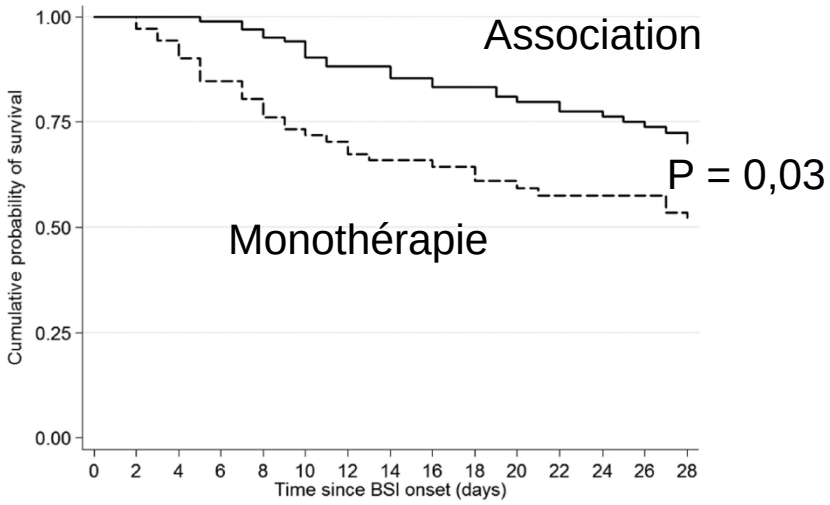
Facteurs associés à la mortalité à J30 de patients ayant une bactériémie à KP-RC

Variable	p	RR (IC 95%)
Choc septique	0,003	4,5 (1,6 – 12,5)
Hémopathie	0,002	8,5 (2,1 – 33)
Isoler KP-RC	< 0,001	7,7 (2,8 – 21,5)
Traitement définitif par coli/tigé/méropénème	0,01	(0,11 -0 ,69)

Liu, J Pers Med, 2021 / Chang, J Inf Pub Health, 2019

Faut-il une association ?

Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems

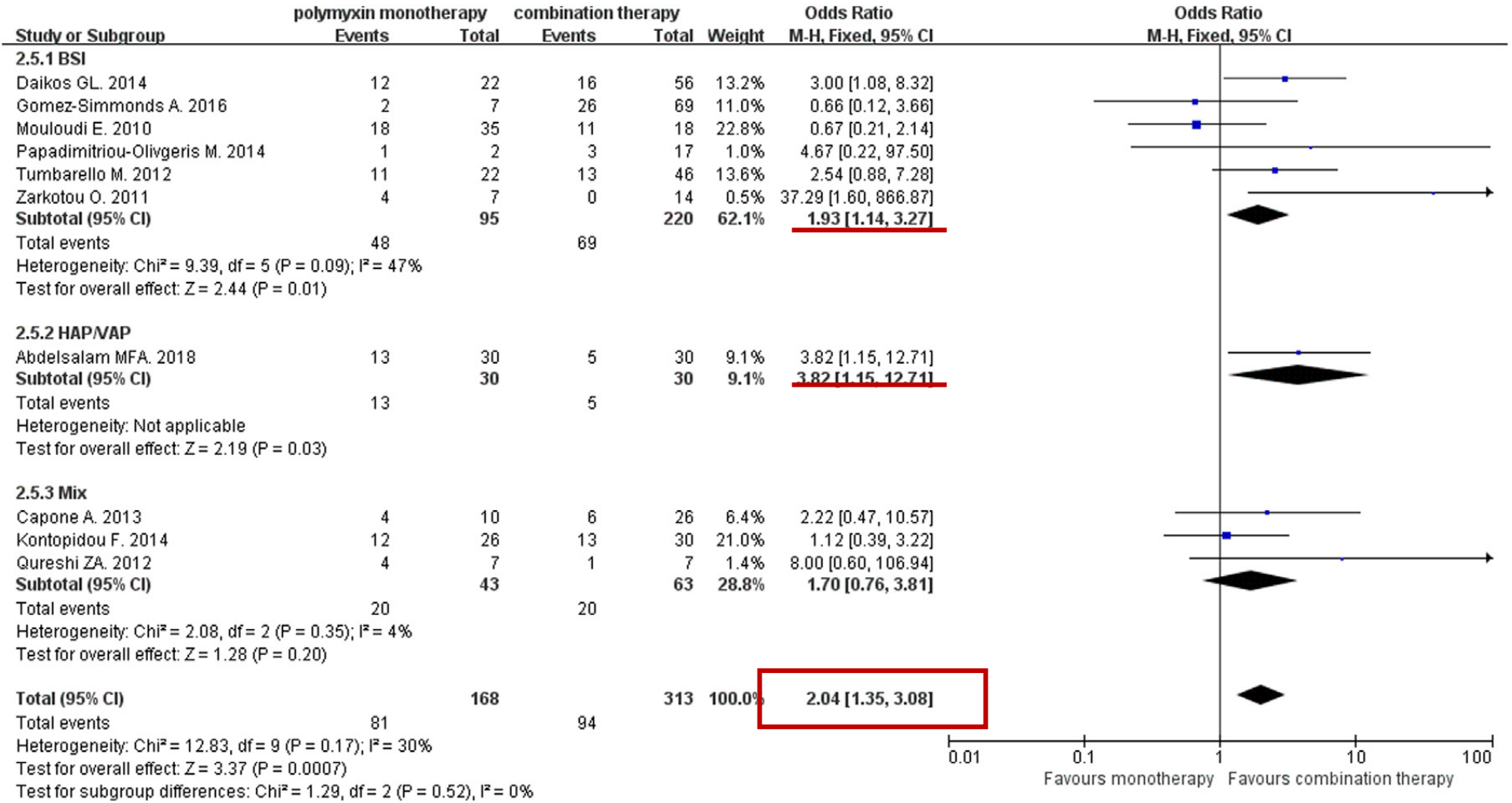


Mortalité

- Pas d'ATB actif = 33,3%
- Monothérapie = 44,4%
- Association = 27,2%
  - Carbapénèmes = 19,3%
  - Sans carbapénèmes = 30,6%

Dalkos, AAC, 2014

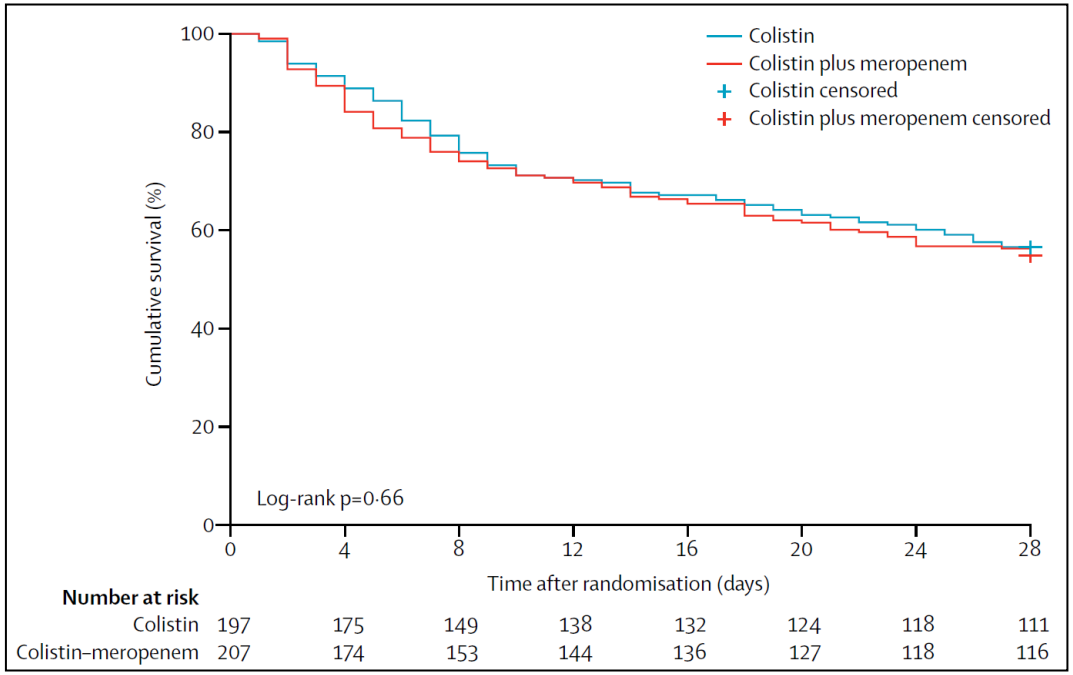
Polymyxin monotherapy versus polymyxin-based combination therapy against carbapenem-resistant Klebsiella pneumoniae: A systematic review and meta-analysis



Hou et al, J Glob Antimicrob Res, 2020

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

- Étude contrôlée randomisée : 406 patients
- Bactériémies, PAVM, HAP, IU à EPC
- Colistine vs colistine + méropénème (2 g x 3 /j)
- Évaluation J14
- Pneumonie + bactériémie : 87%
- A. Baumanii : 77%
- **Pas de différence même en cas d'infection sévère à AB (p=0,4)**
- Plus d'EI si association



Paul et al, Lancet Inf Dis, 2018

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

Belén Gutiérrez-Gutiérrez*, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†

- Cohorte rétrospective sur bactériémies monomicrobiennes à EPC
- 10 pays, 26 hôpitaux
- Comparaison **mortalité J30** entre patients ayant reçu une seule molécule efficace vs plusieurs molécules
- Score INCREMENT de mortalité

- ATB adaptée (<5j) associée à une moindre mortalité vs ATB inadaptée : 38,5% vs 60,6% (p<0,0001)

- **Pas de différence de mortalité globale** (35% vs 41 % ; p = 0,28)

	Appropriate therapy (n=343)	Inappropriate therapy (n=94)	p value
Age (years)	66 (55·5–76·0)	66 (50–77)	0·76
Male sex	197 (57%)	58 (62%)	0·46
Enterobacteriaceae	..	..	0·27
Klebsiella pneumoniae	291 (85%)	84 (89%)	..
Other	52 (15%)	10 (11%)	..
Enterobacter cloacae	24 (7%)	4 (4%)	..
Escherichia coli	14 (4%)	3 (3%)	..
Enterobacter aerogenes	10 (3%)	3 (3%)	..
Citrobacter spp	3 (1%)	0	..
Serratia marcescens	1 (<1%)	0	..
Type of carbapenemase	..	..	0·64
OXA-48	57 (17%)	12 (13%)	..
KPC	253 (74%)	76 (81%)	..
Metallo-β-lactamases	33 (10%)	6 (6%)	..
VIM	30 (9%)	6 (6%)	..
Other	3 (1%)	0	..
Nosocomial acquisition	298 (87%)	87 (93%)	0·13

