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RÉUNION INTERDISCIPLINAIRE DE
CHIMIOTHÉRAPIE ANTI-INFECTIEUSE

LUNDI 13 & MARDI 14
DÉCEMBRE 2021

Palais des Congrès
Paris

www.ricai.fr



R I C A I

Place des nouveaux antibiotiques dans les IOAs

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Liens d'intérêts potentiels E. Senneville

- Support congrès
- Orateur congrès
- Investigateur

- AdvanzPharma
- Bayer
- Cepheid
- Diaxonhit
- Menarini
- MSD
- Novartis-Pharma
- Pfizer
- Sanofi-Aventis
- Shionogi

Anti-Gram positif

- Afabicine
- Ceftaroline/Ceftobiprole
- Daptomycine
- Telavancine
- Dalbavancine
- Oritavancine
- Linezolide / Tedizolide
- Delafloxacin
- Omadacycline

Anti-Gram négatif

- Ceftidéocol
- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Méropénème-vaborbactam
- Imipénème-relebactam

Anti-Gram positif

- Afabicine
- Ceftaroline/Ceftobiprole
- Daptomycine
- Telavancine
- Dalbavancine
- Oritavancine
- Linezolide / Tedizolide
- Delafloxacin
- Omadacycline

Anti-Gram négatif

- Céfiderocol
- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Méropénème-vaborbactam
- Imipénème-relebactam

Nouveaux anti-Gram négatif

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant <i>Pseudomonas aeruginosa</i>	Carbapenem-resistant <i>Acinetobacter baumannii</i>	<i>Stenotrophomonas maltophilia</i>
Cefiderocol	Green	Green	Green	Green	Green	Green
Ceftazidime-avibactam ¹	Green	Red	Green	Yellow	Red	Red
Ceftolozane-tazobactam ¹	Red	Red	Red	Yellow	Red	Yellow
Imipenem-relebactam ³	Green	Red	Yellow	Green	Red	Red
Meropenem-vaborbactam ¹	Green	Red	Red	Red	Red	Red

Tamma P *et al.* JPIDS 2019

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Ceftazidime/avibactam

Ceftolozane/tazobactam

➤ Ceftazidime/avibactam :

- Rico-Nieto A *et al.* Lumbar arthrodesis infection by multi-resistant OXA-48 Klebsiella pneumoniae, successfully treated with implant retention and ceftazidime/avibactam. Rev Esp Cir Ortop Traumatol (Engl Ed). 2018

➤ Ceftolozane/tazobactam :

- Gentile I *et al.* Successful treatment of post-surgical osteomyelitis caused by XDR *Pseudomonas aeruginosa* with ceftolozane/tazobactam monotherapy. J Antimicrob Chemother 2017
- Kurtzhals KE *et al.* Successful treatment of multidrug-resistant *Pseudomonas aeruginosa* pubic symphysis osteomyelitis with ceftolozane/tazobactam. BMJ Case Rep 2017
- Hassan S *et al.* Treatment of a complex orthopaedic infection due to extensively drug-resistant *Pseudomonas aeruginosa*. BMJ Case Rep 2018



Rempenault C *et al.* 2020

Short Communication

Treatment of bone and joint infections by ceftazidime/avibactam and ceftolozane/tazobactam: a cohort study



- Etude observationnelle bicentrique France (2016-2019)
- 15 patients :
 - 9 C/A, âge median 66 ans, Charlson index median = 5
 - 6 C/T, âge median 53 ans Charlson index median = 2
 - un C/T puis C/A
- 5 *Pseudomonas aeruginosa* MDR dans le groupe C/T
- C/A : chirurgie 8/9 et association antibiotique 8/9
- C/T : chirurgie 5/5 et association antibiotique 3/5
- Guérison :
 - C/A = 7/9 (suivi médian 272 jours)
 - C/T = 3/5 (suivi médian 350 jours)
- Effets secondaires : 2 épisodes de confusion (C/A)

Meropénème-vaborbactam

Age (years)	Sex	CRE species (source)	Other susceptibilities	Primary infection	Major comorbidities	ICU	Source control	MVB dosing regimen (CrCl) ^a	Duration of therapy (days)	Clinical response	Microbiological response at Day 3/7	Recurrence free at Day 30/90	Survival at Day 30/90
83	F	<i>K. pneumo</i> (tissue)	AMK, GEN, MIN	PJI	CKD, DM	N	Partial	2 g q12h (31 mL/min)	45	Neg.	ND/ND	-/-	Y/Y
62	M	<i>K. pneumo</i> (urine)	CZA	UTI	DLBCL, IBD	Y	N/A	2 g q12h (22 mL/min)		Neg.	Pos./Pos.	-/-	N/-(unrelated)
38	F	<i>C. koseri</i> (tissue)	AMK, CZA, SXT	Osteomyelitis	DM	N	Yes	Full dose ^b	41	Pos.	ND/ND	UC/-	Y/Y
53	M	<i>K. pneumo</i> (blood)	AMK, CZA, GEN, TET, SXT, TOB	Soft tissue abscess with secondary bacteraemia	CLD	N	Yes	Full dose ^b	14	Pos.	Pos./Pos.	N/-	Y/Y
63	M	<i>E. coli</i> (tissue)	CZA, GEN, LVX	Osteomyelitis	PVD	N	Yes	Full dose ^b	39	Pos.	ND/ND	Y/Y	Y/Y
46	M	<i>E. coli</i> (abscess)	AMK, CZA, SXT	Intra-abdominal abscess	CKD, DM, SOT	N	Yes	Full dose ^b	27	Pos.	ND/ND	Y/Y	Y/Y
52	F	<i>K. pneumo</i> (sputum)	AMK, CZA, GEN	VAP	CAD, CHF, CKD, DM	Y	N/A	Full dose ^b	7	Neg.	Neg./-	-/-	N/-(unrelated)
79	F	<i>K. pneumo</i> (blood)	CZA	CLABSI	CHF, CLD, DM	Y	Yes	2 g q8h (33 mL/min)	17	Pos.	Neg./Pos.	Y/Y	Y/Y
53	M	<i>E. coli</i> (tissue)	AMK, CZA, GEN, SXT, TOB	Osteomyelitis/SSTI	CHF, CLD, CKD, DM, ESRD, V/D	N	Yes	1 g q12h (<15 mL/min)	50	UC	ND/ND	UC/-	Y/Y
62	M	<i>K. pneumo</i> (sputum)	CZA, SXT	PNA	mSCC	Y	N/A	Full dose ^b	8	Pos.	ND/Pos.	Y/Y	Y/Y
36	M	<i>K. aerogenes</i> (abscess)	AMK, GEN, SXT, TOB	Intra-abdominal abscess	None	Y	Partial	Full dose ^b	7	Neg.	ND/ND	-/-	Y/Y
82	F	<i>K. pneumo</i> (tissue)	CZA	Osteomyelitis	CKD, COPD, DM	N	Yes	Full dose ^b	34	Pos.	ND/ND	Y/Y	Y/Y
70	M	<i>K. pneumo</i> (blood)	None	Primary bacteraemia	ALL, CAD, CHF	Y	N/A	Full dose ^b	14	Pos.	Pos./Pos.	Y/Y	Y/Y
90+	F	<i>K. pneumo</i> (urine)	AMK, CZA, GEN, TET, SXT, TOB	UTI	CAD	Y	N/A	2 g q8h (60 mL/min)	5	Neg.	ND/ND	-/-	N/-(related)
68	M	<i>K. pneumo</i> (blood)	AMK, CZA, FDC	Primary bacteraemia	CAD, COPD, PVD	N	N/A	Full dose ^b	27	Pos.	Pos./Pos.	Y/Y	Y/Y

Compassionate use of cefiderocol for carbapenem-resistant *Acinetobacter baumannii* prosthetic joint infection



Antimicrobial/Resistance determinants	MIC (mg/L)							
β -lactams <i>bla</i> _{NDM-1} , <i>bla</i> _{OXA-23} , <i>bla</i> _{OXA-69} , <i>bla</i> _{ADC-25}	AMP	AMC	ATM	CAZ	CTX	CZA	CXM	DOR
	>256	>8	>4	>256	>64	>256	>256	>256
	ETP	FB	FOX	IPM	IMR	MEM	TZP	SUL
Aminoglycosides <i>aac</i> (3')-Ia/ <i>aadA</i> , <i>aph</i> (3')-Ia, <i>aph</i> (3')-Ib/ <i>straA</i> , <i>aph</i> (3')-VIa, <i>aph</i> (6)-Id/ <i>straB</i>	>1	>16	>256	>32	>32	>32	>64	>4
	AMK	GEN	TOB					
Quinolones <i>qnr</i>	LVX	LVX	MXF					
	>1	>1	>1					
Tetracyclines <i>tet</i> (B)	TET	TGC						
>256	2							
Sulphonamides/trimethoprim <i>dfrA1</i> , <i>sul1</i> , <i>sul2</i>	SXT	TMP						
	>4	>256						
Polymyxins 	CST	PMB						
	0.5	0.5						
Others (macrolides, chloramphenicol, fosfomycin)	AZM	CLI	CHL	ERY	FOF			
	>256	>256	>256	>256	64			

