CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

SMIT CHU NANTES

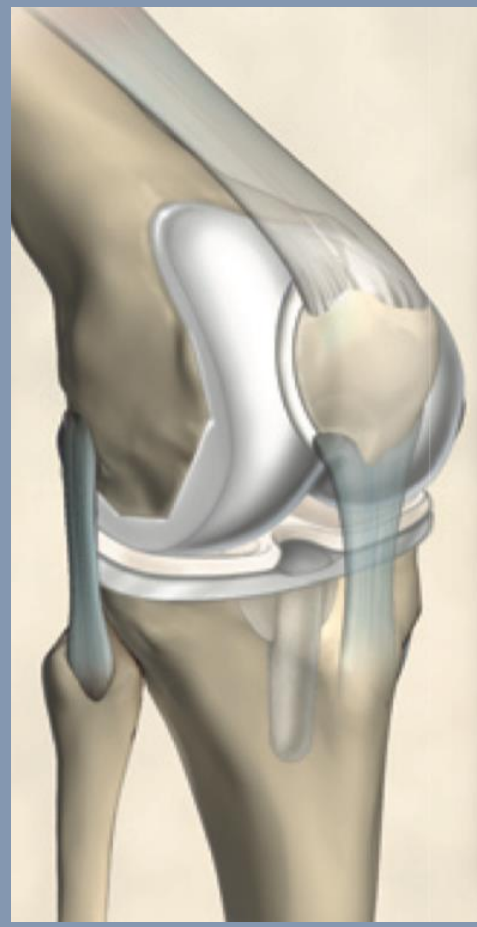
Antibiotiques de longue demi-vie dans les infections ostéo-articulaires

Dr Raphaël LECOMTE

11 mai 2021

Introduction:

- Bactéries cocci gram positifs première cause d'IOA/IPOA



Common causes of prosthetic-knee and prosthetic-hip infection

Gram-positive cocci (approximately 65%)
- Coagulase-negative staphylococci
- *Staphylococcus aureus*
- Streptococcus species
- Enterococcus species

Aerobic gram-negative bacilli (approximately 6%)
- Enterobacteriaceae
- *Pseudomonas aeruginosa*

Anaerobes (approximately 4%)
- Propionibacterium species
- Peptostreptococcus species
- *Finegoldia magna*

Polymicrobial (approximately 20%)

Culture-negative (approximately 7%)

Fungi (approximately 1%)

Del Pozo and Patel NEJM 2009

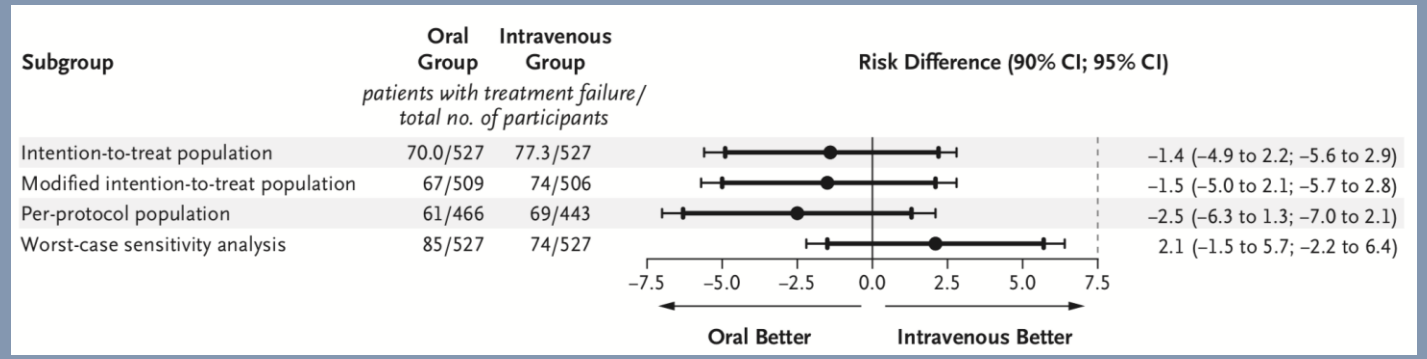
Introduction:

- Bactéries cocci gram positifs première cause d'IOA/IPOA
- Traitement de référence IV
- Relai per os démontré non inférieur (étude OVIVA – IOA/IPOA)

Table 2. Intravenous or Highly Bioavailable Oral Antimicrobial Treatmenion (B-III Unless Otherwise Stated in Text)

Microorganism	Preferred Treatment[a]	Comments
Staphylococci, oxacillin-susceptible	Nafcillin[b] sodium 1.5–2 g IV q4-6 h or Cefazolin 1–2 g IV q8 h or Ceftriaxone[c] 1–2 g IV q24 h	See recommended use of rifampin as a companion drug for rifampin-susceptible PJI treated with debridement and retention or 1-stage exchange in text
Staphylococci, oxacillin-	Vancomycin[d] IV 15 mg/kg q12 h	See recommended use of rifampin as a

23. Two to 6 weeks of a pathogen-specific intravenous antimicrobial therapy (Table 2) in combination with rifampin 300–450 mg orally twice daily followed by rifampin plus a companion oral drug for a total of 3 months for a THA infection and 6 months for a total knee arthroplasty (TKA) infec-



Osmon et al. CID 2012
Li et al. NEJM 2019

Introduction:

- Bactéries cocci gram positifs première cause d'IOA/IPOA
- Traitement de référence IV
- Relai per os démontré non inférieur (étude OVIVA – IOA/IPOA)
- Mais en cas de germes résistants? Terrains particuliers?
- Place pour les antibiotiques à longue demi-vie?

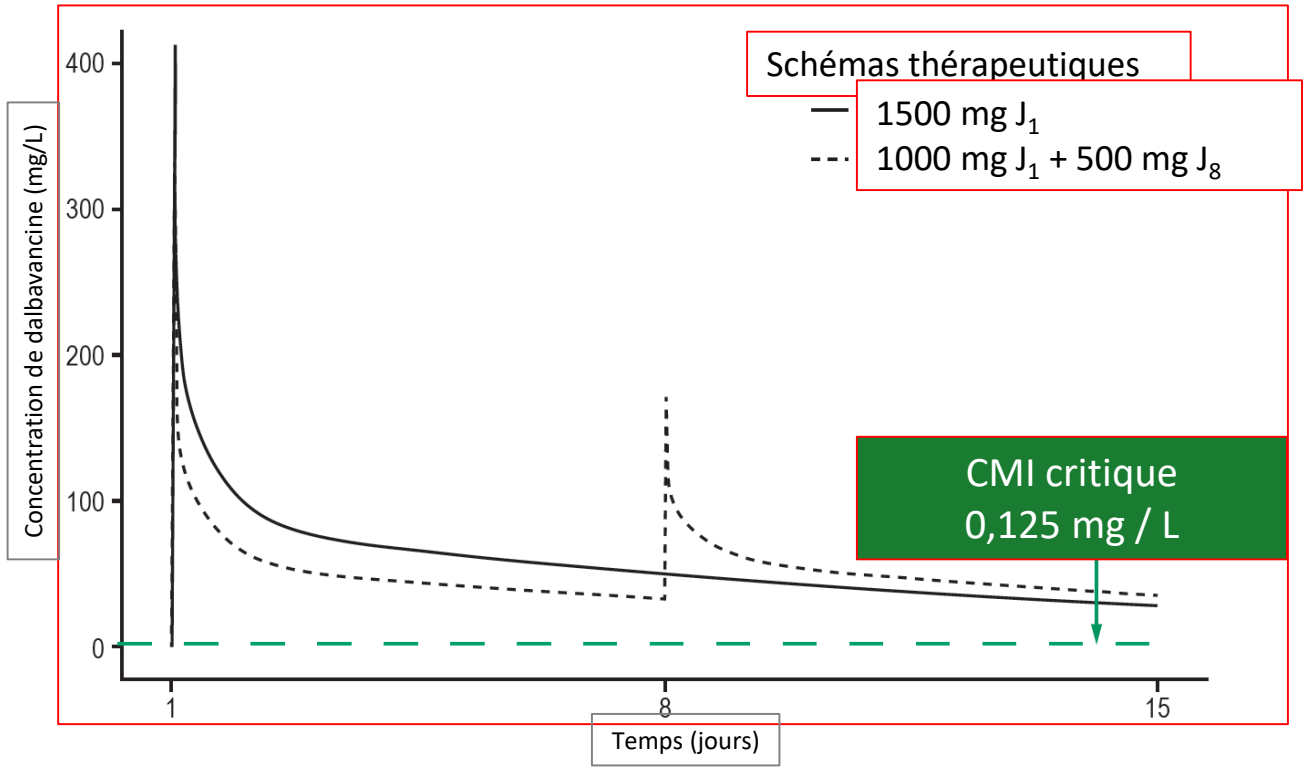
EXAMEN MICROSCOPIQUE DIRECT		
CULTURE ET IDENTIFICATION		
En aérobiose	rares colonies microbiennes d'un seul type	
En anaérobiose	négatif	
Identité bactérie	Staphylococcus epidermidis	
ANTIB. AUTOM. : STAPHYLOCOQUE		
TECHNIQUE SIR	automate Vitek 2	
TEST.CEFOX [FOX] SIR	POSITIF	
OXACILLINE SIR	RESISTANT	
OXACILLINE CMI	>2.	
KANAMYCINE [KMN] SIR	RESISTANT	
KANAMYCINE [KMN] CMI	>32.	
TOBRAMYCINE [TMN] SIR	RESISTANT	
TOBRAMYCINE [TMN] CMI	>8.	
GENTAMICINE [GMN] SIR	RESISTANT	
GENTAMICINE [GMN] CMI	>8.	
OFLOXACINE [OFX] SIR	RESISTANT	
OFLOXACINE [OFX] CMI	>4.	
VANCOMYCINE [VNC/VAN] SIR	SENSIBLE	
VANCOMYCINE [VNC/VAN] CMI	<=0.5	
ERYTHROMYCINE [ERY] SIR	RESISTANT	
ERYTHROMYCINE [ERY] CMI	>4.	
LINCOMYCINE [LCN] SIR	RESISTANT	
LINCOMYCINE [LCN] CMI	>8.	
PRISTINAMYCINE [PTN] SIR	SENSIBLE	
TETRACYCLINE [TET] SIR	RESISTANT	
TETRACYCLINE [TET] CMI	4.	
AC.FUSIDIQUE [FAD] SIR	RESISTANT	
AC.FUSIDIQUE [FAD] CMI	>16.	
COTRIMOXAZOLE [SXT] SIR	RESISTANT	
COTRIMOXAZOLE [SXT] CMI	160.	
FOSFOMYCINE [FOS] SIR	RESISTANT	
FOSFOMYCINE [FOS] CMI	>64.	
LINEZOLIDE [LIN] SIR	RESISTANT	
LINEZOLIDE [LIN] CMI	>4.	
NITROFURANES [NFE] SIR	SENSIBLE	
NITROFURANES [NFE] CMI	<=16.	
RIFAMPICINE [RIF] SIR	RESISTANT	
RIFAMPICINE [RIF] CMI	>2.	
CEFTAROLINE [CPT] SIR	SENSIBLE	
DAPTOMYCINE [DPC] SIR	SENSIBLE	
CMI de BACTERIE AEROBIE		
CMI Ceftaroline	1,000	mg/L
CMI Daptomycine	0,380	mg/L

