JN 22es Journées Nationales d'Infectiologie
Montpellier
et la région Occitanie - Méditerranée
LE CORUM, Montpellier
du lundi 30 août 2021
au mercredi 1er septembre 2021

Résistance bactérienne et nouveaux antibiotiques

Aurélien Dinh
Service des Maladies Infectieuses et Tropicales
Hôpital Raymond-Poincaré, APHP
Université Paris Saclay

Cefiderocol

JAC Antimicrob Resist
doi:10.1093/jacamr/dlab081

JAC-Antimicrobial Resistance

In vitro activity of cefiderocol and comparators against isolates of Gram-negative pathogens from a range of infection sources: SIDERO-WT-2014–2018 studies in France

Thierry Naas [1,2,3]*, Gerard Lina[4,5], Anne Santerre Henriksen [6], Christopher Longshaw[7] and Francois Jehl[8]

	All isolates			NP			cUTI			BSI			cIAI		
Pathogen	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S
Enterobacterales	1330	1344	99.0	344	344	100	383	388	98.7	166	172	96.5	300	302	99.3
E. coli	322	324	99.4	48	48	100	104	105	99.0	38	38	100	114	115	99.1
K. pneumoniae	260	266	97.7	65	65	100	101	103	98.1	35	37	94.6	43	44	97.7
Klebsiella oxytoca	96	96	100	24	24	100	17	17	100	13	13	100	31	31	100
K. aerogenes	90	91	98.9	40	40	100	17	18	94.4	14	14	100	11	11	100
Klebsiella variicola	18	18	100	5	5	100	5	5	100	1	1	100	5	5	100
E. cloacae	89	90	98.9	13	13	100	24	24	100	13	14	92.9	21	21	100
Enterobacter asburiae	9	11	81.8	2	2	100	1	2	50.0	2	3	66.7	1	1	100
Serratia spp.	167	167	100	90	90	100	20	20	100	30	30	100	10	10	100
Citrobacter spp.	137	139	98.6	28	28	100	55	55	100	15	17	88.2	32	32	100
Proteus spp.	89	89	100	17	17	100	27	27	100	3	3	100	19	19	100
M. morganii	37	37	100	11	11	100	3	3	100	1	1	100	12	12	100
Providencia rettgeri	16	16	100	1	1	100	9	9	100	1	1	100	1	1	100
Non-fermenters	681	683	99.7	337	338	99.7	105	105	100	92	93	98.9	62	62	100
P. aeruginosa	341	341	100	166	166	100	42	42	100	30	30	100	54	54	100
Pseudomonas otitidis	1	1	100	—	—		—	—		—	—		1	1	100
A. baumannii	159	161	98.8	66	67	98.5	34	34	100	32	33	97.0	1	1	100
other *Acinetobacter* spp.	71	71	100	23	23	100	23	23	100	17	17	100	2	2	100
S. maltophilia	103	103	100	78	78	100	6	6	100	11	11	100	4	4	100
Burkholderia spp.	6	6	100	4	4	100	—	—		2	2	100	—	—	
Total	2011	2027	99.2	681	682	99.9	488	493	99.0	258	265	97.4	362	364	99.5

- Programme de surveillance SIDERO WT
- Collection des souches de 2014-2018
- 10 laboratoires en France
- Sensibilité en microdilution
- Selon Guidelines/break point EUCAST

Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L Paterson, Simon Portsmouth, Julian Torre-Cisneros, Kiichiro Toyoizumi, Richard G Wunderink, Tsutae D Nagata

- Essai clinique ouvert, randomisé avec un contrôle actif (2:1) et une analyse descriptive
- Patients en état critique et souffrant d'infections diverses (IU, PN, BSI) résistantes aux carbapénèmes
- 29 régimes de contrôle différents utilisés dans 95 centres

	Cefiderocol (n=101)	Best available therapy (n=49)
Sex		
Male	66 (65%)	35 (71%)
Female	35 (35%)	14 (29%)
Age (years)		
Mean (SD)	63·1 (19·0)	63·0 (16·7)
Clinical diagnosis		
Nosocomial pneumonia	45 (45%)	22 (45%)
HAP	20 (20%)	7 (14%)
VAP	24 (24%)	13 (27%)
HCAP	1 (1%)	2 (4%)
Bloodstream infections or sepsis†	30 (30%)	17 (35%)
Bloodstream infection	22 (22%)	9 (18%)
Complicated intra-abdominal infection	3 (3%)	2 (4%)
Skin and skin structure infection	1 (1%)	0
Intravenous line infection	4 (4%)	2 (4%)
Other‡	5 (5%)	1 (2%)
Unknown	9 (9%)	4 (8%)
Sepsis	8 (8%)	8 (16%)
Complicated intra-abdominal infection	2 (2%)	1 (2%)
Skin and skin structure infection	4 (4%)	3 (6%)
Intravenous line infection	0	3 (6%)
Other‡	2 (2%)	1 (2%)
Complicated urinary tract infection	26 (26%)	10 (20%)

	Cefiderocol (n=101)	Best available therapy (n=49)
(Continued from previous column)		
Creatinine clearance (mL/min)		
Mean (SD),	85·8 (79·3)	88·9 (64·2)
Median (range; IQR)	59·2 (9·4–539·26; 33·9–107·9)	69·4 (4·6–270·8; 47·6–119·8)
Empirical treatment failure	58 (57%)	27 (55%)
Previous therapy§		
Antibiotics¶	93 (92%)	49 (100%)
Carbapenems	60 (59%)	26 (53%)
Systemic corticosteroids	44 (44%)	17 (35%)
ICU at randomisation	57 (56%)	21 (43%)
Shock	19 (19%)	6 (12%)
Immunocompromised	27 (27%)	10 (20%)
Positive blood culture	25 (25%)	13 (27%)
APACHE II score		
Mean (SD)	15·3 (6·5)	15·4 (6·2)
Median (range; IQR)	15 (2–29; 11–20)	14 (2–28; 11–20)
≤15	55 (54%)	27 (55%)
16–19	17 (17%)	9 (18%)
≥20	29 (29%)	13 (27%)

	Cefiderocol (n=80)	Best available therapy (n=38)
Number of carbapenem-resistant Gram-negative pathogens from appropriate specimens*		
One	62 (78%)	30 (79%)
Two	13 (16%)	8 (21%)
Three	4 (5%)	0
Four	1 (1%)	0
Type of carbapenem-resistant Gram-negative pathogen		
All patients	N=87†	N=40‡
Acinetobacter baumannii	37 (46%)	17 (45%)
Klebsiella pneumoniae	27 (34%)	12 (32%)
Pseudomonas aeruginosa	12 (15%)	10 (26%)
Stenotrophomonas maltophilia	5 (6%)	0
Acinetobacter nosocomialis	2 (3%)	0
Enterobacter cloacae	2 (3%)	0
Escherichia coli	2 (3%)	1 (3%)