Compassionate Use of Cefiderocol to Treat a Case of Prosthetic Joint Infection Due to Extensively Drug-Resistant *Enterobacter hormaechei*

- Homme 67 ans PTG
- Infection à *Enterobacter hormaechei* XDR
- Phénotype de résistance :
 - CSPase chromosomique ACT-5
 - 3 Blases hyperproduites (CTX-M-15, TEM-1B et OXA-1)
 - Baisse de perméabilité
- Traitement de 1^{er} choix : colimycine-tigécycline (intolérance)
- Switch vers le céfidérocol pour 12 semaines
- Évolution favorable

Autres études

- Alamarat ZI *et al.* **Long Term Compassionate Use of Cefiderocol to Treat Chronic Osteomyelitis Caused by XDR- *Pseudomonas aeruginosa* and ESBL-producing *Klebsiella pneumoniae* in a Pediatric Patient.** Antimicrob Agents Chemother 2019
- Dagher M *et al.* **Case Report: Successful Rescue Therapy of Extensively Drug-Resistant *Acinetobacter baumannii* Osteomyelitis With Cefiderocol.** Open Forum Infect Dis 2020
- Chavda A *et al.* **A compassionate use of cefiderocol to treat osteomyelitis caused by an XDR *Pseudomonas aeruginosa*.** JAC-Antimicrobial Resist 2021
- Cipko K *et al.* **Cefiderocol treatment of *Pseudomonas aeruginosa* and extensively drug-resistant *Acinetobacter baumannii* retained spinal hardware infection causing reversible acute interstitial nephritis.** Int J Infect Dis 2021
- Zingg S *et al.* **Cefiderocol for Extensively Drug-Resistant Gram-Negative Bacterial Infections: Real world Experience from a Case Series and Review of the Literature.** Open Forum Infect Dis 2020
- Bavaro DF *et al.* **Recurrent neurosurgical site infection by extensively drug-resistant *P. aeruginosa* treated with cefiderocol : a case report and literature review.** Infect Dis (Auckl) 2020
- Oliva A *et al.* **Cefiderocol for compassionate use in the treatment of complicated infections caused by extensively- and pan-resistant *Acinetobacter baumannii*.** J Glob Antimicrob Resist 2020

Tédizolide et souches bactériennes d'IOAs

Europe / US

- Souches consécutives 2014 - 2017
- *Staphylococcus aureus* = 59,3%; 58,6% in the USA and 60,4% in Europe
- 29,6% SARM
- CMI 90 tédizolide/linezolide = 0,12–0,25 / 0,5–2 mg/L

Sensibilité des staphylocoques/ EUCAST

MSSA (333)

tedizolid	100.0/0.0
linezolid	100.0/0.0
clindamycin	97.9/1.8
daptomycin	100.0/0.0
erythromycin	73.3/23.4
levofloxacin	93.4/6.6
teicoplanin	100.0/0.0
tetracycline	96.1/3.3
trimethoprim/sulfamethoxazole	100.0/0.0
vancomycin	100.0/0.0

MRSA (140)

tedizolid	100.0/0.0
linezolid	100.0/0.0
clindamycin	77.1/22.9
daptomycin	99.3/0.7
erythromycin	22.9/77.1
levofloxacin	32.1/67.9
teicoplanin	100.0/0.0
tetracycline	84.2/12.9
trimethoprim/sulfamethoxazole	97.1/2.1
vancomycin	100.0/0.0

Methicillin-susceptible CoNS (37)

tedizolid	100.0/0.0
linezolid	100.0/0.0
clindamycin	91.9/8.1
daptomycin	100.0/0.0
erythromycin	73.0/27.0
levofloxacin	97.3/2.7
teicoplanin	97.3/2.7
tetracycline	86.5/10.8
trimethoprim/sulfamethoxazole	94.6/2.7
vancomycin	100.0/0.0

Methicillin-resistant CoNS (71)

tedizolid	98.6/1.4
linezolid	98.6/1.4
clindamycin	52.1/47.9
daptomycin	100.0/0.0
erythromycin	15.5/83.1
levofloxacin	35.2/64.8
teicoplanin	85.9/14.1
tetracycline	77.7/19.7
trimethoprim/sulfamethoxazole	90.6/18.3
vancomycin	100.0/0.0

Long-Term Use of Tedizolid in Osteoarticular Infections: Benefits among Oxazolidinone Drugs

Etude retrospective multicentrique 2017-20219

51 patients, âge moyen 65 ans; ostéo-arthrites (n = 27; 53%), prothèses articulaires (n = 17; 33,3%), ostéite du pied diabétique (n = 9; 18%); 59% sur matériel

Microbiologie : *Staphylococcus* spp. (65%, n = 47; *S. aureus*, 48%)

Rationnel du choix TZD : interaction médicamenteuse (63%), toxicité hématologique

Durée médiane du traitement: 29 jours (IQR 15-44)

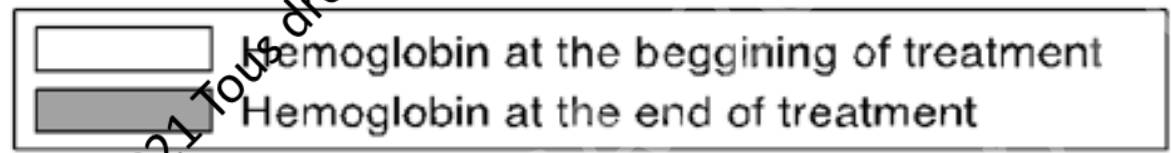
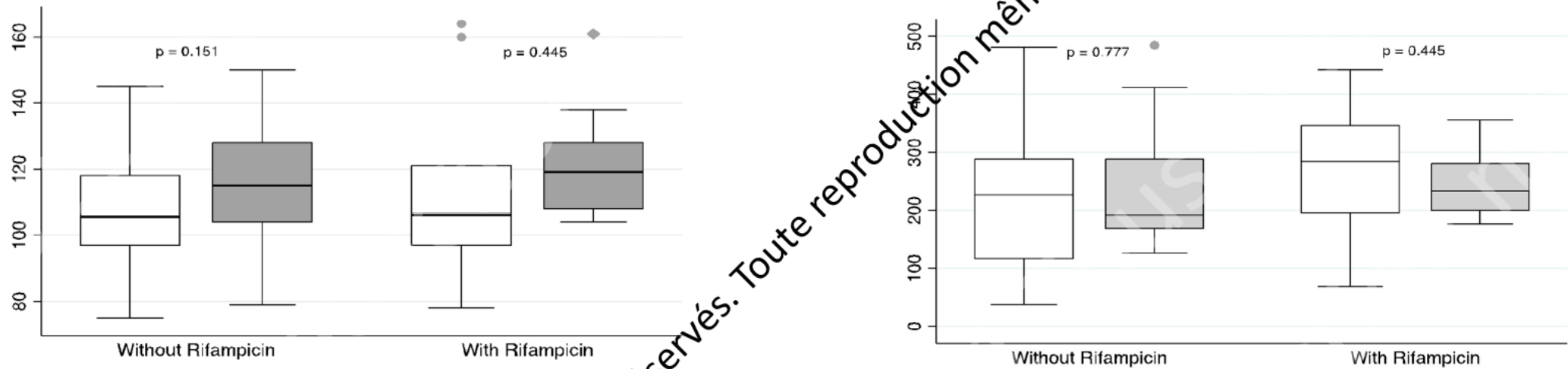
Rifampicine dans 24% des cas

Effets secondaires : n = 3

Pas de modification significative hématologique

Rémission chez 83% des patients (suivi médian de 630 jours)

Long-Term Use of Tedizolid in Osteoarticular Infections: Benefits among Oxazolidinone Drugs



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Tolerance of Prolonged Oral Tedizolid for Prosthetic Joint Infections: Results of a Multicentre Prospective Study