Lancet Inf Dis, 2017

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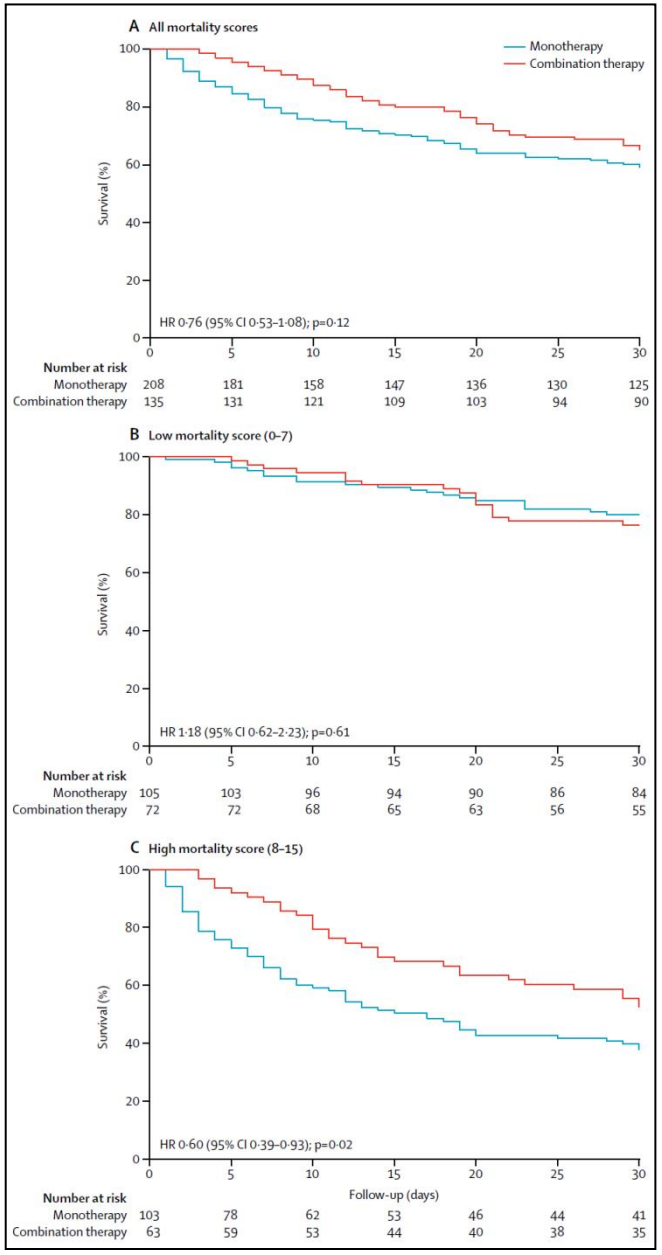
	All patients (n=343)	Low-mortality score (0–7; n=177)	High-mortality score (8–15; n=166)
Monotherapy			
Any	85/208 (41%)	21/105 (20%)	64/103 (62%)
Colistin	40/74 (54%)	12/32 (38%)	28/42 (67%)
Meropenem or imipenem	16/43 (37%)	5/25 (20%)	11/18 (61%)
Other active β-lactams	3/19 (16%)	2/17 (12%)	1/2 (50%)
Cefepime	1/13 (8%)	0/11	1/2 (50%)
Aztreonam	1/4 (25%)	1/4 (25%)	0/0
Ceftazadime	1/2	1/2	0/0
Tigecycline	14/37 (38%)	0/15	14/22 (64%)
Aminoglycosides	11/27 (41%)	1/9 (11%)	10/18 (56%)
Others	1/8 (13%)	1/7 (14%)	0/1
Cloramphenicol	1/1 (100%)	1/1 (100%)	0/0
Ciprofloxacin	0/4	0/3	0/1
Fosfomycin	0/1	0/1	0/0
Levofloxacin	0/2	0/2	0/0
Combination therapy*†			
Any	47/135 (35%)	17/72 (24%)	30/63 (48%)
Tigecycline included	29/82 (35%)	10/45 (22%)	19/37 (51%)
Colistin included	28/74 (38%)	11/36 (31%)	17/38 (45%)
Aminoglycosides included	19/56 (34%)	4/27 (15%)	15/29 (52%)
Carbapenem included	14/37 (38%)	4/19 (21%)	10/18 (56%)
Fosfomycin included	3/9 (33%)	1/4 (25%)	2/5 (40%)
Others	6/17 (35%)	3/11 (27%)	3/6 (50%)



Lancet Inf Dis, 2017

Association pour les bactériémies ?

Design, no. of sites	Included infections	Carbapenemase(s)	Mortality definition	No. of deaths/no. of patients treated with MT (%)	No. of deaths/no. of patients treated with CT (%)	CT protective or not; adjusted OR (95% CI) for mortality with CT[b]
Retrospective, 1 site (Turkey)	BSI due to CRE	Mostly *K. pneumoniae* OXA-48	28-day	2/5 (40)	16/31 (51.5)	MV analysis not performed
Prospective, 9 sites (Italy)	BSI due to ERT[r] *K. pneumoniae* (BSI subanalysis)	Mostly KPC	In-hospital	4/9 (44.4)	11/25 (44)	CT not protective (OR not provided)
Retrospective, 2 sites (Greece)	BSI due to CR *K. pneumoniae*	Mostly KPC, some VIM	28-day	32/72 (44.4)	28/103 (27.2)	CT protective; 0.48 (0.28–0.81)
Retrospective, 3 sites (Brazil)	Infections due to KPC-producing *K. pneumoniae* (BSI subanalysis)	KPC	30-day	15/34 (44.1)	24/44 (54.4)	CT not protective (OR not provided)
Retrospective, 2 sites (USA)	BSI due to CR *K. pneumoniae*	Most (probably) KPC	30-day	18/68 (26.4)	28/73 (38.3)	CT not protective; with BL, 1.8 (0.6–5.6); without BL, 1.1 (0.3–3.6)
Retrospective, 16 sites (worldwide)	BSI due to CPE	74% KPC	30-day	85/208 (40.9)	47/135 (34.8)	CT protective only in high-risk patients; 0.54 (0.32–0.89)
Prospective, 1 site (Spain)	BSI due to KPC-producing *K. pneumoniae*, COL[r]	KPC	30-day	14/32 (43.8)	18/72 (25)	CT protective in septic shock
Retrospective, 1 site (India)	Children, BSI due to CRE; includes inactive drugs	66% *K. pneumoniae*, 72% NDM	30-day	Not specified	Not specified	Crude OR = 0.23 (0.05–1.0); MV analysis not performed
Retrospective, 1 site (Spain)	BSI due to OXA-48 producers	OXA-48	30-day	2/7 (28.5)	13/27 (48.1)	MV analysis not performed
Retrospective, 1 site (Greece)[c]	BSI due to CS and CR *K. pneumoniae* in ICU	Mostly KPC	30-day	18/57 (31.5)	7/38 (18.4)	CT protective; 0.23 (0.07–0.75); also with shock
Retrospective, 2 sites (USA)	BSI due to KPC-producing *K. pneumoniae*; includes inactive drugs	KPC	28-day	11/19 (57.8)	2/15 (13.3)	CT protective; 0.07 (0.009–0.71)
Retrospective, 8 sites (USA)	BSI due to CRE	Mostly KPC	30-day	21/55 (38.1)	22/43 (51.1)	CT not protective (OR not provided)
Retrospective, 4 sites (Greece)	BSI due to CR *K. pneumoniae*, neutropenic patients	Mostly KPC	14-day	5/10 (50)	11/30 (36.6)	CT protective; 0.25 (0.07–0.81)
Prospective, 13 sites (Italy)	BSI due to CR *K. pneumoniae*, hematological patients	Not identified	21-day	69/77 (89.6)	40/72 (55.5)	CT protective; 0.52 (0.35–0.77)
Retrospective, 3 sites (Italy)	BSI due to KPC-producing *K. pneumoniae*	KPC	30-day	25/46 (54.3)	27/71 (34.1)	CT with COL plus TIG-MER protective; 0.11 (0.02–0.60)
Retrospective, 5 sites (Italy)[d]	Infections due to KPC-producing *K. pneumoniae* (BSI subanalysis)	KPC	30-day	80/156 (51.3)	93/291 (32)	MV analysis not performed for BSI
Retrospective, 11 sites (South America)	BSI due to CRE	Mostly KPC	28-day	5/8 (62.5)	17/29 (58.6)	MV analysis not performed
Retrospective, 1 site (Greece)	BSI due to KPC-producing *K. pneumoniae*	KPC	Infection related	7/15 (46)	0/20 (0)	CT not included in MV

Faut-il une association ?

