DES-C Thématique n°10: IOA
Principes du traitement médical: Infection de prothèse articulaire

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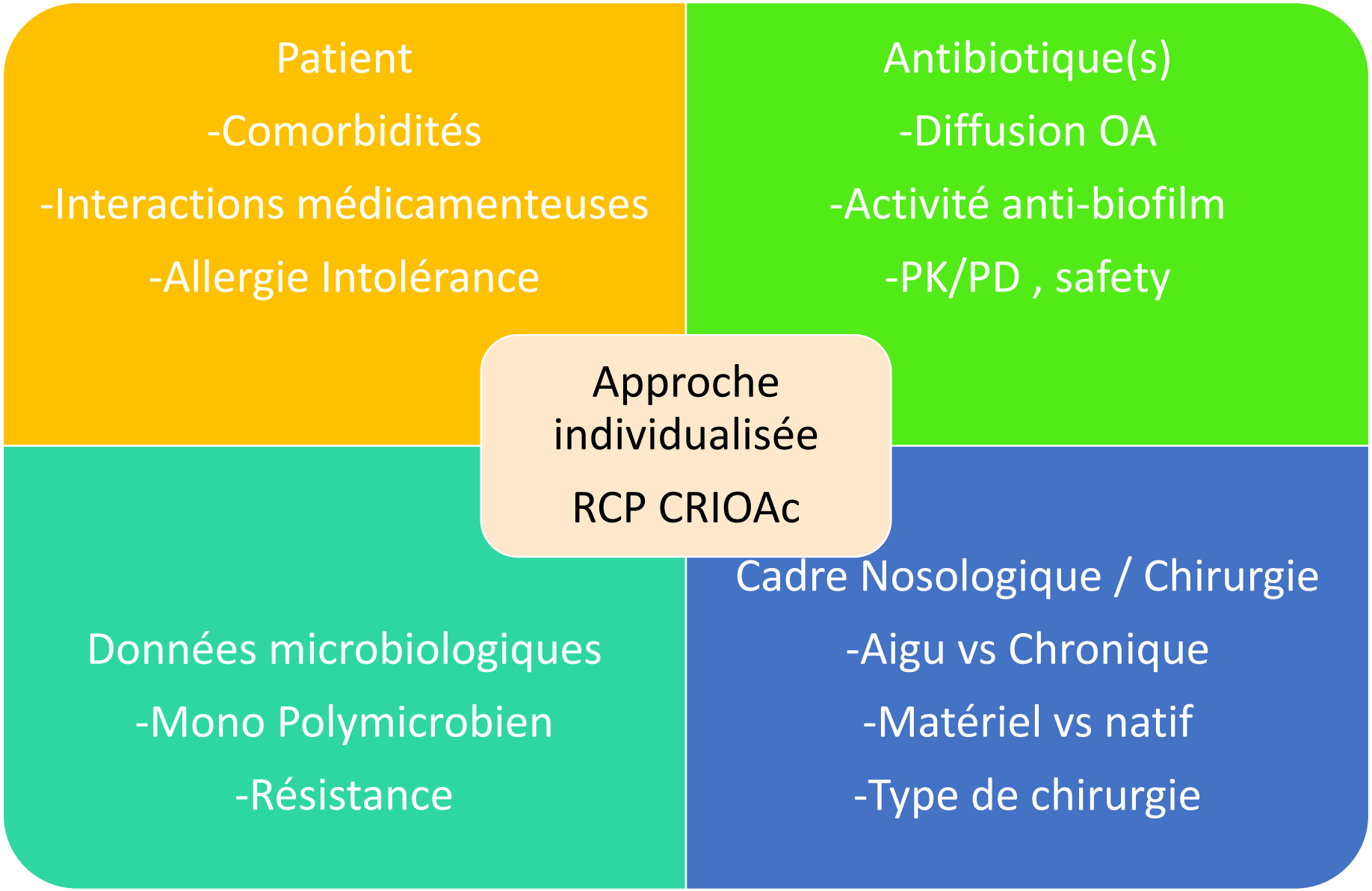
Plan

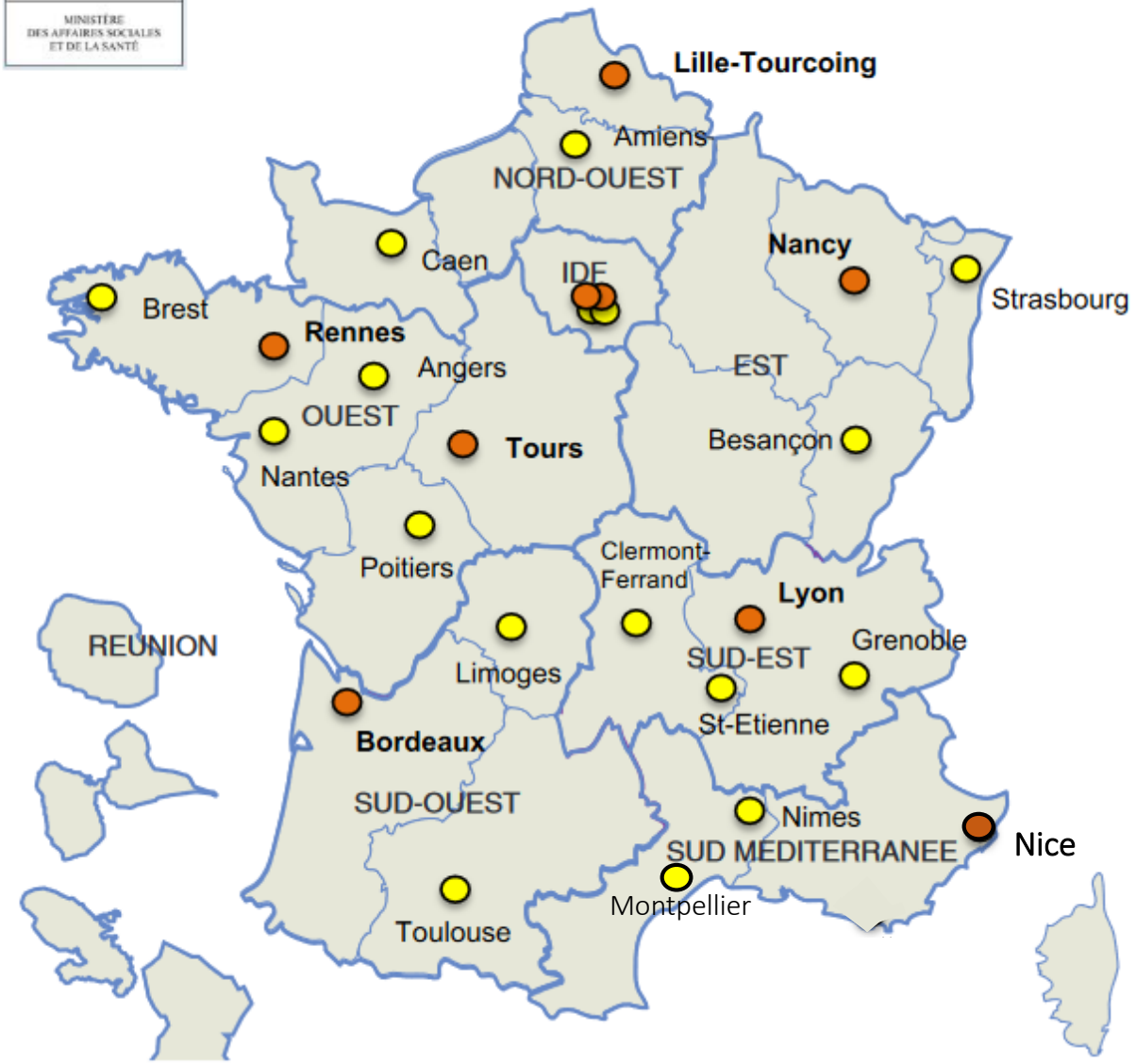
- Introduction
- Diffusion ostéo-articulaire des antibiotiques
- Place de la rifampicine
- Tolérance des traitements
- Traitement probabiliste post-opératoire
- Relais PO
- Durée des traitements
- Lipoglycopeptides à longue demi-vie
- Autres IOA
- Conclusions