Staphylococci, oxacillin-resistant	Vancomycin[d] IV 15 mg/kg q12 h	Daptomycin 6 mg/kg IV q24 h or Linezolid 600 mg PO/IV q12 h

Osmon et al. CID 2012

Dalbavancine: un nouvel anti cocci-gram+

- Lipoglycopeptide
- La dalbavancine inhibe la transglycosylation en se liant au substrat D-ala-D-ala
- Demi-vie d'élimination plasmatique moyenne (T1/2): **14 jours !**
- Coût 2258 euros les 1500 mg



Montali *et al.* Antibiotics 2020

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D.,

- Etudes DISCOVER 1 et 2: Infection de la peau et des tissus mous
- Etude randomisée de non infériorité Dalbavancine versus Vancomycine ou Linézolide (n= 659).

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (–4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	–1.5 (–7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	–0.1 (–4.5 to 4.2)

Boucher *et al.* NEJM 2014

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Bou ... uttagunta, M.D.,

- Etudes DISCOV ... ous
- Etude randomi ... ncomycine ou Linézolide

Table 2. Primary and Se ...

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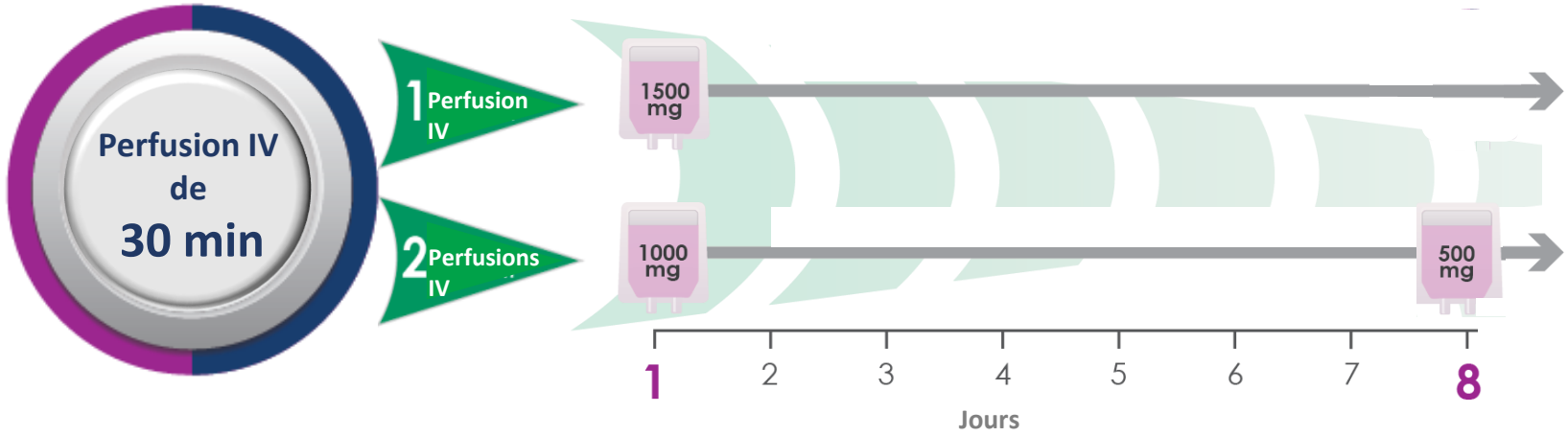
Boucher *et al.* NEJM 2014

Rappel : l'AMM

- La dalbavancine est recommandée chez l'adulte présentant des infections bactériennes aiguës de la peau et des tissus mous à la posologie de **1500 mg** administrés:
  - soit en une seule perfusion IV de 1500 mg
  - soit en une perfusion IV de 1000 mg suivie d'une perfusion IV de 500 mg une semaine plus tard



Tout ce qui va suivre sera hors AMM

Diapositive du Pr David Boutoille

La Dalbavancine dans les infections ostéoarticulaires

Quelles données microbiologique?

Quelles données cliniques dans les IOA?

- Efficacité?
- Tolérance?

Comment utiliser la Dalbavancine?

- Paramètres PK/PD
- Intérêt des dosages

Partie 1: les données microbiologiques

Quel spectre microbiologique?

Journal of Antimicrobial Chemotherapy

Activité de la Dalbavancine sur les cocci gram positifs (27 208 souches), USA Europe 2015-2016

Organism (No. tested)	**MIC90**	**CMI critiques**	**% Sensible EUCAST**
S. aureus (14 319)	0.03	S ≤ 0.125	>99.9
SASM (9 111)	0.03	S ≤ 0.125	>99.9
SARM (5 208)	0.03	S ≤ 0.125	100
Staphylocoques à coagulase négative (1 992)	0.06	S ≤ 0.125	99.6
Streptocoques β-hémolytiques (3 269)	0.03	S ≤ 0.125	100
S. pneumoniae (3 487)	0.015	S ≤ 0.125	
E. faecalis Vanco S (2 022)	0.06	-	
E. faecium Vanco S (531)	0.012	-	

Pfaller *et al.* JAC 2018

Souches cliniques d'infections, USA et Europe (37 hôpitaux, 18 pays), 2015-2016

Journal of Antimicrobial Chemotherapy

Table 1. Antimicrobial activity of dalbavancin tested against the main organisms and organism groups of isolates