Ceftazidime-Avibactam Combination Therapy Compared to Ceftazidime-Avibactam Monotherapy for the Treatment of Severe Infections Due to Carbapenem-Resistant Pathogens: A Systematic Review and Network Meta-Analysis

Author (Published Year) [ref.]	N° of patients Enrolled	N° of Bacteremia (%)	N° of Patients Treated with CZA Alone	N° of Patients Treated with CZA Association	N° of Patients Treated with BAT	BAT	CZA-Associated Antibiotic	Medical Ward
Sousa (2018) [8]	57	26 (46)	46	11	X	X	#	NS
King (2017) [26]	60	23 (38)	33	27	X	X	^	Mix ICU (59%)
Alraddadi (2019) [27]	38	22 (58)	10	X	28	§	X	NS
Caston (2017) [6]	31	31 (100)	X	8	23	^^	^^	Mix ICU (10%)
Shields (2017) [7]	109	109 (100)	8	5	96	++	<>	Mix ICU (50%)
Tumbarello (2019) [5]	208	208 (100)	22	82	104	§§	##	Mix ICU (33.3%)

Pas de supériorité des associations avec CZA versus CZA seul en termes de mortalité

OR = 0,96 (IC95% = 0,65-1,41)

Fiore et al, Antibiotics, 2020

Recommandations (ESCMID 2022)

- Infections sévères :
  - ceftazidime-avibactam
  - méropénème-vaborbactam
- Céfidérocol : infections sévères à souches NDM ou résistance à toutes les autres molécules
- Infections non sévères :
  - Anciennes molécules actives in vitro
  - Si infections urinaires compliquées : AG > tigécycline

Paul et al, CMI, 2022

Recommandations (ESCMID 2022)

- Tigécycline :
  - Ne pas utiliser si bactériémies ou PAVM/PAH
  - Si nécessaires en cas de pneumonie : fortes posologies
- Pas de recommandations en monothérapie :
  - Imipénème-relebactam
  - Fosfomycine

Paul et al, CMI, 2022

Recommandations (ESCMID 2022)

- Pas d'association avec les nouvelles molécules :
  - Ceftazidime – avibactam
  - Méropénème – varobactam
  - Cefidérocol
- Infection sévère et probable NDM : CZA + aztréonam
- Si CZA non disponible et infection sévère : association de molécules actives in vitro :

  colistine / AG / fosfo / tigécycline
- Si infection non sévère et sous réserve de contrôle de la source d'infection : monothérapie par molécule active in vitro

Paul et al, CMI, 2022

Les carbapénèmes ?

Les carbapénèmes ne sont pas recommandés en association pour le traitement des infections à ERC sauf si CMI-méropénème ≤ 8 mg/l, si une dose élevée de méropénème est utilisée en perfusion continue

Paul et al, CMI, 2022 / Lawandi et al, CMI 2022

Recommandations

ERC	ESCMID 2022	IDSA 2021
Infections non sévères	Anciennes molécules	Quinolones, TMP/SMX Aminosides
ERC par NDM	Cefiderocol Cefta/avibatam + AZT	Cefiderocol monothérpaie
Tigécycline	Non recommandée en cas de bactériémies ou PAVM	Doit être évitée
Association	Pas obligatoire	Pas obligatoire

Paul et al, CMI, 2022 / Lawandi et al, CMI 2022

Pseudomonas aeruginosa résistant aux carbapénèmes

Bactériologie : mécanismes de résistance

Table 2 | Prevalence and primary resistance mechanisms expected in *P. aeruginosa* in Spain.

Antimicrobial[a]	% I+R (R)[a]	In order of frequency implicated mechanisms of resistance[b]
PIP-TZ	20-30	↑AmpC (++), ↑MexAB (+), MBL (+), OXAs and other ESBL (+)
CAZ	20-30	↑AmpC (++), ↑ MexAB (+), MBL (+), OXAs and other ESBL (+)
FEP	20-30	↑MexAB/XY (++), ↑AmpC (++), MBL (+), OXAs and other ESBL (+)
TOL-TZ	1-5	MBL (+), OXAs and other ESBL (+) ↑AmpC+mut AmpC (-/+)
ATM	>50 (20-30)	↑MexAB/XY (+++) ↑AmpC (++), OXAs and other ESBL (+)
IMP	20-30 (20-30)	OprD (+++), MBL (+)
MER	20-30 (5-20)	OprD (+++), ↑MexAB (++), MBL (+)
CIP	30-50	QRDR (+++), ↑MexAB/XY (++), ↑MexCD/EF (+)
TOB	20-30	Modified enzyme AMG (++) ↑MexXY (+)
AMK	5-20 (1-5)	↑MexXY (++),modified enzyme AMG (+)
COL	1-2	*pmrAB/phoPQ/parRS* (-/+)

Lipopolysaccharide

Pelag AY, NEJM, 2010 / Mensa, Rev Esp Q, 2018

Molécules

- Nouvelles
  - BL/IBL : ceftolozane-tazobactam
  - Imipénème-relebactam
  - Céfidérocol
- Anciennes
  - Colistine
  - Aminosides
  - Fosfomycine

Maraolo, Expert Review Anti-Infective Therapy, 2017

Ceftolozane-tazobactam

- Nouvelle C3G associée au tazobactam (2/1)
- Spectre :
  - Entérobactéries
    - classe A : TEM, SHV, CTX-M
    - classe D : OXA-BLSE
  - *Pseudomonas aeruginosa*
- Indications (AMM) :
  - Infections intra-abdominales compliquées
  - Infections urinaires compliquées

Maraolo, Expert Review Anti-Infective Therapy, 2017

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant Pseudomonas aeruginosa

Pogue M et al, CID, 2020

- Étude rétrospective multicentrique observationnelle
- CEF/TAZ versus association comportant polymyxine ou aminoside

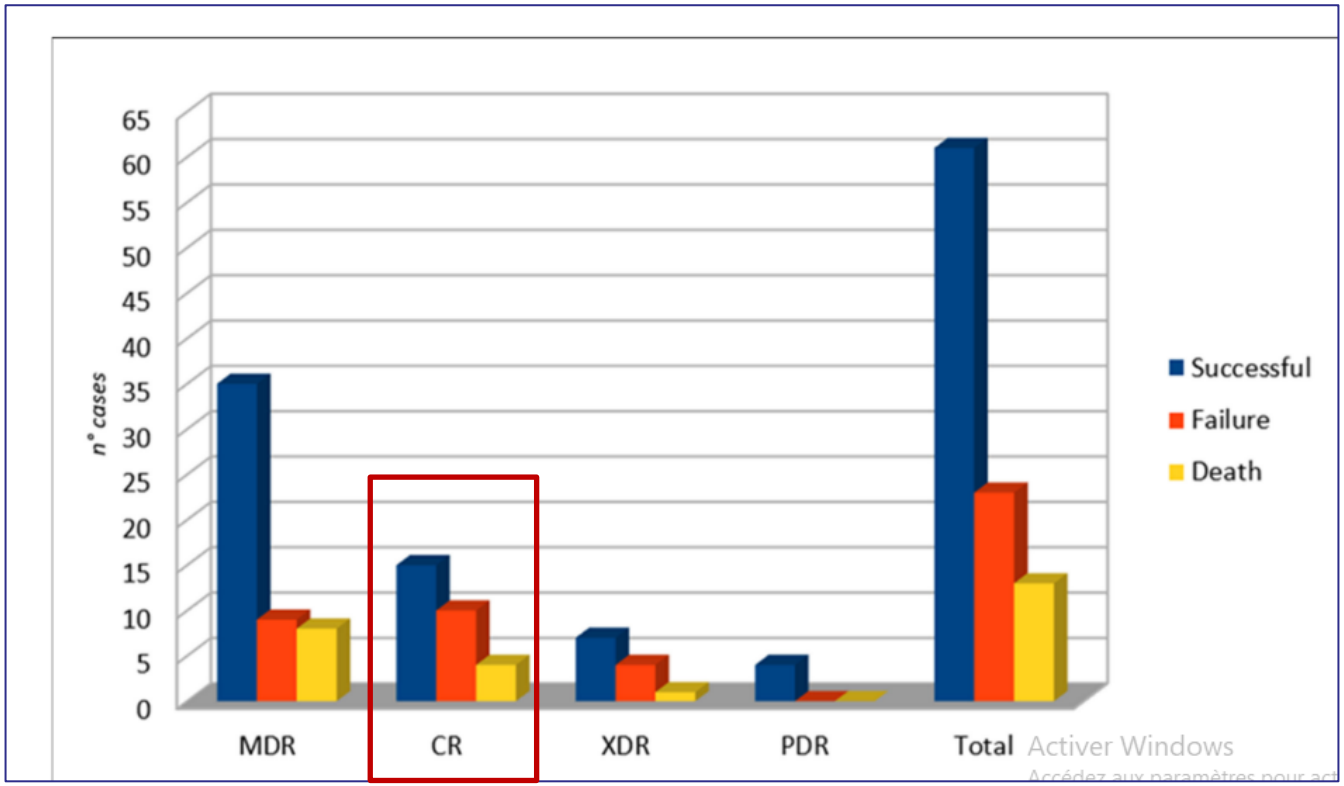
Outcome	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/Aminoglycoside (N = 100)	*P* Value	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Clinical cure	81	61	.002	2.72 (1.43–5.17)	2.63 (1.31–5.30)
In-hospital mortality	20	25	.40	0.75 (0.38–1.46)	0.62 (.30–1.28)
Acute kidney injury	6	34	<.001	0.12 (0.05–0.31)	0.08 (.03–.22)
Risk	2	8	…	…	…
Injury	3	12	…	…	…
Failure	1	14	…	…	…
Renal replacement therapy	0	7	…	…	…

- Conclusion : CEF/TAZ plus efficace et moins toxique

Ceftolozane/Tazobactam for Resistant Drugs Pseudomonas aeruginosa Respiratory Infections: A Systematic Literature Review of the Real-World Evidence

Giaccare, Life, 2021

- 22 publications, 84 épisodes infectieux



Taux global de succès 72,6%

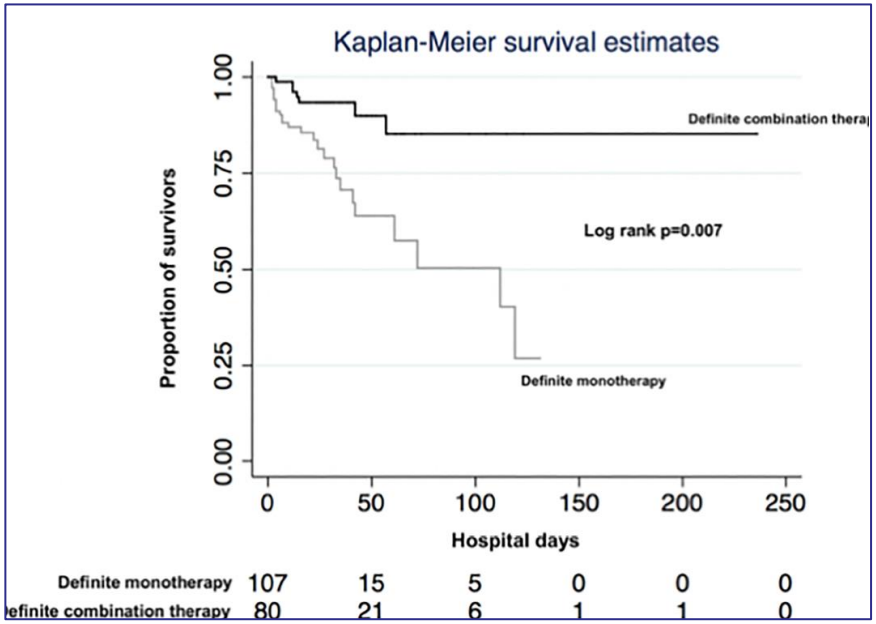
Monothérapie vs Association

- Pourquoi associer ?
  - Synergie in vitro (vitesse de bactéricidie)
  - Prévention d'émergence de mutants résistants
  - Antibiothérapie empirique appropriée
- Pourquoi ne pas associer ?
  - Toxicité des antibiotiques
  - Surinfection
  - Coût