TZD \geq 6 et \leq 12 semaines pour IPOA

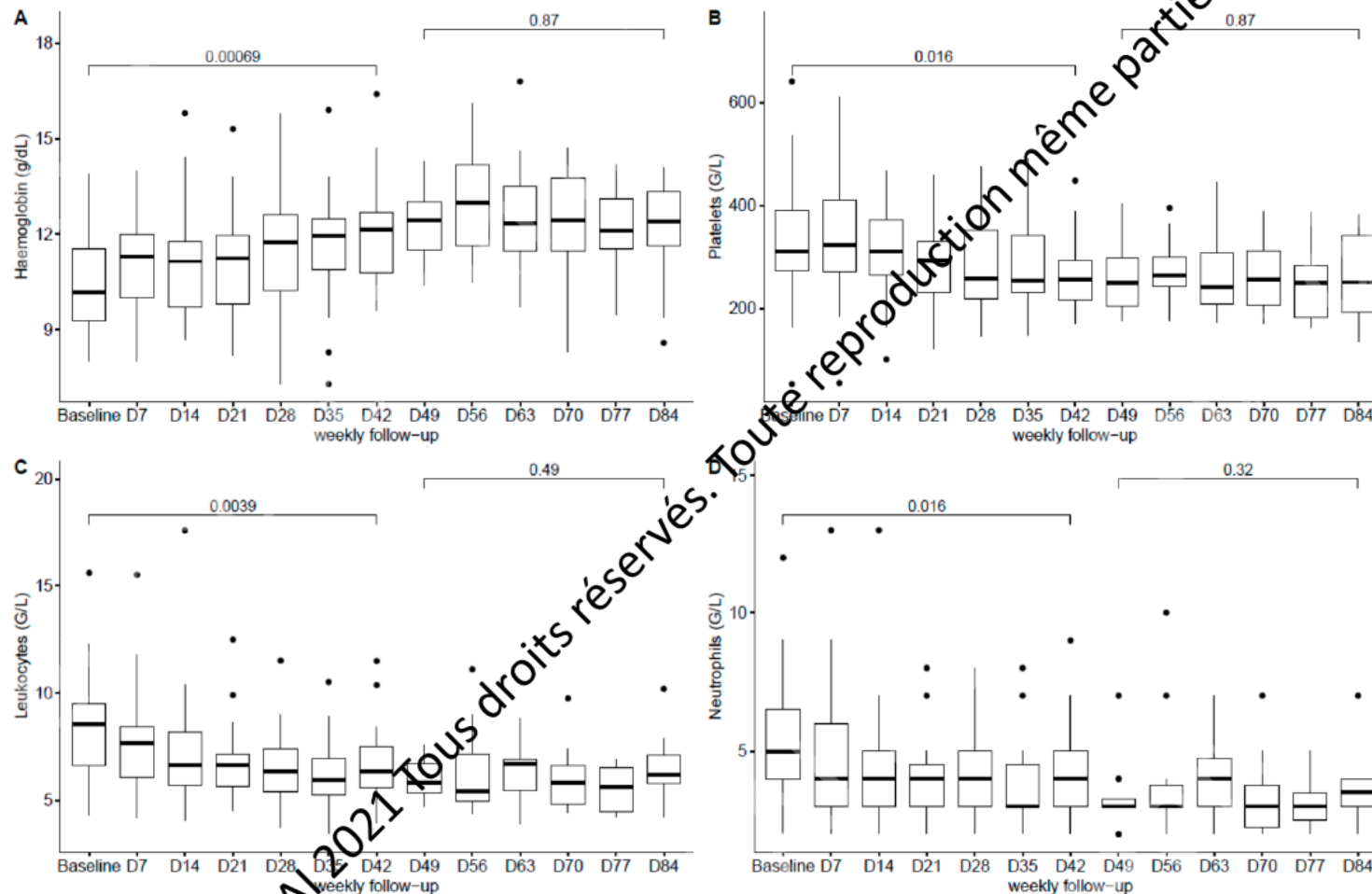
Étude prospective 3 CRIOAC (Lille-Tourcoing Paris-Ambroise Paré et Lyon)

- 33 patients adultes d'âge moyen 73 ans avec IPOA (hanche = 19, genou = 13 et épaule = 1)
- Lavage-synovectomie/R1T/R2T = 11 (33,3%)/17 (51,5%)/5 (15,2%)
- SRM = 21 (dont 7 SARM)
- Durée du traitement = $8,0 \pm 3,27$ semaines (6–12)
- Association à un autre antibiotique dans 54,5% (rifampicine 48,5%)
- 6 arrêts prématurés, dont 2 attribuables potentiellement au TDZ

Tolerance of Prolonged Oral Tedizolid for Prosthetic Joint Infections: Results of a Multicentre Prospective Study

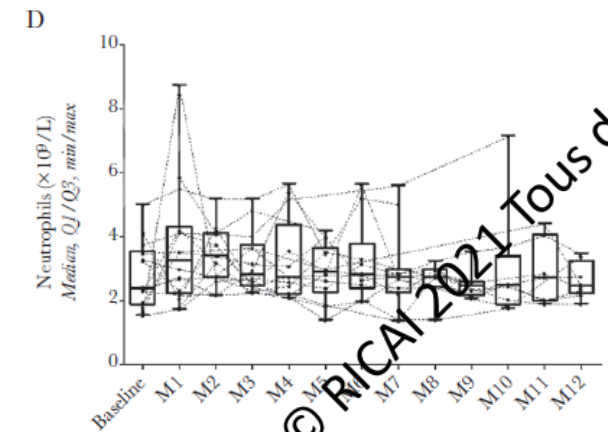
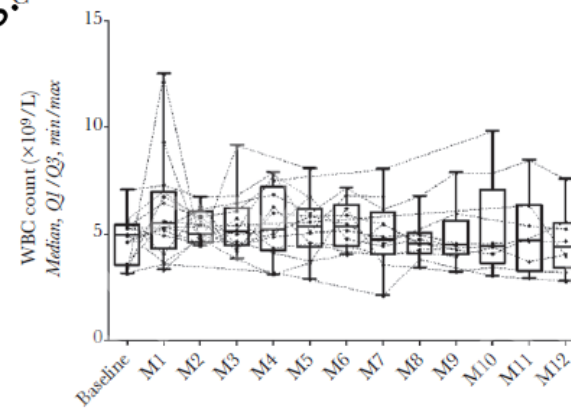
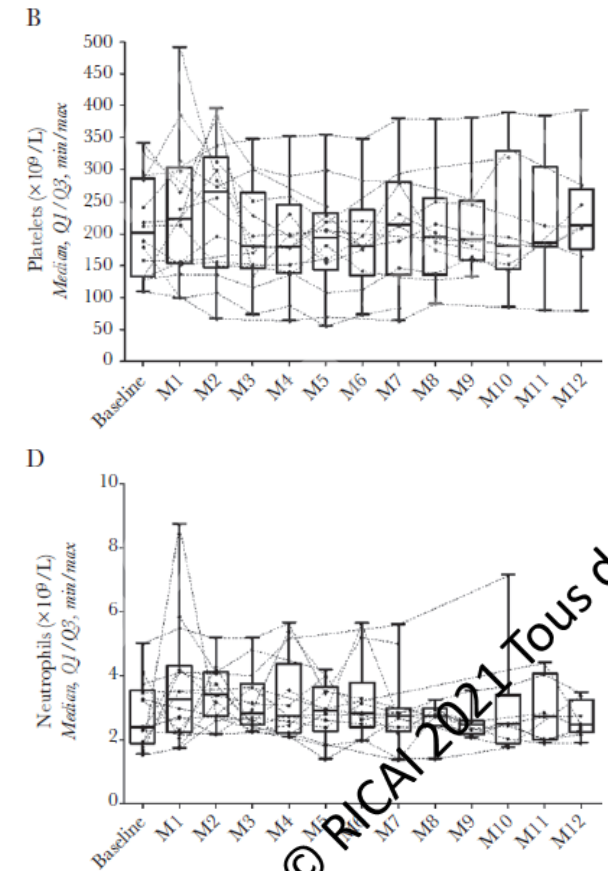
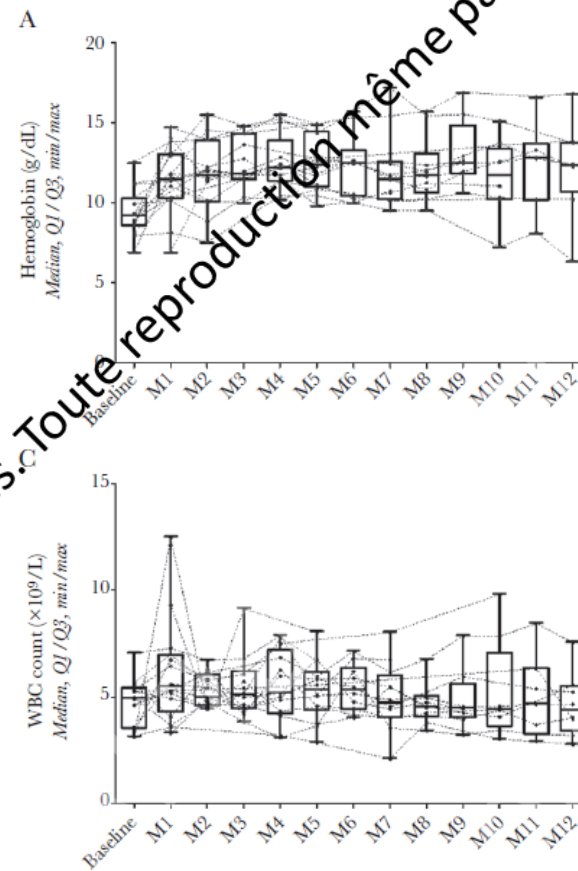
Patients' Characteristics	N° of Patients (%), Total = 33	<i>p</i>
≥1 adverse event	20 (60.6)	
Any combination therapy		0.8
- Yes (<i>n</i> = 18)	11 (61.1)	
- No (<i>n</i> = 15)	9 (60)	
Rifampicin combination therapy		0.9
- Yes (<i>n</i> = 16)	9 (56.3)	
- No (<i>n</i> = 17)	11 (64.7)	
Duration of treatment ≥ 6 weeks		0.8
- Yes (<i>n</i> = 13)	7 (53.8)	
- No (<i>n</i> = 20)	13 (65)	