Organism/organism group (no. of isolates)	No. of isolates (cumulative %) at MIC (mg/L)												MIC_{50}	MIC_{90}
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>2		
S. aureus (14 319)	3 (<0.1)	16 (0.1)	72 (0.6)	1620 (11.9)	11 293 (90.8)	1286 (99.8)	27 (>99.9)	2 (100.0)					0.03	0.03
MSSA (9111)	2 (<0.1)	9 (0.1)	52 (0.7)	1039 (12.1)	7214 (91.3)	782 (99.9)	11 (>99.9)	2 (100.0)					0.03	0.03
MRSA (5208)	1 (<0.1)	7 (0.2)	20 (0.5)	581 (11.7)	4079 (90.0)	504 (99.7)	16 (100.0)						0.03	0.03
S. aureus with vancomycin MIC ≥2 mg/L (44[a])			0 (0.0)	1 (2.3)	13 (31.8)	22 (81.8)	6 (95.5)	2 (100.0)					0.06	0.12
CoNS (1992)	1 (0.1)	13 (0.7)	78 (4.6)	504 (29.9)	953 (77.8)	323 (94.0)	113 (99.6)	5 (99.9)				2 (100.0)	0.03	0.06
E. faecalis (2071)				266 (12.8)	1362 (78.6)	376 (96.8)	20 (97.7)	2 (97.8)	0 (97.8)	0 (97.8)	1 (97.9)	44 (100.0)	0.03	0.06
vancomycin-susceptible *E. faecalis* (2022)				266 (13.2)	1361 (80.5)	374 (99.0)	20 (>99.9)	1 (100.0)					0.03	0.06
vancomycin-resistant (VanA) *E. faecalis* (43)										0 (0.0)	1 (2.3)	42 (100.0)	>2	>2
vancomycin-resistant (VanB) *E. faecalis* (6)				0 (0.0)	1 (16.7)	2 (50.0)	0 (50.0)	1 (66.7)	0 (66.7)	0 (66.7)	0 (66.7)	2 (100.0)	0.06	
E. faecium (936)				72 (7.7)	166 (25.4)	190 (45.7)	100 (56.4)	25 (59.1)	5 (59.6)	7 (60.4)	17 (62.2)	354 (100.0)	0.12	>2
vancomycin-susceptible *E. faecium* (531)				70 (13.2)	160 (43.3)	184 (78.0)	98 (96.4)	19 (100.0)					0.06	0.12
vancomycin-resistant (VanA) *E. faecium* (386)					0 (0.0)	2 (0.5)	1 (0.8)	5 (2.1)	5 (3.4)	7 (5.2)	15 (9.1)	351 (100.0)	>2	>2
vancomycin-resistant (VanB) *E. faecium* (19)				2 (10.5)	6 (42.1)	4 (63.2)	1 (68.4)	1 (73.7)	0 (73.7)	0 (73.7)	2 (84.2)	3 (100.0)	0.06	>2
E. gallinarum/				3 (7.3)	6 (22.0)	10 (46.3)	18 (90.2)	4 (100.0)					0.12	0.12
					15 (83.3)	3 (93.3)	2 (100.0)						0.03	0.06
					319 (99.7)	9 (100.0)							0.015	0.015
					408 (96.3)	101 (99.4)	21 (100.0)						0.015	0.03
S. pyogenes (1553)	40 (2.6)	396 (28.1)	718 (74.3)	277 (92.1)	104 (98.8)	17 (99.9)	1 (100.0)						0.008	0.015
S. agalactiae (1232)	1 (0.1)	8 (0.7)	202 (17.1)	723 (75.8)	217 (93.4)	67 (98.9)	14 (100.0)						0.015	0.03
S. dysgalactiae (484)	1 (0.2)	44 (9.3)	180 (46.5)	149 (77.3)	87 (95.2)	17 (98.8)	6 (100.0)						0.015	0.03
VGS (1063)	179 (16.8)	191 (34.8)	196 (53.2)	214 (73.4)	208 (92.9)	56 (98.2)	16 (99.7)	3 (100.0)					0.008	0.03
S. anginosus group (382)	176 (46.1)	152 (85.9)	42 (96.9)	7 (98.7)	3 (99.5)	2 (100.0)							0.004	0.008
S. bovis group (75)	0 (0.0)	9 (12.0)	13 (29.3)	25 (62.7)	28 (100.0)								0.015	0.03
S. mitis group (526)	2 (0.4)	28 (5.7)	127 (29.8)	157 (59.7)	159 (89.9)	41 (97.7)	10 (99.6)	2 (100.0)					0.015	0.06
S. salivarius group (80)	1 (1.2)	2 (3.8)	14 (21.2)	25 (52.5)	18 (75.0)	13 (91.2)	6 (98.8)	1 (100.0)					0.015	0.06

[a]All isolates had a vancomycin MIC of 2 mg/L.

Le cas des Staph dorés CMIHV: résistance?

Le cas des SCN: attention à la CMI à 0,12

Pfaller *et al.* JAC 2018

Faut-il tester systématiquement la Dalbavancine?

Comité de l'antibiogramme de la Société Française de Microbiologie

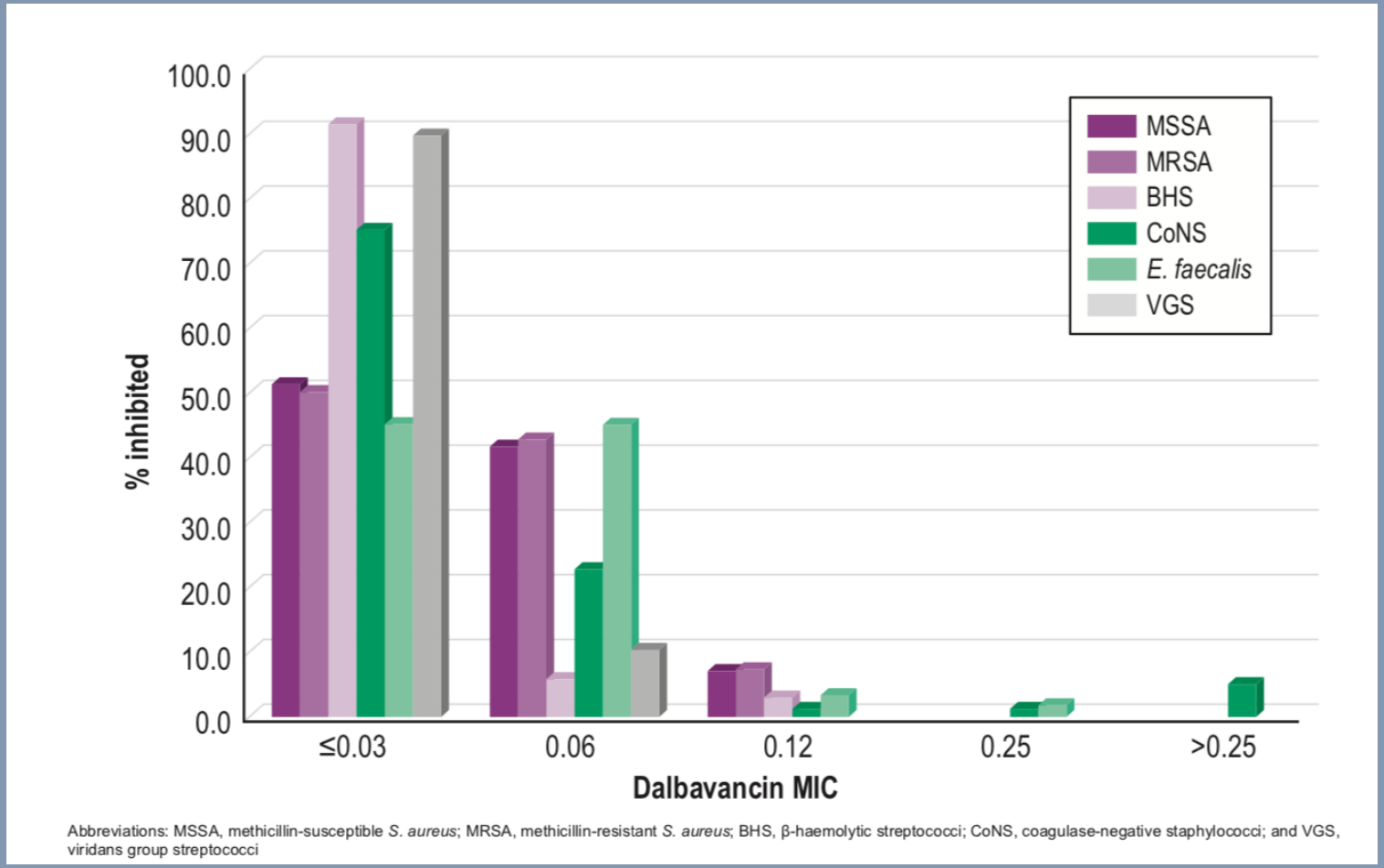
Recommandations 2021
V.1.0 Avril

5. 8. *Staphylococcus* spp.

Glycopeptides (suite)	Concentrations critiques (mg/L)			Charge du disque (µg)	Diamètres critiques (mm)			Notes Chiffres arabes pour les commentaires portant sur les concentrations critiques (CMI) Lettres pour les commentaires portant sur les diamètres critiques d'inhibition
	S ≤	R >	ZIT		S ≥	R <	ZIT	
Dalbavancine[1]	0,125[1]	0,125[1]			Note[A]	Note[A]		1. Mesurer la CMI. Pour déterminer la CMI par micro-dilution, le milieu doit être supplémenté avec du polysorbate-80 à la concentration de 0,002%.
Oritavancine[1] *S. aureus*	0,125[1]	0,125[1]			Note[A]	Note[A]		
Téicoplanine *S. aureus*	2	2			Note[A]	Note[A]		Les souches sensibles à vancomycine sont sensibles à la dalbavancine, à l'oritavancine et à la télavancine.
Téicoplanine *S.* non-*aureus*	4	4			Note[A]	Note[A]		A. La méthode de diffusion (disque et gradient en bandelette) n'est pas utilisable car elle ne permet pas la différenciation entre les souches sensibles de celles de sensibilité diminuée aux glycopeptides.
Télavancine SARM[1,2]	0,125[1]	0,125[1]			Note[A]	Note[A]		
Vancomycine *S. aureus*	2	2			Note[A]	Note[A]		
Vancomycine *S.* non-*aureus*	2	2			Note[A]	Note[A]		

Et les souches isolées d'IOA?