Traugott, Pharmacotherapy, 2011

Combination therapy for treatment of *Pseudomonas aeruginosa* bloodstream infections

- Étude monocentrique
- 2003 à 2013
- 187 bactériémies à PA
- 80 (42%) : combinaison
  - BL : 76%
  - AG : 24%
- Mortalité plus faible (C)
- Bénéfice de la combinaison



Tshudin-Sutter, PLOS, 2018

Outcomes of Appropriate Empiric Combination versus Monotherapy for *Pseudomonas aeruginosa* Bacteremia

- Étude rétrospective multicentrique
- 2002 à 2011 : 384 patients
- Mortalité J30 : pas de différence entre monothérapie vs combinaison
- Pas de bénéfice si PA sensible à au moins un antibiotique

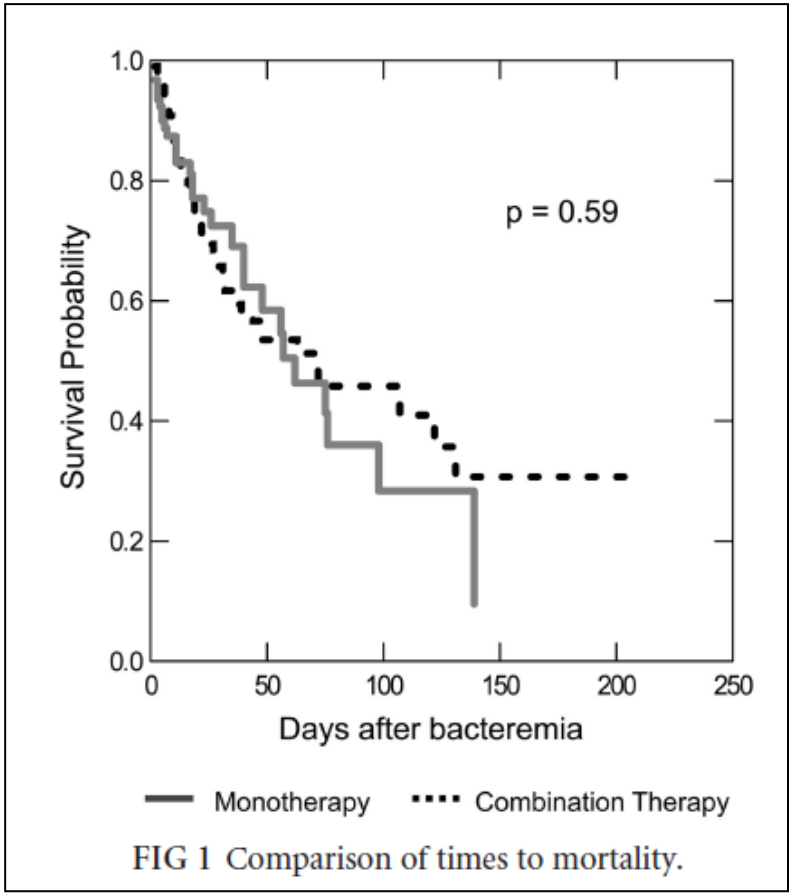


FIG 1 Comparison of times to mortality.

Bowers, AAC, 2013

Impact of Definitive Therapy with Beta-Lactam Monotherapy or Combination with an Aminoglycoside or a Quinolone for *Pseudomonas aeruginosa* Bacteremia

- Étude multicentrique (Grèce, Italie)
- Patients traités par BL versus BL + FQ/AG
- 92 bactériémies à PA
- Pas de différence significative en faveur de la combinaison

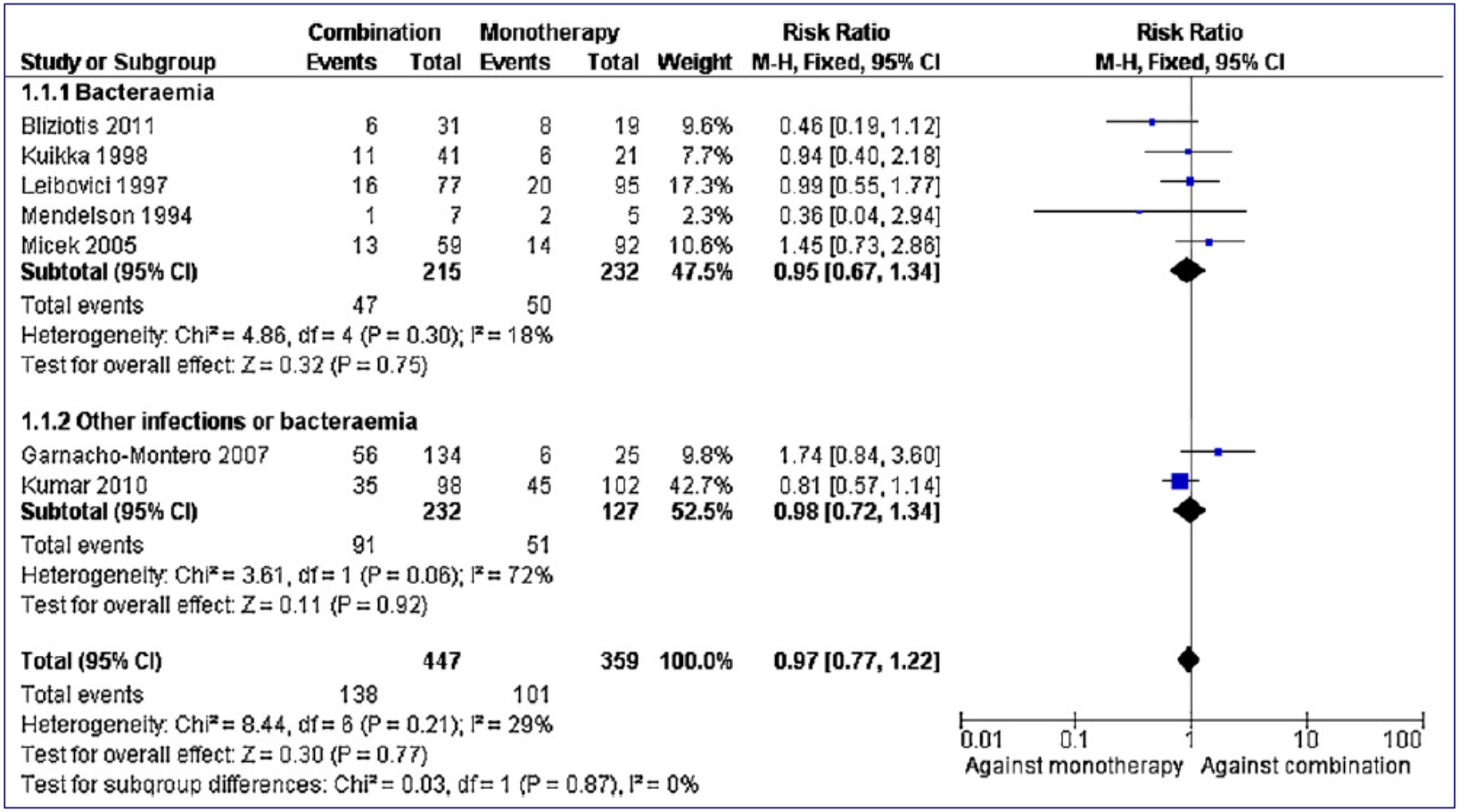
Bliziotis, PLoS ONE, 2011

Table 3. Multivariable analysis of factors possibly associated with treatment success.

Factor	OR	95% Conf. Interval	p-value
Very long (>2 months) hospitalization	0.73	0.01–0.95	*0.046*
Hospitalization in ICU prior to bacteremia	0.67	0.09–4.78	0.69
Age-adjusted Charlson comorbidity index	1.02	0.76–1.38	0.88
HIV	0.59	0.08–4.23	0.60
Combination therapy	3.30	0.63–17.22	0.15

β-Lactam plus aminoglycoside or fluoroquinolone combination versus β-lactam monotherapy for *Pseudomonas aeruginosa* infections: A meta-analysis

- 1721 patients traités par BL versus BL + FQ/AG



Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Bacteraemia						
Bliziotis 2011	6	31	8	19	9.6%	0.46 [0.19, 1.12]
Kuikka 1998	11	41	6	21	7.7%	0.94 [0.40, 2.18]
Leibovici 1997	16	77	20	95	17.3%	0.99 [0.55, 1.77]
Mendelson 1994	1	7	2	5	2.3%	0.36 [0.04, 2.94]
Micek 2005	13	59	14	92	10.6%	1.45 [0.73, 2.86]
Subtotal (95% CI)		**215**		**232**	**47.5%**	**0.95 [0.67, 1.34]**
Total events	47		50			
Heterogeneity: Chi² = 4.86, df = 4 (P = 0.30); I² = 18%						
Test for overall effect: Z = 0.32 (P = 0.75)						
1.1.2 Other infections or bacteraemia						
Garnacho-Montero 2007	56	134	6	25	9.8%	1.74 [0.84, 3.60]
Kumar 2010	35	98	45	102	42.7%	0.81 [0.57, 1.14]
Subtotal (95% CI)		**232**		**127**	**52.5%**	**0.98 [0.72, 1.34]**
Total events	91		51			
Heterogeneity: Chi² = 3.61, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 0.11 (P = 0.92)						
Total (95% CI)		**447**		**359**	**100.0%**	**0.97 [0.77, 1.22]**
Total events	138		101			
Heterogeneity: Chi² = 8.44, df = 6 (P = 0.21); I² = 29%						
Test for overall effect: Z = 0.30 (P = 0.77)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						