PJI = prosthetic joint infection
IPA = infection de prothèse articulaire

Introduction


Patient
-Comorbidités
-Interactions médicamenteuses
-Allergie Intolérance
Antibiotique(s)
-Diffusion OA
-Activité anti-biofilm
-PK/PD , safety
Approche individualisée
RCP CRIOAc
Données microbiologiques
-Mono Polymicrobien
-Résistance
Cadre Nosologique / Chirurgie
-Aigu vs Chronique
-Matériel vs natif
-Type de chirurgie

Réseau des CRIOAc



Mandat 5 ans = 2023-2028

Missions

Soins

RCP

Enseignement

Recherche

Complications - Infection

The Journal of Arthroplasty 34 (2019) S337–S342

Mortality During Total Hip Periprosthetic Joint Infection

Kyle M. Natsuhara, MD *, Trevor J. Shelton, MD, John P. Meehan, MD,

- 23 études
- 19 169 patients
- Taux de mortalité à 1 an 4.22%
- Taux de mortalité à 5 ans 21.12%
- Odds ratio de décès par rapport à la population générale USA : 3.58

Au-delà de la mortalité, par rapport aux patients avec arthroplastie non compliquée d'infection: baisse de la qualité de vie et du niveau d'autonomie

Wildeman P et al. 2021 Clin Orthop Relat Res

The changing epidemiology of bacteraemic osteoarticular infections in the early 21st century

CMI 2015

O. Murillo[1], I. Grau[1], J. Lora-Tamayo[1], J. Gomez-Junyent[1], A. Ribera[1], F. Tubau[2], J. Ariza[1] and R. Pallares[1]

1) *Infectious Disease Service and* 2) *Microbiology Department, Hospital Universitari de Bellvitge, Barcelona, Spain*

	Total (n=601)	1985-1991 (n=70)	2007-2011 (n=183)
Age médian (IQR)	63 (50-74)	49 (24-64)	65 (53-77)
≥ 1 comorbidité	307 (51%)	16 (23%)	107 (59%)
Diabète	153 (26%)	11 (16%)	50 (27%)
Cardiovasculaire	88 (15%)	1 (1%)	42 (23%)
Insuffisance rénale	44 (7%)	0	20 (11%)
Ttt immunosupp.	88 (15%)	6 (9%)	30 (16%)

RESEARCH ARTICLE Open Access

Polypharmacy and adverse outcomes after hip fracture surgery

Maria Härstedt[1], Cecilia Rogmark[2], Richard Sutton[3], Olle Melander[1,4] and Artur Fedorowski[1,5*]

Härstedt *et al. Journal of Orthopaedic Surgery and Research* (2016) 11:151

272 fracture de hanche
à 6 mois

- 36 (13,2%) décès
- 86 (31,6%) réadmission
  - -nombre de ttt = fdr réadmission
  - -AVK diurétique tramadol = fdr chute

Diffusion ostéo-articulaire des antibiotiques

Diffusion ostéo-articulaire des antibiotiques

➢Hétérogénéité des données

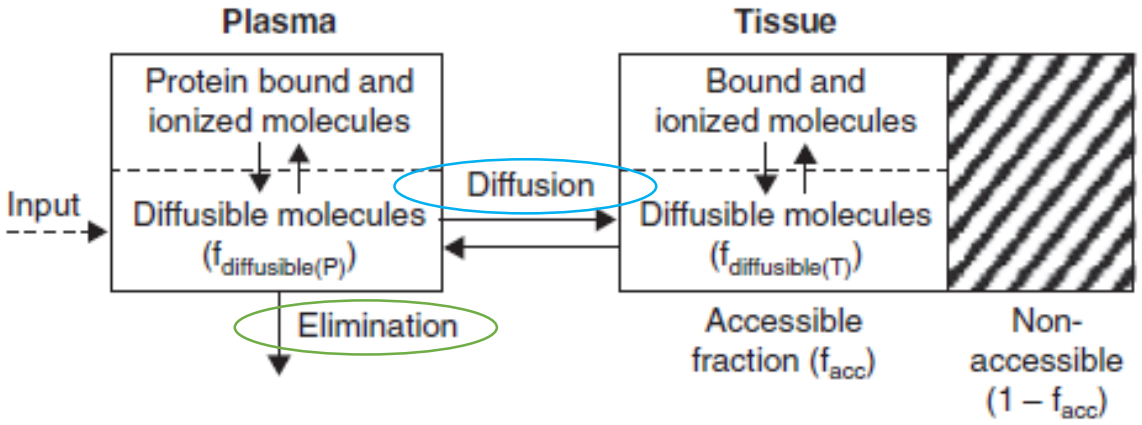
- Données chez l'humain vs modèles animaux
- Os cortical vs Os spongieux (cort. < spon.)
- Avec ou sans inflammation
- Après dose unique vs doses répétées
- Souvent prélèvement unique
- Technique de dosages des antibiotiques
- Estimation de la densité osseuse (mg/kg vers mg/L) pour calcul des ratios C_{os}/C_{plasma} variable (1,3 à 1,9)