- 2011–2016
- Souches d'infections ostéoarticulaires
- USA
- 744 souches



Sader HS, IDWeek 2017, October 4-8, San Diego, CA, USA

Un alternative en cas de résistances aux autres antistaphylococciques majeurs

TABLE 2 Summary of dalbavancin activity tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from U.S. medical centers

Resistance phenotype	No. of isolates (cumulative %) inhibited at dalbavancin MIC (mg/liter) of[a]:					MIC_{50} (mg/liter)	MIC_{90} (mg/liter)
	≤0.03	0.06	0.12	0.25	0.5		
Vancomycin MIC ≥2 mg/liter (n = 1,141)	117 (10.3)	**697 (71.3)**	276 (95.5)	43 (99.3)	8 (100.0)	0.06	0.12
Daptomycin nonsusceptible (n = 48)	3 (6.3)	**25 (58.3)**	16 (91.7)	2 (95.8)	2 (100.0)	0.06	0.12
Telavancin MIC ≥0.12 mg/liter (n = 52)[b]	4 (7.7)	**24 (53.8)**	16 (84.6)	3 (90.4)	5 (100.0)	0.0.6	0.25
Teicoplanin MIC ≥4 mg/liter (n = 143)	14 (9.8)	**73 (60.8)**	33 (83.9)	16 (95.1)	7 (100.0)	0.06	0.25
Linezolid resistant (n = 25)	5 (20.0)	**18 (92.0)**	2 (100.0)			0.06	0.06
All isolates (n = 59,903)	22,066 (36.8)	**33,879 (93.4)**	3,795 (99.7)	155 (>99.9)	8 (100.0)	0.06	0.06

[a]Boldface data represent dalbavancin modal MIC results. The dalbavancin-susceptible breakpoint approved by the FDA for *S. aureus* is ≤0.25 mg/liter (13).
[b]Telavancin was only tested against isolates collected in 2011 to 2016.

Sader *et al.* AAC 2018

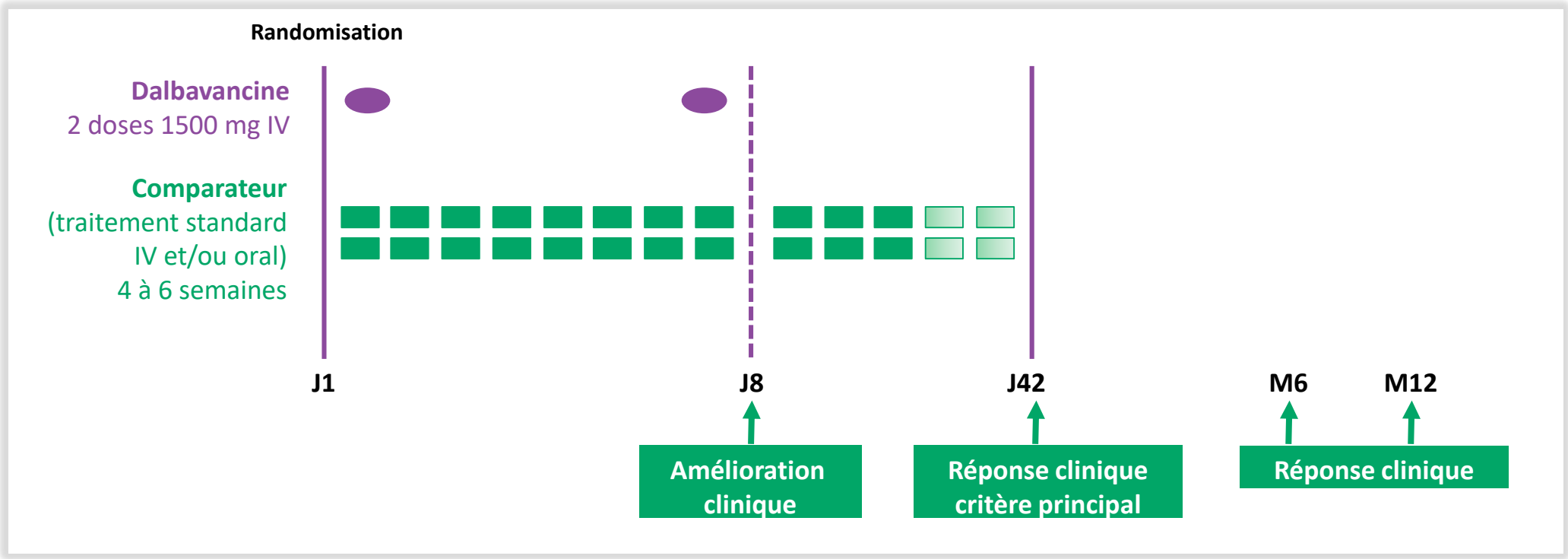
Que retenir sur les données microbiologiques?

- Spectre large sur les CG+:
  - Staphylocoques dorés et SCN
  - Streptocoques
  - Entérocoques
- CMI très basses sauf quelques exceptions:
  - Entérocoques
  - SCN, particulièrement si CMI vancomycine élevée
- Une alternative en cas de résistances aux autres anti-staphylococciques majeurs.

Partie 2: les données cliniques

Infection osseuse de l'adulte : efficacité de la dalbavancine (1)

- Essai randomisé (7:1) ouvert, monocentrique comparant dalbavancine vs traitement standard (mars 2016 - décembre 2017). Ukraine.
- Ostéomyélite <u>SANS</u> matériel



Rappo et al. OFID 2019 Rappo U, ECCMID 2018, Abs. O0697

Infection osseuse de l'adulte : efficacité de la dalbavancine (2)

Caractéristiques des patients

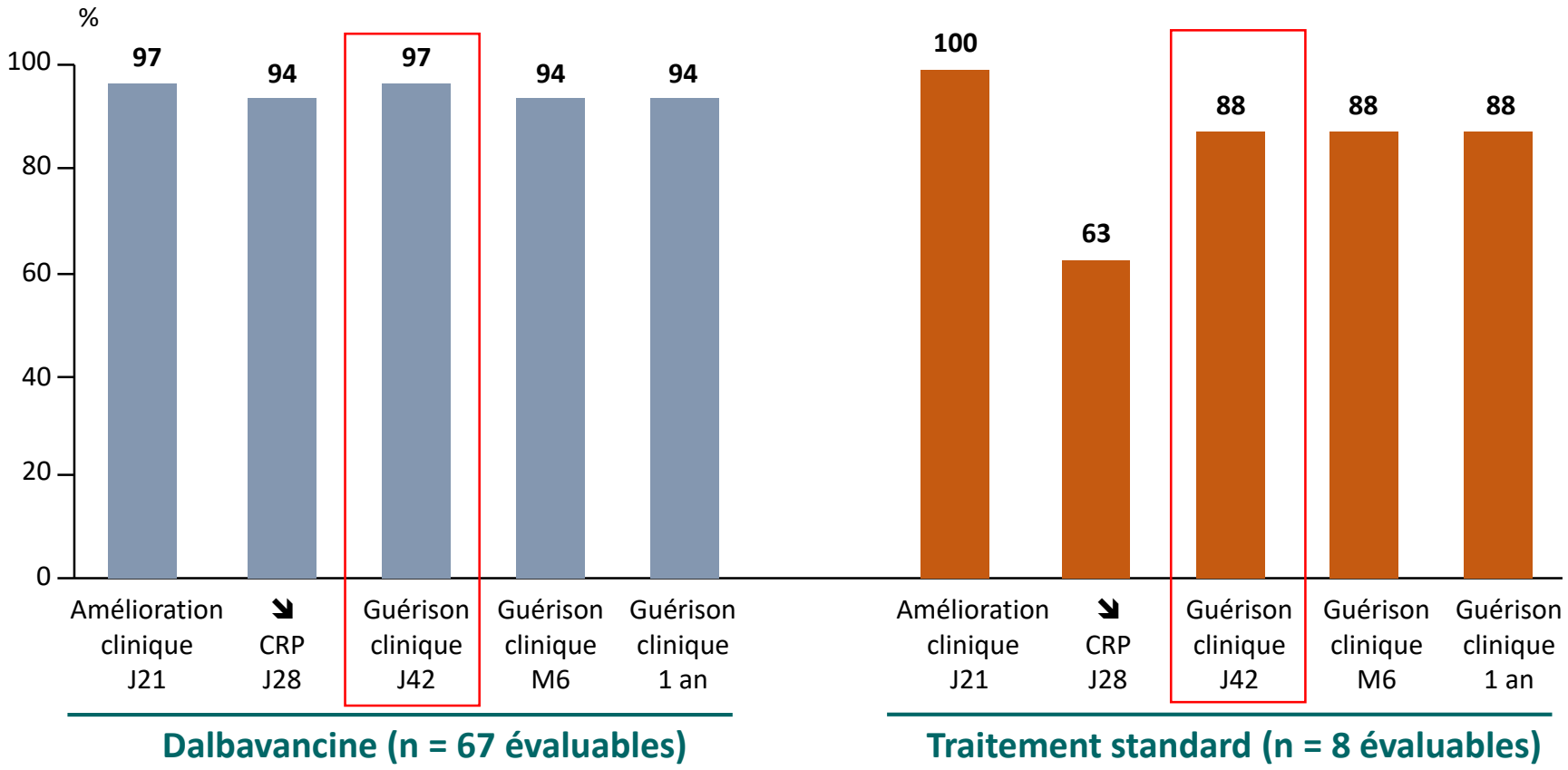
	Dalbavancine (n = 70)	Traitement standard (n = 10)
Age moyen (années)	49,2	54,4
Homme	84,3 %	50 %
IMC (kg/m^2) moyen	26,1	30,7
Diabète	14,3 %	50,0 %
Infection pied diabétique	5,7 %	10,0 %
Vac thérapie	11,4 %	30 %