Vardakas, Int J Antimocrob Agents, 2013

04773 Results from the OVERCOME trial: colistin monotherapy versus combination therapy for the treatment of pneumonia or bloodstream infection due to extensively drug resistant Gram-negative bacilli

OVERCOME : étude contrôlée randomisée double aveugle versus placebo

Colistine seule (placebo) versus colistine + méropénème

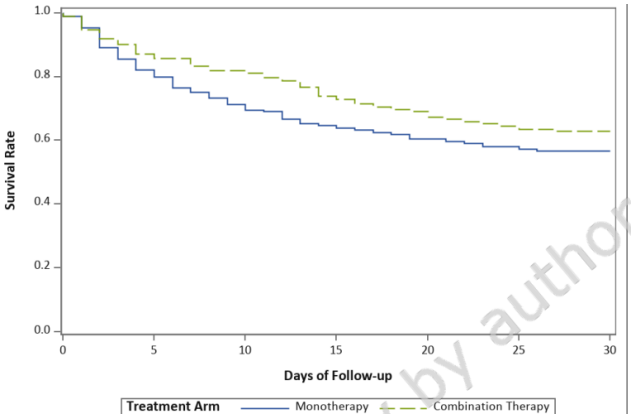
Traitement des pneumonies à BMR (ABRI, PA-RC, ERC)

425 patients, 21 centres, 7 pays

Pas de différence sur

- **Mortalité (43% vs 37%, p = 0,21)**
- **Échec clinique (45% vs 38%, p = 0,18)**

	Colistin N = 214	Colistin + Meropenem N = 211	P value
Age*	68 (60 – 80)	68 (59 – 81)	0.62
Race			0.87
White	108 (50)	108 (51)	
Asian	90 (42)	85 (40)	
Other	16 (7)	18 (9)	
Female	83 (39)	76 (36)	0.56
Infection Type			0.85
Pneumonia	143 (67)	134 (64)	
BSI	61 (29)	64 (30)	
Combined	10 (5)	13 (6)	
ICU at infection onset	149 (70)	144 (68)	0.76
Study pathogen			
CR *A. baumannii*	165 (77)	163 (77)	0.97
XDR *P. aeruginosa*	23 (11)	20 (9)	0.66
CRE	35 (16)	36 (17)	0.80



Kaye et al, ECCMID, 2021

Molécules - Posologies

- Utiliser les bonnes molécules
- Posologies élevées
- PK/PD
- Particularités des malades de réanimation

Maraolo, Exp Rev Anti-infec Ther, 2017

Table 3. Pharmacokinetic alterations in ICU patients.

Absorption (decreased)	
Enteral	
Increased gastric pH	
Altered mesenteric perfusion, vasopressor therapy	
Intestinal atrophy and reduced transport function	
Bowel edema and dysmotility	
Nutrient–drug interactions	
Inhalation, topical, sublingual, intramuscular, and subcutaneously	
Impaired cutaneous and mucosal perfusion	
Use of vasopressors	
Volume of distribution (Vd)	
Increased Vd	Decreased Vd
Edematous states (cirrhosis, acute hepatic failure, nephrotic syndrome, right and left heart failure)	Fluid loss (vomiting, diarrhea, burns, and blood loss)
Aggressive fluid administration	Diuretics
Decreased protein concentration or binding Acute renal failure	Increased protein binding
Drug metabolism and biotransformation	
Decreased	Increased
Impaired liver enzymatic activity (liver dysfunction, hypotension, and blood flow alterations)	Induction of the enzymatic activity (e.g. benzodiazepine carbamazepine, phenobarbital, phenytoin, rifampicin)
Impaired function of drug transporters	High intake of dietary protein
Elimination	
Decreased renal drug clearance	Increased renal drug clearance
Reduced glomerular filtration rate	Proinflammatory cytokines
Reduced proximal tubular drug secretion (tubular injury)	Inotropic agents
	Administration of intravenous fluid
Decreased hepatic drug clearance	
Impaired biliary excretion	

Modalités d'administration

- L'utilisation de **posologies élevées**
- L'administration par **voie intraveineuse prolongée ou continue après dose de charge** pour les molécules suivantes :
  - Pipéracilline-tazobactam
  - Céfépime
  - Ceftazidime
  - Méropénème

Maraolo, Exp Rev Anti-infec Ther, 2017 / HAS 2019

Molécules - Posologies

Antibiothérapie empirique

Antibiotiques	Posologies
Ceftazidime	1-2 g DC + 6 g/24 h CI
Ceftazidime-avibactam	2/0.5 g/8 h EI
Pipéracilline-tazobactam	2/0.25 g DC + 16/2 g/24 h CI
Ceftolozane-tazobactam	1/0.5 or 2/1 g/8 h EI
Méropénème	1-2 g DC + 2 g/8 h EI
Fosfomycine	2-4 g DC + 16-24 g/24 h CI
Colistine	6-9 MU DC + 4.5 MU/12 h
Ciprofloxacine	400 mg/8 h en 30-60 minutes
Amikacine	25 mg/kg/24 h en 60 minutes

Schéma de traitement

Critères pour un sepsis sévère ou choc septique ?

Inoculum bactérien élevé ?

Immunodépression sévère ?

Risque de colonisation par *P. aeruginosa* MDR ?

OUI

BL active contre PA différente de celle utilisée dans les 90 jours précédents :

CEF/TAZ > CZA > Méropénème

> PIP/TAZ ou Ceftazidime

+

Amkacine ou colistine

NON

BL active contre PA : méropénème / PIP/TAZ / Ceftazidime

+

Amikacine ou ciprofloxacine

Monothérapie (IU / IKT veineux)

Mensa et al, 2018, Rev Esp Quimoter

PAVM : antibiothérapie

Situation	Therapeutic class	Agent
Early VAP (< 5 days), without MDR bacteria risk factor*	Non-antipseudomonal β-lactam	Amoxicillin/clavulanic acid† OR Third generation cephalosporin
Late VAP (≥ 5 days), OR Risk factors for MDR bacteria	β-lactam active against *Pseudomonas aeruginosa* AND Non β-lactam antipseudomonal agent	Cefepime 2 g q 8 h OR Ceftazidime 2 g q 8 h OR Piperacillin–tazobactam 4 g q 6 h OR Meropenem 2 g q 8 h Amikacin 25 mg/kg/day OR Ciprofloxacin 1200 mg/day
Known MRSA colonization, or high (> 20%) MRSA prevalence in the unit	Agent active against MRSA	Vancomycin 30–45 mg/kg/day OR Linezolid 600 mg/12 h
Known colonization with carbapenem-resistant Enterobacteriaceae or Pseudomonas aeruginosa susceptible only to new beta-lactam agents	New β-lactam agent	Ceftolozane–tazobactam 3 g q 8 h‡ OR Ceftazidime–avibactam 2.5 g q 8 h‡ OR Meropenem–vaborbactam 4 g q 8 h‡ OR Imipenem–relebactam 1.5 g q 6 h‡

Zaragosa, Crit Care, 2020 / Papazian, Intensive Care Med, 2020

Recommandations PA-RC

	ESCMID 2022	IDSA 2021
Infections sévères	• Ceftolozane-tazobactam • Données in vitro insuffisants pour : cefiderocol, imipénème-relebactam, CZA • Anciennes molécules si efficacité in vitro	• Ceftolozane-tazobactam • Imipénème-relebactam • CZA • Cefiderocol si UTI
Infections non sévères	• Anciennes molécules si efficacité in vitro	• Ceftolozane-tazobactam • Imipénème-relebactam • CZA • Dose unique AG si cystite
Association si nécessaire	Si infection sévère, utiliser en association de 2 agents actif in vitro : • Colistine • AG • Fosfomycine	AG en association avec nouvelles BL/IBL

Paul et al, CMI, 2022 / Lawandi et al, CMI 2022

Acinetobacter baumannii résistant aux carbapénèmes (ABRI)

Acinetobacter : tous les chemins mènent à la résistance

Table 2. Carbapenemases reported in *Acinetobacter baumannii*.

Carbapenemase class	Enzyme	Characteristics
Metallo-β-lactamases (ambler class B; zinc ion at active site)	IMP-like (IMP-1, -2, -4, -5, -6, -8, -10, -11, -19) VIM-like (VIM-1, -2, -3, -4, -11) SIM-1	Class 1 integrons
	NDM-1, NDM-2	Most likely linked to a transposon, Tn*125*, bracketed by two copies of insertion sequence IS*Aba125*, and not plasmid related, in contrast to what is observed in the Enterobacteriaceae
Oxacillinases (ambler class D; serine residue at active site)	OXA-23 cluster (OXA-23, -27 and -49)	Acquired; found either on the chromosome or on plasmids, in association with IS*Aba1* within Tn*2006* and Tn*2008* transposons or with IS*Aba4* in Tn*2007*
	OXA-24/40 cluster (OXA-25, -26, -40 and -72)	Acquired; chromosomal or plasmid, no associated IS elements
	OXA-58	Acquired; found mostly on plasmids in association with insertional sequences IS*ABa1*, IS*AB3* and IS*18*
	OXA-51 cluster (OXA-51, -64, -65, -66, -68, -69, -70, -71, -78, -79, -80, -82 and -143	Intrinsic chromosomally and/or plasmid-located; confers carbapenem resistance when the insertion sequence IS*Aba1* element is inserted upstream of the gene

OXA: Oxacillinase.

Abott I, Expert Rev Anti Infect 2013

Antibiothérapie ?

- Carbapénèmes (antibiotiques de choix)
- Ampicilline-sulbactam
- Colistine
- Tigécycline
- Rifampicine
- Aminosides

Colistine

Colistine

- Garde une activité sur la majorité des souches ABRI
- ABRI parfois sensible qu'à la colistine
- In vitro : synergie entre la colistine et d'autres antibiotiques

Le rationnel des associations ?