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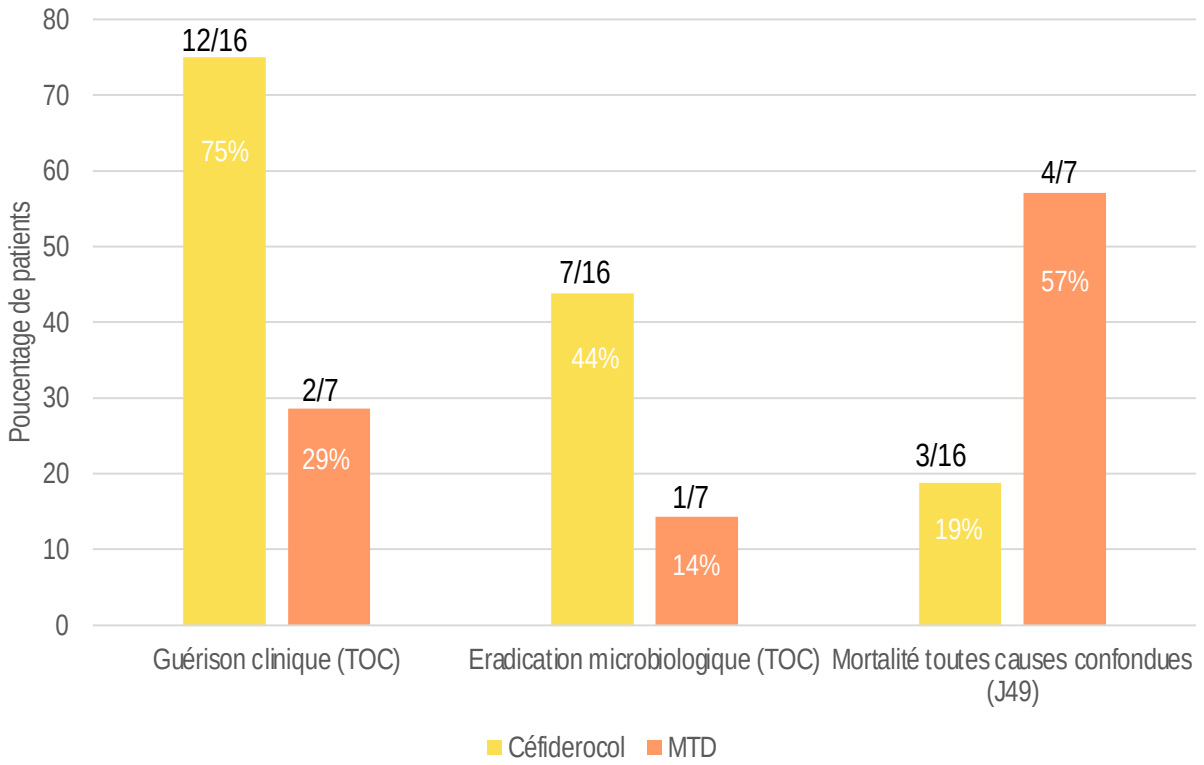
- PN : Guérison clinique dans le groupe céfidérocol 50.0% (20/40) vs 52.6% (10/19)
- BSI/Sepsis : Guérison clinique dans le groupe céfidérocol 43.5% (10/23) vs 42.9% (6/14)
- IU : Eradication microbiologique dans le groupe céfidérocol 52.9% (9/17) vs 20.0% (1/5)
- Mortalité J28 (toute cause) : 33% (13/40) dans le groupe cefiderocol vs 16% (3/19)

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=40)	Best available therapy (n=19)	Cefiderocol (n=23)	Best available therapy (n=14)	Cefiderocol (n=17)	Best available therapy (n=5)	Cefiderocol (n=80)	Best available therapy (n=38)
Clinical outcomes								
End of treatment								
Clinical cure	24 (60%; 43·3–75·1)	12 (63%; 38·4–83·7)	16 (70%; 47·1–86·8)	7 (50%; 23·0–77·0)	13 (77%; 50·1–93·2)	3 (60%; 14·7–94·7)	53 (66%; 54·8–76·4)	22 (58%; 40·8–73·7)
Clinical failure	13 (33%)	7 (37%)	6 (26%)	7 (50%)	1 (6%)	1 (20%)	20 (25%)	15 (40%)
Indeterminate	3 (8%)	0	1 (4%)	0	3 (18%)	1 (20%)	7 (9%)	1 (3%)
Test of cure								
Clinical cure*	20 (50%; 33·8–66·2)	10 (53%; 28·9–75·6)	10 (43%; 23·2–65·5)	6 (43%; 17·7–71·1)	12 (71%; 44·0–89·7)	3 (60%; 14·7–94·7)	42 (53%; 41·0–63·8)	19 (50%; 33·4–66·6)
Clinical failure	16 (40%)	6 (32%)	9 (39%)	7 (50%)	2 (12%)	1 (20%)	27 (34%)	14 (37%)
Indeterminate	4 (10%)	3 (16%)	4 (17%)	1 (7%)	3 (18%)	1 (20%)	11 (14%)	5 (13%)
Follow-up								
Sustained clinical cure	20 (50%; 33·8–66·2)	6 (32%; 12·6–56·6)	9 (39%; 19·7–61·5)	4 (29%; 8·4–58·1)	9 (53%; 27·8–77·0)	3 (60%; 14·7–94·7)	38 (48%; 36·2–59·0)	13 (34%; 19·6–51·4)
Relapse	0	3 (16%)	1 (4%)	1 (7%)	1 (6%)	0	2 (3%)	4 (11%)
Clinical failure	16 (40%)	6 (32%)	9 (39%)	7 (50%)	2 (12%)	1 (20%)	27 (34%)	14 (37%)
Indeterminate	4 (10%)	4 (21%)	4 (17%)	2 (14%)	5 (29%)	1 (20%)	13† (16%)	7† (18%)

Infections à métallo-β-lactamases

Caractéristiques des infections à métallo-β-lactamases

	Céfidérocol	MTD
Total	16	7
Bactériémie	4	1
PN	6	3
IU	6	3
Entérobactéries	10	4
P. aeruginosa	4	3
A. baumannii	2	0



*Incluant NDM, VIM, IMP; PN: pneumonie nosocomiale, IU: infection urinaire, MTD: meilleur traitement disponible
Bassetti 2020 Lancet ID et rapport de l'étude CREDIBLE-CR

Mortalité selon bactérie

	Cefiderocol n/N (%) (95%IC (%))	MTD n/N (%) (95%IC (%))
Tous les patients	34/101 (33,7) (24,6- 43,8)	10/49 (20,4) (10,2-34,3)
Patients avec une infection à *Acinetobacter* spp.	21/42 (50) (34,2- 65,8)	3/17 (17,6) (3,8-43,4)
Patients avec une infection sans *Acinetobacter* *(*comprenant *entérobactéries* ou *P. aeruginosa…)* Entérobactéries *P. aeruginosa*	13/59 (22) (12,3-34,7) 6/28 (21,4) 2/11 (18,2)	6/32 (18,8) (7,2- 36,4) 4/15 (26,7) 2/11 (18,2)

*Parmi ces patients, 30% (16) avaient des souches ayant une CMI au méropénème supérieure à 64 mg/L.
Bassetti 2020 Lancet ID et rapport de l'étude CREDIBLE-CR; 2: Wunderick 2020 Lancet ID

Acinetobacter spp.

Paramètre à l'inclusion	Patients avec une infection à *Acinetobacter*		Patients avec une infection sans *Acinetobacter* (comprenant *entérobactéries* ou *P. aeruginosa*)	
	Cefiderocol	MTD	Cefiderocol	MTD
Age ≥ 65 ans, n (%)	26 (62)	7 (41)	38 (64)	15 (47)
Total APACHE II ≥ 16, n (%)	24 (57)	8 (47)	22 (37)	14 (44)
Choc dans le mois précédent l'inclusion, n (%)	11 (26)	1 (6)	8 (14)	5 (16)
Hospitalisation en USI à la randomisation	34 (81)	8 (47)	23 (39)	13 (41)

Bassetti 2020 Lancet ID et rapport de l'étude CREDIBLE-CR

Cefiderocol as Rescue Therapy for *Acinetobacter baumannii* and Other Carbapenem-resistant Gram-negative Infections in Intensive Care Unit Patients

Marco Falcone,[1] Giusy Tiseo,[1] Manuela Nicastro,[2] Alessandro Leonildi,[3] Alessandra Vecchione,[3] Costanza Casella,[2] Francesco Forfori,[2,4] Paolo Malacarne,[2] Fabio Guarracino,[2] Simona Barnini,[3] and Francesco Menichetti[1]