Tolerance of Prolonged Oral Tedizolid for Prosthetic Joint Infections: Results of a Multicentre Prospective Study



Tedizolide en traitement suppressif

- Étude prospective CRIOAC France
- 17 patients avec une infection d'implant orthopédique (cocci à Gram positif multi-resistant) traités en suppressif
- Durée médiane de traitement de 6 mois



Dalbavancine et IOAS

- **Traitement en deux injections (J1-J15), +/- réinjection**
 - Pas d'accès veineux permanent
- **Tolérance**
 - Pas de monitoring des concentrations sériques si schéma à deux injections
 - Pas d'interaction médicamenteuse
- **Inconvénient**
 - Durée de traitement non modulable

Dalbavancin in-vitro activity obtained against Gram-positive clinical isolates causing bone and joint infections in US and European hospitals (2011–2016)

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)								MIC ₅₀	MIC ₉₀
	≤0.03	0.06	0.12	0.2	0.5	1	2	>2		
<i>Staphylococcus aureus</i> (801)	412 (51.4)	342 (94.1)	47 (100.0)						≤0.03	0.06
MSSA (534)	280 (52.4)	224 (94.4)	30 (100.0)						≤0.03	0.06
MRSA (267)	132 (49.4)	118 (93.6)	17 (100.0)						0.06	0.06
Coagulase-negative staphylococci (160)	110 (68.8)	43 (95.6)	6 (97.4)	1 (100.0)					≤0.03	0.06
<i>S. epidermidis</i> (97)	62 (63.9)	30 (94.8)	5 (100.0)						≤0.03	0.06
<i>S. lugdunensis</i> (21)	18 (85.7)	3 (100.0)							≤0.03	0.06
Other CoNS (42) ^a	30 (71.4)	10 (95.2)	1 (97.6)	1 (100.0)					≤0.03	0.06
<i>Enterococcus faecalis</i> (82)	38 (46.3)	35 (89.9)	5 (95.1)	1 (96.3)	0 (96.3)	0 (96.3)	0 (96.3)	3 (100.0)	0.06	0.12
β-haemolytic streptococci (164)	148 (90.2)	11 (95.0)	5 (100.0)						≤0.03	≤0.03
<i>S. agalactiae</i> (80)	69 (86.2)	7 (95.0)	4 (100.0)						≤0.03	0.06
<i>S. disgalactiae</i> (36)	36 (100.0)								≤0.03	≤0.03
<i>S. pyogenes</i> (48)	43 (89.6)	4 (97.9)	1 (100.0)						≤0.03	0.06
Viridans group streptococci (45) ^b	41 (91.1)	4 (100.0)							≤0.03	≤0.03

Diffusion tissus ostéo-articulaires

Dalbavancin concentration (mean [SD]; no. of samples) post-dose that samples were collected

Tissue	0.5 day	1 day	3 days	7 days	10 days	14 days
Plasma ($\mu\text{g/ml}$) ^a	85.3 (18.9); 31	ND ^b	ND	ND	ND	15.3 (4.1); 31
Synovium ($\mu\text{g/g}$) ^c	25.0 (0); 3	17.9 (7.8); 3	19.5 (4.9); 3	19.2 (8.9); 4	25.0 (0); 2	15.9 (7.9); 3
Synovial fluid ($\mu\text{g/ml}$) ^c	22.9; 1	27.4 (10.8); 4	19.2 (4.9); 3	11.6 (3.3); 2	13.9 (1.0); 3	6.2 (1.7); 2
Bone ($\mu\text{g/g}$)	6.3 (3.1); 5	5.0 (3.5); 5	4.6 (3.8); 5	3.8 (2.7); 5	3.7 (2.2); 5	4.1 (1.6); 5
Skin ($\mu\text{g/g}$) ^c	19.4 (7.9); 2	12.5 (6.5); 3	13.8 (1.4); 2	15.7 (1.0); 2	21.6; 1	13.8 (2.1); 2

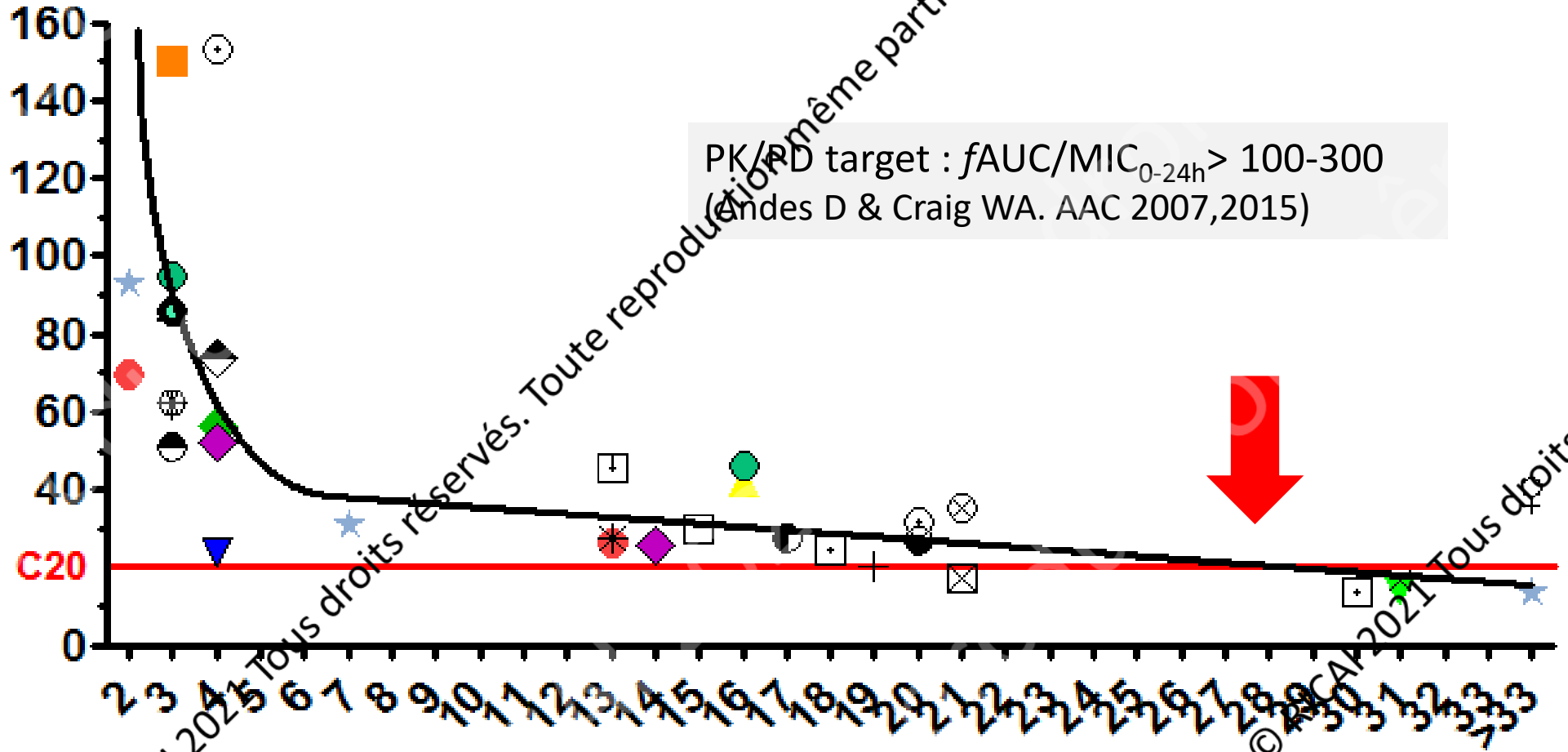
^a Mean (SD) plasma concentrations in 31 subjects at 772 and 1,080 h were 6.2 (2.4) and 3.4 (1.7), respectively.

^b ND, not detected.