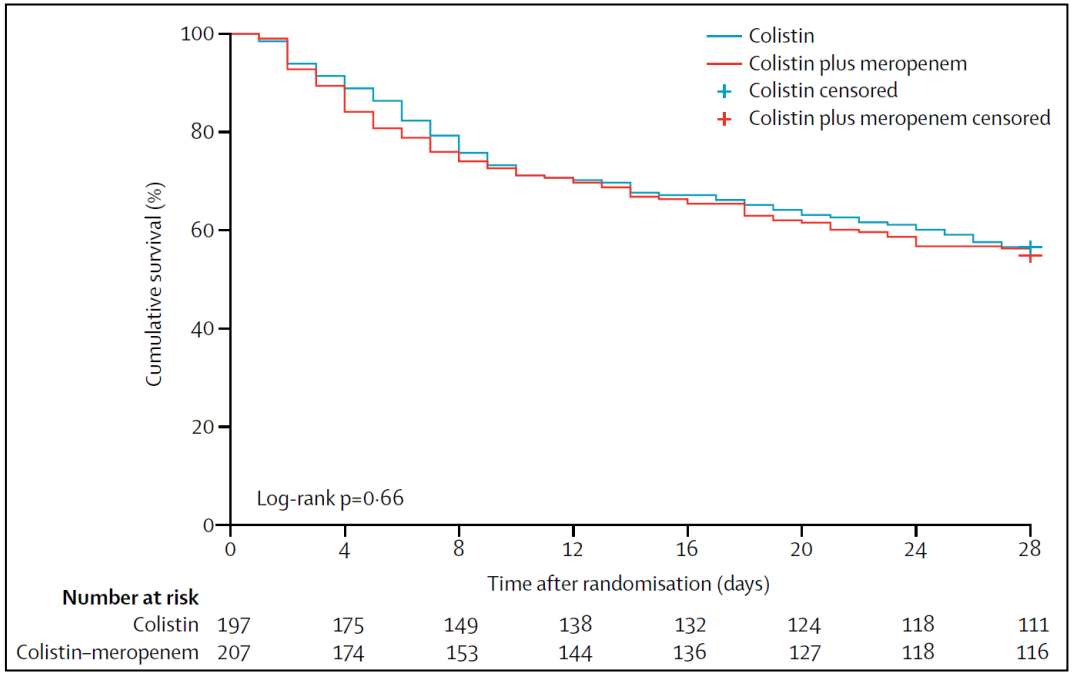
1. Manque de données fiables avec la monothérapie
2. Conséquences graves en cas de retard thérapeutique
3. Patients graves (réanimation)
4. Les antibiotiques qui semblent actif contre les ABRI développent rapidement de la résistance

Tamma et al, CID, 2021

Colistine + méropénème ?

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

- Étude contrôlée randomisée : 406 patients
- Bactériémies, PAVM, HAP, IU à EPC
- Colistine vs colistine + méropénème (2 g x 3 /j)
- Évaluation J14
- Pneumonie + bactériémie : 87%
- A. Baumanii : 77%
- Pas de différence même en cas d'infection sévère à AB (p=0,4)
- Plus d'EI si association



Paul et al, Lancet Inf Dis, 2018

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Short Communication

Colistin-based treatment for extensively drug-resistant *Acinetobacter baumannii* pneumonia☆

Thana Khawcharoenporn[a,*], Nattapol Pruetpongpun[a], Pimsiri Tiamsak[b], Sasinuch Rutchanawech[a], Linda M. Mundy[c], Anucha Apisarnthanarak[a]

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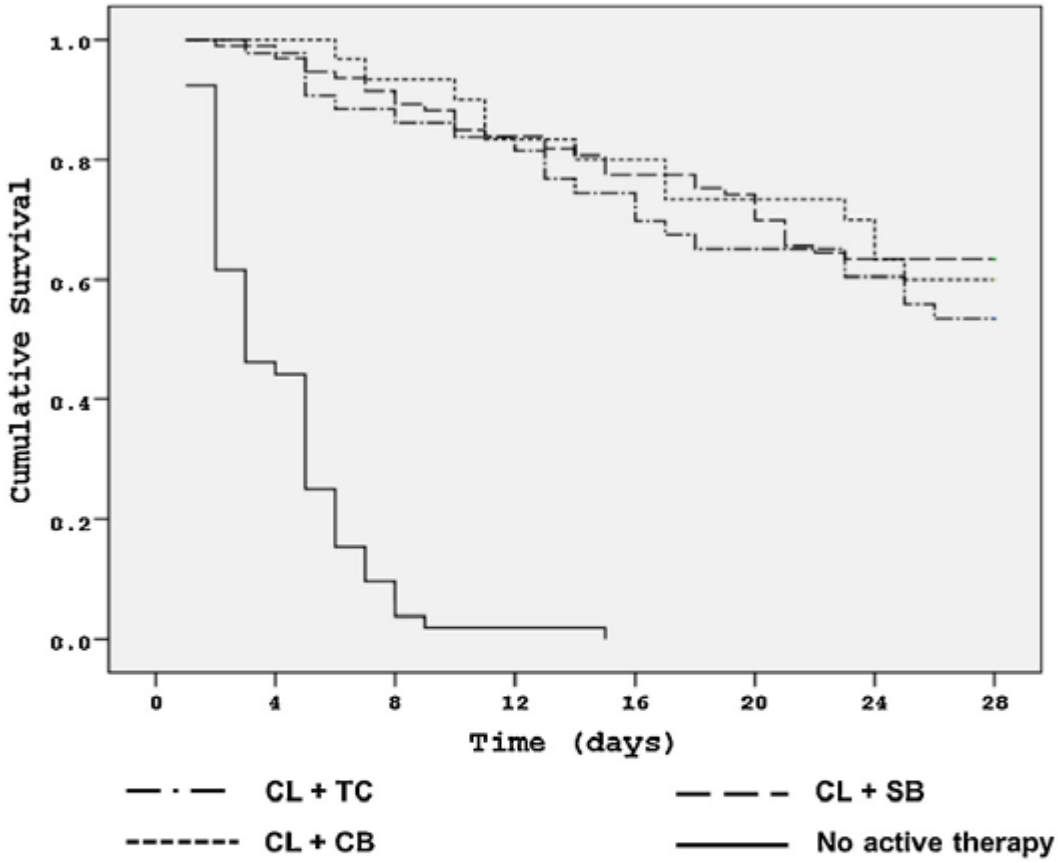


TC vs SB
p = 0.3

TC vs CB
p = 0.53

SB vs CB
p = 0.86

Fig. 1. Kaplan–Meier survival analysis for death at 28 days after the onset of extensively drug-resistant *Acinetobacter baumannii* pneumonia. Comparison between treatment regimens by log-rank test: (i) CL + TC vs. CL + SB, $P = 0.30$; (ii) CL + TC vs. CL + CB, $P = 0.53$; (iii) CL + SB vs. CL + CB, $P = 0.86$; (iv) CL + TC vs. no active therapy, $P < 0.001$; (v) CL + SB vs. no active therapy, $P < 0.001$; and (vi) CL + CB vs. no active therapy, $P < 0.001$. CL, colistin; TC, tigecycline; SB, high-dose sulbactam; CB, high-dose prolonged-infusion carbapenem.

Colistine + méropénème

- IDSA = pas recommandée
- ESCMID = pas recommandée
  - Si CMI méropénème ≤ 8 mg/L, possibilité d'association en utilisant de fortes posologies

Colistine + fosfomycine ?

Preliminary Study of Colistin versus Colistin plus Fosfomycin for Treatment of Carbapenem-Resistant Acinetobacter baumannii Infections

- Essai clinique ouvert comparant colistine versus colistine + fosfomycine (8 gr/j)
- Traitement d'Ab-carba R (76% de PAVM)
- Réponse microbiologique favorable

Col + fosfo	Col	
83%	53%	p = 0.004

Siriatuphet, AAC 2014

Preliminary Study of Colistin versus Colistin plus Fosfomycin for Treatment of Carbapenem-Resistant Acinetobacter baumannii Infections

	Col + fosfo	Col
• Réponse favorable		
– 24 heures	72%	66% (p=0.66)
– Fin	60%	55% (p=0.83)
• Mortalité à 28 jours		
– Toutes causes	47%	57% (p=0.41)
– Dues à l'infection	21%	28% (p=0.63)