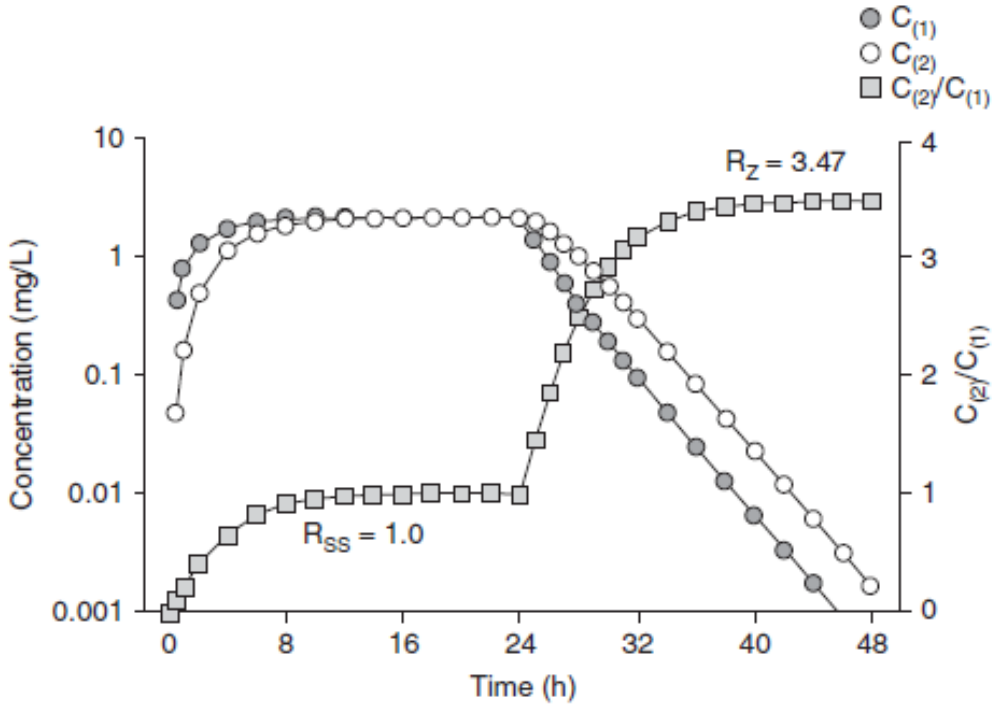
Clin Pharmacokinet 2009

Penetration of Antibacterials into Bone

Pharmacokinetic, Pharmacodynamic and Bioanalytical Considerations

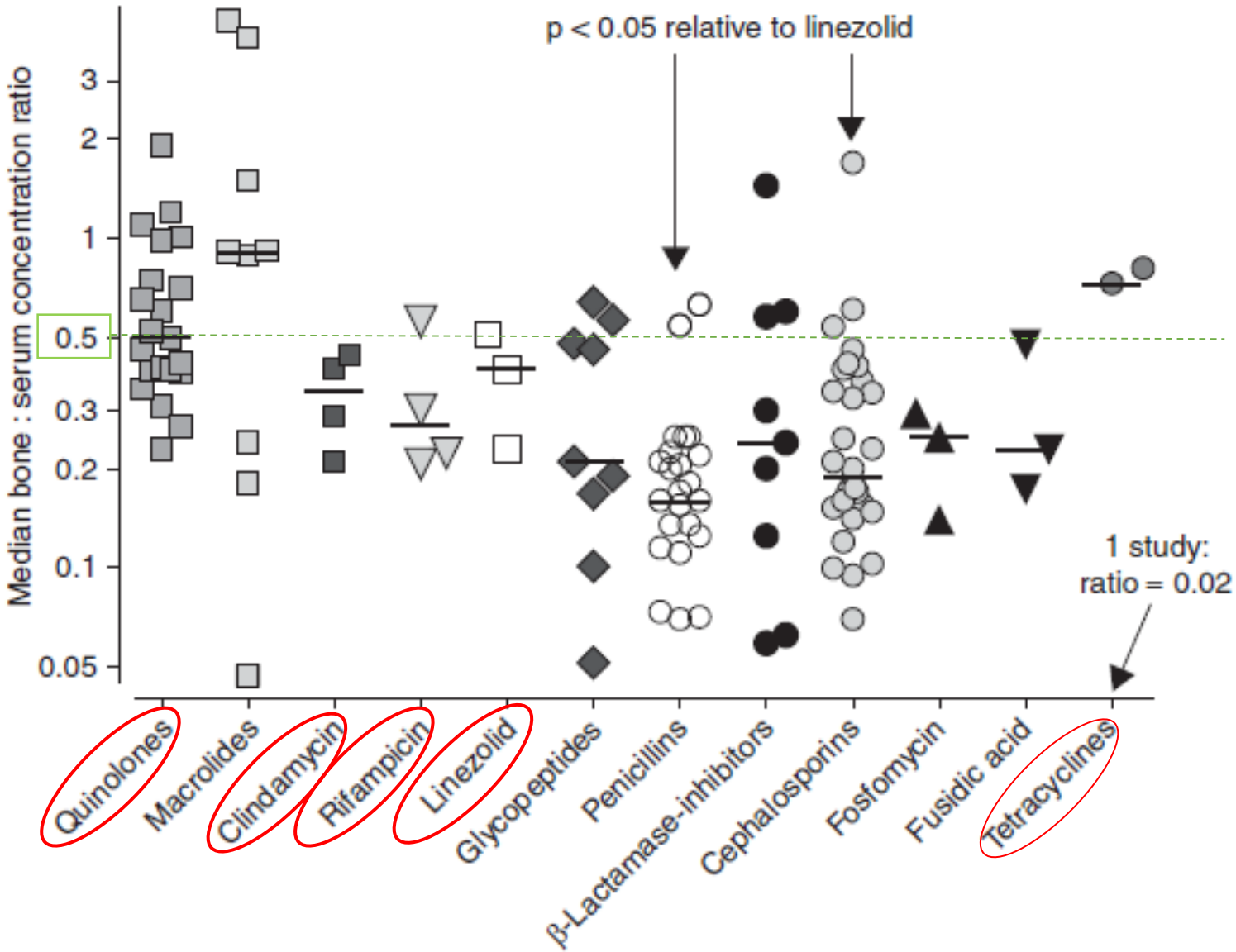
Cornelia B. Landersdorfer,[1] *Jürgen B. Bulitta,*[1] *Martina Kinzig,*[1] *Ulrike Holzgrabe*[2] and *Fritz Sörgel*[1,3]





Simulated plasma and bone tissue concentrations and bone : plasma concentration ratio for a two-compartment model after a 24-hour constant-rate infusion

Human bone : serum or bone : plasma concentration ratios



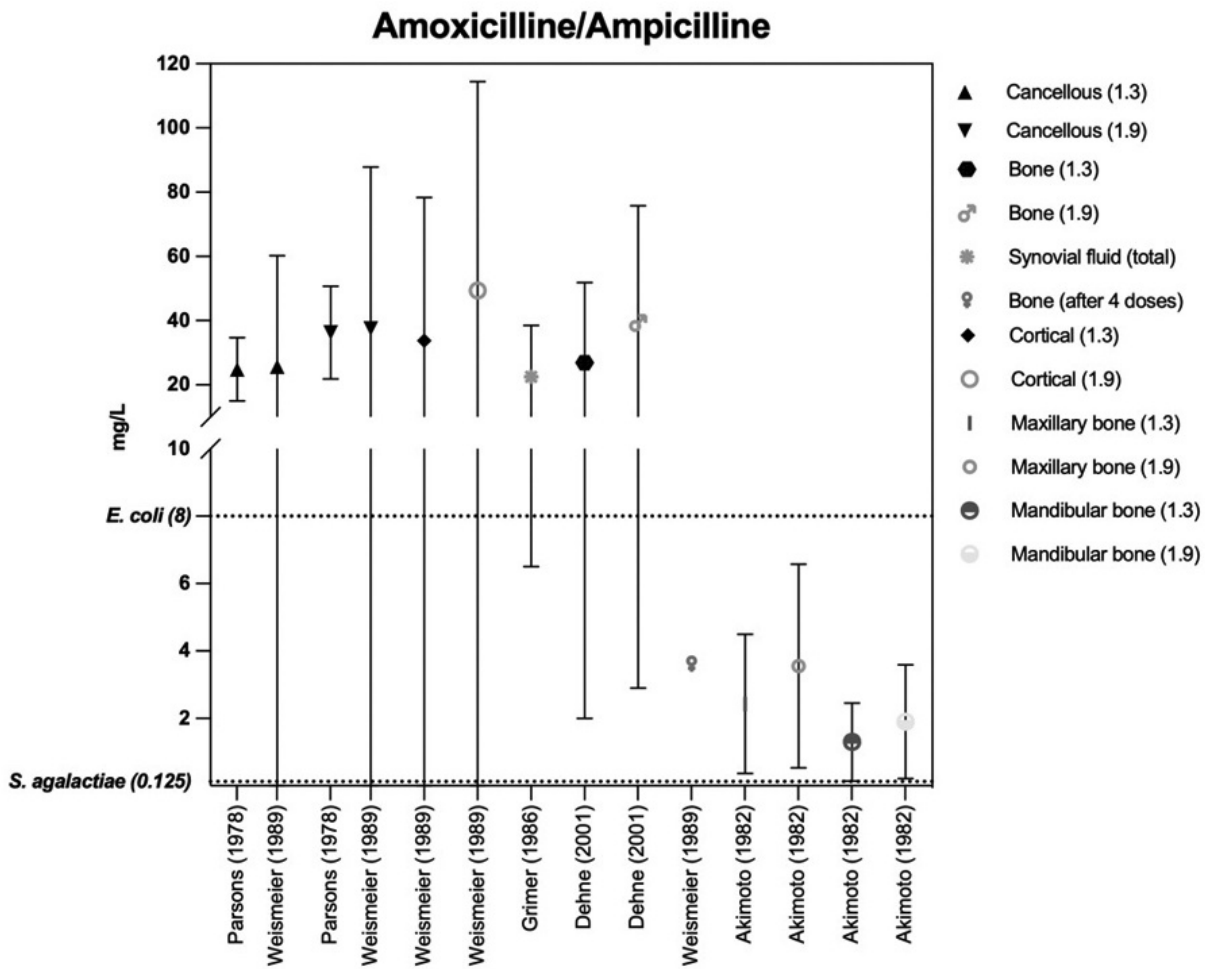
REVIEW

OPEN ACCESS Check for updates

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
2022, VOL. 18, NO. 9, 587–600
https://doi.org/10.1080/17425255.2022.2117607

The mysteries of target site concentrations of antibiotics in bone and joint infections: what is known? A narrative review

Birgit C.P. Koch[a,b,c], Qiaolin Zhao[a,c], Maartje Oosterhoff[a], Jakob van Oldenrijk[d], Alan Abdulla [a,b,c], Brenda C.M. de Winter[a,b,c], Koen Bos[d] and Anouk E. Muller[b,e,f]



Extended-Duration Dosing and Distribution of Dalbavancin into Bone and Articular Tissue

April 2015 Volume 59 Number 4 Antimicrobial Agents and Chemotherapy

Michael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[c]* Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]

Durata Therapeutics, Inc., Branford, Connecticut, USA[a]; Institute for Clinical Pharmacodynamics, Latham, New York, USA[b]; PRACS Institute, Ltd., Fargo, North Dakota, USA[c]

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.