^c Concentrations above the upper limit of quantification are reported as 25 μg unit.

Dalbavancin blood concentrations 1,500mg D1-D14 for the treatment of staphylococcal osteomyelitis

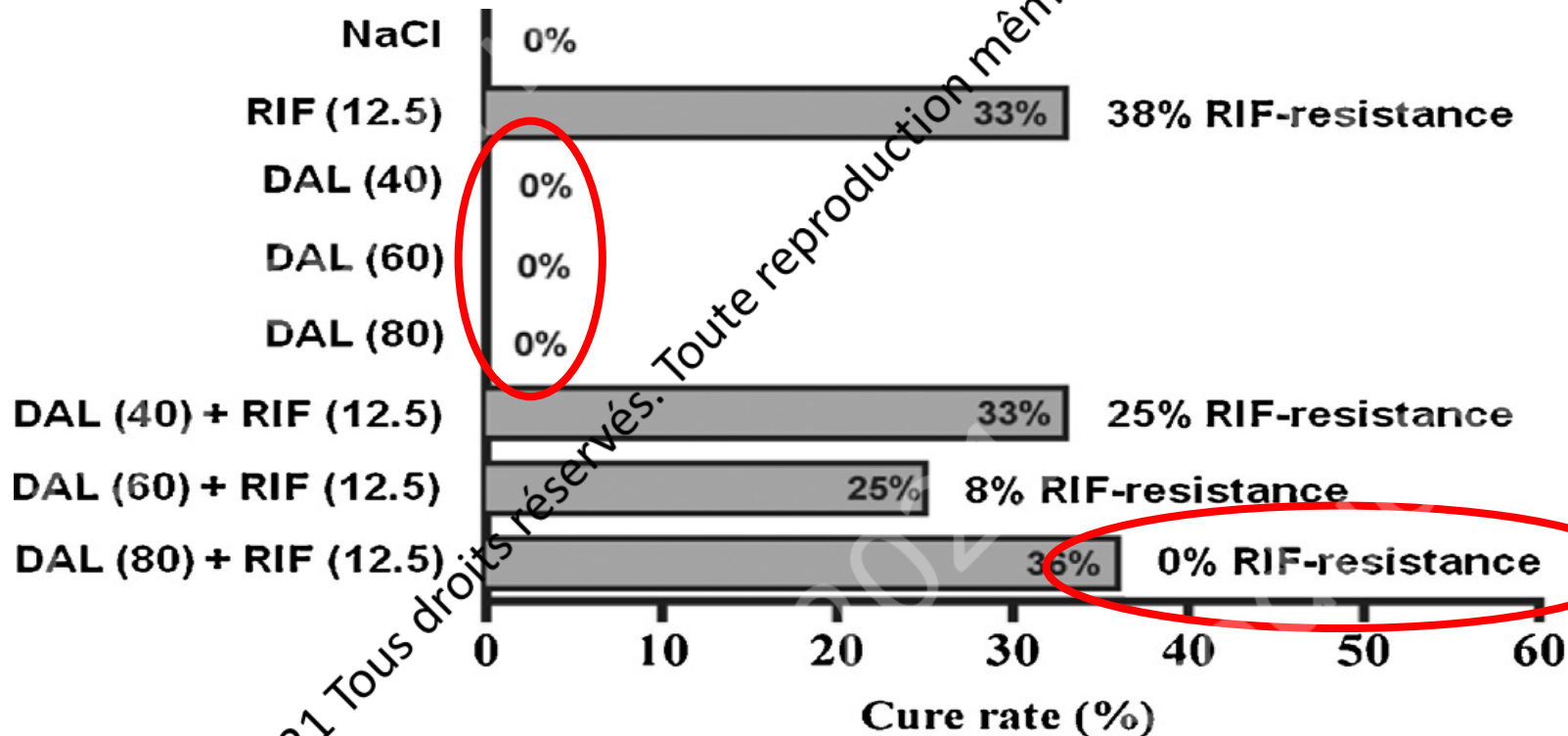
[DALBA] = f(t)



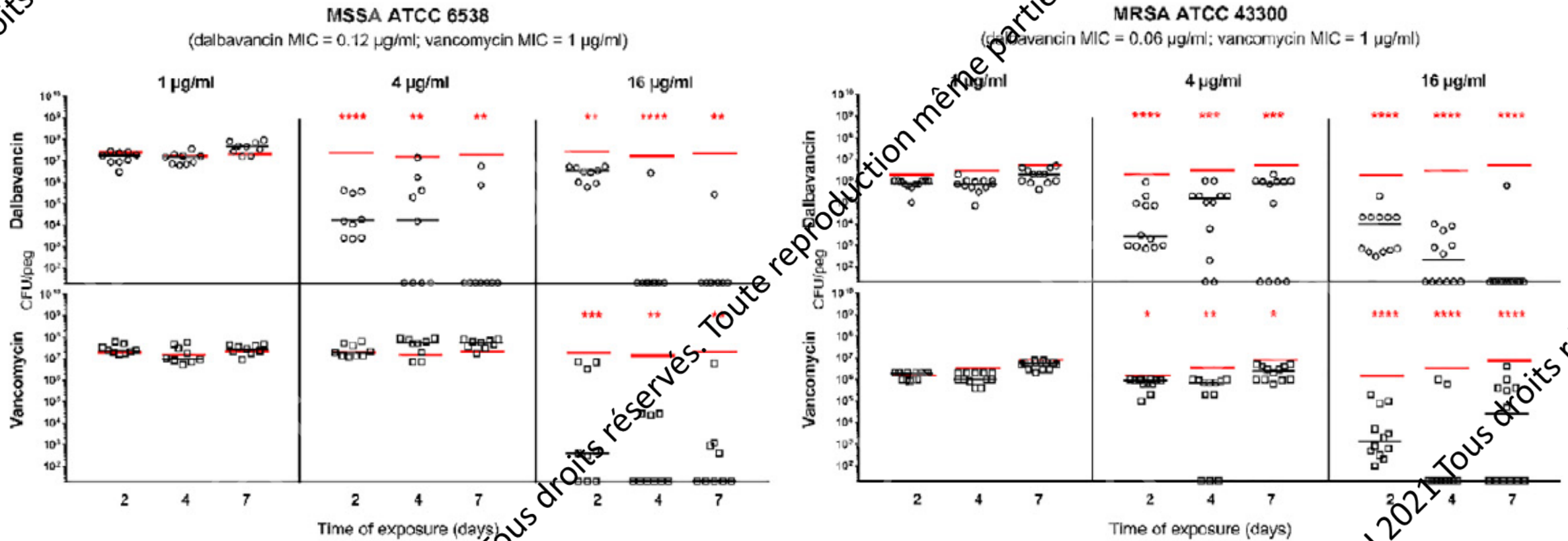
With courtesy of Dr B Hennart, Pharm D, CHU Lille and Dr F Jehl CHU Strasbourg, France

Modèle cage à SARM

- Bactéries planktoniques : monothérapie = réduction (-2 log); -5 à 6 log en association avec la rifampicine
- Biofilm :