- 10 patients en soins critiques : bactériémies ou PAVM due à ABRI, *S. maltophilia*, ou NDM-*K. pneumoniae*
- Guérison à J30 : 70%
- Survie à J30 : 90%
- 2 échecs microbiologiques

Age/ Sex	Underlying Diseases	APACHE II Score	Isolated Pathogen	CFDC MIC, µg/mL	Type of Infection	Initial Treatment Regimen	CFDC Dosage	CFDC Mono-therapy	CRRT	Clinical Outcome at 30 d	30-d Mortality
76/F	Hypertension Bipolar disorder	44	*A. baumannii*	0.25	BSI	COL + TGC	2 g q8h	Yes	Yes	Failure	No
82/M	Cerebrovascular disease Bladder cancer	43	*A. baumannii*	0.5	BSI	COL + TGC + FOS	2 g q8h	Yes	No	Success	No
65/F	Hypertension Obesity	46	*A. baumannii*	0.5	BSI	COL	2 g q8h	Yes	No	Failure	No
33/F	IV drug user	34	*A. baumannii*	0.5	BSI	COL + TGC	2 g q6h	Yes	No	Success	No
82/F	Hypertension Previous stroke	25	*A. baumannii*	0.25	BSI	COL + TGC + MEM	1.5 g q8h	Yes	No	Success	No
75/F	Hypertension Ischemic cardiomyopathy	29	*A. baumannii*	0.5	BSI	TGC + SAM	2 g q6h	Yes	No	Success	No
79/F	Hypertension	39	NDM-producing Kp *Stenotrophomonas maltophilia*	1/0.5	VAP	CAZ-AVI + ATM + FOS	2g q6h	Yes	No	Success	No
44/M	Hypertension Obesity	40	NDM-producing Kp	1	VAP	COL + FOS	2g q6h	Yes	No	Success	No
77/M	Hypertension	36	*A. baumannii* + NDM-producing Kp	0.12/ 2	VAP	COL + CAZ-AVI + ATM	1.5 g q8h	No[a]	Yes	Failure	Yes
72/M	Hypertension	30	*A. baumannii*	0.5	VAP	COL + TGC	2g q6h	Yes	No	Success	No

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Article

Cefiderocol-Based Combination Therapy for "Difficult-to-Treat" Gram-Negative Severe Infections: Real-Life Case Series and Future Perspectives

Davide Fiore Bavaro [1,*,†], Alessandra Belati [1,†], Lucia Diella [1,†], Monica Stufano [2], Federica Romanelli [3], Luca Scalone [4], Stefania Stolfa [3], Luigi Ronga [3], Leonarda Maurmo [4], Maria Dell'Aera [5], Adriana Mosca [3], Lidia Dalfino [2], Salvatore Grasso [2] and Annalisa Saracino [1]

- 13 patients traités du 1er Septembre 2020 au 31 Mars 2021
- 5/13 (38%) USI
- 4/13 (31%) infections post-chirurgicales
- 4/13 (31%) patients ID (2/4: transplantés d'organe; 2/4: hémopathie)

Pt	Age, y	Sex	Cause of Hospedalization	Underlying Diseases
1	68	M	COVID19	Huntington Corea, Imobilization syndrome
2	62	F	COVID19	Fibromyalgia
3	69	M	COVID19	Hypertension, Diabetes
4	78	M	COVID19	Hypertension, COPD, Diabetes
5	75	F	COVID19	Diabetes
6	38	M	Dyspnoea post orotracheal intubation for cerebral hemorragy	Hypertension, Pulmonary Embolism
7	70	M	PTCA due to myocardial Infarction in course of COVID-19	Mild COVID19, Diabetes, Ischemic heart disease
8	64	M	Neurosurgical wound Infection	Previous drainage of post-traumatic subarachnoid hematoma
9	25	M	Subocclusion and volvulus treated with gut surgical resection	Colostomy, Hip and Arm fracture
10	60	M	Sepsis	Hepatic transplantation for HBV-related cirrosis and HCC
11	43	M	Myocardial Infarction and cardiogenic shock, Arrhythmic storm, Acute	Heart transplantation
12	57	M	COVID19	Myelodysplastic syndrome
13	68	M	Pneumonia	Acute Myeloid Leukemia, Chronic Kidney Disease

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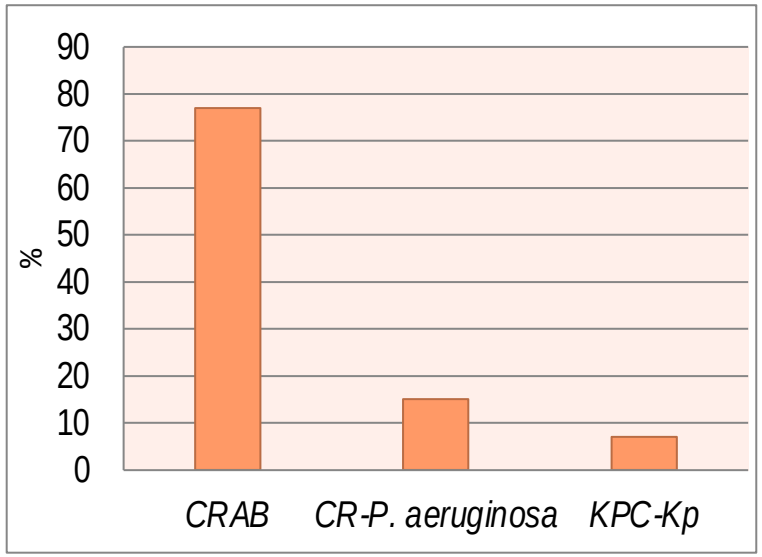
Article

Cefiderocol-Based Combination Therapy for "Difficult-to-Treat" Gram-Negative Severe Infections: Real-Life Case Series and Future Perspectives

Davide Fiore Bavaro [1,*,†], Alessandra Belati [1,†], Lucia Diella [1,†], Monica Stufano [2], Federica Romanelli [3], Luca Scalone [4], Stefania Stolfa [3], Luigi Ronga [3], Leonarda Maurmo [4], Maria Dell'Aera [5], Adriana Mosca [3], Lidia Dalfino [2], Salvatore Grasso [2] and Annalisa Saracino [1]

- Eradication microbiologique : 100%
- Survie J30 : 10/13; 2 décès dus au SARS-CoV-2
- 1 décès due à une infection intercurrente
- Pas de récidive à J30



Pt	Type of Infection	Cefiderocol Based Therapy (Duration, day)	Outcome	Outcome at 30 days
1	CVC-related BSI with Septic Shock	FDC, FOF, TGC (5)	Microbiological Eradication	Death†
2	CVC-related BSI with Septic Shock	FDC, CST, MEM (13)	Recovery	Success
3	CVC-related BSI with Septic Shock	FDC, CST (10)	Recovery	Success
4	CVC-related BSI with Sepsis	FDC, TGC (8)	Recovery	Success
5	CVC-related BSI with Sepsis	FDC, FOF (5)	Recovery	Success
6	VAP	FDC, FOF, TGC (9)	Recovery	Success
7	Bloodstream infection	FDC, CST, FOF (8)	Recovery	Success
8	Neurosurgical Wound Infection	FDC, FOF (10)	Recovery	Success
9	Perihepatic Abscess, Septic Shock	FDC, TGC, DAP, FOF (21)	Recovery	Success
10	Hepatic Abscess, Bloodstream infection	FDC, TGC, CST (17), then FDC, FOF (11) *	Recovery	Success
11	VAP, Bloodstream infection	FDC, TGC, CST, FOF (16)	Microbiological Eradication	Death†
12	Bloodstream infection	FDC, CST (12)	Microbiological Eradication	Death†
13	Pneumonia	FDC, FOF (10)	Recovery	Success

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Open Forum Infectious Diseases