Microbiologie

Bactéries isolées	Dalbavancine (n = 70)	Traitement standard (n = 10)
SASM	54,3 %	50,0 %
SARM	5,7 %	10,0 %
SCN	20,0 %	20,0 %
Entérocoque	11,4 %	10,0 %
Anaérobies	12,9 %	0 %
Streptocoque	4,2 %	10,0 %
Autres Bactéries Gram+	7,6 %	10,0 %
BGN	4,3 %	20,0 %
Non documenté	7,1 %	0 %

Rappo et al. OFID 2019 Rappo U, ECCMID 2018, Abs. O0697

Infection osseuse de l'adulte : efficacité de la dalbavancine (3)



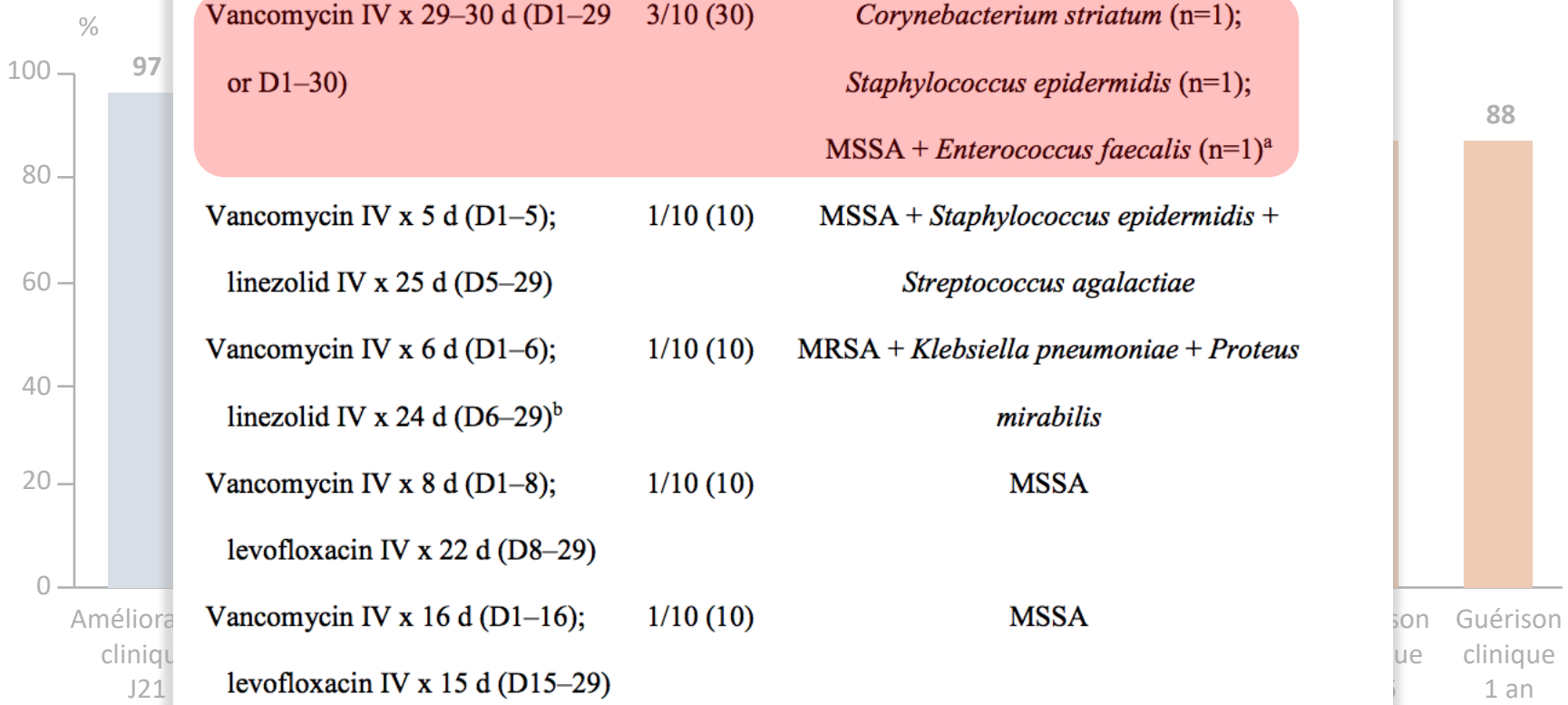
- Clinical cure at day 42 was seen in 65/67 (97%) and 7/8 (88%) patients in the dalbavancin group and SOC group

Rappo et al. OFID 2019 Rappo U, ECCMID 2018, Abs. O0697

Infection osseuse de l'adulte : efficacité de l

Supplementary Table 1. All Treatment Regimens for Patients Receiving Standard of Care (Safety Population)

Regimen	SOC, no./No. (%)	Baseline Pathogen(s) in Bone
Vancomycin IV x 29–30 d (D1–29 or D1–30)	3/10 (30)	*Corynebacterium striatum* (n=1); *Staphylococcus epidermidis* (n=1); MSSA + *Enterococcus faecalis* (n=1)[a]
Vancomycin IV x 5 d (D1–5); linezolid IV x 25 d (D5–29)	1/10 (10)	MSSA + *Staphylococcus epidermidis* + *Streptococcus agalactiae*
Vancomycin IV x 6 d (D1–6); linezolid IV x 24 d (D6–29)[b]	1/10 (10)	MRSA + *Klebsiella pneumoniae* + *Proteus mirabilis*
Vancomycin IV x 8 d (D1–8); levofloxacin IV x 22 d (D8–29)	1/10 (10)	MSSA
Vancomycin IV x 16 d (D1–16); levofloxacin IV x 15 d (D15–29)	1/10 (10)	MSSA
Vancomycin IV × 7 d (D1–7); linezolid IV plus cefotaxime IV x 43 d (D7–49)[c]	1/10 (10)	MSSA + *Pseudomonas aeruginosa* + *Raoultella planticola* + *Serratia marcescens*



- Clinical cu
group an
albavancin

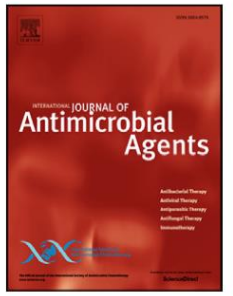
Rappo U, ECCMID 2018, Abs. O0697

Rappo et al. OFID 2019 Rappo U, ECCMID 2018, Abs. O0697

Short Communication

French national cohort of first use of dalbavancin: A high proportion of off-label use

Aurélien Dinh[a,*], Clara Duran[a], Patricia Pavese[b], Lydie Khatchatourian[c], Boris Monnin[d],



- Cohorte issue de française de tous les patients qui ont reçu au moins une dose de dalbavancine
- Juin 2017 – Septembre 2018
- 29 centres
- Définition de l'échec:
  - Persistance signes cliniques
  - ATB suppressive
  - décès

Table 1
Demographics and baseline characteristics and description of dalbavancin use in the study population ($N = 75$)

Characteristic	n (%) [a]
Site of infection	
Disseminated disease [d]	19 (25.3)
BJI	48 (64.0)
Endocarditis	19 (25.3)
Native valve	9 (12.0)
Prosthetic valve	10 (13.3)
SSTI	13 (17.3)
Vascular infection	5 (6.7)
Catheter line infection	4 (5.3)
Bloodstream infection	3 (4.0)
Mediastinitis	2 (2.7)

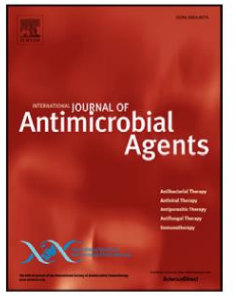
[d] Disseminated disease was considered when at least two different sites were infected.

Dinh et al. IJAA 2019

Short Communication

French national cohort of first use of dalbavancin: A high proportion of off-label use

Aurélien Dinh[a,*], Clara Duran[a], Patricia Pavese[b], Lydie Khatchatourian[c], Boris Monnin[d],



- 64% d'IOA
- 30% SAMS, 7% d'E faecalis

Table 1
Demographics and baseline characteristics and description of dalbavancin use in the study population ($N = 75$)

Characteristic	n (%) [a]
Microbiology analysis	
Documented infections	72 (96.0)
Polymicrobial infections	25 (34.7)
Staphylococcus spp.	69 (95.8)
Staphylococcus aureus	37 (51.4)
MRSA	14 (19.4)
CoNS	32 (44.4)
Staphylococcus epidermidis	24 (33.3)
MRSE	15 (20.8)
Enterococcus faecalis	5 (6.9)
Corynebacterium spp.	5 (6.9)

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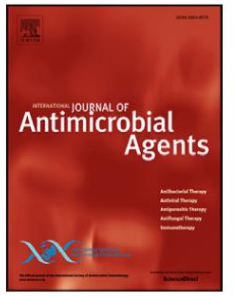

- 64% d'IOA
- 30% SAMS, 7% d'E faecalis
- Utilisation: effets indésirables et liés à la facilité d'utilisation (et non en raison du spectre)

Table 1
Demographics and baseline characteristics and description of dalbavancin use in the study population ($N = 75$)