Siriatuphet, AAC 2014

Colistine + fosfomycine

- IDSA = pas de recommandations

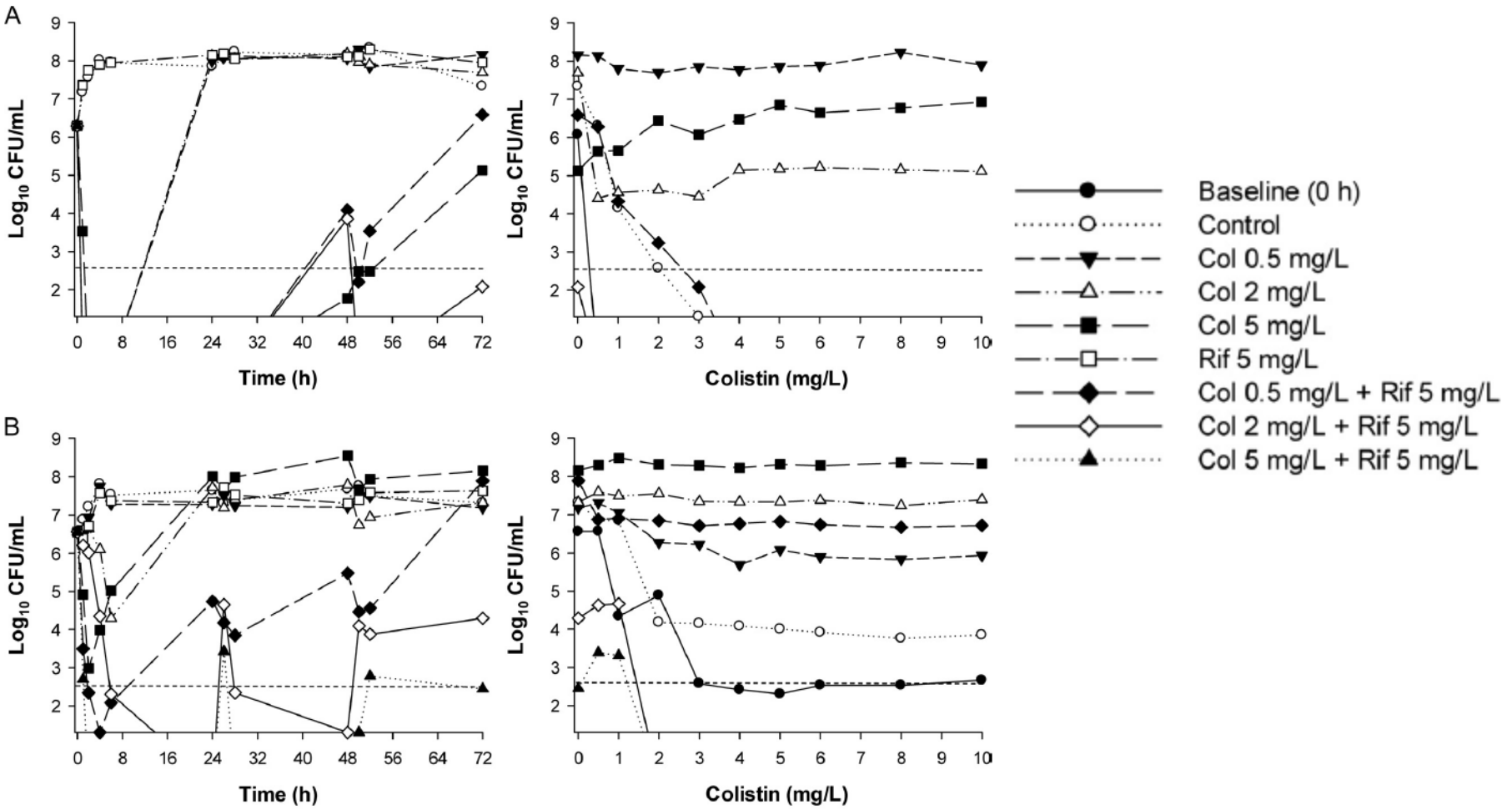
- ESCMID = pas de recommandations

Colistine + rifampicine

- Synergie in vitro
- Synergie pour le modèle murin
- Études cliniques montrant une meilleure éradication microbiologique mais pas d'impact sur la mortalité

Durante-Mangoni, CID, 2014 / Park, J Glob Antimicrob Resist 2019

Synergistic Activity of Colistin and Rifampin Combination against Multidrug-Resistant *Acinetobacter baumannii* in an *In Vitro* Pharmacokinetic/Pharmacodynamic Model



Lee, AAC 2013

Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections

- 29 patients
  - 19 PAVM
  - 10 bactériémies
- Colistine (2MUI x 3) + rifampicine (10 mg/kg x 2/j)
- Réponse clinique et microbiologique dans 22 cas (76%)
- Mortalité : 6 cas (21%)

Bassetti, JAC 2008

Colistin *vs.* the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia

- Étude monocentrique
- 43 patients

	Coli	Coli + Rifa	*p*
Réponse clinique (%)	**40.9**	**52.4**	**0.65**
Réponse microbiologique (%)	59.1	71.4	0.029
Décès à l'hôpital (%)	72.7	61.9	0.67
Mortalité / PAVM (%)	**63.6**	**38.1**	**0.17**

Aydemir H, Epidemiol Infection 2013

Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randimzed clinical trial

- Pas d'impact sur la mortalité

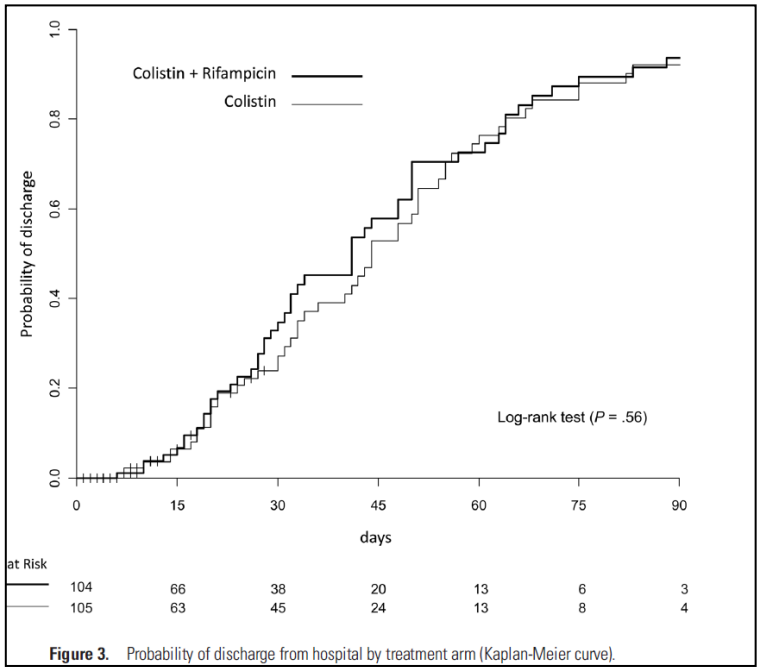


Figure 3. Probability of discharge from hospital by treatment arm (Kaplan-Meier curve).

Table 2. Efficacy Outcomes

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)	*P* Value
Primary outcome			
30-d mortality			
Yes	45 (43.3%)	45 (42.9%)	.95[a]
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	28 (26.6%)	.29[a]
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	.034[a]
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length, d (IQR)	41 (26–61)	44 (27–59)	.96[b]
Development of colistin resistance, %	0	0	. . .

Durante-Mangoni, CID 2013 ; 57 : 349

Colistine + rifampicine

- Éradication microbiologique mais pas de réduction de la mortalité
- ESCMID = non recommandée
- IDSA = non recommandée

Tigécycline

Clinical Experience of Tigecycline Treatment in Infections Caused by Extensively Drug-Resistant *Acinetobacter* spp.

- TG en monothérapie : 71 (65.7%)
- Association de carabapénèmes dans 20 cas (54.1%)

TABLE 5. TREATMENT OUTCOME OF THE PATIENTS

	14-Day mortality	p-*Value*	*30-Day mortality*	p-*Value*
Total patients	36/96 (37.5)		46/87 (52.9)	
Acinetobacter infections	29/71 (40.8)	0.254	38/64 (59.4)	0.053[a]
Non-*Acinetobacter* infections	7/25 (28.0)		8/23 (34.8)	
Pneumonia	19/40 (47.5)	0.122	23/38 (60.5)	0.475[b]
Intra-abdominal infections	4/16 (25.0)		8/16 (50.0)	

Moon, Microbial Drug Resistance 2012

Outcomes in patients infected with carbapenem-resistant *Acinetobacter baumannii* and treated with tigecycline alone or in combination therapy

- Étude rétrospective, 33 patients
- Âge médian : 62 ans (18-87)
- Succès clinique : 23 (69.7%)
- PAVM vs bactériémies (NS)

	Succès	Échec
TG + aminosides	71%	58%
TG + sulbactam	29%	25%
TG seule	0%	17%

Guner, Infection 2011

In vitro synergistic activity of colistin with tigecycline or β-lactam antibiotic/ β-lactamase inhibitor combinations against carbapenem-resistant *Acinetobacter baumannii*

- 50 souches Ab-CR
- Objectif : efficacité in vitro des associations d'antibiotiques

Karaoglan, J Intern Med Res 2014

- Synergie démontrée dans 9 cas / 50
- Pas d'antagonisme !

Table 4. Synergy test results for colistin–tigecycline, colistin–cefoperazone/sulbactam and colistin–piperacillin/tazobactam against carbapenem resistant *Acinetobacter baumannii* strains.

Combination	Test results			Total
	Synergistic effect	Indifferent effect	Antagonistic effect	
Colistin–tigecycline	6 (12)	44 (88)	0	50
Colistin–cefoperazone/sulbactam	2 (4)	48 (96)	0	50
Colistin–piperacillin/tazobactam	1 (2)	49 (98)	0	50

Karaoglan, J Intern Med Res 2014

Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant *Acinetobacter baumannii* infections

- 386 patients Ab-MDR
- 2 groupes
  - TG : 266 patients
    - 108 TG seule
    - 158 TG + IMP ou PIP/TAZ ou C3G anti-pyo
  - Non-TG : 120 patients

- A noter : moins de patients bactériémiques dans le groupe non-TG ($p<0.001$)

Lee, Eur J Clin Microb Infect Dis 2013

Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant *Acinetobacter baumannii* infections

Table 3 Summary of treatments and outcomes among patients with MDRAB in the TG and non-TG treatment groups

	Total (n=386)	Group		p-Value[a]
		Non-TG (n=120)	TG (n=266)	
Treatment				
Duration of antibiotic use[b] (days)	10.0 (7.0, 14.0)	12.0 (9.0, 18.5)	8.0 (6.0, 13.0)	**<0.001**
Switch to other antibiotics[c]	178 (46.1 %)	35 (29.2 %)	143 (53.8 %)	**<0.001**
Death				
No[c]	211 (54.7 %)	64 (53.3 %)	147 (55.3 %)	0.930
Death related to MDRAB infection[c]	142 (36.8 %)	46 (38.3 %)	96 (36.1 %)	
Death not related to MDRAB infection[c]	33 (8.5 %)	10 (8.3 %)	23 (8.6 %)	
Length of hospital stay[b] (days)	40.0 (26.0, 62.0)	37.5 (25.5, 62.0)	43.0 (26.0, 62.0)	0.526
Length of ICU stay[b] (days)	21.0 (10.0, 41.0)	23.5 (10.0, 46.0)	20.0 (10.0, 40.0)	0.338
Microbiological and clinical outcomes				
Microbiological eradication[c]	17 (4.4 %)	14 (11.7 %)	3 (1.1 %)	**<0.001**
Favorable (cure or improvement) [c]	244 (63.2 %)	60 (50.0 %)	184 (69.2 %)	**<0.001**
Unfavorable (stationary or deterioration) [c]	142 (36.8 %)	60 (50.0 %)	82 (30.8 %)	

Lee, Eur J Clin Microb Infect Dis 2013

Chuang *et al. BMC Infectious Diseases* 2014, **14**:102
http://www.biomedcentral.com/1471-2334/14/102

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Effectiveness of tigecycline-based versus colistin- based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis

Yu-Chung Chuang[1,2], Chien-Yu Cheng[3], Wang-Huei Sheng[1*], Hsin-Yun Sun[1], Jann-Tay Wang[1], Yee-Chun Chen[1,4] and Shan-Chwen Chang[1,4]

- Étude cas-témoin : 249 Ab-MDR
  - 119 colistine + (IMP ou AG ou sulbactam)
  - 175 TG + (IMP ou AG ou sulbactam)

Effectiveness of tigecycline-based versus colistin- based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis

Table 4 Multiple variable analysis of risk differences for in-hospital mortality among matched patients with *Acinetobacter baumannii* pneumonia

Variable	Adjusted risk differences % [95% CI]	*p*-value
Colistin vs. tigecycline	−16.4 [−0.9 to − 31.8]	.04
Propensity score	−30.3 [−85.0 to − 24.3]	.28
Age	0.3 [−0.07 to − 0.6]	.11
Male	−11.8 [−29.5 to − 5.9]	.19
Carbapenem combination	−20.8 [−45.8 to − 4.2]	.10

- Surmortalité en fonction des CMI-TG
  - CMI > 2 mg/l : p = 0.01
  - CMI ≤ 2 mg/l : p = 0.81

Tigécycline

- Moins bien que la colistine
- Bonne tolérance (profil rénal)
- Pas de monothérapie
- Se méfier des souches à CMI élevées
- Double dose ?