MAJOR ARTICLE

Cefiderocol Activity Against Clinical *Pseudomonas aeruginosa* Isolates Exhibiting Ceftolozane-Tazobactam Resistance

Patricia J. Simner,[1] Stephan Beisken,[2] Yehudit Bergman,[1] Andreas E. Posch,[2] Sara E. Cosgrove,[3] and Pranita D. Tamma[4]

Isolate[b]	Clinical Summary[c]	TOL-TAZ MIC, mcg/mL		CAZ-AVI MIC, mcg/mL		IMI-REL MIC, mcg/mL		Cefiderocol MIC, mcg/mL	
		a	b	a	b	a	b	a	b
12a-b	16 yo M, ventilator-dependent with *P. aeruginosa* pneumonia. Received TOL-TAZ 3g q8h x 6d (no HD); other β-lactams: meropenem (7d). Alive at day 30: yes.	4	2	32	4	8	8	0.25	0.25
13a-b	53 yo M, 60% body surface area burns with *P. aeruginosa* pneumonia. Received TOL-TAZ 3g q8h x 6d (no HD); other β-lactams: meropenem (10d). Alive at day 30: no.	1	0.5	16	4	4	4	0.5	0.5
14a-b	55 yo F, anoxic brain injury with *P. aeruginosa* pneumonia. Received TOL-TAZ 3g q8h x 7d (no HD); other β-lactams: meropenem (3d). Alive at day 30: yes.	2	8	16	16	8	4	0.5	1
15a-b	74 yo M, ventilator-dependent with *P. aeruginosa* pneumonia. Received TOL-TAZ 3g q8h x 6d (HD); other β-lactams: none. Alive at day 30: yes.	1	256	2	256	4	32	0.12	0.25
16a-b	65 yo M, ventricular assist device with *P. aeruginosa* bacteremia and device-associated infection, device not removed. Received TOL-TAZ 3g q8h x 16d (HD); other β-lactams: meropenem (1d). Alive at day 30: yes.	1	256	8	32	32	4	0.12	1

- Mutations dans région AmpC-AmpR associées à résistance à ceftolozane-tazobactam (TOL-TAZ) et ceftazidime-avibactam (CAZ-AVI)
- 32 paires d'isolats de 16 patients
  - isolats index de *P. aeruginosa* sensibles à TOL-TAZ
  - isolats après traitement par TOL-TAZ
- 4/16 paires : ↗ ≥4x CMI au cefiderocol
- Mutations AmpC E247K : ↗ ≥4x CMI à TOL-TAZ et CAZ-AVI + ↘ ≥4x CMI à IMI-REL
- Altérations sites de liaison d'AmpC **β**-lactamases dérivées de *P. aeruginosa* :
  - Peuvent réduire l'activité de 3 sur 4 nouveaux β-lactamines (ie, ceftolozane-tazobactam, ceftazidime-avibactam, et cefiderocol)
  - Peuvent augmenter susceptibilité à imipenem-relebactam

Comparaison entre molécules

Open Forum Infectious Diseases

REVIEW ARTICLE

Meta-analysis of Clinical Outcomes Using Ceftazidime/Avibactam, Ceftolozane/Tazobactam, and Meropenem/Vaborbactam for the Treatment of Multidrug-Resistant Gram-Negative Infections

Geneva M. Wilson,[1,©] Margaret Fitzpatrick,[1,2] Kyle Walding,[2] Beverly Gonzalez,[1] Marin L. Schweizer,[3,4] Katie J. Suda,[5,6] and Charlesnika T. Evans[1,7]

- 29 études >> 1620 patients
- Pneumonie : 49.8%
- *Pseudomonas aeruginosa*
  MDR : 65.3%

Author, Year	Study Design	Location	Duration of Study, mo	Duration of Treatment	Sample Size	Age, y	SOT, %	Kidney Disease, %	Cancer	Pneumonia	%MDRPA	%CRE
Alosaimy, 2020	Obs. study	USA	20	≥72 h MW	40	58 [34–89][a]	NR	37.5	NR	32.5	NA	84.6
Bassetti, 2019	Obs. study	Italy	21	≥96 h CrT	101	67 [49–94][a]	10.9	30.7	29.7	31.7	69.0	NA
Boseaed, 2020	Obs. study	Saudi Arabia	24	≥96 h CrT	24	57 [36–71][a]	8.3	20.8	20.8	31.6	100	NA
Caston, 2017	Obs. study	Spain	9	NR	12	67 [54–75][b]	NR	25.0	16.7	50.0	100	NA
De la Calle, 2019	Obs. study	Spain	26	≥72 h CrA	23	58.8 [16.0–93][c]	21.7	43.5	21.7	21.7	NA	100.0
Díaz-Sanestro, 2018	Obs. study	Spain	28	CrT for ≥48 h	58	60.8 [14.5][c]	1.7	25.9	32.7	60.3	97	NA
Dinh, 2017	Obs. study	France	9	≥1 dose of CrT	15	49.3 [8–73][a]	33.3	20.0	26.7	46.7	100	NA
Escrig-Verge, 2018	Obs. study	Spain	20	≥72 h of CrT	38	59.5 [19–84][b]	28.9	21.1	28.9	38.8	100	NA
Gallagher, 2018	Obs. study	USA	38	≥24 h of CrT	205	60 [48–70][a]	17.1	28.3	16.1	59.0	100	NA
Guimaraes, 2019	Case series	Brazil	21	≥48 h of CrA	29	50.5[d,e]	24.1	48.3	NR	10.3	NA	100.0
Haidar, 2017	Obs. study	USA	9	NR	21	58 [29–91][b]	38.1	23.8	9.5	76.2	100	NA
Hart, 2019	Case series	USA	41	≥24 h CrT	70	57 [14][c]	67.1	NR	NR	55.7	100	NA
Jorgensen, 2019	Obs. study	USA	48	≥72 h of CrA	203	62 [49–72][a]	NR	32.0	13.3	37.4	31	58
Jorgensen, 2020	Obs. study	USA	48	≥72 h of CrT	259	62 [52–72][a]	NR	NR	9.3	62.9	87	NA
Kong, 2017	Chart review	USA	13	≥24 h of CrA	60	60 [51–89][a]	25.0	31.7	NR	26.7	NA	83.3
Molloy, 2020	Case series	USA	Not reported	Not reported	13	3 mo–19 y[f]	NR	NR	7.7	76.9	100	NA
Monar, 2017	Obs. study	USA	Not reported	≥24 h CrT	34	57 [42–90][a]	44.1	NR	NR	64.7	100	NA
Murrie, 2017	Obs. study	USA	Not reported	Not reported	35	52.9 [18–89][b]	NR	11.4	25.7	47.9	77.0	NA
Nambiar, 2019	Case series	USA	22	Not reported	32	CrA = 61 [11][c] CrT = 48 [19][c]	100.0	12.5	NR	46.9	13.0	87.5
Nathan, 2016	Case series	USA	14	NR	28	57 [18–84][c]	0.0	NR	39.3	28.6	50.0	25.0
Rodriguez-Nunez, 2020	Obs. study	USA, UK, France, Spain	24	≥72 h of CrT,	90	64 [16.2][c]	3.3	14.4	18.9	100	77.0	NA
Sastre, 2017	Case series	USA	10	≥1 dose of CrT	49	65 [51–71][a]	34.7	NR	14.3	69.4	69	NA
Santevlecchi, 2018	Case series	USA	12	≥1 dose of CrA	10	53 [32–79][a]	20.0	NR	10.0	60.0	70	NA
Shields, 2016	Case series	USA	10	≥72 h of CrT	37	64 [26–78][a]	29.7	NR	0.0	32.4	NA	100.0
Shields, 2020	Obs. study	USA	16	MV for ≥48 h	20	56 [31–80][a]	NR	NR	NR	35.0	NR	70.0
Souza, 2018	Obs. study	Spain	20	≥48 h of CrA	57	64 [28–86][a]	NR	21.05	24.56	26.3	NA	100.0
Tumkin, 2017	Case series	Europe and Australia	36	≥1 dose of CrA	38	61 [47–67][a]	13.2	18.42	NR	NR	NA	89.5
Viale, 2020	Obs. study	Italy	24	≥72 h of CrA	41	61 [6.1–93.0][c]	NR	26.09	17.39	43.8	93	NA
Xydis, 2018	Case series	Spain	12	≥72 h of CrT	23	62 [41–70][a]	19.5	21.9	26.8	34.8	100	NA