Characteristic	n (%) [a]
Reason for dalbavancin use	
Clinical failure of previous antibiotic treatment	16 (21.3)
Microbiological failure of previous antibiotic treatment	4 (5.3)
Adverse event of previous antibiotic treatment	26 (34.7)
Multidrug-resistant bacteria	17 (22.7)
Impossible venous access	18 (24.0)
Patient autonomy	29 (38.7)
Early hospital discharge	26 (34.7)
Better compliance	21 (28.0)

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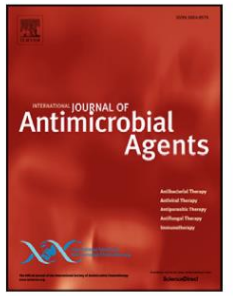

- 64% d'IOA
- 30% SAMS, 7% d'E faecalis
- Utilisation: effets indésirables et liés à la facilité d'utilisation (et non en raison du spectre)
- Utilisé en 2ème voire 3ème intention
- En association avec la rifampicine dans 1/3 des cas

Among the 75 patients, 74 (98.7%) had received prior antibiotic treatment, with a mean of 2.3 ± 1.2 lines (range, 1–8). The

Concomitant antibiotics were used with dalbavancin for 34 patients (45.3%). The most frequently antibiotics used were rifampicin ($n = 12$; 35.3%), trimethoprim/sulfamethoxazole ($n = 10$; 29.4%), fluoroquinolones ($n = 6$; 17.6%) and tetracyclines ($n = 6$; 17.6%).

Une étude de vraie vie avec une utilisation en tout point opposée à l'AMM et aux études randomisées (IOA – Complexe – en association…)

Dinh et al. IJAA 2019

Short Communication

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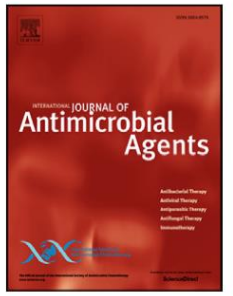

- Outcomes:
  - Suivi moyen 87.8 ±86.9 jours
  - Guérison: pas de signe clinique (avec confirmation pas le médecin).
  - Echec:
    - Persistance ou réapparition des signes
    - ATB suppressive
    - Décès

=> IOA : 76% de guérison

Table 2
Dalbavancin dosing regimen and patient outcome, in total and according to site of infection

	Total ($n = 75$)	BJI ($n = 48$)	Endocarditis ($n = 19$)	SSTI ($n = 13$)
Outcome at last visit [b] [n (%)]				
Cure	54/68 (79.4)	35/46 (76.1)	13/18 (72.2)	9/11 (81.8)
Failure	14/68 (20.6)	11/46 (23.9)	5/18 (27.8)	2/11 (18.2)
Delay since first dose (days) (mean ± S.D.)	87.8 ± 86.9	80.0 ± 73.9	97.9 ± 99.7	102.8 ± 96.6

Only five adverse drug reactions were reported, without any dalbavancin treatment discontinuation. Two adverse drug reactions concurred with hypersensitivity to dalbavancin (erythematous rash, chills and fever after the first infusion). One patient suffered from headaches. An increase in eosinophils level was also reported, which was self-resolving. Lastly, one patient had local inflammatory signs after a single i.v. infusion of 1500 mg dalbavancin.

Dinh et al. IJAA 2019

Données de tolérance:

- Données issues de 3 études pivots:
  - Une étude randomisée de phase 3b (DUR001- 303), (dalbavancin single-dose (1500 mg intravenous [IV]) or two- dose regimen (1000 mg IV on day 1, 500 mg IV on day 8).
  - DISCOVER 1 and DISCOVER 2
  - Nephrotoxicité:
    - >50% d'augmentation de la créatinine sérique ou une augmentation absolue > 0.5 mg/dL at any time point.

Table 3 Adverse event and nephrotoxicity rates across the 3 clinical trials in patients with acute bacterial skin and skin structure infections

Patients	Dalbavancin			Vancomycin[c]	*P* value[d]
	Single dose[a] (*N* = 349) *n*/*N*1 (%)	Two doses[b] (*N* = 998) *n*/*N*1 (%)	Total[b] (*N* = 1347) *n*/*N*1 (%)	(*N* = 651) *n*/*N*2 (%)	
Patients (safety population) experiencing a TEAE (*n*/*N*)	70/349 (20.1)	283/998 (28.4)	353/1347 (26.2)	247/651 (37.9)	< 0.0001
All patients experiencing a TEAE	69/345 (20.0)	278/980 (28.4)	347/1325 (26.2)	25/54 (46.3)	0.0011
TEAE leading to premature discontinuation of study drug	5/345 (1.4)	18/980 (1.8)	23/1325 (1.7)	0	0.3291
Drug-related TEAE	24/345 (7.0)	104/980 (10.6)	128/1325 (9.7)	3/54 (5.6)	0.3134
Serious TEAE	7/345 (2.0)	21/980 (2.1)	28/1325 (2.1)	7/54 (13.0)	< 0.0001
Nephrotoxicity on therapy[e]					
All dalbavancin patients vs patients intravenously administered vancomycin only	15/345 (4.3)	34/980 (3.5)	49/1325 (3.7)	5/54 (9.3)	0.039
Patients receiving IV treatment only[f]	NA	1/58 (1.7)	1/58 (1.7)	5/54 (9.3)	0.0781

IV intravenous, *N* safety population, *N1* safety population with all creatinine values available, *N2* safety population with all creatinine values available in patients who received vancomycin for at least 10 days, *NA* not applicable, *ND* not determined,

Gonzalez *et al.* Infect Dis Ther 2021

Quelles données observationnelles?

- Revue de la littérature
- 12 études observationnelles
- Effectifs faibles

Journal of Antimicrobial Chemotherapy

Table 1. Summary of published real-life experience with dalbavancin in the treatment of osteomyelitis in adult patients

Citation (year)	Study design	Country; no. of sites	No. of patients	Dosage regimen	Clinical success	Adverse events
Bouza *et al.*[18] (2018)	RCS	Spain; 29	overall = 69, OM = 12	variable; median of 4 doses (range 1–9) and duration of 3 weeks (range 1–24)	11/12 (92%) up to 1 month after end of treatment	9/69 mild–moderate (rash, tachycardia and impaired renal function)
Wunsch *et al.*[28] (2019)	RCS	Austria; 3	overall = 101, OM = 30	variable; median of 3 doses (range 1–32)	89% up to 3 months after the end of therapy	3/101 (dyspnoea, fatigue, vertigo, arterial hypertension and reversible increase in creatinine); 1 required treatment discontinuation
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Morata *et al.*[29] (2019)	RCS	Spain; 30	overall = 64, OM = 19	variable; median of 5 doses (IQR 3–8)	17/19 (90%) at latest medical visit (median of 6 months)	7/64 (gastrointestinal distress, rash, phlebitis, asthenia and increased serum creatinine)
Almangour *et al.*[4] (2019)	RCS	USA; 3	31	variable; median of 3 doses (range 1–14)	28/31 (90%) at 3 months after end of treatment	none
Bork *et al.*[6] (2019)	RCS	USA; 2	overall = 21, OM = 11	variable; median of 3 doses (IQR 4.5)	6/11 (55%) at 1 month after end of therapy	3/21 (rash and renal impairment)
Rappo *et al.*[24] (2019)	RCT	Ukraine; 1	dalbavancin = 70, SOC = 10	1500 mg on Days 1 and 8	at 1 year: dalbavancin, 96%; SOC, 88%	no serious adverse events were considered to be related to dalbavancin
Morrisette *et al.*[20] (2019)	RCS	USA; 1	overall = 56, OM = 15, dalbavancin = 40, oritavancin = 14, combination = 2	variable; median of 1 dose (IQR 1–2)	14/15 (93%) at median follow-up of 6.1 months after treatment	6/56 [infusion reactions (itching and rash), nausea, chest tightness, line infiltration with oedema, acute kidney injury or headache]
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Almangour et al. JAC 2020

Quelles données observationnelles?

- 12 études observationnelles
- Effectifs faibles
- Schémas thérapeutiques variables+++

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Almangour et al. JAC 2020

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- Taux de succès élevés
- Rares EI

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Almangour et al. JAC 2020

Et sur prothèse?

Table 1
Demographic information (n = 101).