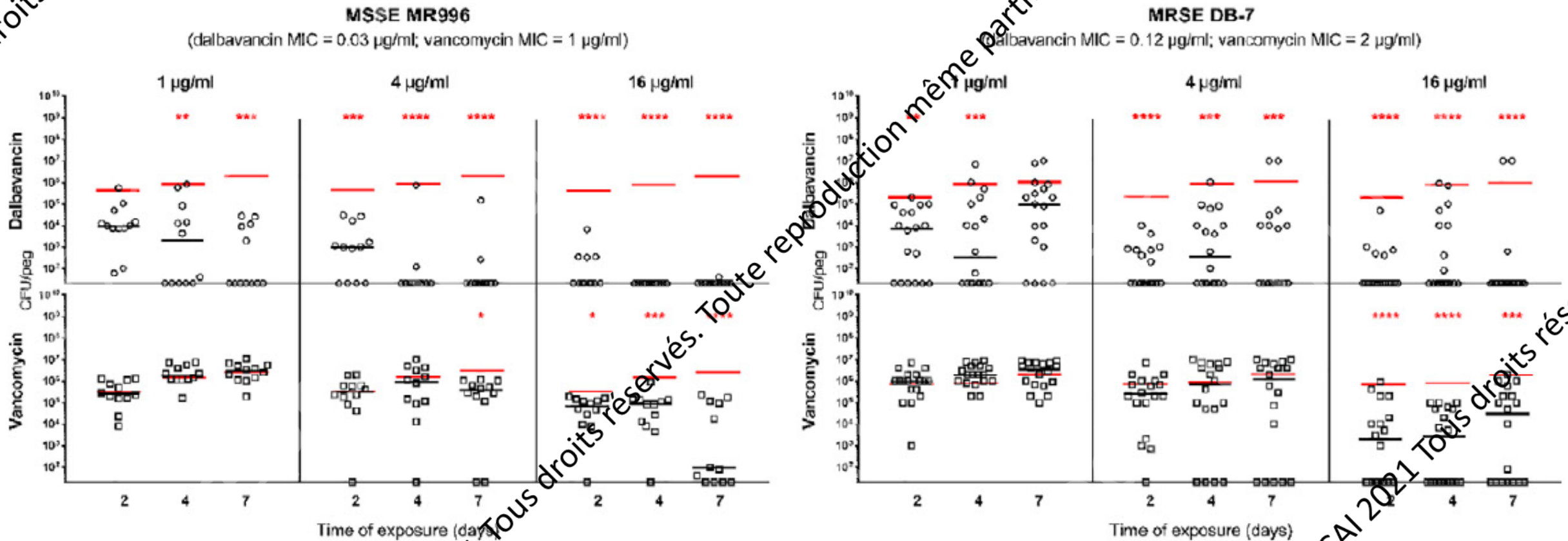


Dalbavancine et biofilm



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Dalbavancine et biofilm



Dalbavancine et biofilm

Références	Souches	Biofilm	Résultats
Fernández et al., 2016 Schmidt-Malan et al., 2016	Isolats cliniques staph IPOAs	6h	DAL: MBIC90 0,12–0,50 , MBBC90 2–4 VAN: MBIC90 2–4 , MBBC90 >128 TDZ: MBIC90 2–4 , MBBC90 >32
Knafel et al., 2017	MRSA MRSE	24h	MRSA: MIC 0,031–0,064 ; MBC 1–4 MRSE: MIC 0,023–0,625 ; MBC 2–16
Neudorfer et al., 2018	Isolats cliniques entérocoques	6h	
Di Pilato et al., 2020	Isolats cliniques <i>S. aureus</i>	7 jours	DAL > VAN
Žiemytė et al., 2020	Isolats cliniques <i>S. aureus</i>	6-9h	Biofilm inhibition. MBIC DAL 0.5–2 Biofilm treatment. Stop ou ↓ biofilm à 8–32
Darouiche et al., 2005	<i>S. aureus</i>	Prophylaxie	28% versus 42% (PCB) p=0,2
Baldoni et al., 2013	MRSA	3 jours	0 effet (éradication 25-36% avec RIF)
Barnea et al., 2016	MRSA	24h	DAL = VAN

Dalbavancine et IPOAs

	DAIR (n = 2)	Prosthesis Removal (n = 27)	Implant Retention and Suppressive Treatment (n = 7)	All Patients (n = 36)
Sex (female)	1 (50%)	11 (40.7%)	3 (42%)	15 (43%)
Age ^{*,1} (years)	69 (67–71)	69 (18–87)	62 (15–92)	67 (15–92)
Number of surgeries before DAL	1	2 (1–4)	2.5 (1–3)	1.8 (1–4)
Treatments				
DAL alone	2 (100%)	11 (40.7%)	5 (71%)	18 (50%)
DAL + rifampin	0	7 (26%)	2	9 (25%)
DAL + other treatments	0	10 (37%)	0	9 (25%)
Etiology				
<i>S. aureus</i> ²	0	5 (18.5%)	1 (14%)	6 (17%)
CoN staphylococci	2 (100%)	6 (22.2%)	2 (29%)	10 (28%)
<i>Enterococcus</i> spp ³	0	4 (14.8%)	1 (14%)	5 (14%)
Anaerobic GP	0	1 (3.7%)	0	1 (3%)
Other GP	0	0	2 (29%)	2 (6%)
Mixed GP	0	10 (37%)	0	10 (28%)
Unknown etiology	0	0	1 (14%)	1 (3%)
Outcome (Success)	1 (50%)	25 (93%)	4 (57%) ⁴	29 (81%)
Follow up (months) ^{*,1}	4 (2–6)	16 (3–40)	6 (3–14)	14 (2–40)

Dalbavancin for treating prosthetic joint infections caused by Gram-positive bacteria: A proposal for a low dose strategy. A retrospective cohort study

Schéma posologique :

- 1500 mg J1
- 500mg J7
- 500mg / 14 jours

Durée :

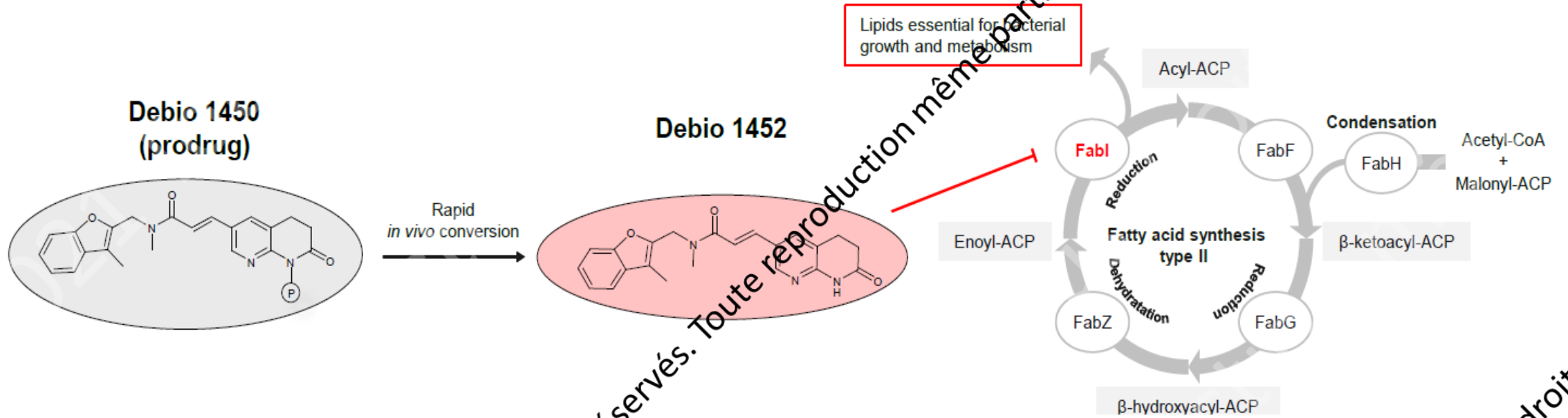
8 Sem. PTH, 12 Sem. PTG

Chirurgie :

R1T/R2T, DAIR, RA1

- 16 patients (8 PTH, 8 PTG)
- *Staphylococcus* spp. et *Enterococcus* spp.
- Pas d'effet secondaire
- Rémission 12/16 (suivi médian 503 jours)

Afabicine (Debio1452)



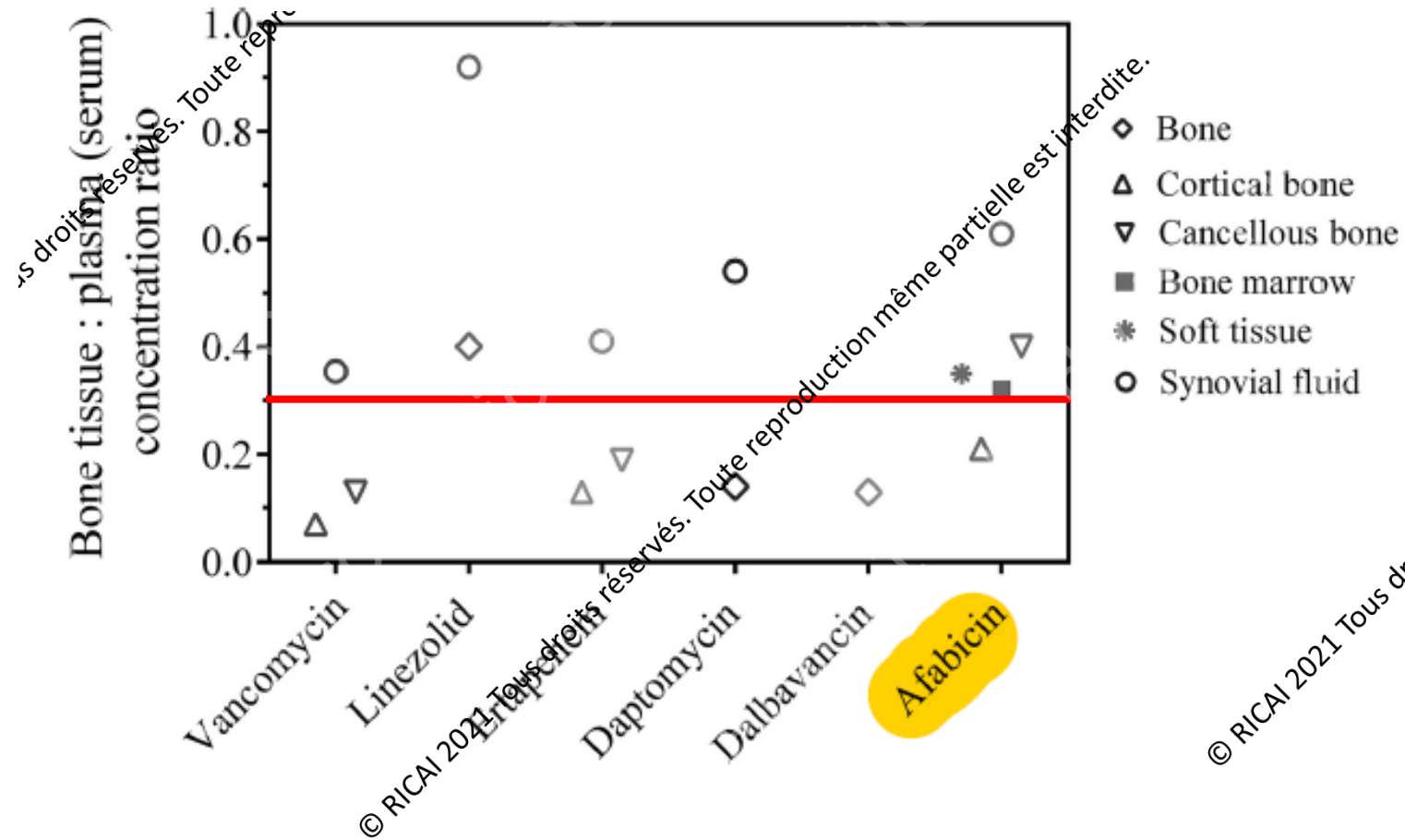
- CMI50 et CMI90 / souches cliniques de *S. aureus* = 0,004 et 0,008 µg/ml
- CMI50 et CMI90 / souches cliniques de SCoN = 0,015 µg/ml et 0,12 µg/ml
- Pas d'influence de la méticillino-résistance