Open Forum Infectious Diseases

REVIEW ARTICLE

Meta-analysis of Clinical Outcomes Using Ceftazidime/Avibactam, Ceftolozane/Tazobactam, and Meropenem/Vaborbactam for the Treatment of Multidrug-Resistant Gram-Negative Infections

Geneva M. Wilson,[1,©] Margaret Fitzpatrick,[1,2] Kyle Walding,[2] Beverly Gonzalez,[1] Marin L. Schweizer,[3,4] Katie J. Suda,[5,6] and Charlesnika T. Evans[1,7]

	Included Studies	Pooled Rate (CI), %	I^2 Value, %
Outcomes			
Clinical success	29	73.3 (68.9–77.5)	72.6
Microbiological success	19	67.9 (58.8–77.4)	87.9
Recurrence rate	14	33.9 (28.2–39.7)	47.3
Clinical success among subset analyses			
C/T-only studies	18	73.8 (67.8–79.7)	78.5
C/A-only studies	12	73.0 (67.7–78.4)	51.9
Salvage therapy patients	12	80.7 (78.0–83.4)	0.0

Ceftolozane tazobactam

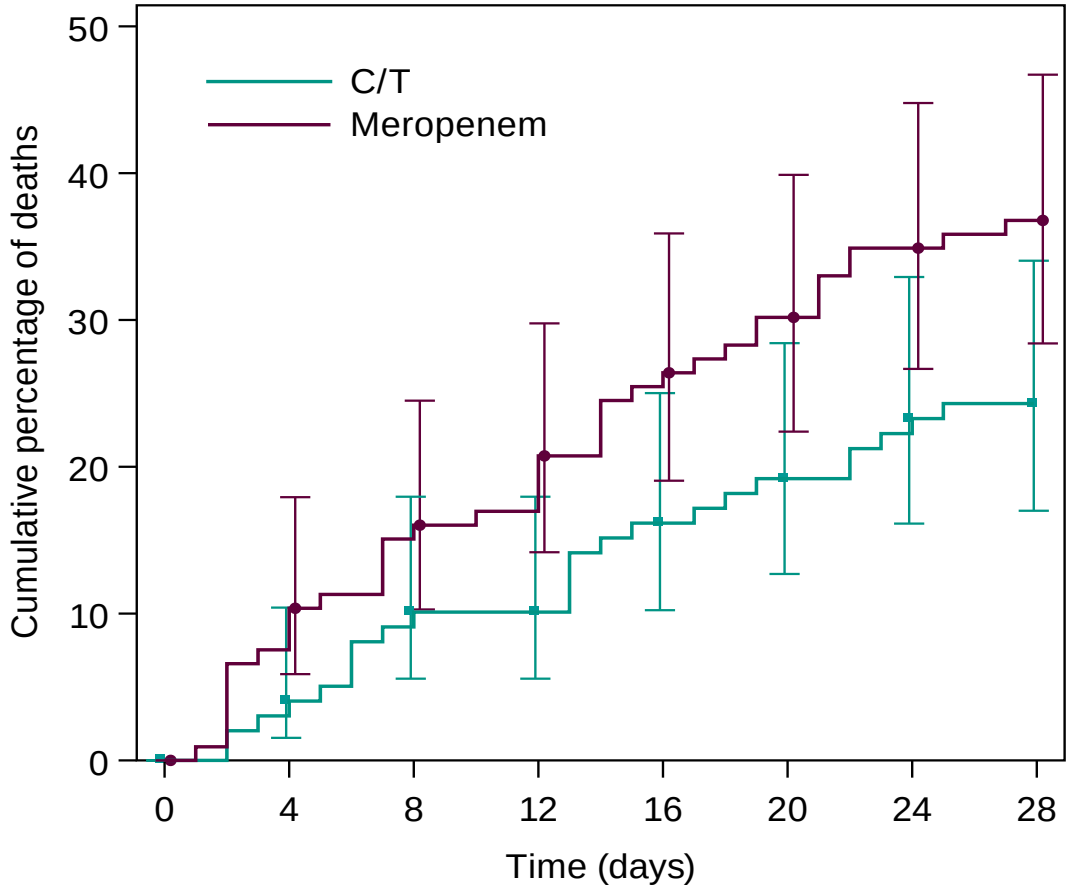
RESEARCH Open Access

Ceftolozane/tazobactam versus meropenem in patients with ventilated hospital-acquired bacterial pneumonia: subset analysis of the ASPECT-NP randomized, controlled phase 3 trial

Jean-François Timsit[1], Jennifer A. Huntington[2], Richard G. Wunderink[3], Nobuaki Shime[4], Marin H. Kollef[5], Ülo Kivistik[6], Martin Nováček[7], Álvaro Réa-Neto[8], Ignacio Martin-Loeches[9,10], Brian Yu[2], Erin H. Jensen[2], Joan R. Butterton[2], Dominik J. Wolf[2], Elizabeth G. Rhee[2] and Christopher J. Bruno[2*]

- Sous groupe d'ASPECT-NP : PAVM
- 99 patients sous ceftolozane/tazobactam vs 108 sous méropénem
- Analyse ajustée sur facteurs confondants : mortalité 2 X plus élevée avec méropénem vs ceftolozane tazobactam
- Facteurs de mauvais pronostic en analyse multivariée : vasopresseur et bactériémie

	C/T	Meropenem
Number of participants	99	108
Number of deaths (%)	31 (31.3)	43 (39.8)



Patients at risk

C/T	99	95	89	89	83	79	75	74
Meropenem	108	95	89	84	78	74	69	67

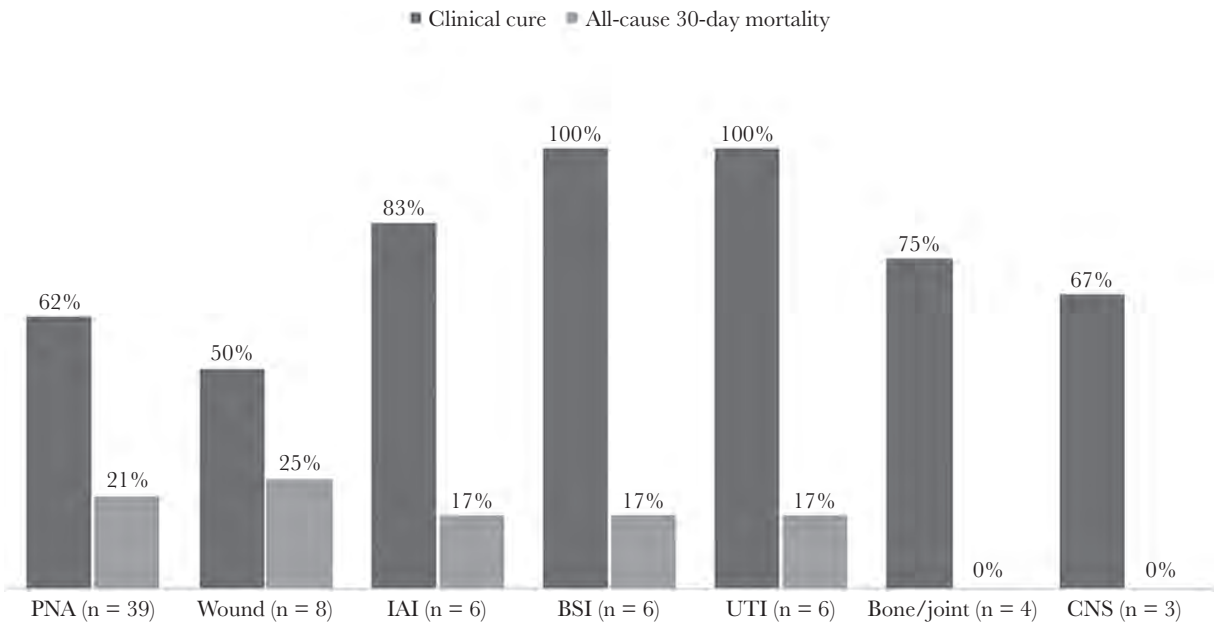
Critical Care 2021

Open Forum Infectious Diseases

MAJOR ARTICLE

A Multicenter Evaluation of Ceftolozane/Tazobactam Treatment Outcomes in Immunocompromised Patients With Multidrug-Resistant *Pseudomonas aeruginosa* Infections