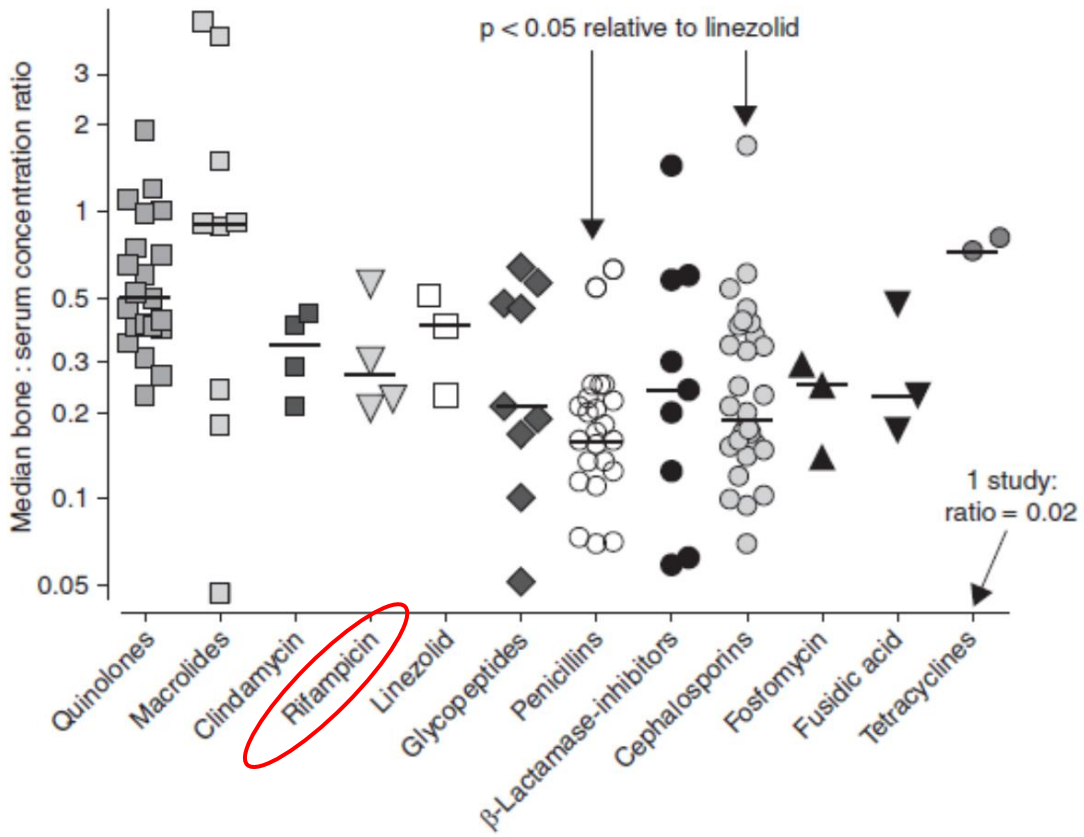
7.4%

27%

Ratio AUC/CMI os/plasma : 13%

CMI_{90} MSSA : 0,06 mg/l

Rifampicine



Rifampicine

Pic plasmatique possible 6 à 10 mg/L

Breakpoint EUCAST *S. aureus* : 0,06 mg/L

Rifampicine et PJI

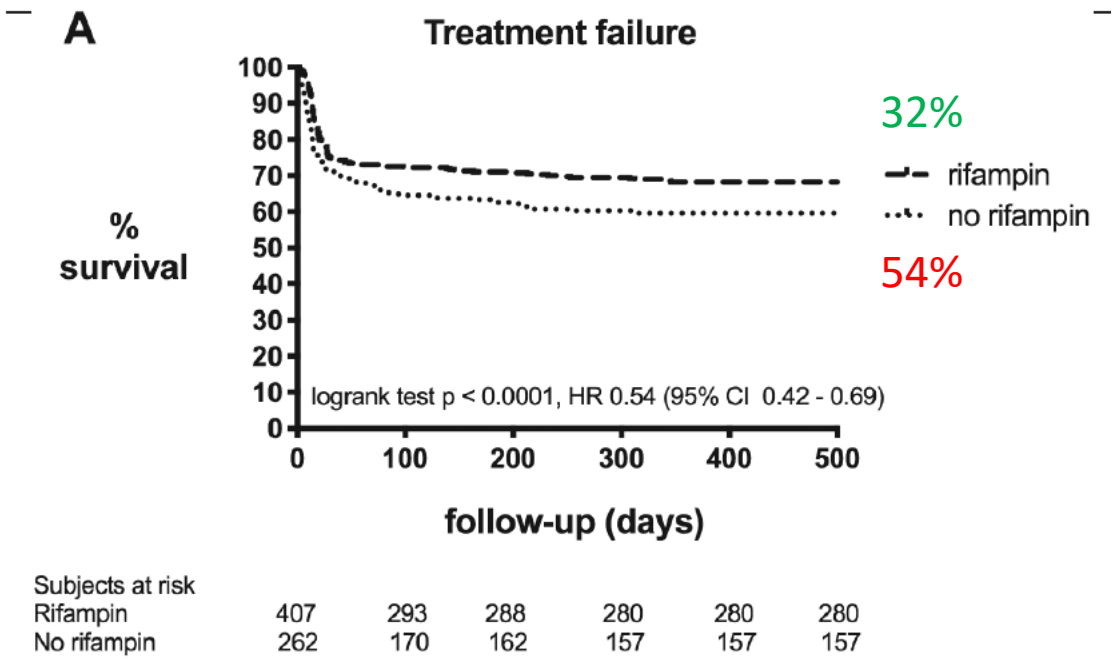
Authors	Sample size	Rifampin effect
Senneville et al. Clin Infect Dis 2011.	98	75% vs 47% success
Holmberg et al. Acta Orthop 2015.	86	81% vs 41% success
Chaussade et al. Int J Infect Dis 2017.	87	HR 0.91 (0.34-2.44)
Lesens et al. Eur J Clin Microb ID 2018.	89	HR 0.21 (0.07-0.63)
Becker et al. J Bone Jt Infect 2020.	79	HR 0.17 (0.06-0.45)
Davis et al. Open Forum ID 2022.	352	OR 1.25 (0.85-1.85)
Espindola et al. Infect Dis Ther 2022.	99	OR 0.2 (0.1-0.7)