(Flamm R *et al.* Antimicrob Agents and Chemother 2015)

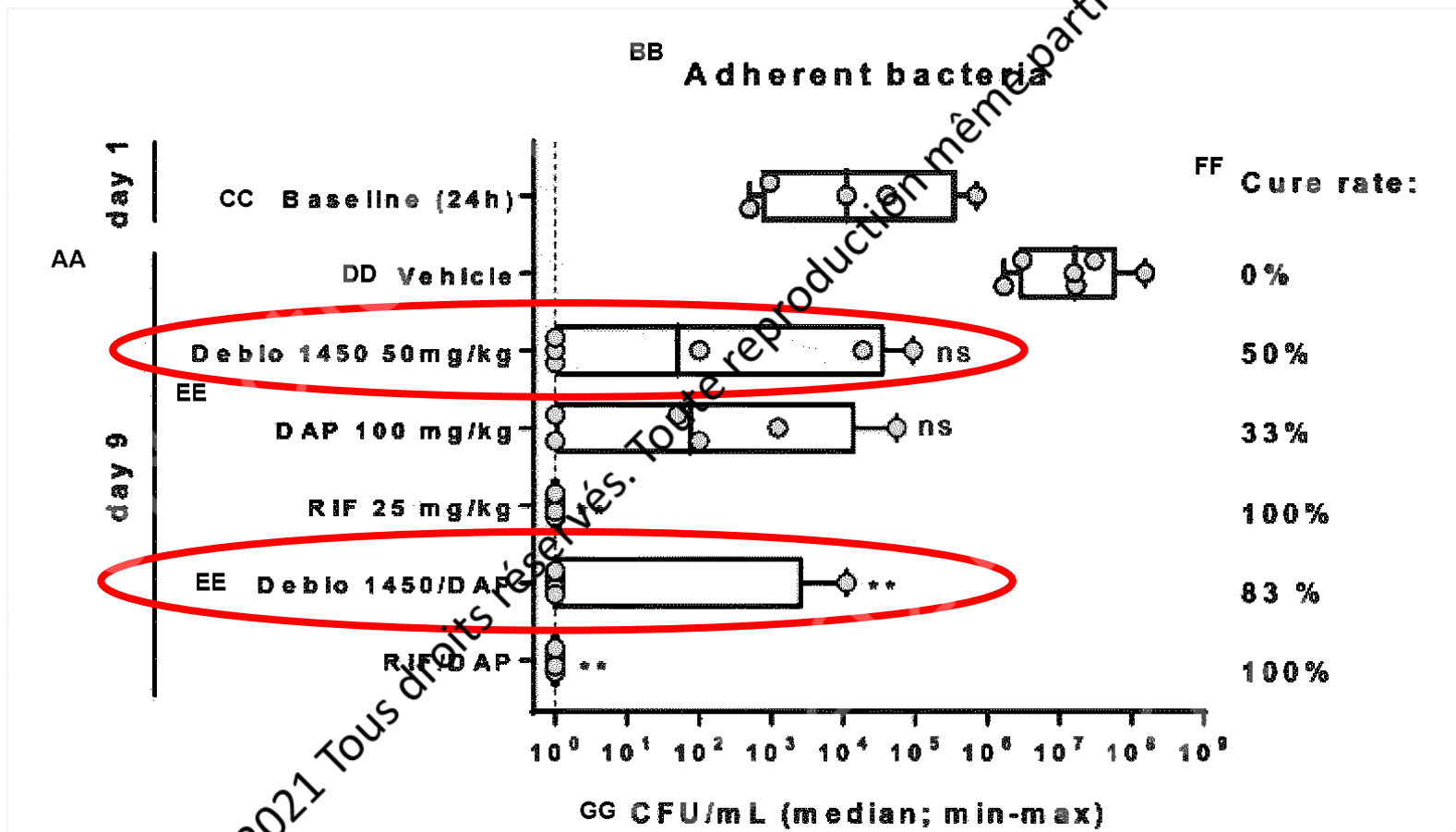
Afabicine (Debio1452)

Parameter	Value(s) for:						
	Plasma (n = 14)	Sparse sampling (from n = 2-4 at each time of resection)					
		Plasma	Cortical bone	Cancellous bone	Bone marrow	Soft tissue	Synovial fluid
AUC _T (ng·h/ml for fluids or ng·h/g for tissues)	20,400 (30.6)	20,100	4,440	8,040	7,060	6,790	12,300
C ₁₂ (ng/ml for fluids or ng/mg for tissues)	1,120 (43.4)	1,500	373	648	640	526	1,210
C _{max} (ng/ml for fluids or ng/mg for tissues)	2,360 (28.0)	2,150	441	841	695	759	1,280
C _{trough} ^a (ng/ml for fluids or ng/mg for tissues)	1,200 (36.7)	—	—	—	—	—	—
t _{1/2} ^b (h)	11.8 (70.1)	—	—	—	—	—	—
t _{max} (median [range]) (h)	2 (0.5-2)	6	6	6	6	6	6
Penetration ratio							
AUC for tissue/AUC for plasma	—	1	0.21	0.40	0.35	0.34	0.61
C _{max} for tissue/C _{max} for plasma	—	1	0.21	0.39	0.32	0.35	0.60
AUC for free tissue/AUC for free plasma ^c	—	1	—	—	—	—	2.88

Diffusion tissulaire de l'Afabcicine



Afabicine et biofilm



Nowakowska J *et al.* (28th ECCMID 2018, Abs. 2471)

Afabicine (Debio1452)

- Traitement d'attente en monothérapie (si suspicion de staphylocoque)
- En association (alternative à oxazolidinones, glyco(lipo) peptides)
- En traitement documenté
- Relais oral (alternative aux oxazolidinones)
- Traitement prolongé (tolérance au long cours ?)