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

- 54 patients DS (50 mg x 2)
- 46 patients DH (100 mg x 2)
- Étude : tolérance, efficacité
- Analyse univariée

	succès	échec	p
DS (%)	34.4	58.5	0.05
DH (%)	65.5	41.1	

De Pascale, Crit Care 2014

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

- Une différence significative n'a été retrouvée que pour le sous groupe des PAVM

Table 3 Logistic regression analysis of factors associated with clinical cure in 63 patients with ventilator-associated pneumonia

Variable	Multivariate analysis		
	Odds ratio	95% CI	*P*-value
SOFA score at infection occurrence	0.66	0.51, 0.87	0.003
Initial inadequate treatment	0.18	0.05, 0.68	0.01
High-dose tigecycline group	6.25	1.59, 24.57	0.009

De Pascale, Crit Care 2014

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

- Pas de différence significative pour la survenue des effets indésirables

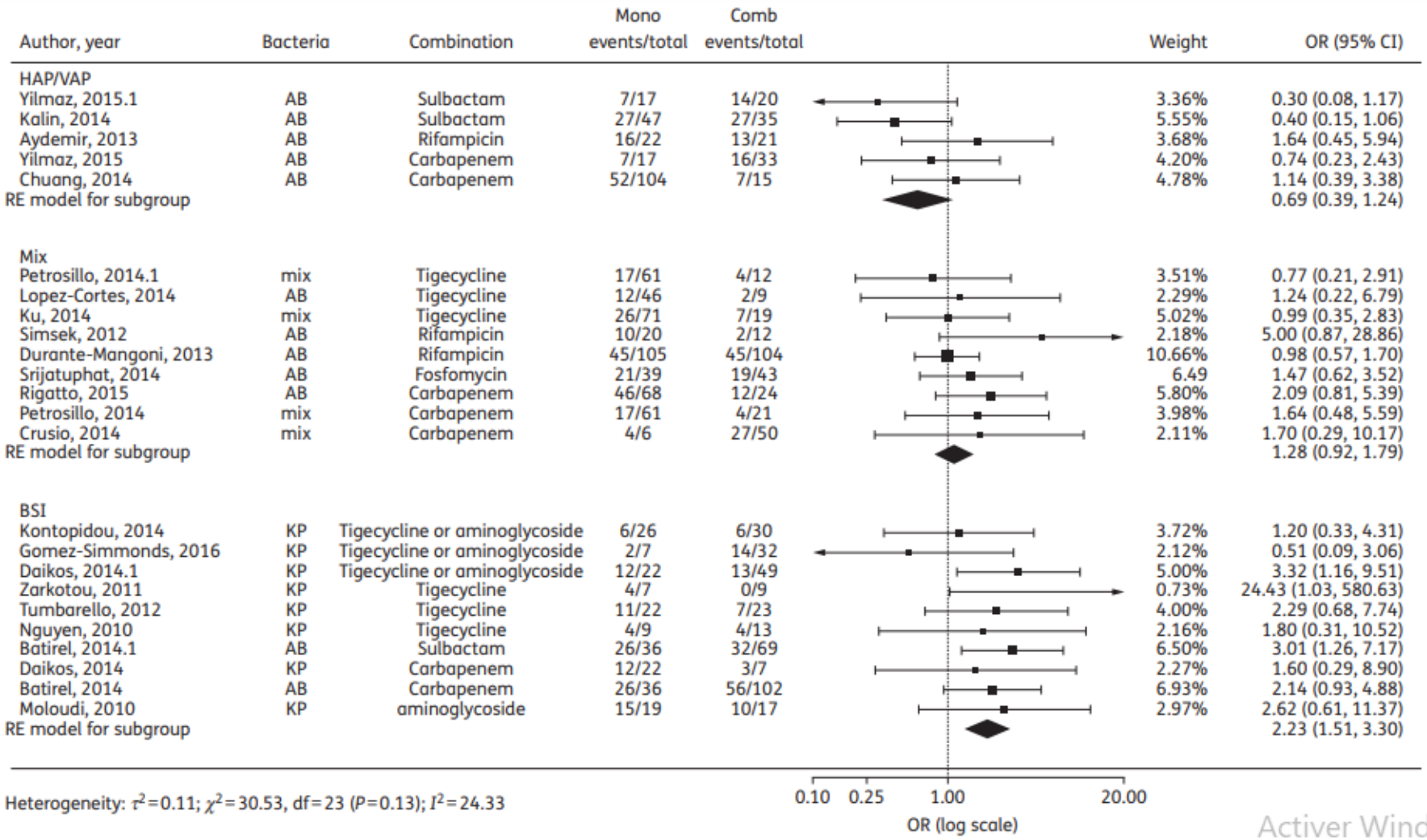
Table 4 Comparison of adverse events in the SD TGC group and HD TGC group

Abnormal laboratory measures (overall population)	Total population (n = 100)	SD TGC group (n = 54)	HD TGC group (n = 46)	*P*-value
BUN increase, n (%)	13 (13)	5 (9)	8 (17)	0.25
Impaired renal function, n (%)	19 (19)	11 (20)	8 (17)	0.8
Impaired hepatopancreatic function,n (%)	18 (18)	9 (17)	9 (19.5)	0.9
Impaired hematological function, n (%)	9 (9)	6 (11)	3 (6.5)	0.5
Abnormal laboratory measures (VAP subgroup)	**Total population (n = 63)**	**SD TGC group (n = 30)**	**HD TGC group (n = 33)**	***P*-value**
BUN increase, n (%)	8 (13)	3 (10)	5 (15)	0.7
Impaired renal function, n (%)	12 (19)	6 (20)	6 (18)	1
Impaired hepatopancreatic function, n (%)	11 (17.5)	4 (13)	7 (21)	0.6
Impaired hematological function, n (%)	4 (6)	1 (3)	3 (9)	0.6

De Pascale, Crit Care 2014

Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis

Zusman, JAC, 2017



Recommandations (ESCMID 2022)

- PAH/PAVM à ABRI : ampicilline/sulbactam
- Si résistance au sulbactam :
  - Colistine
  - Tigécycline forte dose
- Céfidérocol : pas recommandé

Recommandations (ESCMID 2022)

Associations ?

- NON =
  - colistine + méropénème
  - colistine + rifampicine
- Patients sévères : associations de 2 molécules actives in vitro parmi : colistine, aminoside, tigécycline, sulbactam
- Si CMI méropénème < 8 mg/L, envisager une association avec forte posologie en perfusion continue (bonnes pratiques)

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)

Table 2
Potential *in vitro* activity of antibiotics against target carbapenem-resistant Gram-negative bacteria and approved indications

	CRAB	ESBLs	CRPA non-MBL	CRE non-CP	CRE-KPC	CRE-OXA-48	CRE-MBL	Current clinical indications/approval
New antibiotics								
Ceftolozane-tazobactam	No	Yes	Yes	No	No	No	No	FDA and EMA approved for cUTI, cIAI, HAP and VAP
Ceftazidime-avibactam	No	Yes	Yes	+/−	Yes	Yes	No	FDA and EMA approved for cIAI and cUTI, HAP and VAP, and (in EMA only) for the treatment Gram-negative infections in patients with limited treatment options
Meropenem-vaborbactam	No	Yes	No	+/−	Yes	No	No	FDA approved for cUTI, EMA approved for cUTI, HAP and VAP, and for the treatment Gram-negative infections in patients with limited treatment options
Imipenem-cilastatin/ relebactam	No	Yes	Yes	+/−	Yes	No	No	FDA approved for cUTI and cIAI; EMA approved for HAP and VAP and for BSI with a suspected respiratory source, and for the treatment Gram-negative infections in patients with limited treatment options
Plazomicin	No	Yes	+/−	Yes	Yes	Yes	+/−	FDA approval cUTI, EMA application withdrawn
Eravacycline	Yes	Yes	No	Yes	Yes	Yes	Yes	FDA and EMA approved for cIAI
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	FDA cUTI, HAP and VAP; EMA for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
Old antibiotics								
Polymyxins	Yes	Yes	Yes	Yes	Yes	Yes	Yes	FDA: serious infections caused by susceptible strains, when less potentially toxic drugs are ineffective or contraindicated. EMA: treatment of serious infections due to aerobic Gram-negative pathogens in patients with limited treatment options
Aminoglycosides	+/−	+/−	+/−	+/−	+/−	+/−	+/−	EMA and FDA: for the treatment of a variety of bacterial infections
Fosfomycin iv	No	Yes	+/−	+/−	+/−	+/−	+/−	EMA: to treat serious infections when other antibiotic treatments are not suitable. FDA: under review
Aztreonam	No	No	+/−	No	No	No	+/−	EMA and FDA: for the treatment of infections caused by susceptible Gram-negative microorganisms
Tigecycline	Yes	Yes	No	Yes	Yes	Yes	Yes	EMA and FDA: complicated SSTI and IAI (FDA also CAP)
Temocillin	No	Yes	No	No	+/−	No	No	EMA and FDA: orphan drug status for the treatment of infections caused by *Burkholderia cepacia* in patients with cystic fibrosis

Conclusion

Difficultés diagnostiques

- CMI pour toutes les molécules
- Détection des gènes de résistance
- Mécanisme de résistance EPC

Difficultés thérapeutiques

- Carbapénèmes si CMI < 8 mg/L
- Associations si gravité
- Fortes doses
- Carbapénèmes + colistine
- Choix individuel, traitement à la carte :
  - KPC : CAZ/AVI, double carbapénème ?
  - Oxa-48 : CAZ/AVI
  - NDM : aztréonam / AVI