Delaney E. Hart,[1] Jason C. Gallagher,[2] Laura A. Puzniak,[3] and Elizabeth B. Hirsch[1]; for the C/T Alliance to deliver Real-world Evidence (CARE)



- Etude rétrospective multicentrique (n=14)
- Patients immunodéprimés traités ≥24 avec C/T
- *P. aeruginosa* MDR
- 66 patients
- USI : 46%
- Infection respiratoire : 56%
- Mortalité J30 : 19%

Outcome	
Clinical cure, all infection sources (n = 69), No. (%)	47 (68)
Pneumonia, receiving pneumonia dosing (n = 28)	21 (75)
Pneumonia, receiving nonpneumonia dosing (n = 10)	3 (30)
30-d all-cause mortality, all infection sources (n = 69), No. (%)	13 (19)
Pneumonia, receiving pneumonia dosing (n = 28)	5 (18)
Pneumonia, receiving nonpneumonia dosing (n = 10)	3 (30)
Length of C/T therapy, mean ± SD, d	13 ± 11
Length of hospital stay, median (IQR), d	38 (54)

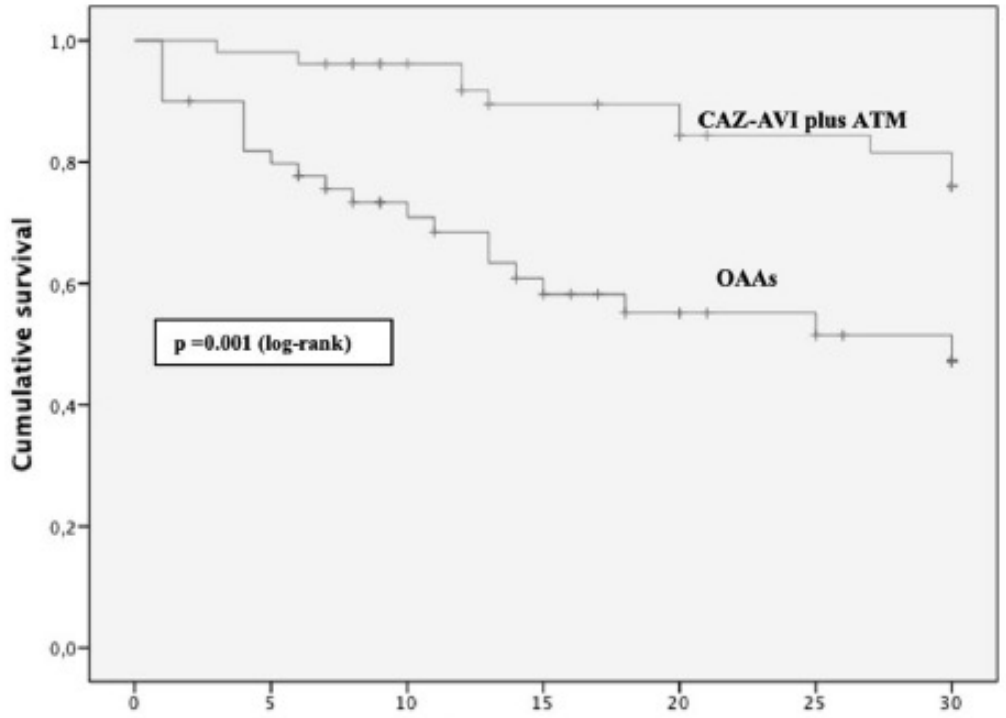
Ceftazidime avibactam

Clinical Infectious Diseases

MAJOR ARTICLE

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

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



Number at risk

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

- Etude prospective observationelle
- Multicentrique : 3 hôpitaux (Italie et Grêce)
- 82 infections à NDM
- 20 infections à VIM
- Mortalité J30 : 19,2% avec CAZ-AVI + ATM vs 44% autre traitement actif

Table 4. Cox Regression Analysis of Factors Independently Associated With 30-Day Mortality

Factor	HR (95% CI)	*P* Value
Cardiovascular disease	6.62 (2.77–15.78)	<.001
Solid organ transplantation	3.52 (1.42–8.69)	.006
SOFA score (1-point increment)	1.21 (1.1–1.32)	<.001
CAZ-AVI + ATM (vs OAAs)	0.17 (.07–.41)	<.001

CID 2021

Méropénem-vaborbactam

Real-world, Multicenter Experience With Meropenem-Vaborbactam for Gram-Negative Bacterial Infections Including Carbapenem-Resistant *Enterobacterales* and *Pseudomonas aeruginosa*

Sara Alosaimy,[1] Abdalhamid M. Lagnf,[1] Taylor Morrisette,[1] Marco R. Scipione,[2] Jing J. Zhao,[2] Sarah C. J. Jorgensen,[1,3] Ryan Mynatt,[1,4] Travis J. Carlson,[5,6] Jinhee Jo,[5] Kevin W. Garey,[5] David Allen,[7] Kailynn DeRonde,[8] Ana D. Vega,[8] Lilian M. Abbo,[8] Veena Venugopalan,[9] Vasilios Athans,[10] Stephen Saw,[10] Kimberly C. Claeys,[11] Mathew Miller,[12] Kyle C. Molina,[12] Michael Veve,[1,13,14] Wesley D. Kufel,[15,16] Lee Amaya,[17,18] Christine Yost,[17] Jessica Ortwine,[19] Susan L. Davis,[1,20] and Michael J. Rybak[1,2,21]

- Etude rétrospective observationnelle multicentrique (n=13 centres) aux USA (octobre 2017-juin 2020).
- Exclusion infection concomitante
- Critère principal : mortalité J30;
- 126 patients (20,5% ID)
- Infection respiratoire (38,1%), IIA (19,0%)
- CRE 78,6%

Outcome[a]	Total Study (n = 126)	PsA Spp. (n = 8)	Non-PsA (n = 118)	CRE Spp. (n = 99)
Efficacy				
30-d mortality	23 (18.3)	0 (0)	23 (19.5)	19 (19.2)
90-d mortality	39 (33.1)	1 (12.5)	40 (31.7)	34 (34.3)
In-hospital mortality	30 (23.8)	1 (12.5)	29 (24.6)	25 (25.3)

Tebipénem

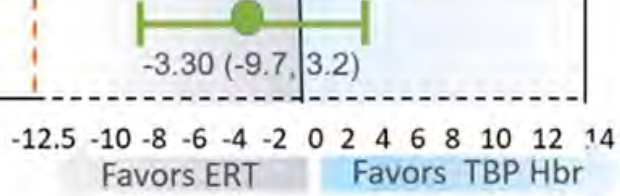
Tebipénème

- Essai randomisé (1:1) double aveugle ADAPT-PO
- TBP (600mgX3/j) vs Erta (1g/j) pour IU compliquées et PNA (durée 7à 10j)

ADAPT-PO primary endpoint:

Clinical cure + microbiological eradication at test-of-cure in micro-ITT population

Endpoint (mMITT Population)	TBP HBr N = 449	Ertapenem N = 419	Treatment Difference (%) (TBP HBr minus ERT, 95% CI)
Overall response at TOC (%/n)	58.8% 264	61.6% 258	-3.30 (-9.7, 3.2)



Micro-ITT = microbiologically modified intent-to treat; TOC = test of cure.