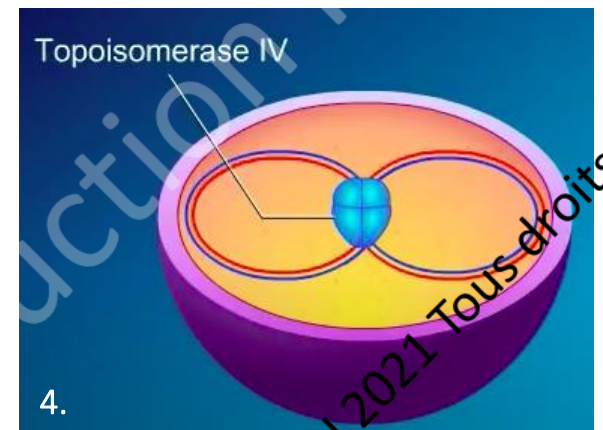
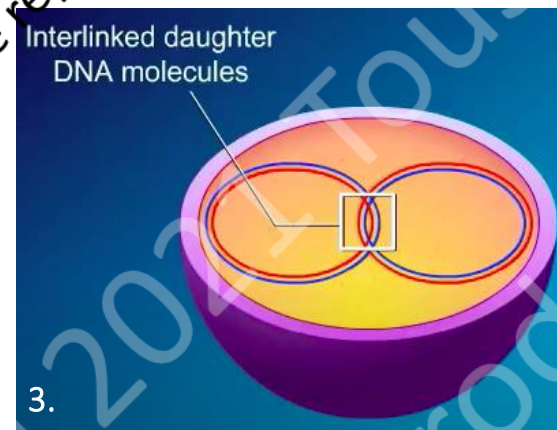
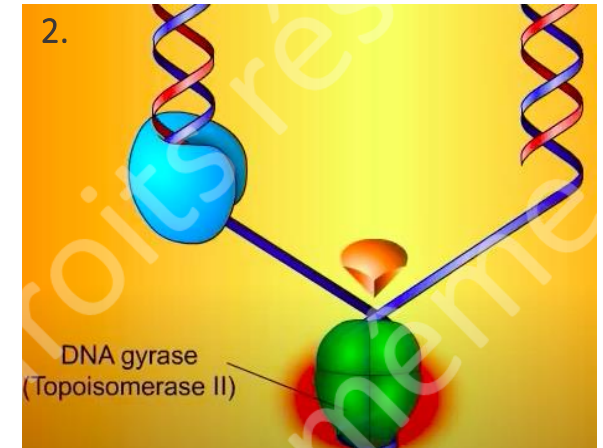
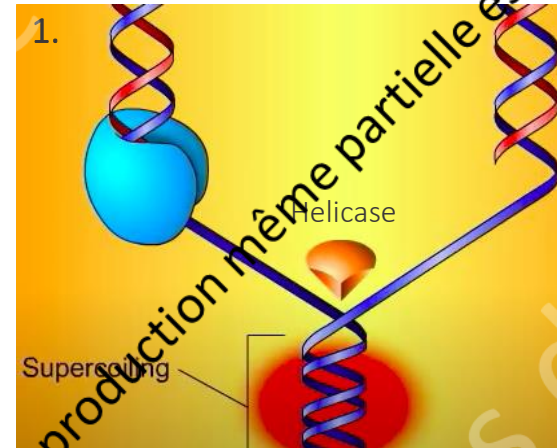
Délaflaxacine : mécanisme d'action

Fluoroquinolones :

- Inhibent ADN gyrase (2.) et topoisomérase IV (4.) bactériennes, enzymes nécessaires à la réplication de l'ADN bactérien
- **Cibent préférentiellement :**
 - **Topoisomérase IV** chez les bactéries à **Gram+**
 - **ADN gyrase** chez les bactéries à **Gram-**

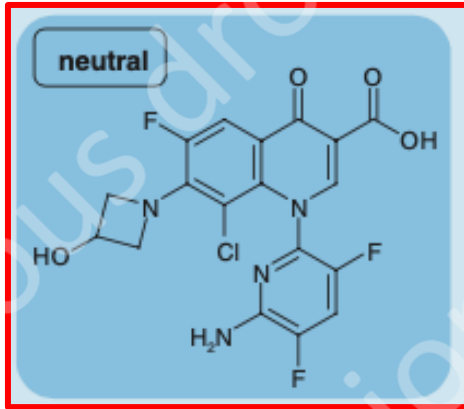
Quofenix :

- Affinité de liaison similaire pour ADN gyrase (2.) et topoisomérase IV (4.)

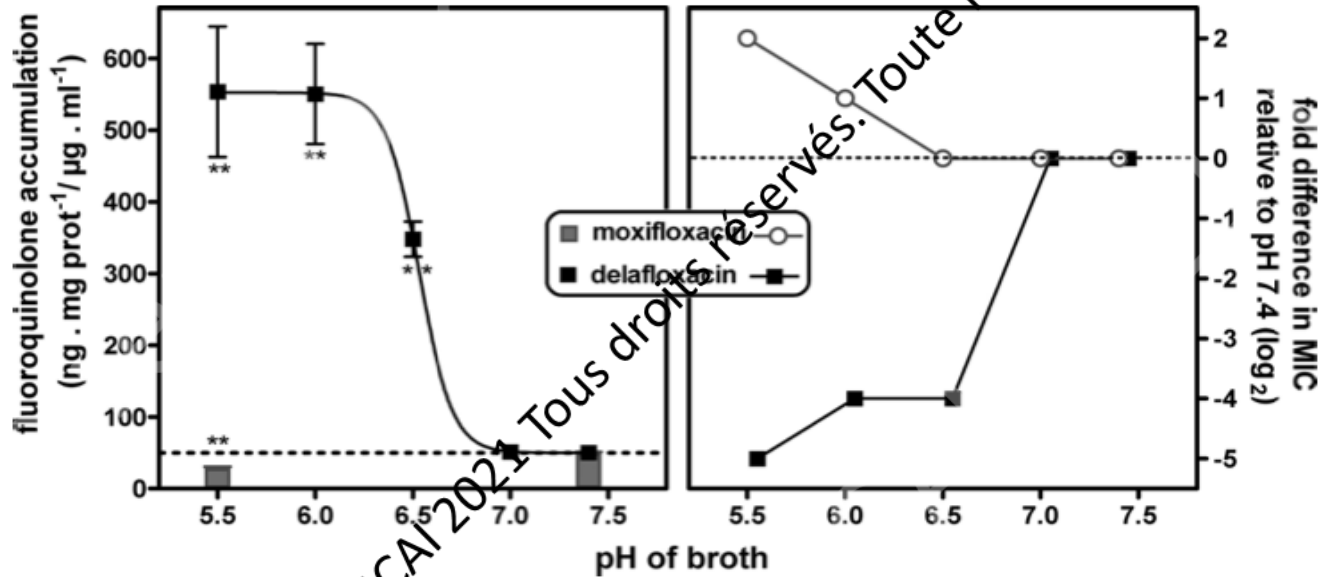
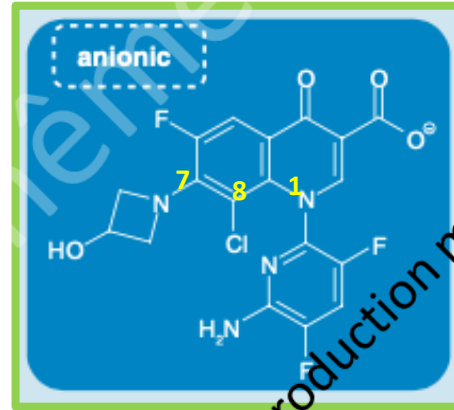


Délafloraxine : structure chimique

En dessous de pH 5,5



À pH neutre



Délafloraxine sous forme non chargée
à pH acide : facilite le passage
transmembranaire⁸



à l'intérieur de la cellule (pH neutre),
la délafloraxine est déprotonée⁸



délafloraxine sous forme anionique



délafloraxine moins diffusible



accumulation intracellulaire⁸

Delafloxacin : activité antimicrobienne

Double inhibition topoisomérase IV (Gram+) et ADN gyrase (Gram-)

Spectre unique :

- staphylocoques
- pneumocoques
- *P. aeruginosa*
- entérobactéries
- anaérobies
- intracellulaires

	CMI ₅₀ (mg/L)	CMI ₉₀ (mg/L)
SASM		
Délafloxacine	≤0,004	0,008
Lévofoxacine	0,25	2
SARM		
Délafloxacine	0,06	0,5
Lévofoxacine	4	>4
<i>P. aeruginosa</i>		
Délafloxacine	0,25	>4
Ciprofloxacine	0,25	>4
<i>S. pneumoniae</i> FQ-R		
Délafloxacine	0,12	0,5
Moxifloxacine	2	4

Van Bambeke F *et al.* Future Microbiol 2015; Tulkens P *et al.* Clin Infect Dis 2019

Apport sur les souches FQ-résistantes

Espèces bactériennes*	N° souches OFLO-R (CMI>4mg/l)	N° souches DELAFLO-S (CMI≤0,25mg/L)	% est inter*	Range CMI DELAFLO (mg/L)
SARM	5	3	60	0,5-1,0
SESM	3	3	100	---
SERM	24	19	79,2	0,30-1,0
<i>S. haemolyticus</i>	2	2	100	---
<i>S. xylosus</i>	1	1	100	---
Total	35	28	80	0,30-1,0

*Données CRIOAC Lille-Tourcoing (souches cliniques IPOAs; Dr Caroline Loiez)

Conclusions

Nouvelles molécules actives sur des bactéries « inaccessibles » : BGN	Cefta-avibactam, cefto-tazobactam, mérovabobactam, imi-relébactam, céfidérocol
Simplification des traitements Staphylocoques	Dalbavancine
Amélioration de la tolérance et observance Staphylocoques BGN	Dalbavancine Céfidérocol / colimycine
Réduction (paradoxale) des coûts	Dalbavancine
Globalement: réduction des déposes (résection arthroplastiques) voire des amputations	Toutes ?