Variable	n (%)
Age, y, median (range)	65 (11–93)
Sex	
Male	57 (56.4)
Female	44 (43.6)
Infection type	
PJI	32 (31.7)
Osteomyelitis (including vertebral osteomyelitis)	30 (29.7)
Endocarditis	25 (24.8)
Native valve	15 (14.9)
Prosthetic valve	6 (5.9)
Cardiac implantable electronic device	4 (4)
ABSSSI	11 (10.9)
CRBSI	3 (3)
Pathogens	
CNS	28 (33)
MSSA	14 (16)
MRSA	8 (9)
Enterococci	7 (8)
Streptococci	5 (6)
Propionibacterium acnes	4 (5)
>1 gram-positive pathogen	16 (15.8)
Mixed infection (gram-positive plus gram-negative)	5 (5)

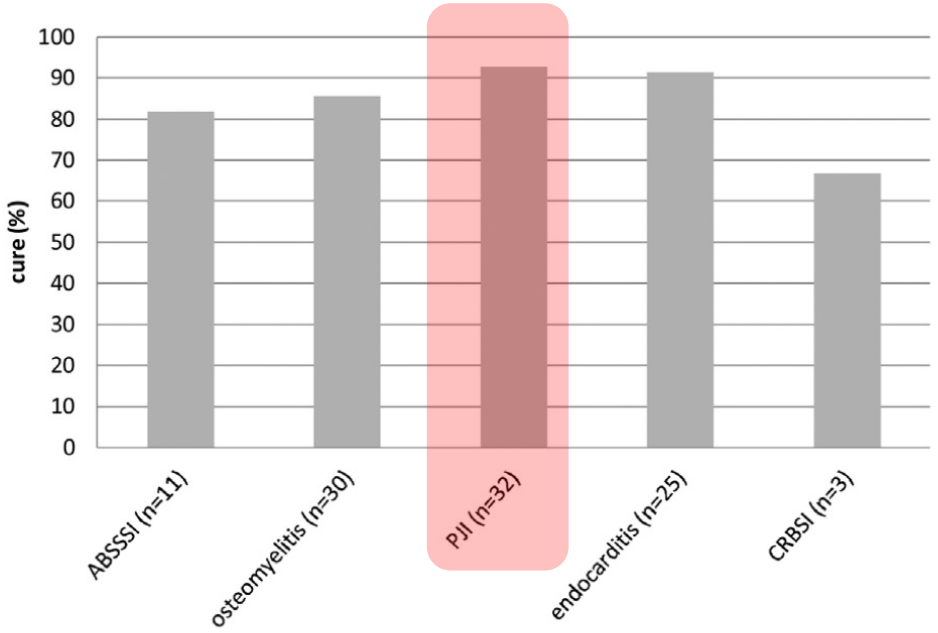


Figure 1. Percentage of cured patients in different indications for dalbavancin use.

Wunsch *et al.* IJCD 2019

Partie 3: les données de pharmacocinétique/pharmacodynamie

Réunion CRIOGO R LECOMTE

Remerciement au Dr Grégoire (pharmacologie CHU Nantes)

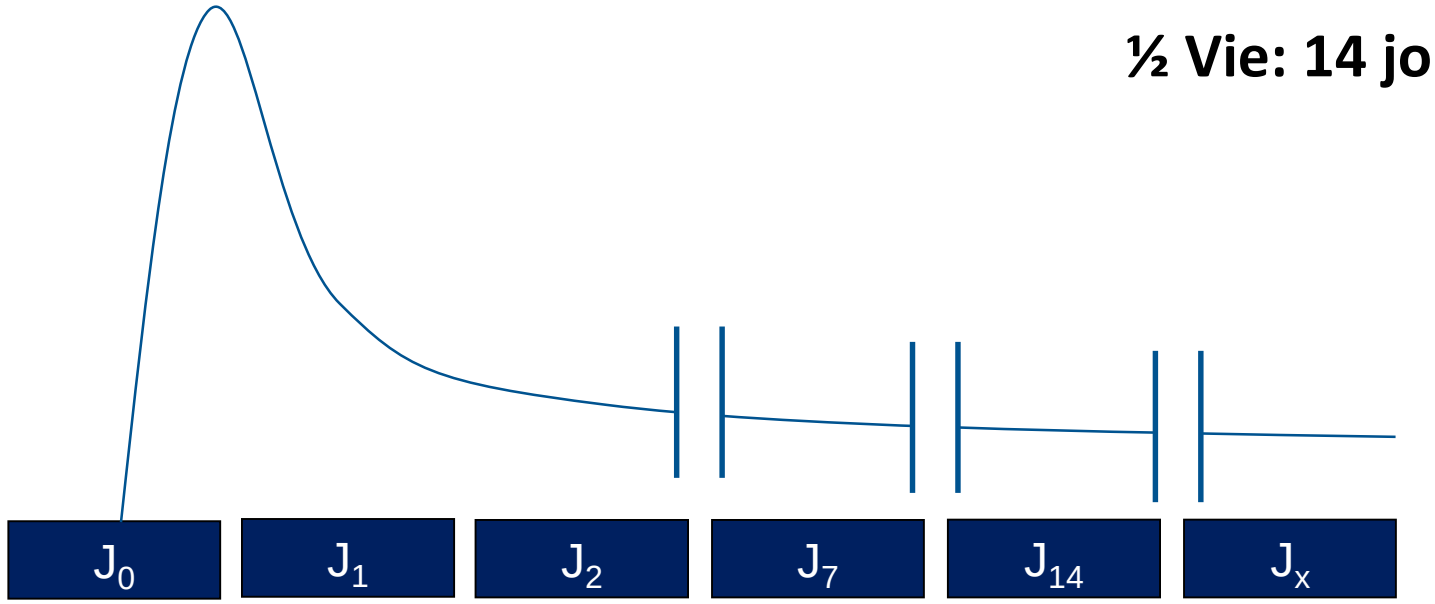
Un schéma d'administration très variable

Table 2
Dalbavancin dosing regimen and patient outcome, in total and according to site of infection

	Total ($n=75$)	BJI ($n=48$)	Endocarditis ($n=19$)	SSTI ($n=13$)	Vascular infection ($n=5$)	CLI ($n=4$)	BSI ($n=3$)	Mediastinitis ($n=2$)
Dalbavancin dosing regimen (n)								
1 dose	15	5	2	5	1	3	2	0
1 g	2	1	0	1	0	1	0	0
1.5 g	13	4	2	4	1	2	2	0
2 doses	44	34	11	7	2	1	1	1
Unknown	2	0	2	0	0	0	0	0
7-day interval								
1 g, 0.5 g	1	0	0	0	1	0	0	0
1 g × 2	1	1	0	0	0	0	0	0
1.5 g × 2	31	29	5	5	0	0	1	1
14-day interval								
1.5 g, 1 g	1	1	1	0	0	0	0	0
1.5 g × 2	7	2	3	2	1	1	0	0
21-day interval								
1.5 g, 0.5 g	1	1	0	0	0	0	0	0
3 doses	2	1	1	0	0	0	0	0
7-day interval								
1.5 g, 0.5 g × 2	1	0	1	0	0	0	0	0
1.5 g × 3	1	1	0	0	0	0	0	0
4 doses	4	3	1	1	0	0	0	0
7-day interval								
1.5 g × 4	1 [a]	0	0	0	0	0	0	0
14-day interval								
1 g, 0.5 g × 3	2	2	0	0	0	0	0	0
1.5 g × 4	1	1	1	1	0	0	0	0
>4 doses (max. 10)	5	3	1	0	2	0	0	0
7-day interval								
1 g, 0.5 g × N	1	1	0	0	0	0	0	0
1.5 g, 0.5 g × N	1	1	0	0	0	0	0	0
14-day interval								
1 g, 0.5 g × N	2	1	1	0	1	0	0	0
1.5 g × N	1	0	0	0	1	0	0	0
Suppressive	3	2	1	0	0	0	0	1
21-day interval								
1.5 g, 0.5 g × N	1	1	0	0	0	0	0	0
1.5 g × 3, 0.5 g × N	1	1	0	0	0	0	0	0
1.5 g × N	1	0	1	0	0	0	0	1

Dinh *et al.* IJAA 2019

Les cibles PK/PD



- **fASC0-24h/CMI > 300 pour les Staphylocoques**
- **fASC/CMI0-24h > 25 pour les Streptocoques**

→ Aucun intérêt du dosage et de la CMI pour les Streptocoques

→ fASC0-24h extrapolable à partir de la concentration résiduelle

Cible PK-PD: Objectif de concentration résiduelle:

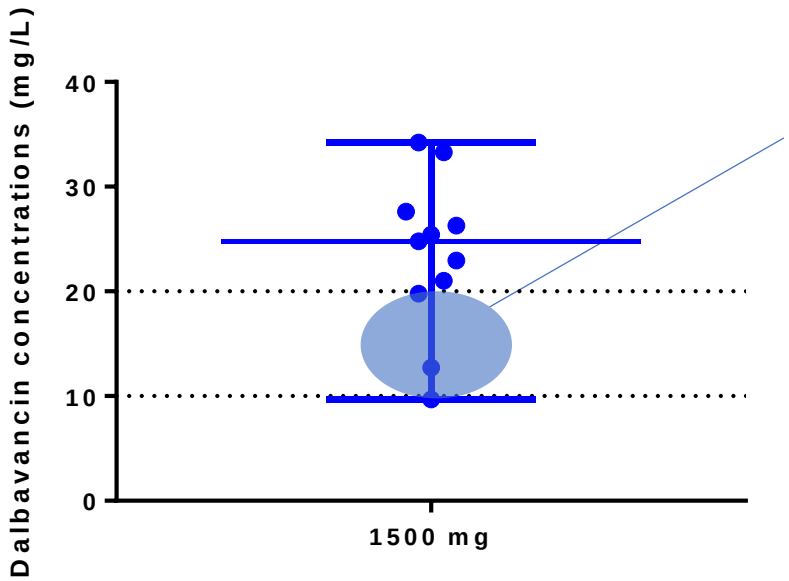
- **Pour une CMI à 0,125 mg/L: ≥ 20 mg/L (≈ fASC/CMI0-24h > 300 au seuil critique)**
- **Pour une CMI à 0,06 mg/L: ≥ 10 mg/L**