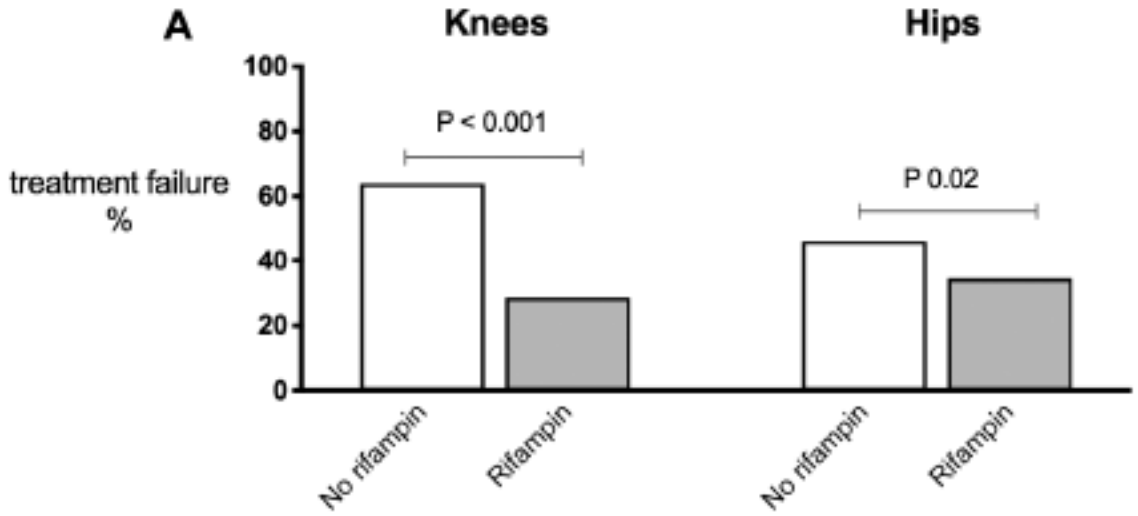
CID 2021:73 (1 November) • Beldman et al

If, When, and How to Use Rifampin in Acute Staphylococcal Periprosthetic Joint Infections, a Multicentre Observational Study

Mark Beldman,[1] Claudia Löwik,[1] Alex Soriano,[2] Laila Albiach,[2] Wierd P. Zijlstra,[3] Bas A. S. Knobben,[4] Paul Jutte,[1] Ricardo Sousa,[5] André Carvalho,[5] Karan Goswami,[6] Javad Parvizi,[6] Katherine A. Belden,[7] and Marjan Wouthuyzen-Bakker[8]

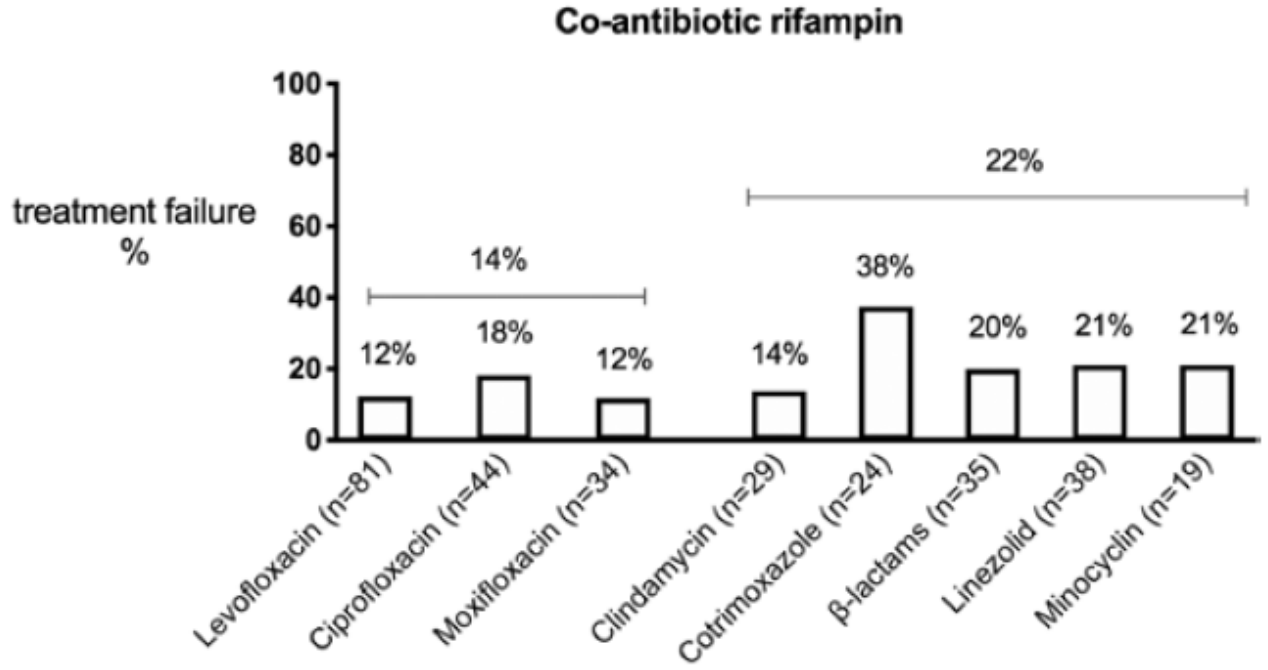
669 patients, 617 infections aiguës, 52 secondaires aiguës
Rifampicine chez 407 (61%) patients





Importance des FQ dans le traitement des IOA associées à du matériel étranger

staphylocoques



Beldman *et al.* 2021 CID

P. aeruginosa

TABLE 2 | Multivariate Cox analysis that includes significant determinants for failure identified in the univariate analysis.

	HR	95% CI	*p*
Optimal surgical treatment*	0.32	0.11–0.98	0.045
IV effective treatment of at least 3 weeks*	0.15	0.004–0.054	0.003
Ciprofloxacin for at least 3 months*	0.23	0.07–0.75	0.015

HR, Hazard ratio; 95% CI, 95% confidence interval.
**After exclusion of the five patients who finally received suppressive antimicrobial therapy.*

Cerrioli *et al.* 2020 Front Med

Tolérance des traitements

Rifampicine (RFP) et Fluoroquinolones (FQ) : (in)tolérance

Etudes / localisation	Taux d'effets secondaires RFP/FQ	Taux d'effets secondaire autres molécules
« Essai randomisé de Zimmerli »	RFP+FQ 28%	
« Série 98 IOAM à *S. aureus* de Senneville »	RFP+FQ 33%	
CHU de Nice, 238 IOA *Staphylococcus* spp	RFP+FQ 14%	CD+RFP 9%, CD+FQ 5.5%
HCL, 200 IOA SAMS	RFP ou FQ 9.5%	

CD: Clindamycine

Zimmerli W et al. *JAMA* 1998
Senneville E et al. *Clin Infect Dis* 2011
Danré A et al. *Joint Bone Spine* 2015
Valour F et al. *Antimicrobs Agent Chemoter* 2014

Safety and Tolerability of Fluoroquinolones in Patients with Staphylococcal Periprosthetic Joint Infections

Nicholas J. Vollmer,[1] Christina G. Rivera,[1] Ryan W. Stevens,[1] Caitlin P. Oravec,[2] Kristin C. Mara,[3] Gina A. Suh,[2] Douglas R. Osmon,[2] Elena N. Beam,[2] Matthew P. Abdel,[4] and Abinash Virk[2]

Clinical Infectious Diseases 2022

MAJOR ARTICLE

156 patients, RFP in both groups

Overall, unplanned drug discontinuation occurred in 35.6% of patients in the FQ group and 3% of patients in the non-FQ group.

Severe adverse effects were reported in 7.8% of patients in the FQ arm and 1.5% in the non-FQ arm, respectively (*P* = .14)

Original article Infectious Diseases Now 53 (2023) 104671

Assessment of the impact of pharmacist-led intervention with antibiotics in patients with bone and joint infection

Philippine Marque [a], Gwenael Le Moal [b], Chloé Labarre [c], Jérémy Delrieu [a], Pierre Pries [c,d], Antoine Dupuis [a,d], Guillaume Binson [a,d], Pauline Lazaro [a,*]

Période contrôle 105 patients
Période intervention 59 patients

- Ré hospitalisation pour un motif en lien avec l'IOA : 23 (22%) contrôle, 3 (5%) intervention
  -hospit pour échec (incluant de l'inobservance, effets secondaires)
- Moins de modifications de traitement dans la période intervention

Original article Infectious diseases now 54 (2024) 104958

Impact of pharmacist-led interventions in a multidisciplinary consultation meeting for bone and joint infection

Anne Elisabeth Royere [a], Xavier Pourrat [a], Louis-Romée Le Nail [b], Marie-Frederique Lartigue [c,d], Adrien Lemaignen [e,f], Vianney Tuloup [a,g,*], Marion Lacasse [f], upon members of the Tours CRIOAC

Traitement probabiliste

Utilité ?