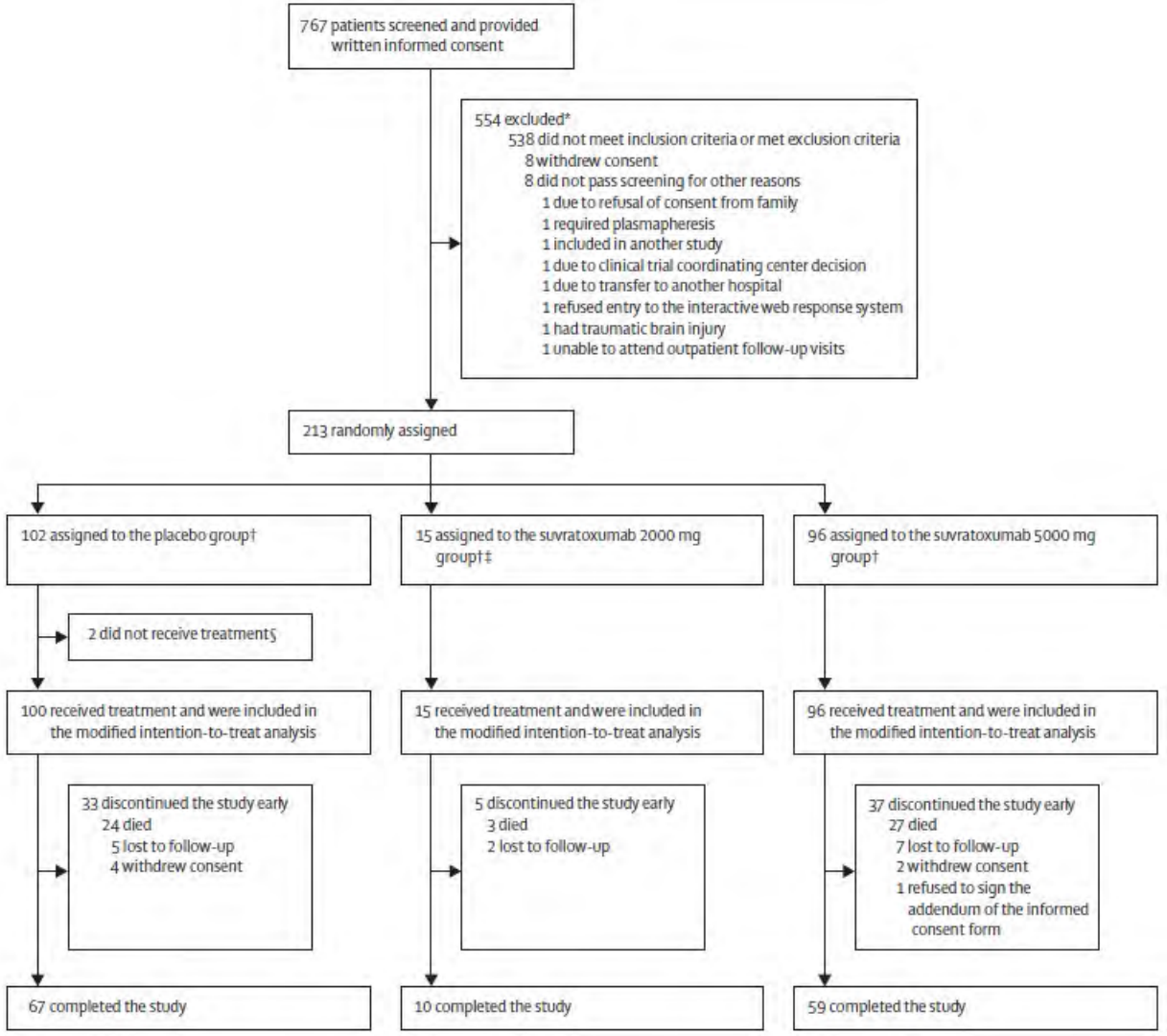
Demonstrated non-inferiority at margin of -12.5%*

Results were similar between treatment arms across all subgroups of patients

IDSA 2020

Anticorps anti-staphylocoque

Efficacy and safety of suvratoxumab for prevention of *Staphylococcus aureus* ventilator-associated pneumonia (SAATELLITE): a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2 pilot trial

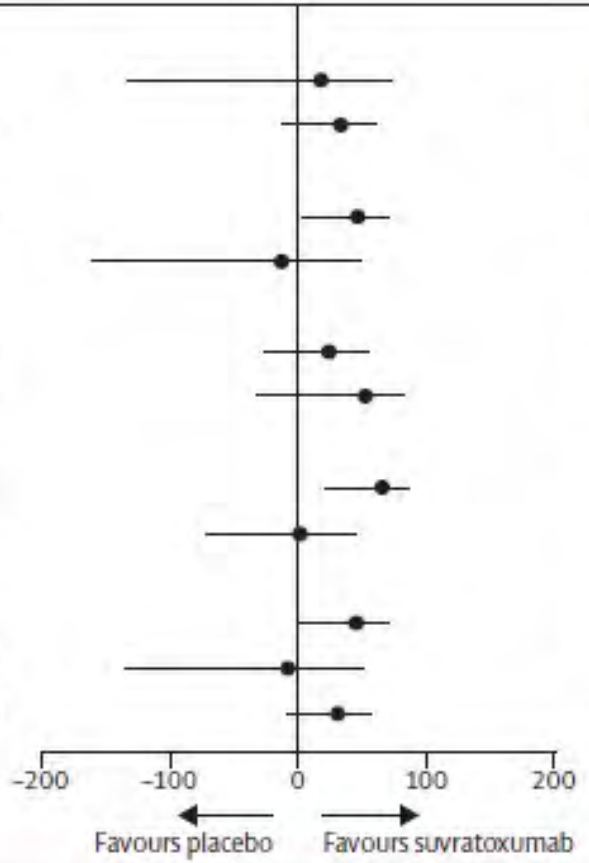


	Placebo group (n=100)	Suvratoxumab 5000 mg group (n=96)
Age, years		
≤65	69 (69%)	59 (62%)
>65	31 (31%)	37 (39%)
Sex		
Female	45 (45%)	37 (39%)
Male	55 (55%)	59 (62%)
Body-mass index		
≤30 kg/m²	73 (74%)	72 (75%)
>30 kg/m²	26 (26%)	24 (25%)
Primary reason for admission to the ICU		
Brain trauma	10 (10%)	8 (8%)
Cardiovascular disorder	5 (5%)	10 (10%)
Infection	3 (3%)	2 (2%)
Neurological disorders	53 (53%)	53 (55%)
Respiratory disease	12 (12%)	9 (9%)
Trauma	14 (14%)	12 (13%)
Other	3 (3%)	2 (2%)
Mean duration of health-care resource use before randomisation, days		
Hospitalisation	6·3 (8·3)	6·9 (8·7)
ICU stay	5·3 (7·4)	5·4 (6·6)
Mechanical ventilation	5·4 (7·2)	5·3 (6·7)
Use of pre-dose antibiotics for *S aureus* infection stratum		
Yes	13 (13%)	12 (13%)
No	87 (87%)	84 (88%)
Mean clinical severity score		
APACHE-II	15·2 (5·2)*	15·1 (5·2)
SOFA	4·5 (2·0)†	4·8 (2·0)
CPIS	3·0 (1·5)†	3·0 (1·3)
Median PCR cycle threshold value (*S aureus* colonisation load)	26·1 (21·0–32·2)	26·7 (21·7–32·1)
Positive tracheal staphylococcal culture	45 (45%)	47 (49%)
MRSA colonisation	6 (6%)	6 (6%)