Dunne *et al.*, *AAC*, 2015
Données RCP

Traitement prolongé (exemple de l'IPOA)

En pratique

Concentrations résiduelles 14 jours après la première administration de 1500 mg



☐ **Pré-requis indispensables: CMI**

Données CHU de Nantes

☐ **2 injections de 1500 mg à 14 jours d'intervalle couvrent 6 semaines de traitement si la CMI ≤ 0,06 mg/L**

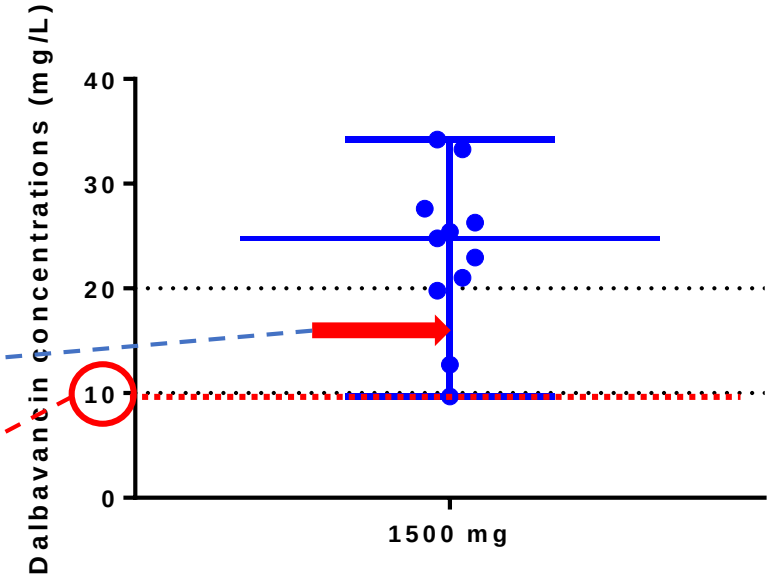
☐ **<u>Dosage en résiduelle à J14</u>:**

→ indispensable si seuil critique à 0,125 mg/L et traitement prolongé

→ cible PK-PD: concentration résiduelle ≥ 20 mg/L

→ si CMI: 0,125 mg/L et concentration résiduelle à J14 < 20 mg/L→ réinjection à J28 nécessaire

Traitement prolongé (exemple de l'IPOA)



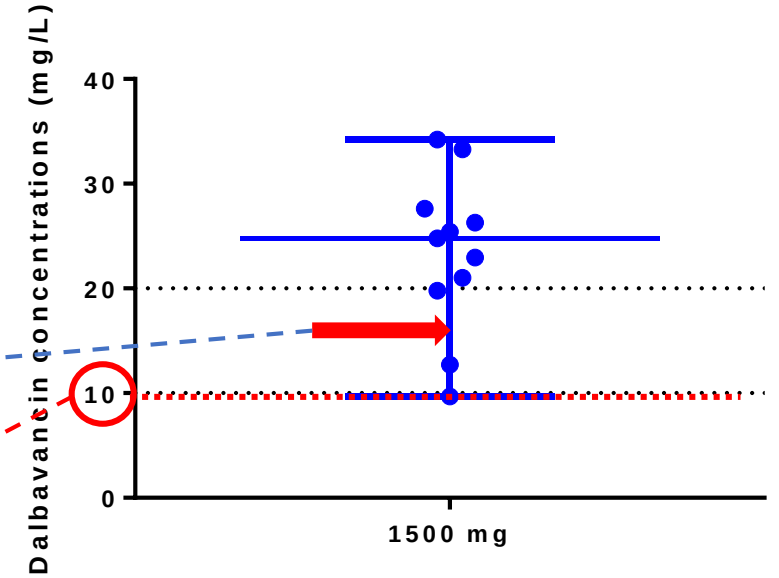
Dosage juste avant l'injection → 16 mg/L

CMI: 0,06 mg/L

J0 1500 mg

J14: 1500 mg

Traitement prolongé (exemple de l'IPOA)



Dosage juste avant l'injection → 16 mg/L

CMI: 0,06 mg/L

J0 1500 mg

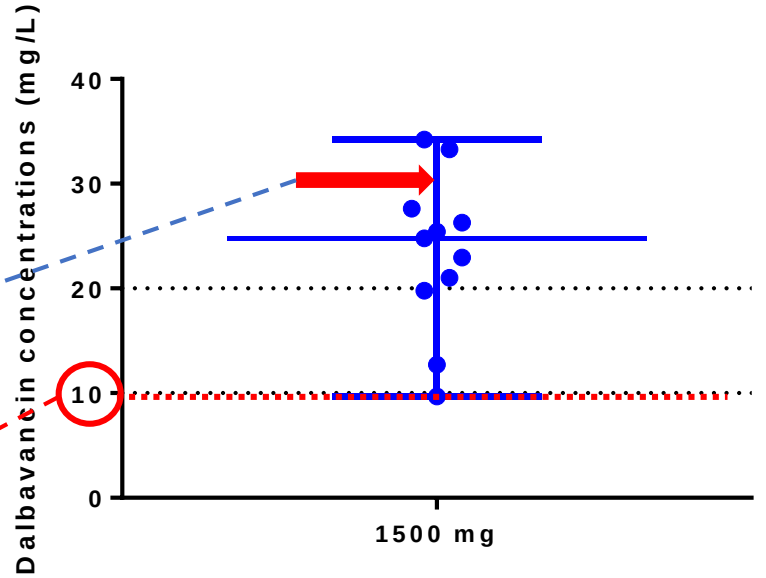
J14: 1500 mg

J28: 1500 mg

Traitement prolongé (exemple de l'IPOA)

Dosage juste avant l'injection → 31 mg/L

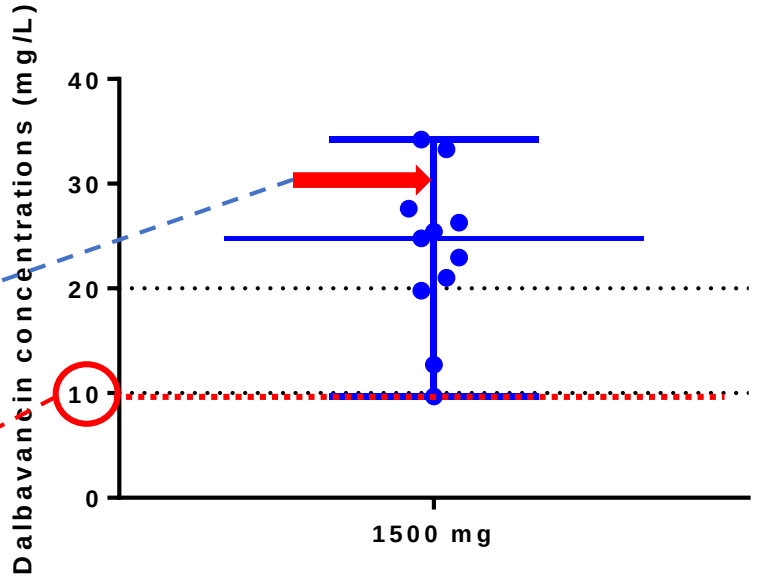
CMI: 0,06 mg/L



J0 1500 mg

J14: 1500 mg

Traitement prolongé (exemple de l'IPOA)



Dosage juste avant l'injection → 31 mg/L

CMI: 0,06 mg/L

J0 1500 mg

J14: 1500 mg

J35: 1500 mg

Diffusion tissulaire

30 volontaires sains dans 6 groupes traités par Dalbavancine 1000mg à différents temps avant une chirurgie programmée

TABLE 4 Dalbavancin tissue concentrations (safety population)

	Dalbavancin concn (mean [SD]; no. of samples) at hours (days) postdose that samples were collected:					
Tissue	12 (0.5)	24 (1)	72 (3)	168 (7)	240 (10)	336 (14)
Plasma (μg/ml)[a]	85.3 (18.9); 31	ND[b]	ND	ND	ND	15.3 (4.1); 31
Synovium (μg/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 (μg/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 (μg/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 (μg/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.

- ☐ **Os: ratio tissue/plasma: 0,27**
- ☐ **Membrane synoviale: ratio tissue/plasma: 1,04**
- ☐ **Ratio AUC os/plasma 13% (Vs 7% pour la vanco)**

Dunne *et al.*, *AAC*, 2015

Take home messages

Microbiologie:

- Spectre large sur les CG +
- CMI dalbavancine à demander si:
  - *E faecium*
  - Staphylocoques avec CMI Vanco ≥ à 2
  - Traitement prolongé

Clinique:

- Intérêt:
  1. germe multirésistant
  2. difficultés d'observance
  3. Problématique de voie d'abord
- Peu de données dans les IOA

Pharmacologie:

- ½ Vie de 14 jours.
- Un schéma de base à 1,5g 2 injection J1 J15 permet de couvrir 6 semaines.
- En cas de traitement > 6 semaines: dosages et CMI indispensables pour déterminer les intervalles de réinjection.

Merci de votre attention

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