Contexte	Type d'IPA	Chir	Evolution	ATB probabiliste inadaptée	Facteurs d'échec	Ref
Espagne monocentrique rétro. 2009-2018, 80 patients	Précoce <3 mois 84%	DAIR	34 échecs 46 succès	14 (41%) 1 (2.2%)	**ATB proba inadaptée** ASA > 2	Barbero-Allende 2021 J Span Soc of Chem
Finlande monocentrique rétro. 2001-2009, 113 patients	Précoce <4 sem 69% Hématogène 31%	DAIR	43 échecs 70 succès	10 (23.3%) 3 (4.3%)	**ATB proba inadaptée** øRFP	Puhto 2015 International Orthop
Australie multicentrique rétro. 2006-2008, 147 patients	Précoce <3 mois	DAIR (76%)	43 échecs 104 succès	30 (70%) 20 (19%)	**ATB proba inadaptée** ATCD d'IPA Durée ATB<90j	Peel 2012 J Hosp Infection

Quelles molécules ?

Molécule anti-Gram -	Nombre de réponses
Carbapénème	1
Céfépime	5
Ceftazidime	1
Pipéracilline-Tazobactam	19
Molécule anti-Gram +	
Daptomycine	10
Linézolide	3
Vancomycine	9

Autres	
Ceftobiprole	2
Gentamicine	1

Le Maréchal M et al. 2021 BMC Inf Dis

A adapter selon l'épidémiologie locale

- Entérobactéries groupe 3 ? Pyo ?
- Choix de la βL, C3G suffisante ?

Anti G -

- Impact écologique céfépime mieux que P/T ?
- Effets secondaires Vanco + P/T ≫ Vanco + Céfépime
- Neurotoxicité du céfépime

Triffault-Fillit, JAC, 2020

Anti G +

SCN Méthi-R

- Gestion de la daptomycine + facile que vancomycine
- Linézolide : Per Os, bien toléré sur des durée courtes, danger des interactions

Relais Per Os, quand ?

Hors bactériémie / endocardite

Time to Positivity of Cultures Obtained for Periprosthetic Joint Infection

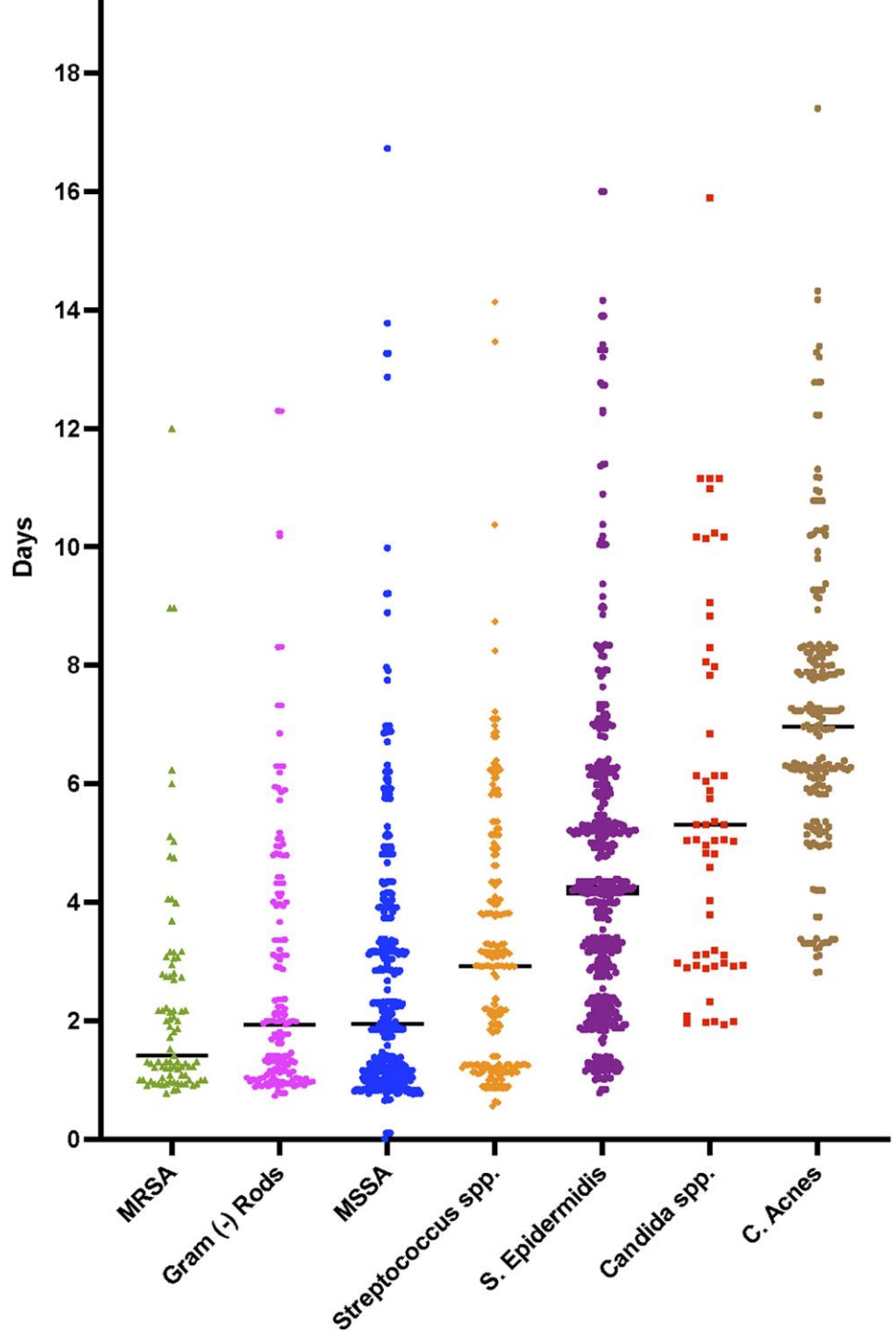
Saad Tarabichi, MD, Graham S. Goh, MD, Luigi Zanna, MD, Qudratullah S. Qadiri, BS, Colin M. Baker, BS, Thorsten Gehrke, MD, Mustafa Citak, MD, PhD, and Javad Parvizi, MD, FRCS

Investigation performed at the Rothman Orthopaedic Institute, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

J Bone Joint Surg Am. 2023;105:107-12 • http://dx.doi.org/10.2106/JBJS.22.00766

536 IOAP chroniques
Temps médian de positivité: 3.3j (IQR 1.9 5.4)

Autre référence: Deroche et al. J Clin Med 2019



ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Li et al. 2019 NEJM

J Antimicrob Chemother 2021; **76**: 3033–3036
doi:10.1093/jac/dkab271 Advance Access publication 18 August 2021

Journal of Antimicrobial Chemotherapy

Fully oral targeted antibiotic therapy for Gram-positive cocci-related periprosthetic joint infections: a real-life before and after study

Alexandre Coehlo[1], Olivier Robineau [1,2,3,4], Marie Titecat[4], Nicolas Blondiaux[4], Hervé Dezeque[4], Pierre Patoz[1], Caroline Loiez[4], Sophie Putman[4], Eric Beltrand[4], Henri Migaud[2,3,4] and Eric Senneville[1,2,3,4]*

Passage de 13 à 9 jours IV en post-op

J Antimicrob Chemother 2024; **79**: 327–333
https://doi.org/10.1093/jac/dkad382 Advance Access publication 19 December 2023

Journal of Antimicrobial Chemotherapy

Prosthetic joint infections: 6 weeks of oral antibiotics results in a low failure rate