B. François *et al.* Lancet ID 2021

Efficacy and safety of suvratoxumab for prevention of *Staphylococcus aureus* ventilator-associated pneumonia (SAATELLITE): a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2 pilot trial

	Placebo group n/N (%)	Suvratoxumab 5000 mg group n/N (%)	Percentage RRR (90% CI)
Use of pre-dose antibiotics for *S aureus* infection			
Yes	4/13 (30·8)	3/12 (25·0)	18·8 (–133·2 to 72·9)
No	22/87 (25·3)	14/84 (16·7)	34·1 (–11·6 to 60·4)
Age (years)			
≤65	20/69 (29·0)	9/59 (15·3)	47·4 (3·5 to 71·4)
>65	6/31 (19·4)	8/37 (21·6)	–11·7 (–160·4 to 49·3)
Body-mass index (kg/m²)			
≤30	19/73 (26·0)	14/72 (19·4)	25·3 (–26·0 to 55·6)
>30	7/26 (26·9)	3/24 (12·5)	53·6 (–31·1 to 83·2)
S aureus* colonisation load (PCR Ct value)			
Low (Ct ≥29)	12/36 (33·3)	4/36 (11·1)	66·7 (21·3 to 86·2)
High (Ct <29)	14/63 (22·2)	13/60 (21·7)	2·5 (–70·4 to 45·3)
Ventilator-associated pneumonia prevention†			
5 bundles	19/59 (32·2)	9/52 (17·3)	46·3 (2·2 to 70·5)
<5 bundles	7/41 (17·1)	8/44 (18·2)	–6·5 (–135·1 to 51·1)
Overall population	**26/100 (26·0)**	**17/96 (17·7)**	**31·9 (–7·5 to 56·8)**



B. François *et al.* Lancet ID 2021

Conclusion

- Cefiderocol (In) CREDIBLE
- Ceftolozane tazobactam >> *Pseudomonas aeruginosa*
- Ceftazidime avibactam >> MBL
- Mero vaborbactam : KPC mais pas que ….
- Tebipenem : « attention aux urologues »
- Anticorps : pas encore

Merci

- Widespread cefiderocol heteroresistance in carbapenem-resistant Gram-negative pathogens
- https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00194-8/fulltext

- Cross-resistance to cefiderocol and ceftazidime–avibactam in KPC β-lactamase mutants and the inoculum effect
- Claire Amaris HobsonAurélie CointeHervé JacquierAlaksh ChoudhuryMélanie MagnanCéline CourrouxOlivier TenaillonStéphane BonacorsiAndré Birgy
- https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00199-3/fulltext

Cross-resistance to cefiderocol and ceftazidime–avibactam in KPC β-lactamase mutants and the inoculum effect

Claire Amaris Hobson [1], Aurélie Cointe [1,2], Hervé Jacquier [1,3], Alaksh Choudhury [1], Mélanie Magnan [1], Céline Courroux [2], Olivier Tenaillon [1], Stéphane Bonacorsi [1,2], André Birgy [1,2,*]

ed in pressed in	Clinical alleles	Mutations	Ancestral allele[a]	Cefiderocol			Ceftazidime–avibactam		
				MIC (mg/L)	Times increase of MIC compared to ancestral allele	MIC (mg/L) at high inoculum (10^7 CFU/mL)	MIC (mg/L)	Times increase of MIC compared to ancestral allele
l allele ancestral	–	–	–	0.25	–	32	0.5	–
	–	–	–	0.12	–	16	1	–
22		–	–	0.25	–	8	0.125	–
		–	–	0.06	–	4	0.19	–
	–	ins165_EL	KPC-3	0.5	4	>32	16	16
	KPC–25	ins165_EL	KPC-2	0.25	1	>32	4	8
	–	ins168_LK	KPC-2	1	4	>32	32	64
	–	ins168_LK + A185T	KPC-3	0.06	–	>32	2	2
	–	ins175_SAIPG	KPC-3	0.5	4	>32	24	24
	KPC–44	ins261_AVVTRAPNKDDKHSE	KPC-2	0.5	2	>32	64	128
	KPC–29	ins269_KDD	KPC-3	0.5	4	>32	32	32
	–	ins274_SEAVI + G147R	KPC-3	0.5	4	>32	32	32
	–	del165-175_WELELNSAIPG	KPC-3	0.25	2	32	24	24
	–	del166-171_ELELNS + A172D	KPC-3	0.5	4	32	32	32
	–	del168-171_ELNS	KPC-3	0.5	4	>32	>256	>256
	–	del168-169_EL	KPC-2	0.5	2	>32	1.5	3
	–	del167-170_LELN + S171P	KPC-2	1	4	>32	24	48
	–	del176-178_DA	KPC-3	0.12	1	32	8	8
	–	del_176-179_DAR	KPC-3	0.5	4	>32	32	32
	–	del239-240_GV	KPC-3	1	8	>32	32	32
	–	del240-241_VY + G239D	KPC-2	1	4	>32	48	96
ous mutations								
		P67L	KPC-2	0.25	1	32	12	24
		R164G	KPC-3	0.5	2	>32	16	16
		R164P	KPC-3	0.5	4	32	32	32
		S171P	KPC-3	0.5	4	>32	24	24
		A172D	KPC-3	1	8	>32	24	24
	KPC-39	A172P	KPC-3	0.5	4	>32	16	16
		A172T	KPC-3	1	8	>32	16	16
		A172T	KPC-2	1	4	>32	16	32
		A172V	KPC-3	0.5	4	>32	12	12
		D176N	KPC-3	0.5	4	>32	12	12
		D176N + Q295S + ins295_NCQIKFTHIYFRLI	KPC-3	0.5	4	4	12	12
		D176Y	KPC-3	0.5	4	>32	16	16
		D176G	KPC-3	1	8	>32	16	16
		D179A	KPC-3	1	8	>32	24	24
	KPC-33	D179Y	KPC-2	2	8	>32	24	48
	KPC-31	D179Y	KPC-3	4	32	>32	48	48
		D179E	KPC-3	0.5	4	32	16	16
		D179G	KPC-3	1	8	>32	16	16
		T243P	KPC-3	0.25	2	32	16	16
		V119M + T243P + V250A	KPC-2	1	4	16	8	16

Résistance cefta avi

- Evolutionary Trajectories toward Ceftazidime-Avibactam Resistance in *Klebsiella pneumoniae* Clinical Isolates
- https://journals.asm.org/doi/10.1128/AAC.00574-21

- Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β-Lactamase–Producing *Enterobacter* spp, *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp, or *Serratia marcescens*: A Pilot Multicenter Randomized Controlled Trial (MERINO-2)
- Adam G Stewart, David L Paterson, Barnaby Young, David C Lye, Joshua S Davis, Kellie Schneider, Mesut Yilmaz, Rumeysa Dinleyici, Naomi Runnegar, Andrew Henderson ... Show more

- A New Twist: The Combination of Sulbactam/Avibactam Enhances Sulbactam Activity against Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) Isolates
- https://www.mdpi.com/2079-6382/10/5/577

- Dalbavancin for the Treatment of Prosthetic Joint Infections: A Narrative Review
- https://www.mdpi.com/2079-6382/10/6/656

- Assessment of Data Supporting the Efficacy of New Antibiotics for Treating Infections Caused by Multidrug-resistant Bacteria
- Dafna Yahav, Noam Tau, Daniel Shepshelovich