Pierre-Marie Roger [1,2]*, Frédéric Assi[1] and Eric Denes[3]

3 jours ou moins IV, 90.8% de succès

Durée de l’antibiothérapie

ORIGINAL ARTICLE

Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection

NEJM 2021

L. Bernard, C. Arvieux, B. Brunschweiler, S. Touchais, S. Ansart, J.-P. Bru, E. Oziol, C. Boeri, G. Gras, J. Druon, P. Rosset, E. Senneville, H. Bentayeb, D. Bouhour, G. Le Moal, J. Michon, H. Aumaître, E. Forestier, J.-M. Laffosse, T. Begué, C. Chirouze, F.-A. Dauchy, E. Devaud, B. Martha, D. Burgot, D. Boutoille, E. Stindel, A. Dinh, P. Bemer, B. Giraudeau, B. Issartel, and A. Caille

Subgroup	6-Wk Therapy	12-Wk Therapy	Risk Difference (95% CI)
	no. of patients with event/total no. (%)		*percentage points*
All patients	32/190 (16.8)	15/188 (8.0)	8.9 (2.2 to 15.6)
Surgical procedure			
Débridement	23/75 (30.7)	11/76 (14.5)	16.2 (2.9 to 29.5)
Two-stage revision	6/40 (15.0)	2/41 (4.9)	10.1 (–3.1 to 23.3)
One-stage revision	3/75 (4.0)	2/71 (2.8)	1.2 (–4.8 to 7.1)
Affected joint			
Hip	19/122 (15.6)	9/117 (7.7)	7.9 (–0.2 to 16.0)
Knee	13/68 (19.1)	6/71 (8.5)	10.7 (–0.9 to 22.2)
Episode of prosthetic joint infection			
First	27/162 (16.7)	13/160 (8.1)	8.5 (1.4 to 15.7)
At least the second	5/28 (17.9)	2/28 (7.1)	10.7 (–7.0 to 28.4)

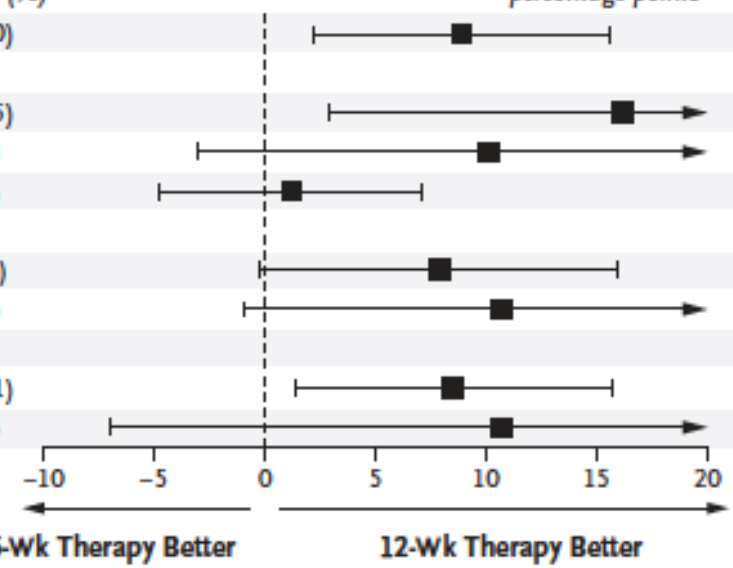
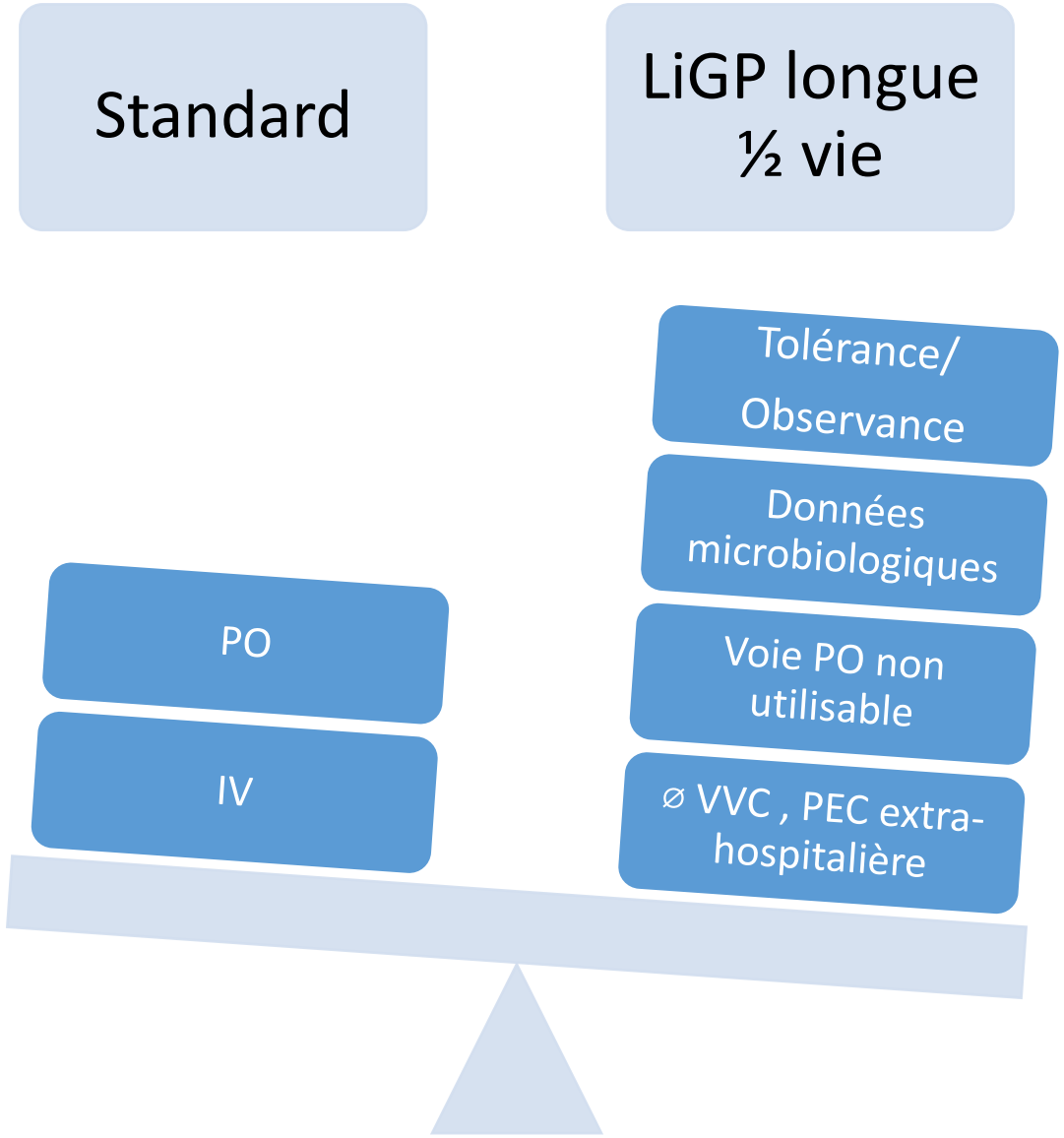


Figure 2. Exploratory Subgroup Analyses of Persistent Infection within 2 Years after the Completion of Antibiotic Therapy (Primary Outcome).

LiGP à longue demi-vie

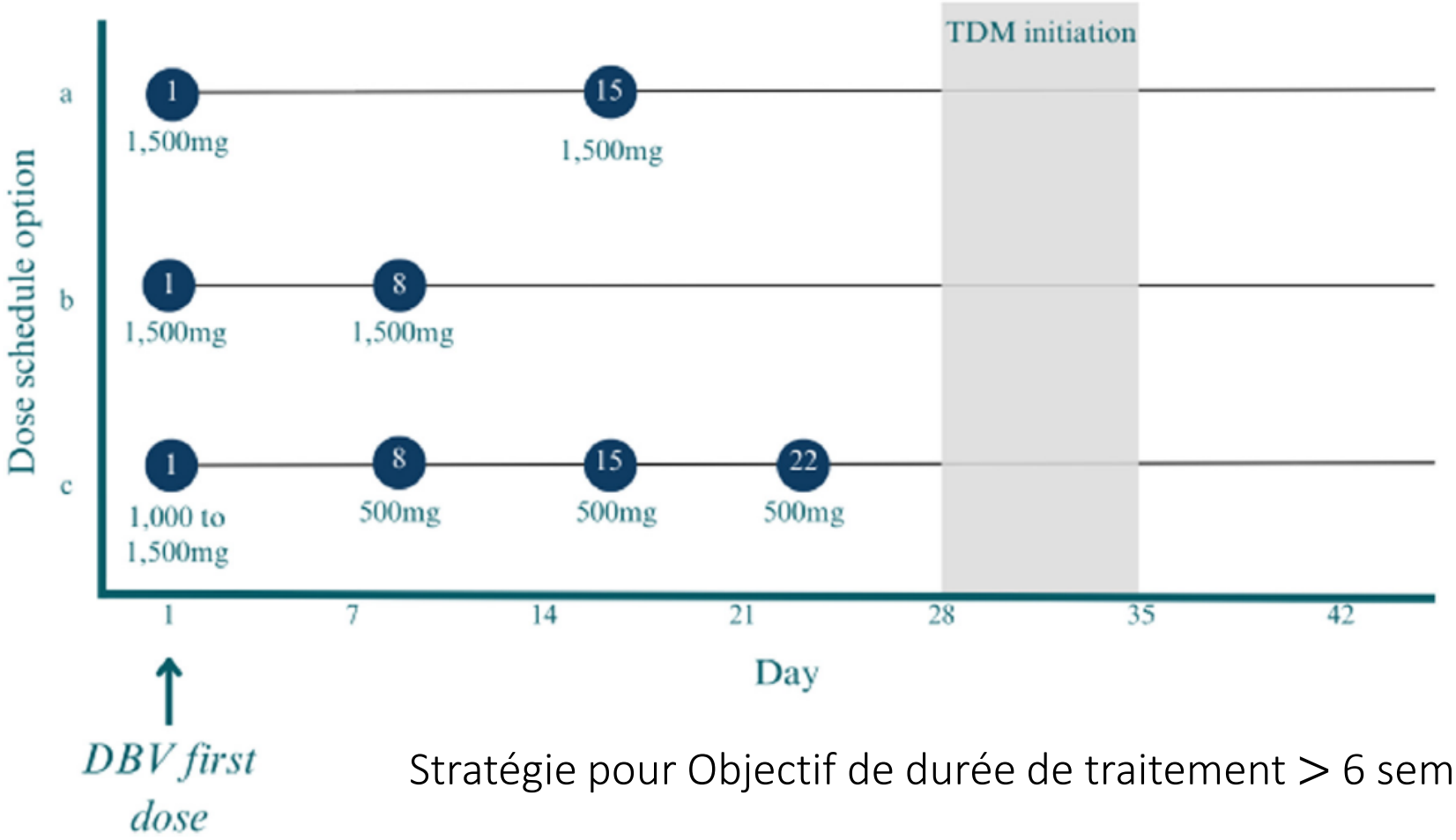
Pourquoi utiliser un LiGP à longue demi-vie?



Expert Opinion on Dose Regimen and Therapeutic Drug Monitoring for Long-Term Use of Dalbavancin: Expert Review Panel

Eric Senneville[a,*], Guillermo Cuervo[b], Matthieu Gregoire[c,d], Carmen Hidalgo-Tenorio[e,f], François Jehl[g], Jose M. Miro[b,h], Andrew Seaton[i], Bo Söderquist[j,k], Alex Soriano[l,h], Florian Thalhammer[m], Federico Pea[n,o]

International Journal of Antimicrobial Agents 62 (2023) 106960



The authors suggest that if the blood serum concentration of dalbavancin is > 8 mg/L, TDM should be repeated in 1 weeks. If the blood serum concentrations of dalbavancin is < 8 mg/L, the next dose of dalbavancin should be given

Stratégie pour Objectif de durée de traitement > 6 semaines

Autres IOA

SPILF update on bacterial arthritis in adults and children

2023

Recommendation 2: Probabilistic antibiotherapy

- purulent synovial fluid (with negative or unavailable direct examination results) + anamnesis compatible with the septic arthritis diagnosis + expert advice
→ cefazolin* or pencillin M (cloxacillin, oxacillin), +/- broadened spectrum if anamnesis suggests a specific bacterium.

Recommendations 1: Treatment durations

- *S. aureus*, and enterobacterales 6 weeks
- *Streptococcus* spp 4 weeks
- *Neisseria gonorrhoeae*: 7 days
- Early arthritis (evolution < 4 weeks), by direct inoculation of the small joints of the hands, following proper surgical hand washing: 14 days in the absence of osteolysis.

Recommendation 4: MSSA oral relay

- The molecule for oral relay is chosen according to antimicrobial susceptibility.
- Only with certain molecules is monotherapy possible.
- If monotherapy, clindamycin is proposed as first-line treatment in the event of sensitivity without inducible MLSb phenotype, that is to say a strain sensitive to clindamycin and erythromycin.
- The levofloxacin/rifampicin or levofloxacin/clindamycin associations may likewise be proposed as first-line treatment.
- In the event of resistance to clindamycin or of an inducible MLSb phenotype, doxycyclin, an oxazolidinon (linezolid, tedizolid) or cotrimoxazol may be proposed.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Short 3-week antibiotic treatment versus 6 weeks in adults with septic arthritis of native joint: a randomized, open label, non-inferiority trial

SHASAR

Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial

*Louis Bernard, Aurélien Dinh, Idir Ghout, David Simo, Valerie Zeller, Bertrand Issartel, Vincent Le Moing, Nadia Belmatoug, Philippe Lesprit, Jean-Pierre Bru, Audrey Therby, Damien Bouhour, Eric Dénes, Alexa Debard, Catherine Chirouze, Karine Fèvre, Michel Dupon, Philippe Aegerter, Denis Mulleman, on behalf of the Duration of Treatment for Spondylodiscitis (DTS) study group**

Conclusions

Levofloxacine		***Staphylococcus spp* :** **IV** ou **PO:** 750 mg/j en une seule administration
		***Enterobacterales* :** **IV** ou **PO**: 500 mg/j en une seule administration

Canouï E et al. JAC 2022

Clindamycine		**IV ou PO** : - poids <70 kg : 600mg/ 8h - poids> 70kg : 900 mg/ 8h

RFP Clinda
Zeller V et al. CMI 2021

Rifampicine		**IV ou PO** : 10 mg/kg/j

-Attente publication résultats EVRIOS
-PK/PD: S. Goutelle RICAI 2021

Recommandations disponibles

PJI

- ICM 2018, à venir ICM 2025
- SEIMC 2017
- SPILF 2008

PVO

- SPILF 2023

AS

- SFR SPILF SOFCOT 2023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RandOmised Arthroplasty infection worlDwide Multidomain Adaptive Platform trial – Synopsis

1.1 Overview of initial trial design (given only as an example, at initial trial launch)

SILOS	DOMAINS			
	Surgical Rx	*Antibiotic duration*	*Antibiotic choice*	*Future domain*
Early* PJI	No randomisation options[1]	For one stage: Total 6 weeks versus 12 weeks post the one-stage For two-stage – 7 days versus 12 weeks post 2nd stage	Backbone regimen with or without adjunctive oral rifampicin	A vs B *(e.g. choice of irrigation fluids; adjunctive vitamin C; antidepressants)*
Late acute* PJI	DAIR versus revision[2]			
Chronic* PJI	One stage versus two stage revision			

Merci